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Trends in Cognitive Sciences

Feature Review

Origins and consequences of cognitive fatigue

Mathias Pessiglione [1,2,*], Bastien Blain [3], Antonius Wiehler [1,2], and Shruti Naik [1,2]

Everybody knows intuitively what mental fatigue is. However, we poorly understand why fatigue emerges with time spent on demanding cognitive work and how such 'cognitive fatigue' impacts neural processing and behavioral guidance. Here, we review experimental investigations that induced cognitive fatigue and recorded its potential markers, including self-report, behavioral performance, economic choice, physiological and neural activity. We then review theoretical models of cognitive fatigue, classically divided into biological and motivational accounts. To explain key observations and reconcile debated theories, we finally propose a conceptual model (dubbed MetaMotiF), in which cognitive fatigue would emerge for biological reasons and yet affect motivational processes that regulate the behavior. More precisely, fatigue would arise from metabolic alterations in cognitive control brain regions, following their excessive mobilization. In turn, these metabolic alterations would increase the cost of cognitive control, which would shift decisions towards actions that require little effort and yield immediate rewards.

Highlights

Cognitive fatigue is not transparently accessed via introspection, is not faithfully communicated through self-report, and does not reliably translate into performance decline.

Preference for low-cost options (rewards at short delay with little effort) in economic choices is a better marker of cognitive fatigue, being sensitive to both task duration and difficulty.

Empirical observations call for a notion of fatigue that is indexed on the cost of cognitive control, defined by opposition to automatic processes.

This notion of cognitive fatigue can offer a reconciliation between biological and motivational accounts that have been in conflict for the last decade.

Cognitive fatigue may have biological origins: exertion of cognitive control may induce some metabolic alteration in the underlying brain regions of the prefrontal cortex.

Cognitive fatigue may have motivational consequences: the elevated cost of cognitive control may discourage actions that go beyond effortless routines and immediate gratifications.

> 'It is always thus, impelled by a state of mind which is destined not to last, that we make our irrevocable decisions.'
>
> [Marcel Proust]

The issue with cognitive fatigue

For decades, science-fiction novels have described worlds in which machines would outsmart humans and take power. The eventual defeat of human intelligence seems even more plausible nowadays, as we witness new feats of artificial intelligence, beating the Go world champion, acing the bar exam, or faking a scientific report. Yet the comparison remains debatable, as we lack a consensual definition of intelligence beyond easy-to-quantify features like computing power and memory capacity. There is, however, one feature of the human brain that makes it clearly inferior to computers: it is susceptible to **fatigue** (see Glossary). While computers can continuously translate input speech in any language (if plugged into a power supply), professional human translators need breaks after less than an hour (without any need for food or sleep). What makes our cognition so fragile? This review addresses two questions: why fatigue emerges with cognitive work and how cognitive fatigue affects subsequent behavior.

Scientific investigation of cognitive fatigue is as old as experimental psychology, with pioneering studies published more than a century ago [1–3]. Even if using cognitive tasks, these studies have typically employed the term 'mental fatigue', in opposition to the physical fatigue that arises during motor tasks (see Box 1 for the different types of fatigue). In the following, we employ the term 'cognitive fatigue' for the specific type of fatigue induced by prolonged and demanding cognitive work. In this context, fatigue has been typically defined as a neurophysiological state that is accompanied by a sensation of discomfort and that compromises the maintenance of task

[1]Motivation, Brain and Behavior team, Paris Brain Institute, Pitié-Salpêtrière Hospital, Paris, France
[2]Sorbonne University, Inserm U1127, CNRS U7225, Paris, France
[3]Sorbonne Economics Center, Paris School of Economics, Paris, France

*Correspondence: mathias.pessiglione@icm-institute.org (M. Pessiglione).

Box 1. The different types of fatigue

In this paper, we focus on cognitive fatigue, understood as the fatigue arising from intense and sustained solicitation of the cognitive control brain system. It remains unclear how cognitive fatigue relates to the other types of fatigue that have been described.

A first type is local neural fatigue, which supposedly affects a specific brain module and not a large-scale generic brain system like that implementing cognitive control. For example, visuo-motor tasks (but not executive functions) were shown to be impaired after 12 h of driving [183]. These fatigue effects have been construed as arising from local sleep, because of the emergence of sleep-like slow waves in the specific brain region targeted by the task [184–186]. Passive visual stimulation can also impair performance relying on specific sub-portions of retinotopic occipital regions [187]. These fatigue effects may be related to local phenomena such as neural adaptation or repetition suppression [188–190]. Our notion of cognitive fatigue is more global regarding both the spectrum of impacted activities and the extent of the underlying brain network.

A second type is physical fatigue, as experienced following manual work or sport practice, with painful sensations in the muscles that compromise the execution of appropriate movements. Physical fatigue is primarily due to muscular alterations resulting from repeated contractions, which degrade the efficiency of motor commands. But there is agreement among exercise physiologists that fatigue during sport performance is not just in the muscles: beyond peripheral fatigue, there is a notion of central fatigue that can interrupt physical effort exertion [191,192]. Indeed, the fatigue induced by cognitive tasks enhances the perception of physical effort and impairs the performance of motor tasks [193–195]. Within the framework of the central governor model, this fatigue is generally interpreted as a signal that prevents the breakdown of body homeostasis [196–198]. However, central fatigue could also be interpreted as representing a need to preserve the cognitive control brain system, which would be required to overcome an automatic tendency to stop exercise when muscles or joints start aching. In endurance sports, cognitive control may be over-solicited to finish a training program, or a competitive race, despite muscular fatigue or pain signals. This hypothesis was confirmed by neural and behavioral signatures of cognitive fatigue (reduced lPFC activation and increased preference for immediate rewards) that were observed in triathletes who were overtrained, relative to normally trained triathletes, using our test protocol [199]. Thus, although peripheral fatigue is clearly a distinct phenomenon, central fatigue may overlap with our notion of cognitive fatigue. Extreme cases of cognitive fatigue might explain the overtraining syndrome, a form of burnout that can lead athletes to withdrawal from competition and even to full-blown depressive episodes [200,201]. Obviously, this does not mean that cognitive fatigue would explain all forms of burnout syndromes, which can be triggered by many other psychosocial factors in interaction with work conditions.

A third type is mental fatigue, as observed in the clinics and scored with questionnaires [8,9]. When fatigue does not go away with rest, it is sometimes qualified as chronic fatigue, by opposition to the acute fatigue that follows strenuous work and that we call cognitive fatigue. Mental fatigue can stem from multiple factors, not only psychosocial stress or sleep deprivation but also infectious diseases like hepatitis, neurologic diseases such as multiple sclerosis, and psychiatric diseases such as mood disorders. Although it is not specifically triggered by performance of a cognitive task, mental fatigue shares some features with cognitive fatigue. Indeed, mental fatigue is usually specified at the subjective level by the impression that most cognitive tasks are too demanding, and at the behavioral level by the avoidance of mental effort and the tendency to seek rest and recovery. Therefore, like cognitive fatigue, mental fatigue could be related to an elevated cost for cognitive control. A notion that may bridge the two sorts of fatigue is cognitive fatigability, understood as a predisposition for a rapid development of fatigue as soon as cognitive control is engaged. For instance, cognitive fatigability is observed in patients with low-grade glioma, who showed an increase in the choice bias (i.e., the preference for immediate rewards), during neuropsychological assessment, when choices of healthy controls were still at baseline indifference levels [202]. This may also be the case of patients with depression, for which fatigue is a key symptom but still poorly understood and treated [203,204]. The sensation that most actions are effortful is often reported by depressed patients, and behavioral tests have demonstrated that physical and mental effort cost is enhanced compared to matched controls [205]. However, the pathophysiological mechanisms underlying mental fatigue might be different from those inducing cognitive fatigue, which we envisage as metabolic alterations of the cognitive control brain system, putatively. Some authors have implicated neurometabolic alterations in mental fatigue, with the suggestion that neuroinflammation, via the release of cytokines, might interfere with astroglial glutamate clearance [206], but such speculations still require empirical confirmation.

performance (see Figure 1 for a standard framework). From this definition follow the two classical markers of fatigue: self-report and performance decline with time-on-task.

