Detailed Study Notes: Episode 453

Nick Gant, PhD - Cognitive Performance: Impact of Caffeine, Nicotine & Creatine

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Introduction to this Episode

The brain plays a central role in both physical and psychological function and performance. The brain also has a very high energy demand. In addition, fatiguing conditions can cause impairment of cognitive performance.

One area of research in neurometabolism related to the potential use of nutrients on improving cognitive function, as well as "rescuing" the fatigue-related declines in performance.

Nick Gant is Director of the Exercise Neurometabolism Laboratory at the University of Auckland. His group uses interdisciplinary approaches from the nutritional sciences and neurosciences to investigate the role of nutrition in brain health and performance. Nick is particularly interested in foods and supplements that prevent brain fatigue and improve physical and cognitive function.

In this episode, the potential impact of creatine, caffeine, nicotine and exogenous ketones were discussed.

Connection to Previous Episodes

Some previous podcast episodes that touch on related topics:

- #438: Diet, Brain Health & Cognitive Function
- #304: Tommy Wood, MD, PhD – Neurodegenerative Disease, Traumatic Brain Injury & Genetics
- #241: Elise Facer-Childs, PhD – Circadian Phenotypes, Brain Function & Athletic Performance

In addition, we have a FAQ on creatine available here: Creatine - Common Questions Answered

Design of the Lab

Dr. Gant outlined some of the core aspects of his lab where they investigate some of the topics discussed in this episode. These include:

- An area for people to study and do cognitive testing and panel type food testing
- An exercise facility where things are environmentally controlled: temperature, light levels, noise levels, etc. are very important to control when assessing brain function.
- Equipped with ability to track the eyes.
- Importantly they can assess brain function during exercise, as opposed to just before/after
- MRI scanner
- Driving simulator – can assess "real-world" impact of interventions
- Virtual reality system attached to all of the exercise equipment so people can be immersed fully in what they're doing, and the researchers can present them with stimuli whilst they're exercising.

What is "Fatigue"?

Fatigue is a multidimensional concept covering both physiological and psychological aspects.

General *"fatigue is very hard to define and it's different for everyone and it's pathological at its extremes".* Physiological fatigue has been well defined in the literature and originates in both the peripheral and central nervous system.

> Gant: *"… when we're fatigued, we have biochemical changes occurring at the level of the muscle or what we would call 'distal to the neuromuscular junction'."* These changes include energy depletion, changes in pH temperature, etc. and they lead to peripheral fatigue. *"But then there's a central component that's easily measured. So, output from the motor areas of your brain (the motor cortex and other areas) is dampened or reduced"*

Some key points:

- The kind of fatigue that accompanies prolonged exercise (and it may be the same for prolonged cognitive work) is an imbalance of certain neurotransmitters
- Most of the consensus is around the brain catecholamines, so, dopamine and noradrenaline (Gant study: Connell et al., 2017)

- When the brain is very active, these catecholamines can become depleted
- Can be altered by substances
    - e.g. caffeine alters both dopamine and noradrenaline
    - Hence why caffeine seems to mitigate the fatigue-induced deficits in performance, as studied at Gant's lab
- Exercise is one of the most demanding tasks for the brain; in terms of signaling the brain has to do, and it generates a huge amount of electricity to recruit a huge amount of muscle. This can be seen by the increase in metabolic rate and the observed blood flow in and out of the brain.

Rescuing Performance: Offsetting Fatigue-Induced Declines in Performance

- In Dr. Gant's lab, to assess the impact of nutrients on central fatigue, protocols of prolonged exercise (~ 3 hours) are used.
- Here, rather than look at the (musculo)skeletal motor system, they measure a separate motor system; known as the ocular motor system (i.e. in the eye).
    - This is useful because then the researchers don't have to worry about the peripheral fatigue in skeletal muscle confounding the results, as the muscles in your eye are incredibly robust to fatigue (consider they're moving many thousands of times a day) and they exercise doesn't really increase the demand.
    - And so a decrease in eye movement speed indicates that there is central fatigue taking place.

