Neuro-computational Impact of Physical Training Overload on Economic Decision-Making

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Title:

Linking endurance sport to intellectual work: the impact of physical training overload on choice neural mechanisms

Short Title:

Executive fatigue induced by sport training

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Summary

Overtraining syndrome is a form of burnout, defined in endurance athletes by unexplained performance drop associated with intense fatigue sensation. Our working hypothesis is that the form of fatigue resulting from physical training overload might share some neural underpinnings with the form of fatigue observed after prolonged intellectual work, which was previously shown to affect th e executive control brain system. Indeed, executive control may be required to prevent any impulsive behavior, including stopping physical effort when it hurts, despite the long-term goal of improving performance through intense training. To test this hypothesis, we induced a mild form of overtraining in a group of endurance athletes, which we compared to a group of normally trained athletes on behavioral tasks performed during fMRI scanning. At the behavioral level, training overload enhanced impulsivity in economic choice, which was captured by a bias favoring immediate over delayed rewards in our computational model. At the neural level, training overload resulted in diminished activation of the lateral prefrontal cortex, a key region of the executive control system, during economic choice. Our results therefore provide causal evidence for a functional link between enduring physical exercise and exerting executive control. Besides, the concept of executive fatigue bridges the functional consequences of excessive physical training and intellectual work into a single neuro-computational mechanism, which might contribute to other clinical forms of burnout syndromes.

Keywords: decision making, executive control, delay discounting, sport training, fatigue, burnout, prefrontal cortex, fMRI, computational modeling

INTRODUCTION

A few decades ago, a marathon superstar at the peak of his career suddenly stopped running for several years, citing mental and physical exhaustion, in the absence of apparent injury. This extreme state of fatigue is at the heart of the so-called overtraining syndrome, a form of burnout that strikes athletes in various types of endurance sport. Beyond subjective fatigue, the overtraining syndrome is objectively characterized by a decrease in performance that persists beyond substantial rest period [1]. It may also be accompanied by cardiac and endocrine modifications, as well as symptoms shared with depression such as apathy, irritability, restlessness, insomnia or loss of appetite [2]. As the underlying mechanisms remain unknown, the overtraining syndrome represents a major issue for both athletes and coaches, and a potential cause of doping practice.

Here, we suggest a neural mechanism that might underlie the effects of excessive physical training. More specifically, our idea is that training overload induces fatigue in the executive control brain system. Executive control is needed whenever routine motor or cognitive processes must be monitored, interrupted and modified so as to better align the behavior to long-term goals [3,4]. Maintaining physical effort for the sake of fitness, when aversive signals such as aching muscles call for stopping, should therefore require executive control. This assumption is difficult to test directly, as it would require monitoring executive control during real-life endurance exercise. However, we reasoned that testing the signatures of a putative fatigue in the executive control brain system might be feasible.

Indeed, we demonstrated in a previous fMRI study [5] that the executive control system is susceptible to fatigue when engaged for a time as long as a workday. The demonstration involved interleaving cognitive tasks meant to induce executive fatigue and choice tasks meant to reveal executive fatigue. This procedure borrowed from sequential task paradigms that have been widely used to assess resource depletion theories [6,7]. Executive fatigue was revealed by two markers recorded during inter-temporal decisions (choices between immediate and larger-later monetary rewards). We observed: 1) at the neural level, a decreased excitability of the lateral prefrontal cortex (LPFC) specifically during choice tasks, and 2) at the behavioral level, an increased preference for immediate rewards in choice tasks.

Importantly, these markers were observed in the absence of any alteration in brain activity or behavioral performance during cognitive tasks. This is consistent with the idea of an executive fatigue, corresponding to an increase in the cost of mobilizing the executive control system, by opposition to an executive dysfunction, as seen in patients with damage to the prefrontal cortex. In other words, our notion of executive fatigue implies that executive control abilities are not lost, but exerted with more parsimony. Thus, they are still mobilized in cognitive tasks where performance has to be maintained, but not necessarily in choice tasks framed as mere expression of subjective preference.

Here, we kept the label 'executive fatigue' for the collection of neural and behavioral signatures previously observed following excessive cognitive work. If physical training overload also leads to executive fatigue, then overtrained athletes should exhibit the same neural and behavioral markers. The presence of these markers would provide evidence that physical exercise over long periods might impact executive control and change temporal preferences. This may be important for cognitive neuroscience in a context where failed replications have casted serious doubt on whether control capacity can be reduced by its utilization at short time scales [8,9]. For the general public, these signatures of executive fatigue would document the neural adverse effects of pushing too far the demand on physical fitness.

We tested these predictions in a mild case of overtraining, called overreaching (OR), since inducing a full-blown overtraining syndrome would be obviously unethical. This state can be considered as a preliminary step, in the pathway to overtraining, which usually vanishes in a week or two if training load is drastically reduced. OR is characterized regarding physical exercise by a decreased maximal power output (MPO) and an increased rating of perceived exertion (RPE), associated in everyday life with enhanced fatigue sensation but no depression-like symptoms [10,11].

To explore the effects of overreaching, we recruited 37 competitive male endurance athletes (mean age around 35 years). Participants were assigned to either the control group with normal training (n = 18) or to the group with training overload (n = 19), in a pseudo-random manner that ensured matching of age and performance level. Their training program (Fig. 1) was supervised during a total of nine weeks by the Insep (French institute for sport performance). The overload concerned a period of three weeks (denoted phase III in Fig. 1) during which the duration of each training session was increased by 40% on average. The general structure of running, cycling and swimming sessions was maintained as usual. Physical performance was monitored during cycling exercises performed on rest days (Pre, Post and Taper in Fig.1), and subjective fatigue was assessed using a psychometric questionnaire [12] every two days.

RESULTS

The effects of training overload on physical performance and effort sensation were assessed during cycling tests that were conducted on the two days following phase III.

On day 1, participants completed on a cycle ergometer an exercise protocol designed to determine their Post MPO, which was compared to the Pre MPO measured before the start of training phase III. MPO corresponds to the maximal workload (in Watts) that participants could sustain when physiological measures reached exhaustion criteria.

On day 2, participants came to the MRI center for two scanning sessions, separated by a 45-min cycling trial, during which participants were instructed to give their best performance, i.e., to cover a maximal distance (see Fig. 2). The aim of including such an intense physical effort was to disentangle the effects of acute (45-min) exercise from long-term (3-week) overload. It also served to test for an interaction between exercise and overreaching, which would occur if OR athletes were more fatigable (even by short exercises) than CTL athletes. Finally, it served to measure perceived exertion, which was rated by participants every five minutes during the cycling time trial, on a visual analog scale [13].

The behavioral and neural markers of executive fatigue were tested on day 2, during fMRI scanning sessions (see Fig. 2). The behavioral marker was preference for immediate rewards, relative to bigger-later rewards, in inter-temporal choices. Before scanning, participants performed a calibration session where choice options were progressively adjusted, following a bisection procedure, in order to find subject-specific indifference points. During scanning sessions, inter-temporal choice task trials were tailored around subject-specific indifference points, so their difficulty was matched across subjects. The neural marker was LPFC activity during choice trials, compared to baseline. Choice trials were intermingled with executive task trials (either N-back or N-switch), on which participants had been trained until passing a threshold of 90% correct responses. There were two reasons for incorporating executive tasks. The first reason was that we needed an independent contrast to isolate executive control regions, which was provided by the difference between hard and easy versions of the tasks (change in N). The second reason was that we intended to test the specificity of fatigue effects on choices, which we observed in our previous study [5]. Indeed, fatigue left unaffected brain activity recorded during performance of executive tasks. The idea is that compensatory mechanisms may be recruited to maintain performance, in tasks where there is an objective correct response (N-back and N-switch), but not in tasks where the response is an expression of subjective preference (inter-temporal choice).

