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Present bias in economic choice demonstrates increased cognitive fatigability of glioma patients

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Running title: Fatigability in low-grade glioma

Abstract

Fatigue is a frequent symptom in many clinical conditions that is still poorly understood despite having a major impact on quality of life. Here, we propose a novel approach using model-based analysis of choice behaviour to extract fatigue markers. We applied this approach to the case of low-grade glioma, with the aim of testing the hypothesis that fatigability in this condition may manifest as limited control over choice impulsivity.

Patients with intact or resected glioma (n=29) and matched healthy controls (n=27) performed a series of behavioural tasks included in a 4h-long neuropsychological assessment. Intertemporal choices, opposing smaller-sooner to larger-later monetary rewards, were intermixed with tasks designed to test cognitive and motor performance and to assess fatigue with subjective ratings. All dependent variables were analysed with generalised linear models testing the main effects of group and time-on-task, as well as their interaction.

While absent in standard measures of fatigue (subjective rating and objective performance), a significant group-by-time interaction was observed in the rate of impulsive choices: contrary to controls, patients developed a preference for the smaller-sooner option in the course of neuropsychological assessment. This preference shift was captured by computational modelling as an increase in the present bias, a parameter that assigns an additive bonus to immediate rewards.

Thus, choice impulsivity was the only reliable marker that reflected the enhanced fatigability of patients relative to controls. These results suggest that the impact of glioma (or its resection) on brain functioning limits the exertion of cognitive control during decision-making. More generally, they pave the way to using model-based analysis of choice behaviour for future investigations of the many clinical conditions plagued with fatigue.

Keywords: low-grade glioma, fatigue, impulsivity, decision-making, delay discounting, cognitive control, computational modelling

Abbreviations: IDH = Isocitrate Dehydrogenase

Introduction

Mental fatigue is a frequent complaint in most neuropsychiatric conditions and many other diseases [1]. Despite its major impact on functional recovery [2], fatigue is still poorly understood and treated. A main difficulty is the assessment of fatigue, which relies on self-report or subjective questionnaires such as the fatigue severity scale [3]. While these instruments are handy and useful to help patients express their trouble, they show modest validity and reliability [4]. The reasons are that fatigue is a sensation whose meaning varies across patients and which may be neglected or exaggerated (particularly when insight is compromised as often observed in case of cognitive deficit). The expression of fatigue can also be biased by the desire to please the caregivers, or confounded with related psychological states such as low motivation or bad mood [5]. Another, even more subtle, possible confound is with fatigability, which can be defined as a rapid increase of fatigue in the course of cognitive or social activity [6]. Thus, there is a need for reliable markers of the objective fatigability that may impair brain functioning in many neuropsychiatric conditions, whether or not patients report it on subjective scales and questionnaires.

The aim of the present paper is to develop a more objective approach to fatigability, in the case of patients with low-grade glioma. Since the 2017 WHO classification, IDH-mutated glioma are considered as a homogeneous group, comprising astrocytoma and oligodendroglioma (respectively without and with 1p19q codeletion). These tumours are characterized by long occult and then silent periods [7] before diagnosis is made, usually after a revealing seizure in a patient typically aged between 30-50 years. Whenever feasible, maximal safe resection is the first treatment option [8]. Timing and choice of subsequent therapies (reoperation, chemotherapy, radiation therapy, combined chemoradiotherapy) should then be tailored according to multivariate individual parameters [9]. More specifically, the decision should rely on a comparison of the benefit (increased survival) – risk (functional impairment) ratio between available options. If the majority of patients at distance from surgery show cognitive performance close to normal, as evidenced by the high rate of work resumption, fatigue is still frequently experienced and reported by these patients, with a major impact on their quality of life [10,11]. A recent, extensive review (19 studies, 917 cases, 7 self-assessment instruments) showed that 39 to 70% of patients with a diffuse low-grade glioma suffer from this symptom [12]. Importantly, patients expressed subjective fatigue despite a

variety of treatments: partial or complete surgery (80% of cases), followed by radiotherapy (68%), chemotherapy (11%) or a combination.