Study: Fatigue related impairments in oculomotor control are prevented by caffeine
Connell et al., 2016, Scientific Reports 6(1):26614

- In this study the researchers examined central fatigue in the oculomotor system after prolonged exercise.
- They looked at the involvement of central neurotransmission by giving the participants caffeine during the exercise session.
- Study design: double-blind, randomized, repeated measures, crossover design
- During 180 min of stationary cycling, 11 cyclists consumed a either:

    a. Caffeine solution
    b. Placebo solution
- ‘Saccadic eye movements’ are a sort of rhythmic oscillation of the eyes.
    a. For example, when you read your eyes do not travel smoothly over the print. Rather they make short jumping movements called “saccades”.
- Saccadic eye movements were measured using infra-red oculography (a technology used to measure horizontal and vertical eye movements)

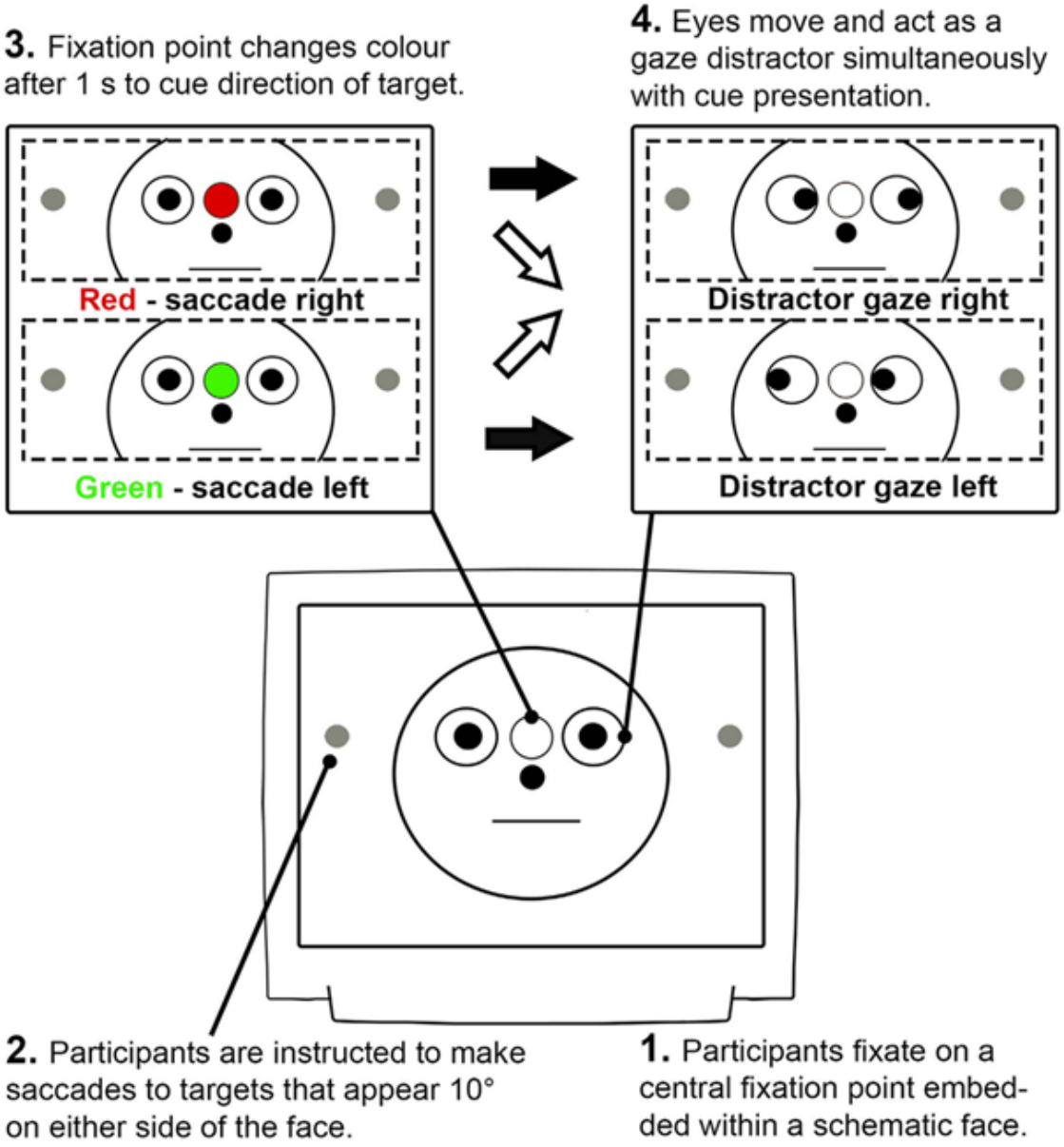
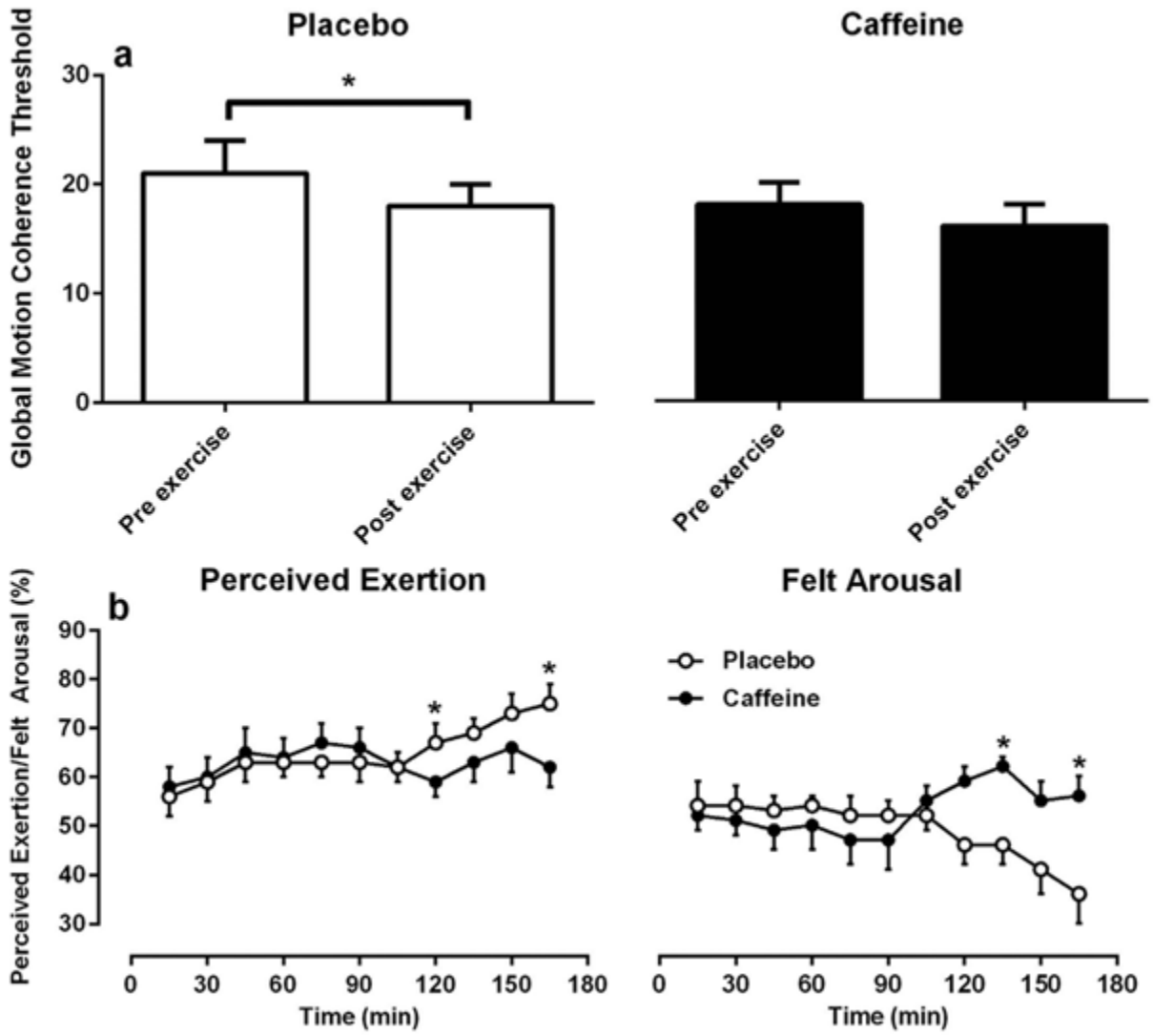