Overreaching effects on cycling exercise. As predicted, MPO was significantly reduced by training overload (Fig. 3A, left), but not by normal training (OR group: ΔMPO = -13.26±2.88 W, t_{18} = -4.61, p = 0.00022; CTL group: ΔMPO = 3.60±2.74 W, t_{17} = 1.2, p = 0.25), with a significant difference in training effect (ΔMPO) between groups ($F_{1,32}$ = 16.3, p = 0.00031). Training overload also had the expected impact on perceived exertion (see Fig. 3A, right), which was higher in OR relative to CTL participants (OR: RPE = 15.59±0.16; CTL: RPE = 14.74±0.29; OR vs. CTL: t_{34} = 2.56, P = 0.014). Altogether, results from cycling exercises confirmed that training overload was effective: it decreased physical performance while increasing effort sensation.

Note that in the OR group, MPO measured after the last phase (Taper) was even higher than in the Pre baseline (ΔMPO = 7.68±3.67 W, t_{18} = 2.15, p = 0.046). Thus, athletes fully recovered their physical capacity after training overload, showing that our manipulation was harmless in the end.

Overreaching effects on psychometric questionnaire. The overreaching state induced by training overload measures were corroborated by psychometric questionnaires (Brunel mood scale) that participants filled every two days (Fig. 3B). Note that baseline fatigue level (at the start of the training program) was matched between groups. The increase in subjective fatigue between the beginning and the end of phase III was higher in OR relative to CTL participants (OR: Δfatigue = 3.78±0.98; CTL: Δfatigue = 0.21±0.74; OR vs. CTL: $F_{1,30} = 6.89$, $P = 0.014$), whereas there was no difference in the evolution of depression score ($F_{1,30} = 0.72$, $p = 0.4$).

Overreaching effects on behavioral task performance. Bayesian model selection indicated that for both groups, the best account of choices made during calibration was provided by exponential discounting of reward with delay, plus an additive parameter, termed immediacy bias (IB), which captures the preference for immediate options, irrespective of reward and delay (see Table 1).

When comparing between groups the proportion of impulsive choice made during the calibration procedure, we observed a marginally significant difference, with a higher proportion of impulsive choice following training overload (OR: Pim = 0.46±0.026; CTL: = 0.38±0.031; difference: OR vs. CTL: t35 = -1.99, p = 0.054). Note that such model-free comparison is limited because choices were progressively adjusted to indifference points through our adaptive design. We thus compared fitted parameters (posterior means) between groups, and observed a specific difference in the immediacy bias (Fig. 3C), which –in line with our key behavioral prediction– was higher following training overload (OR: IB = 0.4±0.21; CTL: IB = -0.34±0.16; OR vs. CTL: $t_{35} = -2.77$, $p = 0.0089$).

All the other parameters (Table 2), as well as the quality of fit (see Fig. 4, left), were similar in the two groups. This suggests that training overload increased the attraction of immediate rewards, but not the way option values were estimated and compared. In particular, the weight assigned to delay (discount factor) and the stochasticity of choices (temperature parameter) were not significantly affected by training overload.

However, such a difference in the immediacy bias between groups might come from a sampling issue (the CTL group being by chance more patient than the global population, and/or the OR group being more impulsive than the global population). To address this question, we included as a reference a third independent control group of participants (n = 106), who were tested with similar calibration procedures, for other purposes. Across all control participants, we conducted permutation tests (1,000,000 iterations) to estimate the exact probability of observing by chance a bias parameter of at least the same mean, with a sample of the same size, as that of the OR group. This permutation procedure gave us a p-value of 0.025. We therefore conclude that the observed bias parameter was unlikely to reflect a sampling issue, and more likely to represent a true effect of training overload.

During scanning sessions, we observed no significant difference between groups in executive task performance. We illustrate this absence of effect using correct response rate pooled across tasks (Fig. 5A), but similar null results were obtained when analyzing tasks separately, or comparing response time instead of accuracy, or focusing on switch cost. However, we observed a trend for a remaining specific group difference in the immediacy bias (OR vs. CTL: $F_{1,35} = 3.99$, $p = 0.054$), despite the adjustment of choice options following calibration (see Fig. 4). Regarding our secondary question, namely the effects of acute exercise, we found no significant difference between scanning sessions, neither in executive task performance nor in inter-temporal choices and no interaction between session and group (see table S1). Thus, 45 minutes of cycling, although athletes approached physical exhaustion, was insufficient to affect executive control or to interact with the state of executive fatigue.

Overreaching effects on neural activity. To investigate the neural underpinnings of fatigue effect on choice impulsivity, we isolated the executive control network using the conjunction between choice-related activity (against baseline) and the difference in difficulty (hard minus easy tasks), as was done in our previous study [5]. The logic of this analysis was to locate brain regions that are normally involved in both executive processing and inter-temporal choice (in the control group). These regions would be candidate for mediating the impact of executive fatigue on choice impulsivity, as they would be both responsive to executive demand and recruited during inter-temporal decision-making. Thus, activity level extracted from these regions served as a reference to assess the effects of training overload. As expected [5,14–20], we observed significant conjunction in a bilateral prefronto-parietal network (Fig. 5B; see Table S2), including the middle frontal gyrus (MFG) and the inferior parietal lobule (IPL).

We focused on the left MFG cluster, as it perfectly overlapped with the unique brain region that was found in the previous study [5] to both activate in the conjunction analysis and deactivate during choices in relation with behavioral fatigue effects. Neural activity was extracted using a general linear model that controlled for task factors such as delay, reward level, eventual choice and response time (see methods). Choice-related activity (but not task-related activity) in the independent left MFG cluster (defined from previous study) was significantly reduced following training overload (OR: $\beta = 0.15 \pm 0.50$; CTL: $\beta = 1.86 \pm 0.43$; OR vs. CTL: $F_{1,35} = 6.36$, $p = 0.016$). As seen with behavioral variables, there was no effect of acute exercise (no main effect of session and no interaction; see Table S3) on neural activity. The difference between group in choice-related left MFG activity was not observed in other clusters such as the left IPL or the right MFG (see Fig. S1 and Table S4). Also, left MFG activation with the difficulty of executive tasks was not different between groups (see Fig. 5C and Table S3). Moreover, the interaction between task and group was significant, indicating that training overload mainly impacted choice-related activity (CTL: $\Delta\beta$ = 1.35±0.43; OR: $\Delta\beta$ = -0.20±0.48; CTL vs. OR: $F_{1,35}$ = 5.81, p = 0.021).

Thus, training overload effects were predominant in the left MFG cluster and during the inter-temporal choice task. The fact that left MFG activity was independent from reward and delay levels (see Fig. S2) suggests that training overload did not affect temporal discounting. This is consistent with the computational modeling analysis showing an effect on the immediacy bias but not on the discount factor. We did not find any increase in choice neural activity in the OR group compared to the CTL group, even at a very liberal threshold ($p<0.05$ at the voxel level, extent threshold of 4 voxels at the cluster level), even with a lower spatial smoothing that would be more sensitive to activity in small subcortical regions such as the ventral striatum.