Here, we first review experimental studies using these straightforward measures of cognitive fatigue, which have yielded somewhat inconsistent results and problematic interpretations, as already pointed out [4,5]. We next describe more recent studies that have introduced novel measures of cognitive fatigue, using computational modeling of choice behavior, as well as neural and

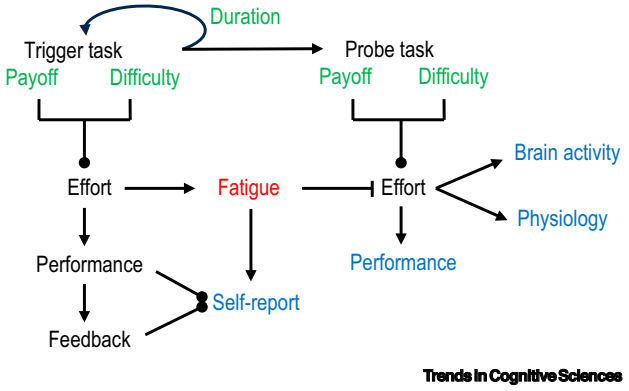

Figure 1. Conceptual framework for the study of cognitive fatigue. Cognitive fatigue is defined here as an objective neurophysiological state that is (i) triggered by the effort exerted to perform some cognitive task, (ii) accompanied by some unpleasant subjective experience, and (iii) manifested as the reluctance to repeat the same kind of effort. Note that cognitive fatigue is not the same thing as the reported fatigue sensation, which is known to be contaminated by other psychological phenomena related to performance and feedback, such as frustration, demotivation, loss of confidence, etc. Experimentally, cognitive fatigue can be induced and revealed using trigger and probe tasks, following two main paradigms. In the time-on-task paradigm, the same task (e.g., N-back) is used all along for triggering and probing fatigue. In the sequential task paradigm, the probe task (e.g., economic choice) involves the same kind of process (cognitive control) but differs from the trigger task (e.g., N-back or N-switch), hence avoiding the confound with boredom. The key experimental factors (task payoff, difficulty, and duration) that can be manipulated to vary the amount of effort exerted and therefore the level of fatigue induced are shown in green. The main classes of measures (self-report, performance, physiology, and brain activity) that can be used to assess the presence of fatigue are shown in blue. Stronger conclusions can be drawn if several measures are integrated because neurophysiological effects depend on whether fatigue results in disengagement (ending with deteriorated performance) or compensation (ending with maintained performance). Positive influence, modulation, and negative influence are respectively indicated with arrows terminated by triangles, circles, and dashes.

Glossary

Choice bias: a computational parameter of the choice model that adds a bonus to the value of particular options (low-cost options in the case of fatigue).
Cognitive control: a set of processes that regulate the behavior when automatic routines are not available for facing a situation or not appropriate for reaching a goal.
Effort: mobilization of mental or physical processes required to achieve a certain goal.
Fatigue: a neurophysiological state that is induced by mental or physical activity and specified by a predisposition to seek rest and avoid effort.

physiological recordings. Then we turn to theoretical explanations of cognitive fatigue, which can be divided into biological and motivational accounts. Because these theories suffer from some contradictions and limitations, we end by presenting an integrative model that might better explain the origins and consequences of cognitive fatigue.

Consequences of cognitive fatigue

Self-report

When cognitive fatigue is probed via introspection, it is generally referred to as mental fatigue (or just fatigue), even if induced by a cognitive task, because it is the term used in everyday language, hence understood by people asked for self-reporting. The subjective sensation of mental fatigue can be simply assessed as a score rated on a visual analogue scale going from top shape to full exhaustion. This is the quantification tool that is most used in experiments assessing fatigue [6]. In the clinics, mental fatigue is typically assessed with questionnaires that enable computing a score on a psychometric scale [7–11]. These analogue and psychometric scales are important for patients to express their complaints when plagued with mental fatigue. Indeed, mental fatigue has been reported in most neurologic conditions (e.g., stroke, degenerative disease), psychiatric conditions (e.g., depression, anxiety), and beyond (e.g., cancer, infectious disease).

However, self-report methods suffer from several limitations that mitigate their validity as fatigue quantification tools. First, it can be difficult to detect one's own fatigue state. This is evidently difficult for children who may refuse to rest or sleep even when they cannot focus on anything, or for patients who suffer from compromised insight, as is frequent in dementia or psychosis. But it may also be difficult for any of us, as illustrated by people who continue working without realizing they have developed severe burnout. Second, different individuals may have different interpretations of anchors and labels on rating scales, as well as possible responses on psychometric questionnaires. This may not be problematic for the follow-up of an individual's fatigue over time but may compromise the comparison of fatigue levels between individuals. Other issues are demand effects: in some situations, participants guess when they are expected to report fatigue.

This might explain why an increase in self-reported fatigue with time-on-task is always observed, even when the behavior remains unaffected [12–14]. This demand effect itself varies with the social desirability bias, which drives some participants to mask their fatigue if it is more important for them to avoid showing weakness. For these reasons, the reliability of self-reports, in both experimental and clinical settings, has been questioned [15–21].

Finally, self-reports often mix fatigue with other psychological states such as frustration, demotivation, boredom, or drowsiness. For example, participants may report feeling more fatigue after making an error in a cognitive task [22] because they confuse fatigue with frustration or feel a need for self-justification. This sort of mix can be spontaneously made by participants when rating their fatigue on a visual analogue scale, or induced by fatigue questionnaires, which often include items that de facto assess other constructs, such as reduced motivation in the Multidimensional Fatigue Inventory [23]. This constellation of subjective states might be grouped under the umbrella term of fatigue, which would turn it into a 'multi-faceted' construct [24–28]. Here, we aim to avoid such confusion by treating cognitive fatigue as a neurophysiological state accessible to objective measurement.

Performance

Initial studies of cognitive fatigue focused on performance drops occurring at time scales of less than 1 h [29,30]. However, declines in performance were not systematically observed, particularly when participants were sufficiently motivated or if their responses could be improved through training [31–35]. Moreover, even when performance decline was observed, critics argued the effect could be related to other phenomena such as frustration, boredom, or loss of interest. The difficulty is thus in isolating fatigue from other possible correlates of time-on-task, without relying on self-reports, which are susceptible to the same confounds.

We believe this is feasible because tasks that induce cognitive fatigue have distinctive properties. For instance, frustration typically arises when a task is too difficult for performance to be successful. In contrast, boredom and drowsiness typically emerge when a task is too easy or monotonous, such that the stimulus-response mapping can be automatized. Cognitive tasks that are efficient to induce fatigue present intermediate difficulty levels: they are feasible but require **effort**. Here, we treat effort as the mobilization of processes needed to attain a goal [36], not as a subjective sensation [37]. In two words, fatiguing tasks involve **cognitive control** [38–41], defined as the set of processes that regulate the behavior when automatic stimulus-response mapping is not available or appropriate [42]. Because cognitive control involves the mobilization of additional processes (on top of sensorimotor transformations), it necessarily represents a form of effort. In everyday life, cognitive control is typically required when we must abandon our habits because the context, rule, and/or goal have changed.

