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Cognitive Neuroscience: No Gain, Much Pain

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What do hard intellectual work and intense physical training have in common? New research suggests that both types of effort exhaust the brain's executive control system, leading to reduced excitability of the lateral prefrontal cortex and stronger preference for immediate rewards in economic decision-making.

A few years ago, a 26-year-old female athlete was selected to compete in a sprint cycling race. She underwent an intensive training program lasting several months, with steady increase in cycling performance. However, suddenly, her performance began to decline, and she eventually reported intensive fatigue, inability to perform and depressed mood [1]. Now consider the following, seemingly completely different story: a scientist has been working all night to meet an important grant deadline. The next morning, after hours of intellectual work and little rest, he/she goes to the supermarket and buys a chocolate cake instead of the healthy low-carb salad he/she originally intended to purchase (a pattern probably not unfamiliar to some readers, and certainly not to the author of this text).

The story of the young athlete describes a case of the so-called overtraining syndrome (Figure 1). This syndrome is characterized by intense subjective fatigue, drop in performance that continues beyond longer rest periods, cardiac and hormonal alterations as well as, sometimes, restlessness, insomnia, mood changes and other signs of depression. Overtraining syndrome can affect professional athletes, but it can also happen to soldiers [2] and lay sportspersons [3]. The case of the mentally exhausted scientist presents (anecdotal) evidence that intellectual work might affect consumer purchasing behavior: a tired mind may prefer immediate hedonic pleasures over outcomes that are more favorable in the long run, such as good health [4].

What do these two cases have in common? Perhaps more than most people would think. A paper by Blain and colleagues [5] in this issue of *Current Biology* argues that both phenomena may share a similar cause: a weakened executive control system in the brain. Their current study builds on previous work [6] in which they showed that six-hour-long cognitive work increased impulsive decision-making during so-called intertemporal choice [7], i.e., with growing cognitive fatigue, participants progressively preferred smaller-sooner over larger-later monetary rewards. This cognitive fatigue effect on impulsive choice was mediated by an effort-related downregulation of the lateral prefrontal cortex (LPFC), a brain region crucially associated with executive self-control during economic decision-making [7–9].

In the current study, Blain and colleagues [5] suggest that similar executive fatigue mechanisms might be responsible for the overtraining syndrome in athletes. They argue that intact executive control is needed, in general, whenever routine motor and intellectual processes have to be monitored and adapted to meet long-term goals. This not only applies to economic intertemporal decision-making, but also to heavy physical training where signs of muscle ache and joint pain have to be ignored for the sake of continued training in order to meet long-term fitness goals. Blain *et al.* therefore hypothesized that physical training overload, like cognitive overload, excessively requires and, hence, exhausts executive control functions. If this was true, training overload should lead to increased impulsive intertemporal decision-making and decreased excitability of the LPFC, similar to what is observed after cognitive fatigue.

They tested their hypothesis by inducing a mild case of overtraining, called overreaching, in male endurance athletes. Athletes underwent a special cycling training program. After a baseline and taper phase, the athletes were either exposed to a three-week physical training overload phase with a 40% increase in training duration, or a three-week control phase where training was done as usual. Throughout training, fatigue and depression were constantly monitored, and the maximal power output (the maximum workload achieved under exhaustion) was assessed before and after the training overload phase, or control phase, respectively. Shortly after the overload/control phase, the athletes' brain activity was scanned with functional magnetic resonance imaging (fMRI) while they performed executive control tasks interleaved with intertemporal decisions. The executive control tasks measured typical executive functions, such as working memory (the ability to transiently retain and manipulate task-relevant information) or rule switching (shifting back and forth between stimulus–response mappings). The interleaved intertemporal choice trials comprised decisions between smaller-sooner or larger-later monetary rewards.