In addition, choice-related left MFG activity was correlated across participants with the immediacy bias estimated during scanning sessions in the OR group (r = -0.36, t_{17} = -4.32, p = 0.0005). Although the coefficient should be interpreted with caution, due to the small sample size[21,22], this significant correlation establishes a link between the neural and behavioral markers of executive fatigue (Fig. S3). Note that the left MFG ROI was selected from the previous study, by conjunction between executive- and choice-related activities, to avoid non-independence issues. Moreover, this correlation is independent from the difference between groups, as it is restricted to the OR group. It shows that athletes who exhibited lower activity in left MFG during decision-making had a stronger bias in favor of immediate over delayed rewards.

DISCUSSION

Our findings indicate that physical training overload reduces the excitability of left MFG and the capacity to resist temptation of immediate reward in inter-temporal choice. These conclusions rely on significant differences between overtrained and normally trained groups of athletes, in both brain activity and behavioral performance, during choice tasks. There were trends for interactions between groups and sessions, in the sense that overtrained athletes were more fatigued after a one-hour cycling exercise, but these trends were not significant. The association of neural and behavioral differences between groups was corroborated by an independent correlation, observed within the overtrained group, between reduced left MFG activity and enhanced immediacy bias. Although this correlation does establish a link between neural and behavioral effects of overtraining, it does not imply that the neural effects were mediating the behavioral effects. Unfortunately, we could not apply here the kind of mediation analysis conducted in our previous study [5], because the consequences of overtraining were assessed between participants, and because we did not get baseline impulsivity measurement (prior to training). The absence of baseline measurement is a potential limitation to the conclusions, but comparison to other datasets in healthy volunteers ensured that the difference was due to overtrained athletes being more impulsive than the normal population.

The difference in choice impulsivity was best captured by the additive bias in the exponential discounting model [23]. Interestingly, the two parameters of this ($\beta\delta$) model were previously mapped onto opponent brain systems involved in the valuation of immediate versus delayed reward. These opponent systems therefore had opposite influences on choice, with a more ‘future-oriented’ system including the lateral prefrontal cortex and a more ‘present-oriented’ system including the ventral striatum. Interpreted in such a framework, increased choice impulsivity in overtrained athletes would correspond to a less active ‘future-oriented’ system (decrease in left MFG activity) rather than a more active 'present-oriented' system (no increase in ventral striatum activity). Indeed, we did not observe any brain region that would have been more active in overtrained athletes during economic choice.

We previously suggested the notion of executive fatigue as a label for the two choice-related markers (increased impulsivity with decreased MFG activity) observed in the absence of any change in behavioral performance or brain activity during cognitive tasks. As all neural and behavioral markers were present in the overtrained group, we conclude and physical training overload can also induce executive fatigue. This notion of executive fatigue is different from physical fatigue, because it can be induced by purely intellectual work [5]. It is also different from stress or sleep deprivation, which failed to influence inter-temporal choices in previous experiments [24,25]. Executive fatigue should also be distinguished from loss of motivation, since it does not affect the arbitrage between reward and delay, as shown by computational modeling of choice behavior, and because it impacts activity in a brain region (left MFG) that was not sensitive to reward. Finally, executive fatigue does not imply that the choice process itself is impaired, as would be reflected by a higher stochasticity, but rather that preference is shifted in favor of immediate reward.

This new concept of executive fatigue should be contrasted to existing theories of 'limited willpower' or 'resource depletion'. These theories postulate that exerting self-control may deplete a common limited resource and consequently affect performance in any subsequent task that also involves self-control [6,7]. However, the time scale typically envisaged in resource depletion theories is that of minutes (e.g., [26]). Meta-analyses and multi-lab replication attempts have seriously questioned that depletion effects can be obtained in sequential task paradigms at such short time scale [8,9]. Consistently, we observed here no effect of 45-min cycling on working memory, task switching, choice impulsivity or brain activity. These results therefore suggest that exerting executive control might indeed affect subsequent recruitment of executive control but at a time scale that is much longer than usually considered (here, three weeks). We nonetheless acknowledge that our participants were well-trained endurance athletes, who had exceptional recovery capacity and highly competitive spirit. It remains possible that recreational cyclists would have shown earlier fatigue effects, as suggested by a previous study investigating interactions between acute exercise and cognitive abilities [27].

Theories assuming that a resource is depleted by self-control have not identified what the resource may be at the biological level [28]. Blood glucose has been proposed as a suitable candidate resource, with some supporting evidence initially [6,29]. However, the beneficial effects of glucose ingestion have been hard to replicate [30,31] and it was later suggested that they might be more psychological than biological [32,33]. In our study, glucose is unlikely to have played a role because participants had free access to food and drinks during both training and experiment days. Instead, we suggest a specific neural basis for our concept of executive fatigue, with a precise anatomical location, in the left MFG. It is remarkable that such different tasks as training for triathlon and making inter-temporal choice precisely interfered in a single brain region. Indeed, other regions of the parieto-prefrontal executive network recruited by inter-temporal choices did not show any fatigue effect. It is the same MFG region that mediated the increase in choice impulsivity induced by prolonged working memory and task-switching performance [5], and the same MFG region on which transcranial magnetic stimulation (TMS) induced a present bias in inter-temporal choice [16,34]. Our findings therefore concur to designate the left MFG as the weak spot of the brain executive control system [15,20], being susceptible to fatigue.

Yet our data are silent about why the MFG is harder to activate with fatigue. This may not necessarily come from a local dysfunction of MFG neurons. Indeed, MFG activity could be down-regulated by other brain systems for adaptive reasons, possibly because exerting executive control would exhaust some energetic supply or accumulate some metabolic wastes. It has been suggested for instance that stopping executive control might avoid the accumulation of Amyloid-β peptide and allow its clearance during rest or sleep, such that neural cells remain functional [35]. More generally, executive fatigue might have origins in any of the numerous physiological changes that have been reported following excessive sport exercise. One interesting (but still debated) possibility is the release of inflammatory cytokines [36,37], which are known to affect motivational processes [38,39]. Yet the mechanisms through which peripheral physiological changes would affect specific prefrontal cortex functions remain to be explored.

Alternatively, down-regulation could be adaptive at a functional rather than biological level, for instance to avoid opportunity costs [40,41], i.e. to avoid losing the benefits of using executive control resources for other purposes. Yet the latter hypothesis would imply that the opportunity cost of executive control increases with time on task, which seems quite an arbitrary assumption. Further studies are thus required to understand why the MFG is susceptible to fatigue, whereas other brain regions such as the visual cortex can work all day long without any behavioral consequence. In any case, the impact of fatigue can be construed as an increase in the cost of recruiting the MFG, and thus exerting control. The implication is that control resources can still be mobilized in a state of fatigue but for higher benefits. This would explain why performance was maintained during executive control tasks, in which a precise financial payoff was associated to every correct response. By contrast, the benefit of making a sound decision in inter-temporal choice might have been too elusive to recruit executive control. Such a view is consistent with suggestions that the effects of time-on-task on cognitive performance and related brain activity are not robust [42,43], and that the consequences of mental fatigue are better conceived as shifts in cost-benefit arbitrages [44,45].