In the laboratory, studies of cognitive fatigue employ behavioral protocols that involve response inhibition, conflict monitoring, working memory, reasoning and planning, task-switching or dual-tasking [38,43–46]. Quantifying the level of cognitive control required by these tasks is not always straightforward. A general intuition is that the level of cognitive control depends on the amount of additional information needed, on top of the stimulus, to identify the correct motor response following the instructions [47]. For instance, a 0-back task ('press this button whenever a letter is on screen') requires less control than a 1-back task ('press this button whenever the letter on screen is the same as the last one') because in the latter case, the correct response is conditioned by the stimulus presented in the previous trial. It is important to distinguish these cognitive control tasks from monotonous tasks that just involve maintaining low levels of vigilance, as when driving a car or monitoring surveillance cameras, which may induce drowsiness but not necessarily fatigue [48,49]. This distinction between activities generating fatigue versus

drowsiness has been conceptualized as overload versus underload tasks [50,51]. Note that the case of vigilance tasks is complicated because fighting to maintain attention against automatic responses to boring stimuli (such as mind wandering or falling asleep) can by itself require cognitive control [52,53].

Even if frustration and drowsiness can be avoided, avoiding boredom or loss of interest remains a delicate matter. One strategy is to employ a sequential task paradigm, where a first task is meant to induce fatigue and a second one to reveal fatigue, through the comparison of performance with a control condition where no fatigue is induced. In this paradigm, the second task should renew interest, such that lower performance can be attributed to fatigue and not boredom. Historically, the sequential task paradigm has primarily been used in the framework of the so-called ego depletion theory [54,55]. The theoretical assumptions are that: (i) the two tasks tap into a shared resource dubbed 'ego' for self-control (sometimes 'strength' or 'willpower'), (ii) the level of this resource diminishes with its utilization (by the first task), and (iii) performance (in the second task) depends on the resource level. Thus, the ego depletion effect refers to a decrease in second-task performance that is more pronounced after a depleting first task than after a non-depleting first task.

We discuss conceptual issues in subsequent text, but the first shortcoming of this theory is that empirical support remains hotly debated. Although some meta-analyses [56,57] concluded that the effect is significant across studies, others pointed to potential publication biases [58] and questionable research practices [59]. Critically, some multi-laboratory pre-registered studies failed to replicate the effect [60,61] while others found only a small effect when testing extra-large samples [62,63]. One reason for skepticism is that many studies reported effects over short time scales (counted in minutes, not hours) after tasks that do not appear very demanding, like eating a radish instead of chocolate [54]. A self-control capacity that is so susceptible to depletion in benign situations seems incompatible with the constraints of modern professional life, and probably with the harsh environments faced by our species during its evolution.

Choice

When we started our own research on cognitive fatigue 10 years ago, we first took inspiration from studies using the sequential task paradigm and went through a series of replication failures. To give us a better chance to demonstrate fatigue effects, we then kept the structure of the sequential task paradigm but changed two critical features: the time scale of fatigue induction (increased to about 6 h) and the second task meant to reveal fatigue (turned into economic choice). The inspiration for these changes came from field observations about decisions that drift during a workday. In a famous study [64] of parole decisions made by experienced judges, positive rulings (in favor of prisoners) were reported to drop from 65% to 0% within the three daily work sessions, returning to 65% after each of the two food breaks between sessions. This particular study has been criticized because the order of application files processed by judges was not random [65]. However, there are other reports of similar decision drifts in other domains, even if less spectacular. For instance, the prescription of antibiotics for respiratory infections, made by trained doctors, was shown to increase with work hours during the day, even in cases for which antibiotics are not indicated (such as influenza), while the rate of these cases did not vary across time [66].

These field observations are not controlled experiments, so we cannot attribute decision drift to cognitive fatigue with any confidence. Thus, we set up an experiment [67] in which decisions were probed every minute for 6 h (the approximate duration of a short workday), while fatigue was induced using cognitive control tasks that recruit the lateral prefrontal cortex, lPFC [68,69]. Two groups performed the same tasks for the same time, but with different levels of difficulty, which induced different levels of fatigue (Figure 2A). The tasks were equally boring for the two