Image from: [Connell et al., 2016, Scientific Reports 6(1):26614]

- In the study, exercise *decreased* saccade velocity (speed of eye movement) by 8% (as measured in the placebo trial).
- This effect was reversed by caffeine, whereby velocity was *increased* by 11% after exercise.
- This led the authors to conclude that:
    a. The human oculomotor system is impaired by strenuous exercise of the locomotor system.
    b. Caffeine exerts a protective effect on oculomotor control, which could be related to up-regulated central neurotransmission.



Graphs from: [Connell et al., 2016, Scientific Reports 6(1):26614]

Fatigue, Hypoxia & The Brain

- Dr. Gant is of the position that (at least the central component of) fatigue is very much linked to the decreased tone of the neurotransmission systems.
- And that of the total exercise-induced fatigue, about 10% is related specifically to the brain.
- To test the impacts on “brain-regulated fatigue”, Gant and colleagues use a **hypoxia protocol**.
- The brain is very metabolic flexible: it's quite well adapted to using different energy sources during exercise.
- So rather than restrict a fuel source, the researchers restrict the oxygen available. This is a hypoxia protocol.
- They expose participants in the lab to air that is about 10% oxygen (that's about half of the normal ~21% oxygen content of normal air) for around 90 minutes.
- They can then test cognitive and motor performance while in this impaired state. One example is the use of the driving simulator mentioned in the episode.
- The degree of cognitive impairment that is achieved within that time frame can be significant.
    - Dr. Gant mentioned how most of their participants are university students, yet the hypoxia protocol can reduce their cognitive function to a point where neuropsychological tests would suggest they'd fail to cope with the normal demands of independent living.
- The lab has looked at creatine supplementation as a potential method of rescuing the performance declines from hypoxia…

Creatine Supplementation Enhances Cognitive Performance during Oxygen Deprivation

- Creatine is also neuroprotective in vitro against anoxic/hypoxic damage.
- Dietary creatine supplementation has been associated with improved symptoms in neurological disorders defined by impaired neural energy provision.

Study: Turner et al., 2015

Study Design & Methods:

- For one week, 15 healthy adults were supplemented with either:
    - Creatine - 20 g/d (taken as 4 servings of 5g across the day)
    - Placebo
- Over this time-frame, the creatine supplementation led to an increase in brain creatine stores by an average of 9.2%.
- A hypoxic gas mixture (i.e. gas of 10% oxygen content) was administered for 90 minutes.
- See graphical representation of the design on the next page.