The consequence of impulsive economic choice could itself be deemed adaptive, if immediate rewards were instrumental to eliminate fatigue, as glucose is for reducing hunger. Yet in our paradigm it remains unclear how a small amount of money could be used to improve overreaching symptoms, so we consider as a bias the shift observed in favor of immediate rewards. Another slightly different perspective could be that fatigue place subjects in a state of need, pushing them to seek immediate rewards in order to restore their mood or some overarching hedonic variable which they monitor on the long run. This hedonic regulation is reminiscent of the spontaneous oscillations between pursuing 'have to' versus 'want to' goals [46] and may be the basis of the trade-off between work and leisure that is at the heart of labor theory [47].

In conclusion, our findings provide the first demonstration that physical training overload induces some fatigue in the executive control brain system, associated with more impulsive economic decisions. They suggest a neural mechanism that might explain not only why overtrained athletes fail to overcome pain or fatigue signals, but also why they are at risk of doping, which may help with immediate performance but compromise long-term achievements. They could also account for the rise of fatigue syndromes observed in amateurs of extreme sports such as ultra-trail, who may put in danger not only their heart and knees, but also their brains. Finally, these findings could perhaps be extended to other types of work overload, and therefore have applications not only for sport coaching but also for work management and health care, since excessive work is one of the possible routes to burnout syndrome. We should keep in mind, however, that our overtrained participants were (fortunately) not in a full-blown burnout state. It remains possible, and even likely, that factors other than executive fatigue come into play for a transition to long-term burnouts. Further research is needed to investigate those putative factors.

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Author Contributions

BB, CH, YLM and MP designed the experiment. CS, AA and YLM supervised the training program. BB and CS collected the behavioral and fMRI data. BB and MP analyzed the data and wrote the paper.

Competing Interests statement

Nothing to declare.

Figure Legends

Fig. 1. Training procedures.

Participants (37 male triathletes in total) were divided into two groups, following slightly different training procedures. The loads assigned to the different training phases correspond to variations in daily exercise duration (in proportion to subject-specific standard), while exercise intensity was kept constant. The critical manipulation is the 40% increase in training load during the three weeks of phase III, in the overreaching (OR) but not in the control (CTL) group. The other phases were identical in both groups, with a two-week baseline phase of usual training at the beginning, and two tapering phases (recovery periods) before and after the critical phase III. The maximal power output (MPO) was evaluated on rest days before and after phase III, as well as after phase IV (as indicated by cyclist icons). The fMRI experiment (indicated by brain icon) was conducted on the day following post-phase III MPO measurement (see details in Fig. 2).

Fig. 2. fMRI experiment procedures.

Tasks are illustrated at different time scales from bottom to top. Participants performed two sessions of behavioral tasks in the MRI scanner, before and after cycling (45-min time trial at maximal speed). Sessions were divided into six 7-min runs, each including five blocks of executive tasks (N-back or N-switch) intermingled with inter-temporal choices (IC). Executive tasks were 3-back (3-B) and 12-switch (12-S) in the hard condition (for a total of 8 blocks, in red), versus 1-back (1-B) and 1-switch (1-S) in the easy condition (for a total of 4 blocks, in blue). The first three runs of a session implemented one executive task (N-back or N-switch), and the last three runs the other one. In each block a series of 16 to 32 different letters was presented on screen, each starting a new trial. The task to be performed was instructed at the beginning of the block. In N-back tasks, participants indicated whether the current letter was the same as the one presented N trials before (irrespective of case and color). In N-switch tasks, participants categorized the current letter as either vowel versus consonant or upper versus lower case, depending on its color. In this case, N designates the number of switches (color changes) during the block. At the end of the block participants made three self-paced choices (with a 5s limit) between immediate and delayed monetary rewards.

Fig.3. Behavioral validation of overreaching effects

(A) Results of cycling tests conducted after phase III (see Fig. 1). Graphs show the change in maximal power output (MPO, left) measured during the incremental cycling test on day 1, and how ratings of perceived exertion (RPE, right) vary during the cycling time trial on day 2 separately for the control (CTL, green) and overreaching group (OR, purple) groups.

(B) Results of fatigue psychometric assessment. Graphs show the change in fatigue score (extracted from Brunel mood scale) observed between the beginning and the end of phase III (see Fig.1).

(C) Results of temporal discounting calibration. Graphs show the posterior mean of immediacy bias, a parameter integrated in the choice model to account for preference between present and future, irrespective of rewards and delays. Plain and dotted lines as well as the shadowed area in between illustrate mean and confidence intervals of the immediacy bias observed in a larger, independent cohort of healthy volunteers (n=106). Error bars and shaded areas correspond to intersubject SEM. Black stars denote p-values (* < 0.05, ** < 0.01, *** < 0.001).

Fig. 4 Psychometric functions and model fits.

Graphs show observed choice rate (dots with error bars) and modeled choice probability (lines with shaded areas) for immediate rewards (IR), as a function of modeled relative values (difference between subjective values of immediate and delayed rewards). Error bars and shaded areas represent intersubjects SE. Overreaching (OR) and control (CTL) groups are shown in purple and green, respectively. Left, middle and right panels correspond to calibration, first fMRI and second fMRI sessions, respectively.

Fig. 5. Neural underpinnings of overreaching effects.

(A) Behavior observed during fMRI. Top graphs show the immediacy bias (posterior mean of model parameter fitted on inter-temporal choices) and bottom graphs the executive performance (correct response rate in hard versions divided by correct response rate in easy versions of executive tasks) separately for the control (CTL, green) and overreaching group (OR, purple) groups (see also Table S1). (B) Whole-brain fMRI activity. Statistical maps show the conjunction between choice-related activity (against baseline) and effect of difficulty (hard versus easy version of executive tasks) in the control group. Significant activation (voxel-wise threshold: $P < 0.001$ uncorrected, cluster-wise threshold: $P <$

0.05 FWE corrected) was observed in a dorsal parieto-prefrontal network including the middle frontal gyrus (MFG), the pre-central gyrus (PCG) and the inferior parietal lobule (IPL). The MFG cluster overlaps with the unique brain region (shown in red) from the same conjunction that was susceptible to executive fatigue in a previous study [5]. The sagittal section (bottom) corresponds to the blue line on the glass brain (top); it shows functional activations overlaid on anatomical scans averaged across subjects. The x, y, z coordinates refer to the MNI space (see also Table S2). (C) Neural activity extracted from the MFG cluster. Graphs show regression estimates (β) extracted from the cluster shown in red, for neural activity observed during inter-temporal choices with respect to baseline (top) and for neural activity observed during hard versions of executive task relative to easy versions (bottom; see also Table S3). Error bars and shaded areas correspond to intersubject SEM. Black stars denote a p-value < 0.05, daggers denote a trend. S1 and S2 refer to fMRI sessions conducted before and after cycling exercise, respectively.

Tables

$P(IR) = \frac{1}{1+e^X}$		$X = \frac{1}{\beta}\left[\frac{DR}{1+kD} - IR\right]$	$X = \frac{1}{\beta}\left[DRe^{-kD} - IR\right]$	$X = \frac{1}{\beta}\left[\frac{DR}{1+kD} - IR\right] - bias$	$X = \frac{1}{\beta}\left[DRe^{-kD} - IR\right] - bias$
Calibration	EF	0.086 (0.013/0.022)	0.22 (0.12/0.21)	0.13 (0.032/0.15)	0.57 (0.83/0.41)
	EP	0	0.0037 (0/0.89)	0 .00020(0/0.03)	0.99 (0.99/0.95)
fMRI sessions	EF	0.076 (0.12/0.014)	0.072 (0.014/0.013)	0.17 (0.014/0.29)	0.68(0.85/0.68)
	EP	0 (0.003/0)	0	0 (0/0.032)	1 (1/0.97)

Table 1. Results of Bayesian model comparison.