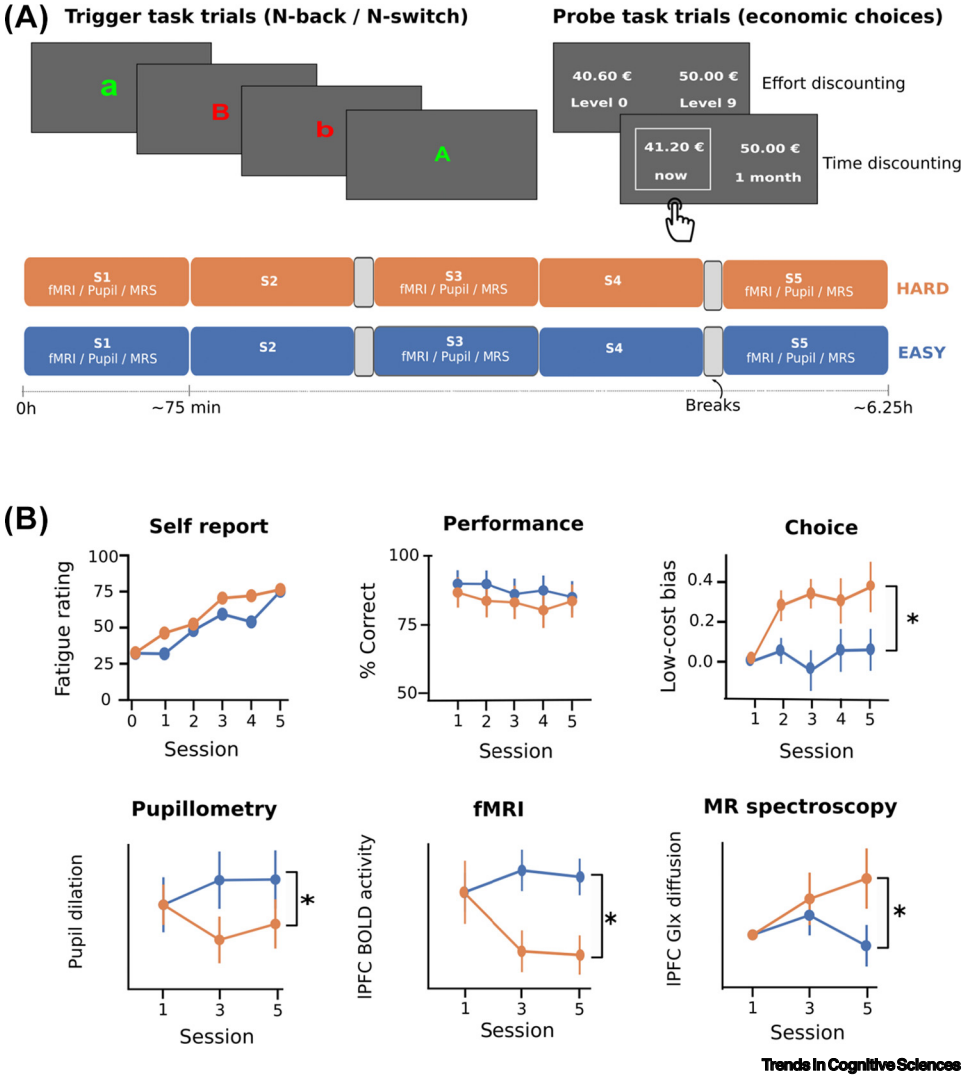

Figure 2. A comprehensive investigation of cognitive fatigue. (A) Experimental protocol used to induce and reveal cognitive fatigue. In this protocol (used in [67,74]), participants perform cognitive control tasks (N-back and N-switch) meant to induce cognitive fatigue, and economic choice tasks meant to reveal cognitive fatigue. Cognitive control tasks are performed on a series of colored letters presented on screen one by one. In the N-back task, participants indicate whether the letter is the same as the letter presented N trials before it. In the N-switch task, participants categorize the letter in either vowel versus consonant or upper-case versus lower-case, depending on its color (green or red). In both tasks, the difficulty can be varied by changing N (number of trials to remember or number of switches between categorization rules). Two groups of participants performed these tasks for the same time (about 6 h) but with different difficulty levels: 1-back and 1-switch (5% of trials) in the easy version (blue sessions), 3-back and 12-switch (50% of trials) in the hard version (orange sessions). In each 1-min block, participants also performed economic choices, between a small reward associated with little cost and a bigger reward associated with a higher cost (either time or effort). Brain activity was recorded during the first, middle and last sessions using functional MRI [67] or MR spectroscopy [74]. (B) Behavioral and neurophysiological consequences of cognitive fatigue. Each plot shows data averaged per session and per group (easy versus hard conditions), with standard errors. Behavioral measures (pooled over datasets collected in [67,74]) include rating of subjective fatigue on a visual analogue scale, performance in N-back and N-switch tasks (percentage of correct responses), and choice bias (bonus parameter added to the value of low-cost options in the choice model, see Box 2). Note that the day before the experiment, participants were trained to perform cognitive control tasks (above a criterion of 90% correct) and calibrated on economic choices, such that options could be individually tailored to start around indifference points (50% choice rate) at the beginning of the test day. Neurophysiological measures include

(Figure legend continued at the bottom of the next page.)

groups, or if anything, more boring in the less challenging version. To test for a decision drift, we used inter-temporal choices opposing immediate to delayed monetary rewards. The rationale was that the choice of immediate rewards (i.e., impulsive choice) was known to be countered by lPFC activation [70,71] and released by lPFC inhibition via transcranial magnetic stimulation [72,73]. We reasoned that cognitive fatigue would manifest more clearly in choices framed as expressions of subjective preferences (with no right or wrong answer) than in performance levels during cognitive control tasks, which participants would want to maintain even if it meant exerting additional effort.

The classical expected outcomes of cognitive fatigue, subjective experience, and performance decline, were inconclusive (Figure 2B). Subjective rating of experienced fatigue increased across sessions, but similarly for the two difficulty levels, comporting to the idea that self-report does not allow valid between-participant comparison. Participants fulfilled the expectation that fatigue should increase during the day, but the magnitude of the change in their rating was not informative about how hard they had to work. Performance showed a slight decline, but again similar in the two groups, with the correct response rate remaining above 90%, even after 6 h. This high and stable performance level can be explained by a strong motivation: participants were told that they would be paid for each correct response.

The main result was a significant group-by-session interaction in impulsive choice rate. Participants doing high-load tasks were more likely (around 60%) to pick the immediate reward at the end of the day [67]. In contrast, impulsive choice rate remained constant in participants doing low-load tasks. This fits well with the idea that fatigue impedes the recruitment of cognitive control, which is necessary to resist the temptation of immediate gratification. The interaction was later replicated [74] and extended to effort: participants doing high-load tasks were not only less willing to wait, but also less willing to engage in physical or mental effort for bigger rewards. To better specify the effects of cognitive fatigue, we fitted computational models to choice data (Box 2). The parameter that captured the fatigue effect, showing a group-by-session interaction, was the **choice bias** – a bonus added to low-cost options (with no delay, no effort). Thus, in our experiments, the best behavioral marker of cognitive fatigue was an exacerbation of choice impulsivity, meaning a shift in subjective preferences towards smaller rewards obtainable at shorter delay and with lesser effort. Note that impulsive choice here means picking the low-cost option, not deciding faster (indeed, choice response time did not change across experimental sessions). Our results comfort the idea that economic choices better reveal the cost of cognitive control than self-reports of effort sensation [75].

Physiology

Many studies have looked for physiological markers of cognitive fatigue, the most common targets being the eye and heart, which can both provide indirect measures of effort exertion related to the activity of the autonomic nervous system. A popular measure is pupil dilation, which has been linked to the engagement of mental effort [76–79] and to the release of noradrenalin by the locus coeruleus [80–85]. Other measures such as heart rate, heart rate variability, and cardiovascular response are derived from electrocardiography and taken as reflecting the balance between sympathetic and parasympathetic drive [86–91].

hemodynamic activity [67], pupil dilation [74] and Glx (glutamate/glutamine) diffusion [74] recorded during economic choices. Brain measures were extracted from a lateral PFC region of interest (left middle frontal gyrus). For computational and neurophysiological measures, data were normalized to the grand mean of the first session (because absolute values are meaningless). Among all measures, significant duration-by-difficulty (i.e., session-by-group) interaction was observed (*) for choice-related measures (choice bias, pupil dilation, lPFC activity and lPFC Glx diffusion), but not for self-reported fatigue nor for cognitive task performance. Abbreviations: €, euro; lPFC, lateral prefrontal cortex; MR, magnetic resonance.

Box 2. Computational accounts of how fatigue emerges and affects choices

Regarding the origins of cognitive fatigue, our model [74] postulates a metabolic alteration resulting from cognitive control exertion. Whether the neurometabolic alteration is (i) the accumulation of a potentially toxic substance X (such as glutamate), or (ii) the depletion of an energetic substrate X (such as lactate), it can be written as the sum of two opposite dynamic processes:

Accumulation : $dX/dt = +\beta_C.C - \beta_X.X$ [I]

Depletion : $dX/dt = -\beta_C.C + \beta_X.X$ [II]

with β_C being the accumulation or depletion rate of X related to the exertion of cognitive control, and β_X the passive clearance or refill rate through molecular mechanisms. A key assumption of the MetaMotiF model is that X concentration, which corresponds to the level of cognitive fatigue, affects the cost of cognitive control. The formalization of how the effort cost relates to X concentration would go beyond the scope of this paper. In short, the idea is that X concentration needs to be regulated, because going too far in X accumulation or depletion would alter the functioning of the cognitive control system, which would be detrimental for the individual in case some important challenge arises and must be efficiently tackled. This regulation would be operated both at a molecular level and at a whole-brain level by a motivational tradeoff system, which would integrate the costs and benefits of cognitive control exertion (Figure 3C).

Among the potential consequences of cognitive fatigue, the effect on choices can be captured with standard computational models [74]. In their simplest forms, these models include (iii) a function that estimates the subjective value of each option by discounting expected rewards with delay and effort costs, and (iv) a function that maps subjective values onto choice probabilities for the different options.

Value function : $V = R/(1 + k_D.D) - k_E.E^2$ [III]

Choice function : $P_i = 1/(1 + \exp(-\beta_V.(V_i - V_d + \text{bias}))$ [IV]

with V the subjective option value, R the reward magnitude, D the delay of reward delivery, E the effort cost, P_i the probability of choosing the immediate and effortless small reward (option with subjective value $V_i = R_i$). Individual preferences are captured by adjusting the free parameters of the value function, that is, the weights of delay and effort (k_D and k_E, also called discount factors). The stochasticity of choices is captured by the weight of option values (β_V, also called inverse temperature). Behavioral data indicate that cognitive fatigue increases the propensity to choose immediate rewards that can be obtained without effort, presumably because these are default options that are selected when no cognitive control is applied to decision making. In computational models, this higher propensity is captured by an increase in the choice bias, a bonus parameter added to the subjective value of no-delay no-effort rewards in the choice function.