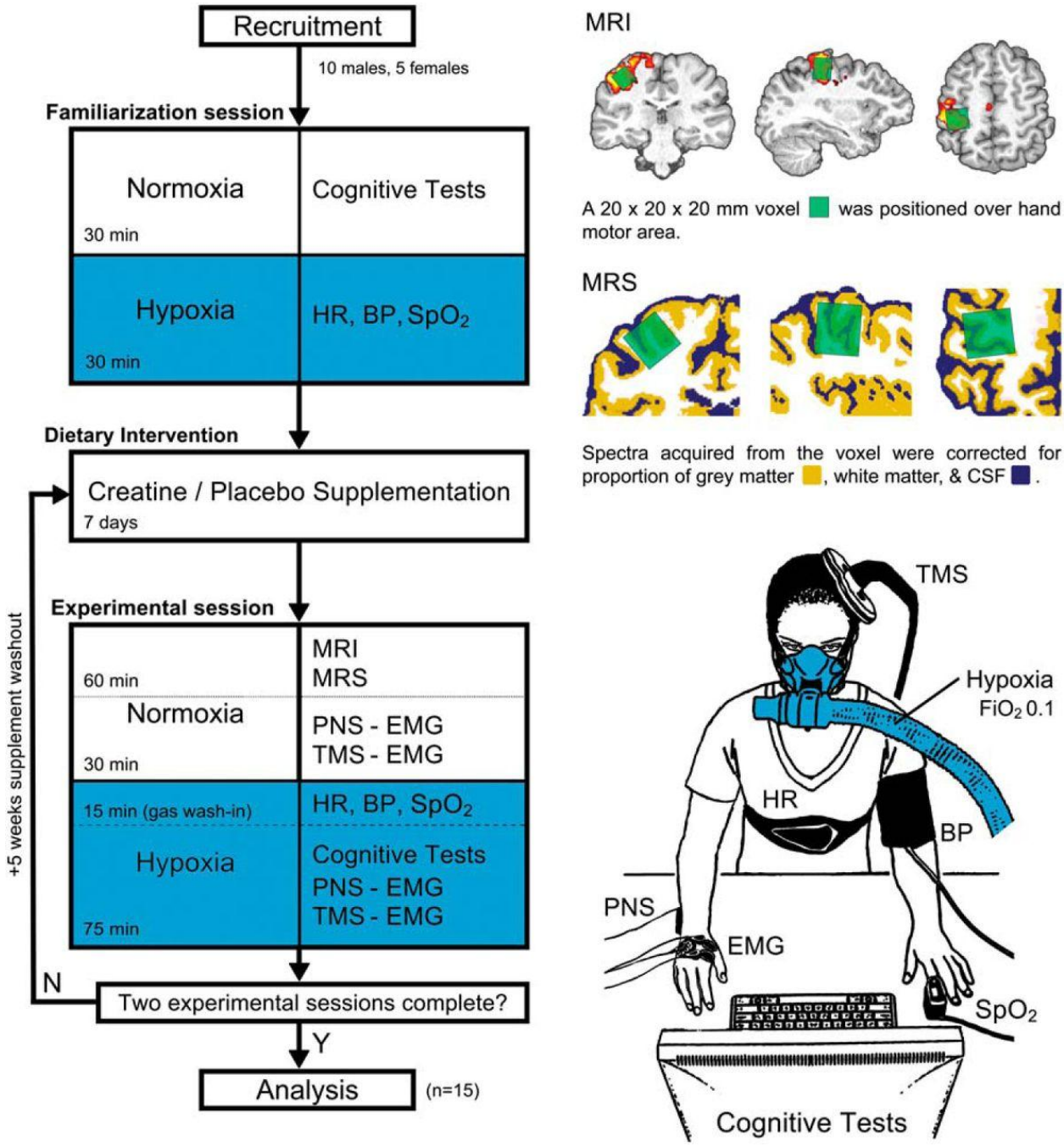


Image from: [Turner et al., 2015]

Study Results:

- This caused a global oxygen deficit and impaired a range of neuropsychological processes.
- However, the hypoxia-induced decrements in cognitive performance (specifically attentional capacity) were restored when participants were supplemented with creatine.