The four models combine two discounting functions (hyperbolic vs. exponential) and two possibilities for inclusion of an immediacy bias (present or absent) in the softmax choice function (see methods). IR and DR are immediate and delayed reward magnitudes, D is delay. β, *k* and *bias* are free parameters (choice stochasticity, discount factor and immediacy bias, respectively). The comparison was based on choices made by the two groups of participants taken together, separately for the calibration and fMRI sessions. EF is expected frequency and EP exceedance probability, provided for all participants and for each group separately (CTL/OR).

Parameter	CTL	OR	Difference	t-value	df	p-value
Immediacy bias	-0.34±0.16	0.40±0.21	-0.74	-2.77	35	0.0089
Discount factor	0.045±0.0083	0.040±0.0075	0.0050	0.45	35	0.66
Choice stochasticity	8.11±0.55	9.23±0.54	-1.12	-1.45	35	0.15
Balanced accuracy	0.70±0.019	0.70±0.011	0	-0.0003	35	0.99

Table 2. Comparison of model parameter estimates and quality of fit for choices made during calibration session.

Models were fitted on the calibration session, separately for the control (CTL) and overreaching (OR) groups. Parameters from top to bottom are denoted *bias*, *k* and β in the models (see Table 1). Balanced accuracy is the percentage of choices correctly predicted by the model, calculated separately for impulsive and patient choices before averaging. Note that balanced accuracy is low because options were adjusted to indifference points. Results are given as inter-subject means ± standard errors. Groups were compared using two-sample two-tailed t-tests; df is degree of freedom.

STAR METHODS

Participants

The experimental design of the study was approved by the Ethical Committee of Hôpital de la Pitié-Salpêtrière. Fourty-two well-trained male triathletes ([$\dot{V}O_{2max}$] = 64.1 ± 4.9 ml·kg^{-1}·min^{-1}) volunteered to participate in this study. They were paid a fix amount of 400€, plus one option that was selected in a random trial of the choice task. All subjects had regularly competed in triathlons for at least 3 years and were training a minimum of 10 hours per week. Their performance level over the short (Olympic) distance triathlon (i.e., 1.5-km swimming / 40-km cycling / 10-km running) ranged between 2 h and 2 h 20 min, which roughly corresponds to national level of competition). Before participation, subjects underwent medical assessment by a cardiologist to ensure normal electrocardiographic patterns and obtain a general medical clearance. All subjects were free from chronic diseases and were not taking medication. After comprehensive explanations about the study, all subjects gave their written informed consent to participate.

Subjects were assigned to either the control group (CTL) or the overreaching group (OR) so as to match performance level, habitual training volume, and past experience in endurance sports. Five participants were excluded due to sleeping or excessive movements in the scanner or failure to comply with instructions about behavioral tasks. In the end, our dataset included 18 CTL subjects (age = 36±1.5) and 19 OR subjects (age = 35±1.2).

To provide a reference point for the immediacy bias in the general population, we included groups of participants with similar age, sex and education level, who were tested with the same choice tasks in independent studies.

Training procedures

An overview of training procedure is shown in Fig 1. The training of each participant was monitored for a period of nine weeks in total, which was divided into four distinct phases. The two first phases (I and II) were similar in the OR and CTL groups. During the third phase (III), the OR group completed a 3-week overload program designed to deliberately induce fatigue: the duration of each training session was increased by 40% (e.g., a 1-hour run including 10 repetitions of 400 m at the maximal aerobic running speed was converted into an 85-min run including 14 repetitions of 400 m at the maximal aerobic running speed). Participants reproduced the same training program during each week of the overload period, which was kept as usual, except for the increase in duration. The CTL group repeated its usual training program during this third phase (III). Thereafter, all participants completed a 2-week taper period (IV), where their normal training load (I) was decreased by 40%, following the guidelines for optimal tapering in endurance sports [48].

During training, fatigue and depression were monitored by asking participants to fill the Brunel mood questionnaire [12] every two days. We used a sub-selection of items to measure the change in depression score (during the last two days, how often did you feel: “Miserable”, ”Unhappy”, “Depressed”, “Unable to fall asleep”, “Insomniac”) and in fatigue score (“Collapsed”, ”Energetic” (-), “Tired”, “Exhausted”, “Having heavy legs”) between the beginning and end of each phase. Fatigue and depression scores were not different between groups at the beginning of the training program.

During phase I, all subjects were familiarized (on separate days) with both the cognitive tasks going to be performed during fMRI scanning, and the maximal power output (MPO) test (described below). The MPO test was performed on three occasions: before phase III (Pre), after phase III (Post) and after phase IV (Taper), on the same day of the week and at the same time of the day. To ensure that performance variations across MPO tests were due to the global training regimen and not to the training session performed the day before testing, the subjects were required to abstain from training during a 24-h period before each MPO testing session. The day after Post MPO test, all participants completed two 45-min fMRI sessions during which they performed cognitive tasks. The two sessions were interspaced with a 45-min self-paced cycling time trial.

Cycling exercises

All MPO tests were performed using an electronically-braked cycle ergometer (Excalibur Sport, Lode®, Groningen, The Netherlands). The incremental exercise protocol started with a 6-min warm-up at a workload of 100 W, and then increased by 25 W every 2 minutes until voluntary exhaustion to estimate MPO. Subjects wore a facemask covering their mouth and nose to collect all expired breath (Hans Rudolph, Kansas City, MO) and calculate $\dot{V}O_{2max}$ using a metabolimeter (Quark, Cosmed®, Rome, Italy). Complete exhaustion was confirmed by physiological criteria [49] – that is, a plateau in $\dot{V}O_{2max}$ despite an increase in PO. MPO was calculated as MPO = W_{last} + 25 (t/120)[50], where W_{last} is the last completed workload and t the number of seconds sustained in W_{last}. $\dot{V}O_{2max}$ was defined as the highest 30-sec average of breath-by-breath values[51].

The 45-min self-paced time trial (TT) was completed between the two fMRI sessions. Participants were instructed to achieve their best performance. Before the TT, participants respected a 15-min warm-up (10 minutes at a workload of 100 W and 5 minutes at 50% of the Post MPO). Both warm-up and TT were performed on participants' own bike mounted on a braked Cyclus2 ergometer (RBM GmbH, Leipzig, Germany). To mimic field conditions, the triathletes were provided with distance, speed, PO, cadence information and *ad libitum* sport drinks and water. Every five minutes during the TT, subjects' rating of perceived exertion (RPE) was recorded using the 6-to-20 point Borg's scale[13]. This scale measures effort sensation, with 6 corresponding to sitting in a chair, and 20 to the maximal effort ever experienced.

fMRI experiment

Participants came to the lab on the second day after the end of phase III. On this day, they performed an inter-temporal choice calibration procedure to elicit their indifference curve. Inter-temporal choices were real in the sense that the chosen option in one pseudo-randomly selected trial was actually implemented (any trial could be drawn, except those where a delay longer than one year had been selected). Subjects then performed two sessions of executive tasks while fMRI data were acquired. Each session lasted for about 45 minutes (5 mins of setup, 10 mins of structural MRI acquisition before the first and after the last session, + 30 mins of functional MRI during task performance). Sessions were divided into three consecutive runs of N-switch blocks (two 12-switch runs separated by one 1-switch run) and three consecutive runs of N-back blocks (two 3-back runs separated by one 1-back run). Each run comprised five successive blocks. The task to be performed was indicated by a 5-s instruction screen presented at the beginning of each block. The length of blocks was randomly varied between 16 and 32 trials (24 on average, duration = 43s) for N-switch tasks and between 18 and 26 trials (22 on average, duration = 40s) for N-back tasks. The order of N-switch and N-back tasks was counterbalanced across subjects. Every 50s on average (at the end of blocks), another 5-s instruction screen indicated to participants that they would have to make three successive inter-temporal choices, giving a total of 90 choices per session. The options proposed in inter-temporal choices were tailored based on the results of the calibration session conducted just before the fMRI experiment.