Blain *et al.* [5] first established that their overreaching induction was successful: maximal power output was diminished in the overreached compared to the normally trained athletes, while feelings of exertion and fatigue were increased. Crucially, they observed that the overreached athletes had a stronger present-bias during intertemporal choice; that is, they revealed a much greater preference for immediate rewards than their conventionally trained counterparts. Blain and colleagues then searched for brain regions that were involved in both executive processing and intertemporal choice. They identified exactly the same spot within the left LPFC, the middle frontal gyrus, that they found in their previous study on mental exhaustion [6]. Most importantly, neural activity in this area was reduced following training overload, but only during intertemporal decision-making, not during executive task performance, suggesting that physical fatigue selectively weakened neural systems subserving self-control during economic decision-making. The hypothesized link between brain and choice-behavior was supported by the observation that decision-related LPFC activity was correlated across athletes with their tendency to prefer immediate rewards: the lower the activity in LPFC, the higher their bias for immediacy. Overall, these results beautifully complement and expand the authors' previous findings [6] by showing that physical exhaustion weakens the brain's executive control system in a manner similar to the effect of mental exhaustion, thus reducing the participants' ability to resist the temptation of immediate gratification. A propos, it is important to add that no harm was done; all athletes were fully recovered two weeks after training overload.

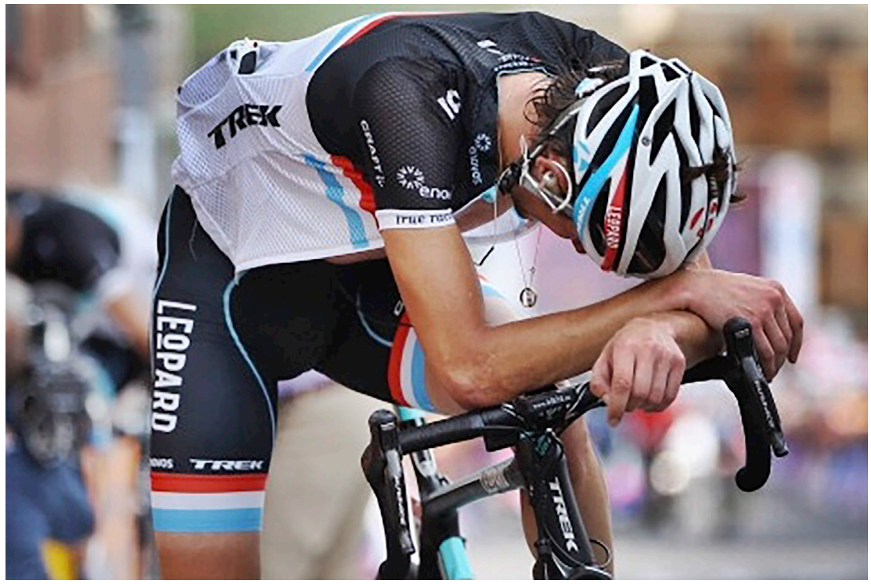

Figure 1. Overtraining syndrome in endurance athletes.
Extreme physical effort can induce overtraining syndrome in endurance athletes — a form of burnout characterized by extreme fatigue and depression-like symptoms. A new paper [5] suggests that intense physical training, much like excessive intellectual work, can exhaust the brain's executive control system, thus producing the symptoms of overtraining syndrome (photo used with friendly permission from https://www.bikechaser.com.au/news/chronic-training-syndrome-identification-explanation/).

These results are important for several reasons. First, they shed light on the putative mechanisms behind overtraining syndrome. The novel insights gained in this study build on existing knowledge that tiredness after physical activity is often more than mere metabolic exhaustion; it can be generated by central mechanisms. Blain *et al.* [5] expand this knowledge by identifying executive fatigue as a putative central causative factor that can lead to those extreme forms of tiredness as seen in overtraining syndrome. But the truly important new message of this paper is that executive fatigue is a domain-general phenomenon that can be triggered by a number of strains, namely intellectual as well as physical work. Therefore, their results go beyond merely explaining a relatively isolated athletes' disorder; they have implications for understanding much more general and widespread conditions related to excessive intellectual and/or physical effort, such as burnout and depression.