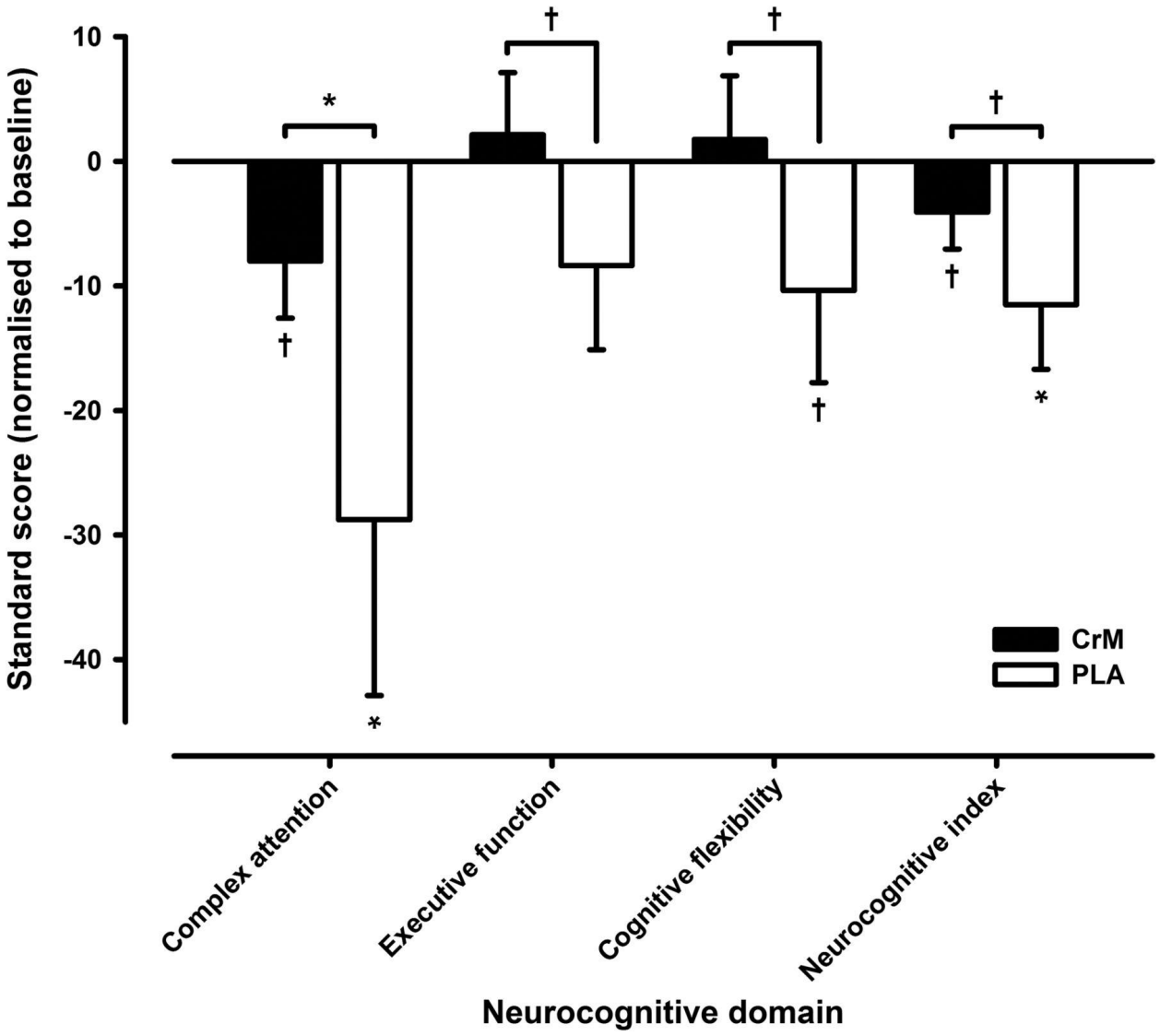


Image from: Turner et al., 2015

Concussion, TBI & Substrate Use

- Sports-Related Concussions (SRCs) are mild traumatic brain injuries (TBIs) that can occur when a force to the head/body causes an acute and temporary deterioration of brain functions. Not all impacts reach the level to cause concussive symptoms, so such traumas would be considered a ‘subconcussive’ impact.
- Sport concussion (SC) causes an energy crisis in the brain by increasing energy demand, decreasing energy supply, and altering metabolic resources
- With an acute TBI there's some neuronal damage. Those neurons are “ripped away” from their support network of glial cells. The glial cells connect those neurons to the blood vessels. They store energy; e.g. astrocytes store meaningful amounts of glycogen. So, the neurons may move and get torn away from that. So, they're torn away from something that's connected to the vessel that has glycogen (and remember glucose is the substrate that the neuron uses). So this damage causes a window of “metabolic vulnerability”
- During that time people are mostly symptomatic. If they try to do too much cognitive work, they develop stress, headaches, fatigue. If they try to do physical work, they typically develop a headache or they have some coordination problems.
- Oxidative glycolysis or the production of lactate from astrocytes is probably impaired in some way by the damage that occurs to the tissue structurally.
- There are far more glial cells in the brain than neurons. Glial cells are required to be the link between the supply of glucose and the neuron, the site where it needs to be used.
- For these reasons, it has been hypothesized that there could be a benefit of supplying an alternative substrate such as creatine or exogenous ketones…

Concussion, TBI & Creatine

And so as there is less glucose (glycogen) available for neurons to use, there could be benefit to providing an alternative fuel source, which is where creatine may have use. So creatine could provide a substrate that's there in the neuron, that does not require oxygen, and does not produce any waste product that needs to be cleared into the vasculature.