Behavioral tasks

For executive tasks, participants were instructed to reach the best possible performance level (correct response rate) with the shortest possible response time. On the week before the experiment as well as on the day of the experiment (before MRI sessions) they read the instructions and were trained to perform all versions of executive tasks until they reached a performance criterion (4 consecutive blocks above 90% of correct responses), or until they reached a maximal duration of three hours.

In both the N-back and N-switch tasks, letters appeared successively at the center of the screen. They could be vowels (e,a,i,o,u,y) or consonants (b,c,g,k,m,p), written with either upper or lower case, and with either red or green color. On every trial, the letter was displayed for 900 ms, corresponding to the time window during which participants could give their response, followed by a blank screen lasting for 400 ms.

For the N-back task, participants were instructed to indicate when the current letter was the same as that presented N trials before. The 'yes' and 'no' responses were given by pressing left or right arrow on the keyboard (key-response associations being counterbalanced across participants). Difficulty was manipulated by changing N from 1 (easy version) to 3 (hard version). The sequence of letters was pseudo-randomized so as to get one third of 'yes' and two thirds of 'no' trials, among which half was made of traps (2- or 3-back repeats in the 1-back version, and 1- or 2-back repeats in the 3-back version). Color and case were varied but had to be ignored in this task.

For the N-switch task, color served as a contextual cue telling participants whether to perform a vowel/consonant or an upper/lower case discrimination task. As an example, a subject had to indicate consonant (left arrow) versus vowel (right arrow) when the letter was green, or upper case (left arrow) versus lower case (right arrow) when it was red. Colors, discrimination tasks and response keys were fully counterbalanced across participants. Letters were pseudorandomly distributed over trials in order to balance the frequency of each task (vowel/consonant or upper/lower case discrimination) and the side of correct response (left or right). The difficulty was imposed by the frequency of switches (color changes) from one per block in the easy version to 12 per block (40% of trials) in the hard version.

Just before the experiment, participants performed a calibration session with real choices. They were told that one of the choices made either during the calibration or during test sessions would be randomly drawn and implemented. This was actually done except that randomization was biased in order to exclude delays longer than one year. The amount of money that they could get varied between 1€ and 100€, which was quite significant relative to the fixed payoff (400€ for the entire experiment).

Choice task trials were intermingled with executive task trials (three per minute on average). There were 90 choices per fMRI session, thus a total of 180 choices in the entire experiment. Every trial, participants had a maximum of 5 s to state their preference between a small immediate reward (with variable amount) and a delayed reward (with variable reward and delay). The location (left or right) of the immediate and delayed options on the screen was counterbalanced across trials. There were ten possible delays (3 days, 1 week, 2 weeks, 3 weeks, 1 month, 3 months, 6 months, 1 year, 5 years and 10 years) and three possible delayed rewards (50€, 75€, 100€), which were presented in a randomized order. The immediate rewards were derived from subject-specific indifference points, which describe how each of the delayed reward is discounted with delay. These indifference points were obtained using a bisection procedure (with 11 steps for each delayed reward and each delay) that was implemented in the calibration session following on our previous study [5]. In each session of the experiment, three immediate rewards were presented for each of the ten delays and each of the 3 delayed rewards: one around the indifferent point, one above and one below. The two options of a choice were therefore close in (discounted) value, maximizing the sensitivity to potential fatigue effects, as it was previously implemented for TMS studies [52]. Between sessions, the amounts proposed as immediate rewards were randomly varied by +/- 1€ to avoid repeating choices and hence automatic responding. Note that delays and reward levels were different in the calibration procedures used for the other datasets included as a reference point for the immediacy bias. The immediacy bias is nevertheless comparable across datasets, because it is an additive parameter (on top of reward and delay terms in the computation of subjective value).

Behavioral data analysis

Two main dependent variables were analyzed: first executive performance (correct choice rate in hard relative to easy executive tasks, N-back and N-switch trials pooled together), second the parameters of the best choice model (present bias, discount factor and choice temperature). For each variable the main analyses tested the main effect of training overload (comparison between groups), the main effect of acute physical exercise (comparison between sessions), as well as the interaction between these two factors. Main effects and interactions were assessed using two-way ANOVA, with session as a within-subject factor and group as a between-subject factor. For comparisons involving only one factor (such as comparing between groups the model parameters fitted on the calibration choices), we used two-tailed t-tests. We checked that all significant results were maintained when we replaced t-tests by non-parametric tests

(Wilcoxon rank sum tests). For testing the effect of training overload on the immediacy bias, we also computed the exact probability of obtaining at least the same mean, in a group of the same size, from random sampling (1,000,000 iterations) within the cohort of control participants (n=106).

Computational modeling

To fit impulsive choices (selection of immediate reward IR vs. delayed reward DR), we used a standard softmax function of the relative value (RV) between the two options. This standard model was compared to a variant including an additive immediacy bias that captures a preference for the present independently from rewards and delays (eq 1 vs eq 2). In both cases, RV was weighted by a temperature parameter β that adjusts the stochasticity of choices. To calculate RV, we compared two classical delay discounting models, where rewards decrease hyperbolically vs. exponentially with delay (see eq 3 vs. eq 4). In both cases, sensitivity to delay (D) was captured by a discount parameter k. The four models were:

$$P(IR) = \frac{1}{1+\exp\left(\frac{RV}{\beta}\right)}\ ,(eq\ 1); \quad P(IR) = \frac{1}{1+\exp\left(\frac{RV}{\beta}-bias\right)}\ ,(eq\ 2); \quad RV = \frac{DR}{1+kD} - IR,\ (eq\ 3);$$

$$RV = DR \times \exp(-kD) - IR,\ (eq\ 4).$$

The four models (two softmax times two discounting functions) were fitted to choices made during the calibration session (210 choices) and during each MRI session separately (90 choices each) by the two groups of participants. Models were inverted by minimizing free energy, using a variational Bayes approach under the Laplace approximation [53,54], as implemented in the VBA Matlab toolbox [55], available at http://mbb-team.github.io/VBA-toolbox/). This algorithm not only inverts nonlinear models to provide posterior distributions on fitted parameters, but also estimates their evidence, which represents a trade-off between accuracy (goodness of fit) and complexity (degrees of freedom). The log-evidences, estimated for each participant and model, were submitted to a group-level random-effect analysis [56]. This analysis was used to generate exceedance probability, which measures the plausibility that a given model is more frequently implemented by participants that any other model in the comparison set. For the calibration session choices, priors were set between 0 and .1 for the discount rate parameter k, and between 0 and 10 for the choice stochasticity parameter β, with variance being adjusted so as to get a flat prior. For the immediacy bias parameter, prior distribution was centered on 0, with a variance equal to 1 (or 0 for the model without bias). For the MRI session choices, priors were centered on the posterior means estimated on calibration choices. An illustration of best model fit is provided in Fig. 4.