Importantly, the increased bias with cognitive fatigue affects all choices, irrespective of the delay and effort associated with the bigger reward and without changing their level of stochasticity (meaning that cognitive fatigue does not affect the other free parameters of the model). Indeed, between the first and last sessions of our protocol, cognitive fatigue manifests as a shift in the psychometric choice function [74]. This effect can be contrasted with that of time pressure (obtained by reducing the response time window to 70% of spontaneous response time), which manifests as a change in the slope of the psychometric choice function (Figure I). Thus, cognitive fatigue induces a preference for effortless options yielding immediate rewards, whereas time pressure makes choices more stochastic.

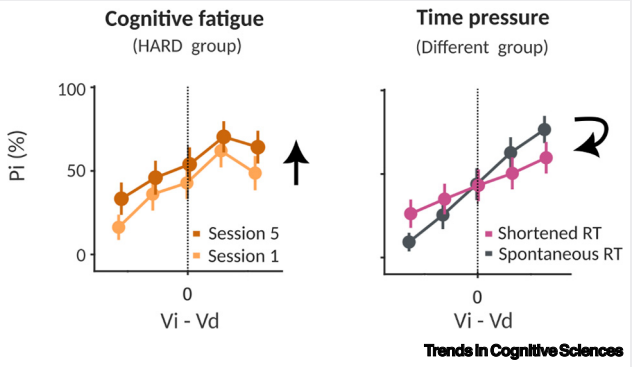

Figure I. Dissociation of cognitive fatigue and time pressure effects on choice behavior. Abbreviation: Pi, probability of choosing the immediate reward; RT, response time; Vd, value of delayed reward; Vi, value of immediate reward.

Consequently, many studies have used eye-tracking and electrocardiographic devices to document cognitive fatigue [92–94]. Some results appeared consistent across studies, such as the reduction of pupil dilation with time-on-task [33,95–97], which may indicate diminished effort exertion. In our own research [74], we observed that fatigue in the hard work condition was associated with reduced pupil dilation during economic choices, but not during cognitive control tasks (Figure 2B). This is consistent with the interpretation that cognitive control was sustained during tasks, to maintain high performance levels, but relaxed during choices, such that low-cost options (no effort, no wait) were more frequently preferred.

Other eye-tracking measures, such as blink rate and saccade velocity, have also been observed to vary with fatigue, albeit in the context of vigilance tasks that may confound fatigue with drowsiness [98]. Cardiac measures have yielded mixed results, with some studies reporting a decreased heart rate and increased heart rate variability [99,100], suggesting effort reduction, and others a stronger cardiovascular response [101,102], suggesting additional effort exertion. These opposite patterns can be interpreted as two different strategies employed when facing fatigue [103]: either disengagement (decreasing effort, resulting in performance decline) or compensation (increasing effort, resulting in performance maintenance).

If cognitive performance is not monitored, however, these interpretations remain problematic because they rely on a reverse inference (from physiology to effort). Factors other than effort exertion, such as stress versus sleepiness, might trigger the reaction of the autonomic nervous system and hence the change in physiological markers. In addition to autonomic arousal, physiological measures can also be confounded with low-level factors, such as luminance in the case of pupil dilation.

Brain activity

To identify neural signatures of cognitive fatigue, most studies have monitored electroencephalography (EEG) activity during task performance. According to meta-analyses [104–106], the most reliable signature is an increase in theta-band oscillations over central electrodes, with possible extensions to the alpha band and frontal and posterior electrodes. However, the high variability observed in effect size across participants precludes using this signature to build reliable fatigue detectors at the individual level. Also, it could be argued that these signatures are not specific to cognitive fatigue but rather shared with drowsiness [107–109], since they have been observed in both studies using cognitive tasks [40,110,111] and studies using driving or flying simulators [112–114]. Yet mid-frontal theta-band oscillations have also been suggested to reflect activity in the mid-cingulate cortex that drives the recruitment of cognitive control [115–117]. In this perspective, decrease or increase of mid-frontal theta-band activity would be interpreted as disengagement of or compensation by cognitive control exertion [118–120], while an increase in alpha-band activity would indicate attention shifting off the task or mind wandering [121–123].

The neural correlates of cognitive fatigue emerging during task performance have also been tracked using fMRI. Consistent observations across studies are decreased activity in the brain network associated to cognitive control, versus increased activity in the default mode network, which can spill over a subsequent task and last during the post-task rest period [124–127]. In our own experiment [67], the activity of the middle frontal gyrus (a cognitive control brain region located within the lPFC), diminished across the workday but only during economic choices, not during cognitive tasks. This is another piece of evidence that, in a fatigued state, cognitive control is maintained whenever important (for producing correct responses) and disengaged whenever possible (for expressing subjective preferences). Furthermore, the neural and behavioral effects of cognitive fatigue were correlated across participants: those who ended the day with a steeper decrease in their lPFC activity were

also more impulsive in their choices. There was no other significant change with time-on-task: no evidence for compensation during tasks by increased activity in cognitive effort brain regions, or for demotivation during choices with decreased activity in reward-related areas.

In sum, empirical evidence suggest that cognitive fatigue emerges from tasks involving cognitive control, with sufficient duration and difficulty, and manifests as a reluctance to exert cognitive control, which (i) can be sensed and reported, but without quantitative precision, and (ii) can result in disengagement of cognitive control, but only when consequences are deemed tolerable. In this case, fatigue may be observed through cognitive performance decline, preference shift toward low-control choice options, or decreased neural and physiological activities associated with cognitive control. Thus, a good theory of cognitive fatigue should account for this entire set of observations at the behavioral and neurophysiological levels. With these considerations in mind, we may now ask why we have such fatigable brains.

Origins of cognitive fatigue

As Hockey [5] wrote: "Remarkably, given that fatigue has been studied formally for well over 100 years, there is still no scientifically mature theory of its origins and functions.". This does not mean that we are short of theories, but simply that among the wealth of theories suggested so far, none has proven fully satisfactory. There are two grand classes of theories providing an account of cognitive fatigue, which differ in the reason why performance of demanding cognitive tasks is stopped at some point: in biological theories, this is because prolonged cognitive work would provoke some alteration of cerebral functions, whereas in motivational theories, this is because prolonged cognitive work would turn maladaptive for maximizing personal benefits.

Biological theories

An intuitive idea is that cognitive fatigue stems from the depletion of some resource, by analogy with machines, which would not work without a source of energy, such as fuel for engines. This idea is related to the concept of effort, classically defined as a resource or process that is mobilized to attain a certain goal [36,128]. If resources are missing, effort cannot be exerted, hence, performance declines. In initial accounts, resources were defined at a cognitive level: for example, attentional or computational resources have been conceived as the number of units in a reservoir that one can allocate to a given task [129–131]. However, when pressed to identify measurable variables to make the model falsifiable, some authors turned abstract cognitive resources into concrete biological entities. This happened with proponents of ego depletion theory, who translated the loss of self-control resources into a lack of blood glucose [132–134].