Overall, there is very limited human research looking at diet or nutritional supplements in the recovery from a sports concussion, or for preventing chronic TBI or other deleterious outcomes in the long-term. Therefore it is difficult to know if nutritional interventions can help, and if so, what nutrients and doses should be used. Based on mechanistic rationale and experiments in rodents, some nutrients can be hypothesized to help brain recovery through reducing neuroinflammation, providing energy, and restoring creatine levels. However, any specific recommendations can’t be made with much confidence.

However, for athletes who wish to err on the side of caution and try some potential strategies, then some that could potentially help and that have no real risk of causing harm would be to consume a high-dose (0.4 g/kg) of creatine in the initial days after a concussion (or fight). If this actually will help has yet to be definitively shown.

Ketones: Concussion & TBI?

As is the case with creatine, due to the potential benefit for an alternative substrate for the brain to use in the post-concussive period, supplementation of exogenous ketones has been suggested as a potential beneficial intervention.

In addition to the hypothesis of providing an alternative energy source at a time of low glucose availability, other hypotheses have been made on the basis that potentially ketones themselves change the concentrations of certain neurotransmitters like GABA and glutamate. And having a different neurological profile during that time may be beneficial.

However, at the time of recording this interview, Dr. Gant highlighted that there was a lack of evidence on this issue, and so it was completely unknown if exogenous ketone provision could improve outcomes of head trauma.

[Side note: If you want to hear about exogenous ketones being investigated in sports performance, then it was discussed in episode 195 of the podcast with Dr. Brendan Egan]

Impact of nicotine on cognitive function

- Anecdotally some people will tend to use nicotine for certain work-based tasks to be more productive.
- There may be substantial impacts at the level of the brain, including on cognition. However, as nicotine is highly addictive, it is probably unethical to recommend its use to people on the basis of it improving mental performance or it acting as a ‘nootropic’.