MRI data acquisition

T2*-weighted echo planar images (EPIs) were acquired with BOLD contrast on a 3.0 T magnetic resonance scanner (Siemens Verio). A tilted-plane acquisition sequence was used to optimize sensitivity to BOLD signal in the orbitofrontal cortex (44). To cover the whole brain with sufficient temporal resolution (TR = 2.180s) we used the following parameters: 40 slices, 2.5 mm thickness, 1mm interslice gap. Structural T1-weighted images were coregistered to the mean EPI, segmented and normalized to the standard T1 template and then averaged across subjects for anatomical localization of group-level functional activation. EPI images were analyzed using statistical parametric mapping (SPM8) environment (Wellcome Trust Center for NeuroImaging, London, UK). Preprocessing consisted of spatial realignment, normalization using the same transformation as anatomical images, and spatial smoothing using a Gaussian kernel with a full width at a half-maximum of 8 mm.

MRI data analysis

In order to identify regions involved in both executive tasks and inter-temporal choices, we regressed subject-level preprocessed fMRI time series against the following GLM. Two first categorical regressors (one for each difficulty level) were included to model blocks of executive task trials with boxcar functions. They were parametrically modulated by the block number within a session (to capture any fatigue effect across blocks). A third categorical regressor was included to model choice trial onsets with a stick function. It was modulated by four parametric regressors including immediate reward (IR), delay, response time and eventual choice (1 for patient and -1 for impulsive choice). These parametric regressors were meant to capture specificities of each particular trial, whereas the categorical regressor captured common processes involved in performing an inter-temporal choice. All regressors of interest were convolved with a canonical hemodynamic response function (HRF). The GLM also included subject-specific realignment parameters in order to correct for motion artifacts, adding six regressors of non-interest.

Linear contrasts of regression estimates (betas) were computed at the subject level, and taken to group-level random-effect analysis. Subject-level contrasts were categorical regressors against implicit baseline, which captured easy task-related activity, hard task-related activity and choice-related activity. A conjunction analysis (logical AND) was conducted at the group level between the difficulty contrast (1 on hard and -1 on easy task-related regressors) and the choice contrast (1 on choice-related regressors). Unless otherwise specified, activations maps were thresholded at both the voxel level ($p<0.001$, uncorrected) and the cluster level ($p<0.05$ after family-wise error correction for multiple comparisons, corresponding to a minimum of 333 voxels).

The main region of interest (ROI), in the left MFG (red cluster in Fig. 5), was delineated from a previous study [5] to avoid non-independence issues. This ROI was defined as the intersection between 1) clusters that showed significant conjunction between activation with task difficulty and during choice, and 2) clusters in which choice-related activity showed significant interaction between task difficulty and time on task (higher decrease in choice-related activity in subjects performing hard tasks relative to subjects performing easy tasks). To test for the specificity of overreaching effect on left MFG activity, we checked other ROI within the executive control network involved in inter-temporal choice. These ROI were defined as 8mm spheres (using MarsBar toolbox) centered on local maxima of choice-related activity in the control group (maximizing the probability to observe a difference between groups). They included the inferior parietal lobules bilaterally and the right MFG (see results in Fig. S1). Regression estimates were extracted from all these ROIs and compared between groups and sessions using two-tailed t-tests. The only significant effect was a difference between OR and CTL groups in the left MFG. We also checked that activity in the left MFG cluster was not affected by any parametric regressor of the GLM (block number, immediate reward, delay, response time, choice type). In particular, left MFG activity was not related to reward or delay (see Fig. S2), in keeping with the computational analysis showing that fatigue effect on choices was independent from these factors. To establish a link between the behavioral and the neural effects of executive fatigue, we tested across-subjects correlation between the fitted immediate bias in inter-temporal choice and the choice-related activity in MFG, using robust regression tool implemented in Matlab (see Fig. S3).

References

1. Meeusen, R. *et al.* Prevention, diagnosis, and treatment of the overtraining syndrome: joint consensus statement of the European College of Sport Science and the American College of Sports Medicine. *Med. Sci. Sports Exerc.* **45**, 186–205 (2013).
2. Armstrong, L. E. & Vanheest, J. L. The unknown mechanism of the overtraining syndrome. *Sports Med.* **32**, 185–209 (2002).
3. Miller, E. K. & Cohen, J. D. An integrative theory of prefrontal cortex function. *Annu. Rev. Neurosci.* **24**, 167–202 (2001).
4. Botvinick, M. & Braver, T. Motivation and Cognitive Control: From Behavior to Neural Mechanism. *Annu. Rev. Psychol.* **66**, 83–113 (2015).
5. Blain, B., Hollard, G. & Pessiglione, M. Neural mechanisms underlying the impact of daylong cognitive work on economic decisions. *Proc. Natl. Acad. Sci. U. S. A.* **113**, 6967–6972 (2016).
6. Muraven, M. & Baumeister, R. F. Self-regulation and depletion of limited resources: Does self-control resemble a muscle? *Psychol. Bull.* **126**, 247 (2000).
7. Englert, C. The strength model of self-control in sport and exercise psychology. *Front. Psychol.* **7**, (2016).
8. Carter, E. C. & McCullough, M. E. Publication bias and the limited strength model of self-control: has the evidence for ego depletion been overestimated? *Front. Psychol.* **5**, 823 (2014).
9. Hagger, M. S. *et al.* A multi-lab pre-registered replication of the ego-depletion effect. *Perspect. Psychol. Sci.* 2 (2015).
10. Meur, Y. L. *et al.* A multidisciplinary approach to overreaching detection in endurance trained athletes. *J. Appl. Physiol.* **114**, 411–420 (2013).
11. Lewis, N. A., Collins, D., Pedlar, C. R. & Rogers, J. P. Can clinicians and scientists explain and prevent unexplained underperformance syndrome in elite athletes: an interdisciplinary perspective and 2016 update. *BMJ Open Sport Exerc. Med.* **1**, e000063 (2015).
12. Lan, M. F., Lane, A. M., Roy, J. & Hanin, N. A. Validity of the Brunel Mood Scale for use With Malaysian Athletes. *J. Sports Sci. Med.* **11**, 131–135 (2012).
13. Borg, G. A. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* **14**, 377–381 (1982).
14. McClure, S. M., Laibson, D. I., Loewenstein, G. & Cohen, J. D. Separate neural systems value immediate and delayed monetary rewards. *Science* **306**, 503–507 (2004).

15. Kool, W., McGuire, J. T., Wang, G. J. & Botvinick, M. M. Neural and Behavioral Evidence for an Intrinsic Cost of Self-Control. *PLOS ONE* **8**, e72626 (2013).

16. Hare, T. A., Hakimi, S. & Rangel, A. Activity in dlPFC and its effective connectivity to vmPFC are associated with temporal discounting. *Front. Neurosci.* **8**, 50 (2014).

17. Wesley, M. J. & Bickel, W. K. Remember the future II: meta-analyses and functional overlap of working memory and delay discounting. *Biol. Psychiatry* **75**, 435–448 (2014).

18. Jimura, K., Chushak, M. S., Westbrook, A. & Braver, T. S. Intertemporal Decision-Making Involves Prefrontal Control Mechanisms Associated with Working Memory. *Cereb. Cortex* 1–12 doi:10.1093/cercor/bhx015

19. Koechlin, E., Ody, C. & Kouneiher, F. The architecture of cognitive control in the human prefrontal cortex. *Science* **302**, 1181–1185 (2003).