But the principle scientific merit of the work by Blain *et al.* [5] lies in its potential to settle a current dispute in the cognitive control literature. A popular theory, called 'limited willpower hypothesis' or 'ego-depletion', states that self-control draws on a limited resource that can be depleted by its utilization [10]. Hence, much like a muscle temporarily loses its strength after intensive physical training, self-control would be progressively and transiently weakened the more it is exerted. This hypothesis is typically tested in sequential-task paradigms where participants complete a sequence of self-control tasks and are expected to show deteriorating self-control abilities in later tasks. However, multiple attempts to replicate ego-depletion effects have failed, or produced only very weak effect sizes [11], and recent meta-analyses cast serious doubts whether the ego depletion phenomenon exists at all [12]. The work by Blain *et al.* [5,6] might reconcile some of the conflicting lines of evidence while also offering novel insights. It suggests that executive control abilities can indeed be exhausted by excessive intellectual or physical work. But, in contrast to previous claims [10,13], the time-scale needed to induce executive fatigue would not be in the range of minutes, but rather hours (for intellectual work) or even weeks (for physical work). In addition, Blain *et al.* observed high task-specificity, but no general decay in self-control capacity: executive fatigue did *not* change performance in many of the cognitive control tasks typically used in the ego depletion literature, such as working memory or rule switching tasks; the effects of executive fatigue were confined to economic choice and its neural correlates. Finally, counter to previous suggestions in the ego-depletion field [13], their results are more compatible with the idea that executive fatigue is the consequence of a neural process rather than the depletion of an actual resource, such as blood glucose.

Of course, like most exciting studies, Blain *et al.* [5] leave some questions unanswered, and additionally raise new ones. For example, it is unknown why the LPFC, but no other brain regions, were especially susceptible to fatigue. Also, the exact nature of the relationship between physical work, impulsive choice and LPFC downregulation remains somewhat unclear. The authors' preferred interpretation is that training overload reduced LPFC excitability, which in turn decreased the athlete's ability to resist the temptation of immediate rewards. However, it is equally plausible that another, yet unknown mechanism arbitrated the effect of training on time preference and LPFC excitability independently. A mediation analysis to determine the exact brain–behavior relationship, as done in their previous study [6], would have shed light on this matter, but their experimental design did not allow such an analysis. A further interesting question to be addressed in future research is if the time course of recovery of executive functions is similar after cognitive or physical work, and how recovery can be accelerated. But independent of these considerations, the study's evidence that both mental and physical work can induce executive fatigue and alter economic decision-making is important news, not only for practitioners researching overtraining syndrome and burnout, but for any scientist studying cognitive control.

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Molecular Evolution: RNA Splicing Machinery Moonlights in Junk Removal

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A close relative of vertebrates solves the problem of gene-disrupting transposable element insertions by splicing them out at the RNA level. Why is such an elegant solution so rare across eukaryotes?

In nearly all eukaryotes, protein-coding nuclear genes are interrupted by non-coding sequences called spliceosomal introns, which are removed from RNA transcripts by a huge RNA–protein complex called the spliceosome [1]. Genomic sequencing of diverse eukaryotes has revealed remarkable conformity of core splicing signals: nearly all introns begin GT (or rarely GC/A/G) and end AG, a finding robust to taxonomy and intron age, length, and gene function. In this issue of *Current Biology*, Henriet *et al.* report the first genome-wide exception: in the chordate *Fritillaria borealis*, 93.3% lack canonical GT–AG splice sites, including 62.6% with AG–AC or AG–AT [2]. Further scrutiny revealed that many or most of these noncanonical introns derive from DNA transposable elements (TEs). Thus, in addition to the ancestral function of removing canonical GT–AG introns, the *F. borealis* spliceosome has evolved a secondary 'moonlighting' function in genome defense, removing interrupting TEs from gene transcripts. In contrast to previous reported cases of precise TE splicing, which are restricted to TE sites that adhere to pre-existing spliceosomal recognition rules [3–5], *F. borealis* TE splicing is potentially quite general, targeting terminal TE sequences (CAG/CTG) that are common across diverse families of TEs.

This report marks the first genome-wide exception to GN–AG splice