Carbohydrate mouth-rinsing: motor performance and sensory perception

Study: Turner et al., 2014

- The presence of carbohydrate in the human mouth has been associated with the facilitation of motor output and improvements in physical performance.
- Oral receptors (distinct from taste receptors) have been identified as signaling nutrient availability.
- In the Turner et al. study, the researchers looked at the brain areas potentially involved, by providing people with oral exposure to carbohydrate (but not swallowing) in combination with doing a motor task.
- The trial had 10 healthy participants and was a double-blind, counterbalanced trial.
- Functional magnetic resonance imaging (fMRI) of the brain was used to identify cortical areas responsive to oral carbohydrate during rest and activity phases of a hand-grip motor task.
- Areas of activation associated with CHO exclusively were observed over the primary taste cortex and regions involved in visual perception.
- Regions in the limbic system associated with reward were also significantly more active with CHO.

An illustration of the experimental protocol:

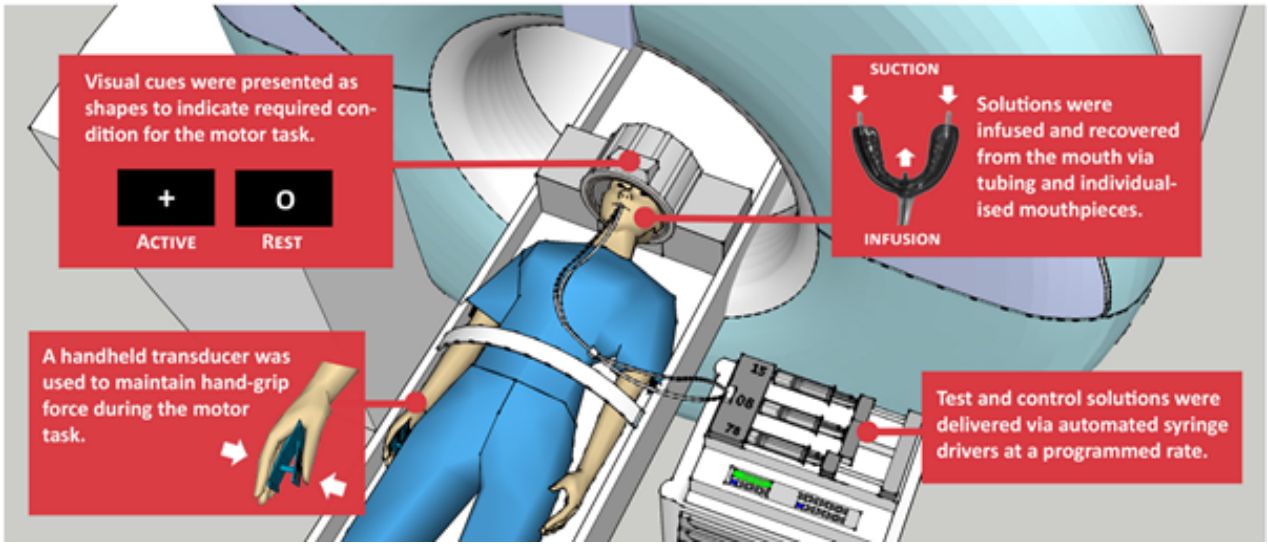


Image from: Turner et al., 2014

Summary/Conclusions

- Demands on the brain caused by exercise-induced fatigue or hypoxia can lead to decrements in cognitive performance and motor tasks.
- Some of the fatigue-related declines in performance may be down to changes in neurotransmission and brain substrate use.
- Creatine and caffeine have been shown to potentially be able to “rescue” some of this lost performance.
- Brain trauma as caused by concussion or sub-concessive impacts (e.g. in sport) can damage neurons and lead to changes in substrate use and other aspects of brain physiology.
- Hypotheses have been put forward in relation to the potential for creatine to mitigate some of the harm and/or aid in recovery from head trauma.
- Some promising research exists, but whether supplementation improves outcomes (or what doses would be effective) is unknown as of yet.
- Some sports organizations (e.g. the UFC Performance Institute) recommend the use of creatine post-trauma (around 0.4 g/kg/d), on the theoretical basis described.
- Exogenous ketones have also been hypothesized to help, but there is a lack of evidence at this time.