The glucose depletion theory is problematic for several reasons. One reason is that glucose is a very general resource for the brain (and other organs): as it provides energy for all cognitive functions, it is unclear why it would specifically affect self-control [135]. Another reason is that energetic consumption by the brain is believed to be roughly similar whether the person is working hard or just resting [136], so it is not clear why cognitive control would affect blood glucose [137–139]. But the main issue is perhaps the absence of undisputed evidence that glucose consumption helps to attenuate fatigue effects. Some early experiments suggested that soft drinks could help to counter the ego depletion effect, that is, the performance drop in the probing task that follows the depleting task [140], but the empirical evidence was later questioned [141,142]. Moreover, follow-up experiments showed that soft drink in the mouth, without swallowing and subsequent digestion into energetic resource, could also counter the ego depletion effect [143–145], pointing to a psychological mechanism rather than a biological one. Prior beliefs and psychological manipulations, such as instructing participants about potential after-effects of self-control exertion, can also activate or eliminate behaviors mimicking ego depletion [146,147].

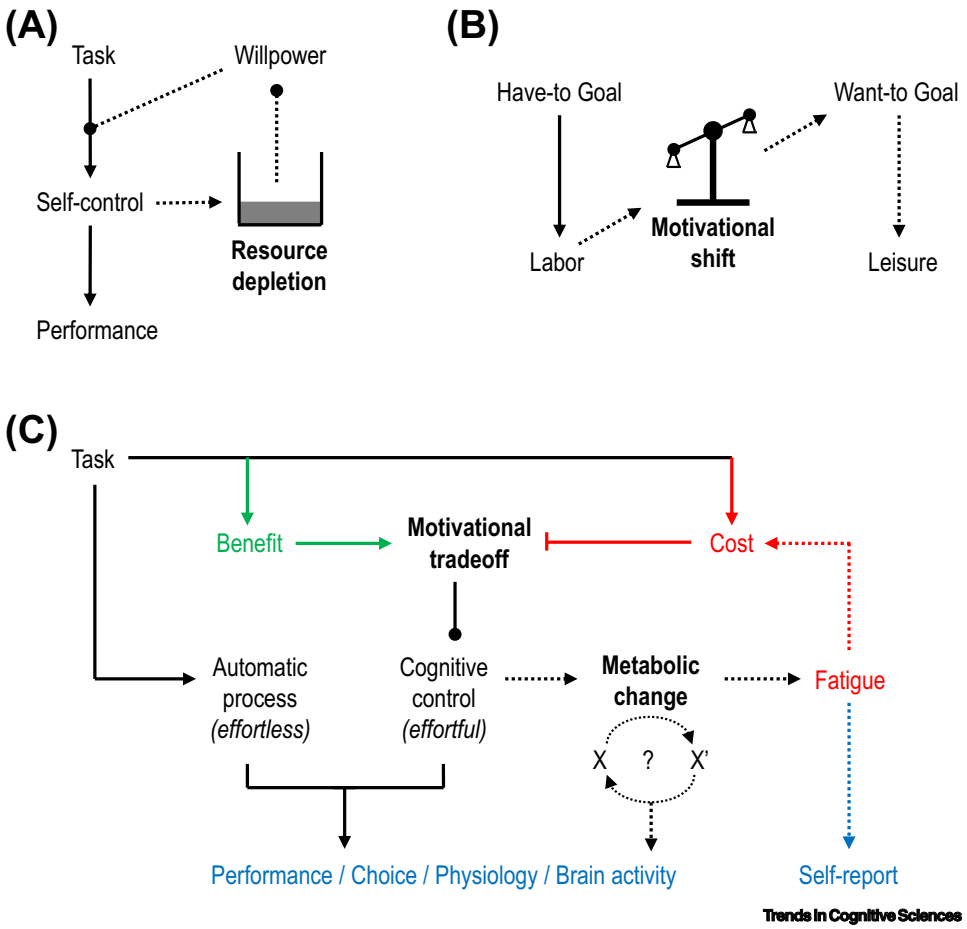

Figure 3. Theoretical accounts of cognitive fatigue. In all three diagrams, dashed lines denote mechanisms underlying the emergence of cognitive fatigue. Arrows terminated by triangles, circles, and dashes respectively indicate positive influence, modulation, and negative influence. (A) A biological resource depletion model. The engagement of self-control is triggered by the task that must be performed but is conditioned on the strength of willpower. The exertion of self-control during task performance is fueled by some resource that is progressively depleted. As resource depletion decreases the strength of willpower, it compromises the exertion of self-control and hence the performance of subsequent tasks. Various resources, such as blood glucose, have been suggested to underlie willpower in the literature. At rest, the resource tank would spontaneously replenish until enabling again the exertion of self-control. This illustration is based on the description of ego depletion theory [134]. (B) A motivational shift model. The engagement of labor activity is driven by the activation of some 'have-to' goal. After some time spent in labor, a motivational shift deactivates the current 'have-to' goal and activates some 'want-to' goal that drives the engagement in some leisure activity. A reverse shift of goals would explain the return to labor. This illustration is adapted from the description of the 'process model' [161]. (C) A metabolico-motivational model (MetaMotiF). The engagement of cognitive control is adjusted on the basis of a motivational arbitration between expected benefits of task performance and expected effort costs, which depends on task difficulty and fatigue level. The exertion of cognitive control improves task performance relative to that obtained with automatic routines and improves economic decisions relative to choosing default options. However, cognitive control exertion induces some change in metabolite X, which can be either some potentially toxic substance that is accumulated or some energetic substrate that is depleted. The variations in X are proportional to both the intensity and duration of cognitive control exertion. In turn, this neurometabolic alteration increases the cost of cognitive control that is weighed against the expected benefit in the motivational tradeoff. The objective fatigue level is nothing but the degree of neurometabolic alteration, which may partially inform what is subjectively experienced and reported as a fatigue sensation. Depending on the expected benefit, cognitive control can be maintained, resulting in enhanced effort sensation, or disengaged, resulting in performance decline and choice bias. During rest periods, molecular mechanisms would restore baseline levels of metabolite X, such that the cost of cognitive control would return to a minimum. This illustration is an elaboration of the model presented in a neurometabolic study of cognitive fatigue [74].

Even if the glucose depletion theory is wrong, the general idea (illustrated in Figure 3A) that cognitive fatigue is linked to the depletion of some metabolic resource in the brain cannot be entirely discarded. Other sources of energetic supply have been advanced, such as glycogen stored in the astrocytes, which may provide neurons with lactate [148–150]. The conceptual issue remains to explain why cognitive control would be particularly demanding of that metabolic resource. Another possibility is that the metabolic alteration associated with cognitive fatigue is not due to the depletion of some energetic supply but the accumulation of some potentially toxic substances, which might compromise cognitive control efficiency. It has been suggested, for example, that prolonged cognitive control exertion may lead to the accumulation of Aβ-amyloid peptide in interstitial spaces, which is detrimental to neural cell functions [151]. Another suggested candidate is adenosine, a by-product of glucose consumption that might interfere with electrophysiological properties of neurons [152].

In our own research, we used magnetic resonance spectroscopy (MRS) to track brain metabolites during cognitive control tasks and economic choices [74]. In participants performing difficult versions of the tasks, we observed that glutamate diffusion increased across the day in the lPFC, the cognitive control brain region in which fMRI activity diminished with cognitive fatigue [67], but not in the visual cortex region probed for comparison, and not in participants doing easy versions of the same tasks (Figure 2B). Furthermore, the increase in glutamate diffusion in the lPFC was correlated across participants with the increase in their propensity to select immediate and effortless rewards. The interesting point is that diffusion is higher in open compartments such as synaptic clefts than in closed compartments such as intracellular vesicles. Therefore, increased glutamate diffusion can be interpreted as glutamate accumulation in the synapse. This would explain cognitive fatigue because synaptic glutamate might interfere with information transmission between neurons. Alternatively, the critical factor may be the exhaustion of intracellular glutamate, which is needed for passing the information to the next neuron. The latter explanation would thus be another instantiation of a resource depletion theory. However, it should be noted that metabolic spectra were far from being exhaustive, such that we might have missed the key substance that generates cognitive fatigue, which could be any metabolite that covaries with glutamate.