20. McGuire, J. T. & Botvinick, M. M. Prefrontal cortex, cognitive control, and the registration of decision costs. *Proc. Natl. Acad. Sci.* **107**, 7922–7926 (2010).

21. Cremers, H. R., Wager, T. D. & Yarkoni, T. The relation between statistical power and inference in fMRI. *PLOS ONE* **12**, e0184923 (2017).

22. Friston, K. Sample size and the fallacies of classical inference. *NeuroImage* **81**, 503–504 (2013).

23. Laibson, D. Golden eggs and hyperbolic discounting. *Q. J. Econ.* **112**, 443–478 (1997).

24. Haushofer, J. *et al.* No Effects of Psychosocial Stress on Intertemporal Choice. *PLoS ONE* **8**, e78597 (2013).

25. Libedinsky, C. *et al.* Sleep deprivation alters effort discounting but not delay discounting of monetary rewards. *Sleep* **36**, 899–904 (2013).

26. Baumeister, R. F., Bratslavsky, E., Muraven, M. & Tice, D. M. Ego depletion: is the active self a limited resource? *J. Pers. Soc. Psychol.* **74**, 1252 (1998).

27. Chang, Y. K., Labban, J. D., Gapin, J. I. & Etnier, J. L. The effects of acute exercise on cognitive performance: A meta-analysis. *Brain Res.* **1453**, 87–101 (2012).

28. Vadillo, M. A., Gold, N. & Osman, M. The Bitter Truth About Sugar and Willpower: The Limited Evidential Value of the Glucose Model of Ego Depletion. *Psychol. Sci.* **27**, 1207–1214 (2016).

29. Gailliot, M. T. *et al.* Self-control relies on glucose as a limited energy source: willpower is more than a metaphor. *J. Pers. Soc. Psychol.* **92**, 325 (2007).

30. Kurzban, R. Does the brain consume additional glucose during self-control tasks? *Evol. Psychol.* **8**, 147470491000800200 (2010).
31. Lange, F. & Eggert, F. Sweet delusion. Glucose drinks fail to counteract ego depletion. *Appetite* **75**, 54–63 (2014).
32. Job, V., Walton, G. M., Bernecker, K. & Dweck, C. S. Beliefs about willpower determine the impact of glucose on self-control. *Proc. Natl. Acad. Sci.* **110**, 14837–14842 (2013).
33. Molden, D. C. *et al.* Motivational versus metabolic effects of carbohydrates on self-control. *Psychol. Sci.* **23**, 1137–1144 (2012).
34. Figner, B. *et al.* Lateral prefrontal cortex and self-control in intertemporal choice. *Nat. Neurosci.* **13**, 538–539 (2010).
35. Holroyd, C. B. The waste disposal problem of effortful control. *Motiv. Cogn. Control* 235–260 (2016).
36. Angeli, A., Minetto, M., Dovio, A. & Paccotti, P. The overtraining syndrome in athletes: a stress-related disorder. *J. Endocrinol. Invest.* **27**, 603–612 (2004).
37. da Rocha, A. L. *et al.* The proinflammatory effects of chronic excessive exercise. *Cytokine* **119**, 57–61 (2019).
38. Harrison, N. A. *et al.* A Neurocomputational Account of How Inflammation Enhances Sensitivity to Punishments Versus Rewards. *Biol. Psychiatry* **80**, 73–81 (2016).
39. Draper, A. *et al.* Effort but not Reward Sensitivity is Altered by Acute Sickness Induced by Experimental Endotoxemia in Humans. *Neuropsychopharmacology* **43**, 1107–1118 (2018).
40. Kurzban, R., Duckworth, A., Kable, J. W. & Myers, J. An opportunity cost model of subjective effort and task performance. *Behav. Brain Sci.* **36**, 661–679 (2013).
41. Boureau, Y.-L., Sokol-Hessner, P. & Daw, N. D. Deciding How To Decide: Self-Control and Meta-Decision Making. *Trends Cogn. Sci.* **19**, 700–710 (2015).
42. Ackerman, P. L. *Cognitive fatigue: Multidisciplinary perspectives on current research and future applications.* (American Psychological Association, 2011).
43. Hockey, R. *The psychology of fatigue: work, effort and control*. (Cambridge University Press, 2013).
44. Massar, S. A. A., Csathó, Á. & Van der Linden, D. Quantifying the Motivational Effects of Cognitive Fatigue Through Effort-Based Decision Making. *Front. Psychol.* **9**, (2018).
45. Müller, T. & Apps, M. A. J. Motivational fatigue: A neurocognitive framework for the impact of effortful exertion on subsequent motivation. *Neuropsychologia* **123**, 141–151 (2019).

46. Inzlicht, M., Bartholow, B. D. & Hirsh, J. B. Emotional foundations of cognitive control. *Trends Cogn. Sci.* **19**, 126–132 (2015).
47. Kool, W. & Botvinick, M. A labor/leisure tradeoff in cognitive control. *J. Exp. Psychol. Gen.* **143**, 131 (2014).
48. Bosquet, L., Montpetit, J., Arvisais, D. & Mujika, I. Effects of tapering on performance: a meta-analysis. *Med. Sci. Sports Exerc.* **39**, 1358 (2007).
49. Howley, E. T., Bassett, D. R. & Welch, H. G. Criteria for maximal oxygen uptake: review and commentary. *Med. Sci. Sports Exerc.* **27**, 1292–1301 (1995).
50. Kuipers, H., Verstappen, F. T., Keizer, H. A., Geurten, P. & van Kranenburg, G. Variability of aerobic performance in the laboratory and its physiologic correlates. *Int. J. Sports Med.* **6**, 197–201 (1985).
51. De Pauw, K. *et al.* Brain mapping after prolonged cycling and during recovery in the heat. *J. Appl. Physiol.* **115**, 1324–1331 (2013).
52. Essex, B. G., Clinton, S. A., Wonderley, L. R. & Zald, D. H. The impact of the posterior parietal and dorsolateral prefrontal cortices on the optimization of long-term versus immediate value. *J. Neurosci.* **32**, 15403–15413 (2012).
53. Friston, K., Mattout, J., Trujillo-Barreto, N., Ashburner, J. & Penny, W. Variational free energy and the Laplace approximation. *NeuroImage* **34**, 220–234 (2007).
54. Daunizeau, J., Friston, K. J. & Kiebel, S. J. Variational Bayesian identification and prediction of stochastic nonlinear dynamic causal models. *Phys. Nonlinear Phenom.* **238**, 2089–2118 (2009).
55. Daunizeau, J., Adam, V. & Rigoux, L. VBA: A Probabilistic Treatment of Nonlinear Models for Neurobiological and Behavioural Data. *PLoS Comput. Biol.* **10**, e1003441 (2014).
56. Rigoux, L., Stephan, K. E., Friston, K. J. & Daunizeau, J. Bayesian model selection for group studies — Revisited. *NeuroImage* **84**, 971–985 (2014).
57. Deichmann, R., Gottfried, J. A., Hutton, C. & Turner, R. Optimized EPI for fMRI studies of the orbitofrontal cortex. *Neuroimage* **19**, 430–441 (2003).
58. Weiskopf, N., Hutton, C., Josephs, O., Turner, R. & Deichmann, R. Optimized EPI for fMRI studies of the orbitofrontal cortex: compensation of susceptibility-induced gradients in the readout direction. *Magn. Reson. Mater. Phys. Biol. Med.* **20**, 39–49 (2007).