Motivational theories

Biological theories have been challenged because of the observation that fatigue effects can be countered by increasing the motivation of participants, for example, by offering additional incentives to maintain performance levels [31,153–156]. This suggests that resources are not truly depleted in a fatigue state. Pushing the argument, several authors proposed to ban the notion of resource, once described as a 'theoretical soup stone' [157], that is, an explanatory factor that is neither necessary nor sufficient. Instead, they suggested that fatigue is just a motivational adjustment that drives people to give up their ongoing labor [5].

Motivational theories come in various flavors. Building on both the labor/leisure framework from economic decision theory [158] and the exploitation/exploration framework from foraging behavior theory [159,160], the so-called 'process model' [161] equates fatigue with a shift from 'have-to goals' to 'want-to goals' (Figure 3B). The rationale is that natural selection should have favored a mechanism ensuring a balance between the need to exploit known sources of reward and the need to explore new places and find other sources of reward. In this scenario, fatigue would be the signal that triggers the transition from exploitation (or labor) to exploration (or leisure). The idea is appealing, as it fits with the common intuition that after a good hard workday, we indulge in immediate gratifications. This idea seems corroborated by reports that appetitive responses to food rewards are enhanced by self-control depletion [162] or that cognitive fatigue manifests itself as a preference shift from delayed to immediate rewards [67]. However, the mapping of the labor/leisure dilemma onto the exploitation/exploration dilemma is not so intuitive. One

could argue that exploration is more demanding in cognitive control than exploitation because, by definition, exploration cannot rely on automatic stimulus-response routines. Indeed, neuroimaging studies have shown that switching to exploration behavior involves brain regions involved in cognitive control [163–165]. Therefore, the prospect of exploring new opportunities may seem aversive after a strenuous workday, while exploitation of well-established gratifying activities may seem attractive. Consistent with these considerations, other authors have proposed that the internal state triggering the motivational switch to exploratory behaviors is not fatigue but boredom [166].

Additionally, the process model suffers from some conceptual shortcomings. The first is that the model does not explain what information is integrated in the generation of the fatigue signal. In other words, there is no mechanistic process in the model, despite its appellation. A possible mechanism would be that some brain system estimates the time spent working and converts this estimate into a proportional fatigue signal, but this system would be blind to work difficulty. Alternatively, optimal foraging theory derived a strategy (following the marginal value theorem) that prescribes switching to exploration when the reward rate of the current patch passes below the average reward rate in the habitat [167,168]. As this theorem accounts for a wide range of foraging behaviors [169], exploration may actually be triggered by the comparison of reward rates, not by a putative fatigue signal. It could be argued that fatigue is nothing but a subjective estimate of reward rate, yet this would not explain why fatigue emerges during task performance with a constant reward rate, as in our protocol (Figure 2A). The natural situation in which the (objective or subjective) reward rate diminishes with time, as when collecting food from a restricted patch, is not so frequent in modern jobs that nonetheless generate fatigue. The second shortcoming of the process model is that cognitive fatigue is supposed to explain why we give up on exerting control and turn to more impulsive behavior. To qualify as an explanation, fatigue must be something more than this behavioral change. Stating that the behavioral change is due to fatigue defined as a motivational shift, from some goal (of facing labor) to some other goal (of indulging leisure), sounds tautological. Indeed, it is always possible to explain a change of behavior by a change of goal. As goals are abstract constructs that are not measurable, they may be the sort of useless stones that should be taken out of the theoretical soup if we want the model to be falsifiable. In any case, the process model does not provide any good reason why the motivational shift should be experienced as fatigue, rather than other sensations such as boredom or frustration.

Other motivational theories of cognitive fatigue have adopted a cost–benefit framework [170,171]. The central assumption is that the decision to engage or persist in a cognitively demanding task is based on a net value function that integrates the expected efforts and rewards attached to task performance. This effort/reward tradeoff is at the core of many motivational processes in both healthy people and patients with neurologic or psychiatric conditions [172,173]. It implies that cognitive control carries an inherent effort cost that must be compensated by some reward outcome for task performance [158,174]. In this framework, cognitive fatigue would correspond to a shift in the expected net value of task performance. If the payoff (i.e., the reward rate) is constant, the shift must be driven by an increase in the effort cost. The issue is therefore to elucidate the nature of the effort cost associated with cognitive control exertion, in a way that would explain why it would increase with its utilization. Initial formulations have been vague, suggesting that the 'energetical cost of performance' [170], or the 'inherent disutility of work' [161], should increase with time-on-task. Yet the reason why it should be the case is unclear, if we keep in mind that what matters for the decision to prolong performance is the expected cost of future efforts, not the cumulated cost of past efforts.

A more formal model has proposed that mental effort may essentially be an opportunity cost [175]. More precisely, the effort cost of allocating one unit of an information processing system to a given task is defined as the foregone utility of allocating this unit to the next-best task.

There is an implicit notion of limited resource in this framework (the number of units available), which creates an allocation problem because, even if one unit can process different tasks, it cannot do so simultaneously. The beauty of the model is that it explains why sensations of mental effort only arise with cognitive control exertion and not with other cognitive functions: using it yields an opportunity cost, precisely because as a multi-demand system, it represents a resource shared by many cognitive activities [176]. However, there is no depletion of resource with time-on-task in this model: performance drops because task utilities are updated, such that a new optimum emerges in which some units are disengaged from the main task to enable engagement in a secondary task, such as daydreaming. Although the model provides a computationally coherent account of effort regulation, there are shortcomings in how it would explain cognitive fatigue. A first limitation (acknowledged by the authors) is that it may equally well explain other negative experiences associated with prolonged task performance, such as boredom or frustration about the tempting opportunities that must be missed. If tempting alternatives (like a smartphone in the pocket) indeed generate fatigue, the reason may not be that they add to the opportunity cost, but that more cognitive control is required to keep focus on the task. A second limitation is that, under this model, fatigue (i.e., increase in mental effort cost) can only arise through learning, which implies that work sessions should always start with overestimated priors about the current task utility, or underestimated priors about the alternative task utilities. There is no reason why this condition should always be fulfilled, particularly in work conditions that are experienced daily or in experimental protocols for which participants are heavily trained (and which still generate cognitive fatigue). Also, if the utility of novel tasks was always overestimated, the model would not explain how cognitive fatigue induced by a first task can impact performance in a different task.

Integration of biological and motivational theories

On the one hand, pure motivational theories are short of mechanistic explanations for why cognitive fatigue scales with the duration and difficulty of task performance. Some change in the mind/brain must occur to drive the switch of motivational priorities. In other words, to signal when to stop labor and start leisure, some brain system must be sensitive to the integral of cognitive demand over time-on-task. Another issue is that the willingness to stop cognitive performance can occur even with an intact appetence for the reward attached to the task [177]. While markers of cognitive control exertion vary with time-on-task, reward-related brain activity seems stable [67,178], suggesting that fatigue is linked to an enhanced effort cost, not a diminished sensitivity to the task payoff. Besides, pure motivational accounts seem implausible in cases where cognitive fatigue reaches such a level that it prevents patients from enjoying any entertainment activity, restricting their agenda to professional activities.

On the other hand, assuming that motivation plays no role and that task disengagement is a deterministic consequence of some biological alteration is obviously wrong. Evidence is overwhelming that, even in an advanced fatigue state, people can find the strength to prolong effort when the stakes are high enough. It is also well documented that people generally stop hard work and switch to easier activity before being exhausted. Yet this does not mean that the idea of resource depletion should be abandoned; it simply suggests that the brain anticipates and avoids reaching a full exhaustion. Consider the analogy of a driver bringing their car to a gas station. At that moment, the car can still move forward, but this is no argument for denying the existence of a depletable gas tank. The gauge is indeed an important factor that a driver integrates with other constraints and goals to make an informed decision about when to stop.

The solution, therefore, is to integrate biological and motivational theories: the willingness to exert cognitive control may be based on the anticipation of a cost–benefit tradeoff, which may be shifted by some alteration of the brain related to task performance. This solution is far from

novel. It is indeed difficult to find in the literature a biological theory that would entirely dismiss that engagement in a cognitive task depends on motivational factors. Even proponents of ego depletion theory would acknowledge that motivation could maintain performance when resources are low [179]. More recent models have also been proposed in which the engagement of cognitive effort depends on a tradeoff between costs and benefits, the costs being related to neurometabolic alterations [148,152,180]. These models follow the same general principles but differ in how they account for the cost of cognitive operations, and which metabolic changes are induced by cognitive effort.

To exemplify this general line of thought, we sketched a metabolico-motivational model of cognitive fatigue dubbed 'MetaMotiF' (illustrated in Figure 3C), as an attempt to put together the various pieces suggested by seemingly opposite theories. In line with predominant views [36,181,182], our model postulates that the allocation of cognitive control is adjusted to maximize a tradeoff between expected costs and benefits. We prefer not to make strong claims about brain localizations, but the region usually called 'dorsal anterior cingulate cortex' is an obvious candidate for the implementation of this cost/benefit arbitration [174], while the lateral prefronto-parietal network likely implements the exertion of cognitive control [47]. The key assumption here is that cognitive control exertion would induce, in the associated brain regions, some metabolic change, which could be an accumulation of potentially toxic substances (possibly glutamate in the synaptic cleft) or a depletion of supply for aerobic glycolysis (and a possible switch to other energetic providers). These metabolites are normally monitored and regulated at the molecular level, for instance with glutamate reuptake in the neurons or lactate shuttles from the astrocytes. On top of these primary molecular mechanisms, the model postulates a secondary mechanism at the whole-brain level, which would simply consist of regulating cognitive control exertion, based on a cost estimate informed by the neurometabolic state. Cognitive fatigue could therefore be reduced to how much the metabolic state of the cognitive control brain system is degraded (i.e., how far it is from the baseline state).

Thus, although it would be caused by a biological alteration, the effect of fatigue on the behavior would appear as a motivational shift caused by an increase in the cost of cognitive control. The additional cost might relate to either the metabolic change impairing the efficiency of cognitive control (such that more effort would be necessary to maintain performance), or the regulation system anticipating the risk of losing cognitive control capacity (and missing future opportunities that may manifest before toxic waste is eliminated or energetic supply is replenished). So far, only two of the mechanisms depicted in the box-and-arrow diagram have been mathematically formalized: how cognitive control may induce metabolic alteration and how the cost of cognitive control may bias affect economic decisions (see Box 2 for equations). There are evident missing pieces in this formalization, notably the link between the neurometabolic state and the cost of cognitive control, which require further mathematical modeling.

Even as a box-and-arrow diagram, the MetaMotiF model provides qualitative explanations for key observations related to cognitive fatigue: why longer and more difficult tasks generate more fatigue (because exerting more cognitive control may aggravate metabolic alterations), why fatigue pushes towards disengagement of cognitive control (because the expected costs related to metabolic alterations may surpass the expected benefits), why motivation can counter the fatigue effect (because important expected benefits may remain higher than the expected costs) and why rest can dissipate fatigue (because regulatory mechanisms at the molecular level may reset the metabolic state to normal baseline). In sum, through the integration of biological and motivational theories, the MetaMotiF model can account for a collection of observations about how cognitive fatigue affects behavioral, physiological, and neural activities.

It must be acknowledged, however, that the generation of the fatigue sensation is not accounted for in our model. It could be that we have direct conscious access to the neurometabolic state of the cognitive control system (or equivalently, to the cost signal), although this seems implausible given the unreliability of self-reports and their contamination by other sources of information. It could also be that we are only conscious of the result of the cost–benefit arbitration, meaning that we notice our fatigue when we realize that we are not ready to engage cognitive effort. This would explain why economic choices, which trigger the cost–benefit arbitration process, better reveal cognitive fatigue than direct ratings.

It must also be acknowledged that without neurometabolic measurement the model is not falsifiable. This is why we need more experiments measuring brain metabolites, in human or non-human primates, during prolonged performance of cognitive control tasks. New experiments could test the central prediction of the model that metabolic spectra in cognitive control brain regions should change with the emergence of fatigue, as a function of task duration and difficulty. Further evidence is needed to consolidate the specificity of the claim that cognitive fatigue is related to neurometabolic alteration of the cognitive control network (and not other brain systems). An additional prediction of the model is that metabolic changes in the cognitive control brain system should condition cost–benefit arbitrations that drive task performance and economic choice. Therefore, interventions that counter these metabolic changes should prevent the emergence of cognitive fatigue and its behavioral consequences.

Concluding remarks

In this paper, we have outlined a conceptual framework in which the cost of cognitive control is the key index of cognitive fatigue. The origins of cognitive fatigue relate to metabolic alterations in the cognitive control brain system. The consequences of cognitive fatigue are most clearly expressed in choices between options that involve different levels of cognitive control. This includes choosing how much effort should be allocated to ongoing work in time-on-task or sequential task paradigms. Still, a vast number of questions remain unanswered (see Outstanding questions). For instance, we ignore which is the key neurometabolic variable that cognitive fatigue would be meant to regulate by signaling the need to stop working. We also lack a clear explanation for why exertion of cognitive control, but not other brain functions (such as perception), would trigger this metabolic change. In any case, our model would only account for cognitive fatigue defined as an objective state of the brain. How this objective state relates to the subjective experience, reported as a fatigue sensation, remains to be elucidated. Finally, further conceptual elaboration would be needed to understand how other states of the mind/brain, such as boredom, may affect our decisions. This can be of importance if, as Marcel Proust pointed out, these transitory states drive us to make irrevocable decisions that may impact our entire life.

Outstanding questions

What are the commonalities between the different types of fatigue that have been described (cognitive fatigue, chronic fatigue, physical fatigue, local fatigue, etc.)? Which type of fatigue involves metabolic alteration in the prefrontal cortex?

What is the key metabolic alteration that the brain intends to regulate by generating a cognitive fatigue signal that drives work cessation? Why is this regulation so important? Is it for stopping the accumulation of some toxic substance or for stopping the exhaustion of some energetic supply?

What are the distinctive properties of the cognitive control system that make it susceptible to metabolic alteration? Why would other brain systems be immune to this type of fatigue? Can we train our brain and make it less vulnerable to cognitive fatigue?

What are the neurocognitive features that make certain persons more resistant to cognitive fatigue? Are they related to the cognitive control brain machinery? Do they condition success in endurance sports and intellectual professions?

What are the best markers for detecting cognitive fatigue? If introspection is limited and performance confounded with nuisance factors, shall we turn to economic decisions, fMRI/EEG activity in the prefrontal cortex, or physiological manifestations of effort allocation?

What is it that we perceive when we experience cognitive fatigue? Is it some continuous representation of the neurometabolic state, or is it some punctual estimate of the effort cost inferred when we consider exerting cognitive control?

What are the dynamics of recovery from cognitive fatigue? How can we make it faster? Shall we just enjoy leisure, or simply rest, or is it better to take a nap? Would drugs targeting neuromodulators help?

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