To better understand the still unexplained and untreated fatigability of patients with IDH-mutated glioma, we turned to specific objective tests. Our assumption was that these patients suffer from an increased fatigability of the cognitive control brain system. Indeed, previous studies have suggested that cognitive control abilities, investigated with mental flexibility, problem solving or working memory tasks, are particularly vulnerable to fatigue [13–16]. Cognitive control can be defined as the regulation of automatic routines responding to the present environment, in a manner that enables achieving goals more distant in the future. It is operated by a large-scale brain system that chiefly includes the lateral prefrontal cortex, with the addition of midfrontal, parietal and temporal regions[17,18]. As many everyday activities involve cognitive control, patients would be maintained in a permanent state of fatigue, unless they just rest or limit their activity to habitual behaviour.

A typical challenge for cognitive control is switching between tasks that require different responses to the same stimuli, such that stimulus-response mapping cannot be made automatic [19,20]. Measuring performance decrement with time on task during this sort of cognitive control tests has been classically employed as a way to assess fatigability. However, performance measures, such as response time or accuracy, have been criticized as being elusive markers of fatigue, showing deterioration with time on task in some studies, but stability or even improvement in others (see [21] for an overview). These inconsistencies may relate to possible confounds, as performance decrement can be compensated by training and/or aggravated by boredom or sleepiness. They may also relate to how much effort participants invest in the task, which can explain why performance decreases with time on task in some individuals but not others, for instance young adults but not older people [22,23]. Critically, performance decrement can be counteracted by motivation, when the benefits of good performance in a task overcomes the costs [24]. Thus, choice tasks probing the current cost of exerting cognitive control can be expected to provide better markers of cognitive fatigability than performance decrement.

In previous studies [25,26], we have demonstrated that direct assessment of preference in inter-temporal choice provides a better measure of cognitive control fatigue than performance decrement. These choices consist in expressing a preference between a smaller-sooner and a larger-later reward (e.g., 10€ now vs. 15€ in a week). Failure to recruit cognitive control during these choices has been shown to favour impulsivity, i.e. preference for immediate

rewards [27,28]. Consistently, in participants performing difficult cognitive control tests (including task switching) for several hours, accuracy remained constant but preference was progressively shifted toward immediate rewards [25]. This effect of fatigue was associated with decreased activity of cognitive control brain regions (in the lateral prefrontal cortex) during decision making. Critically, it was not observed in a different group of participants performing the same tasks for the same duration but with a lower level of difficulty, hence discarding a potential confound with boredom.

Here, we employed similar inter-temporal choices to assess fatigability in patients with IDH-mutated glioma. We took the opportunity of a neuropsychological assessment that was part of their clinical schedule to alternate these choices with cognitive tasks. Our prediction was that, compared to matched healthy controls, patients would exhibit an increased choice impulsivity in the course of neuropsychological assessment, which would be specified via computational modelling as a higher bias for immediate rewards. As alternative measures of fatigue, we included clinical questionnaires and subjective reports on a visual analog scale, plus handgrip squeezing and task switching for potential deterioration of motor and cognitive performance.

Methods

We report how we determined our sample size, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all data exclusions, all manipulations, and all measures in the study.

Participants

Patient group

In the neurosurgery department of Lariboisière Hospital (Paris), low-grade glioma patients undergo neuropsychological evaluations on a regular basis, both before and after surgery, as a standard of care. Starting from June 2018, we decided to include high-level cognitive tasks in our standard neuropsychological evaluation, intermingled with intertemporal choices which were previously shown to provide a good fatigability marker in healthy controls [25]. We thus retrospectively reviewed the data collected during neuropsychological assessments between 1st of June 2018 and 1st of March 2021 in IDH-mutated glioma patients. Patients with progressive disease or ongoing adjuvant therapy at the time of their assessment were

excluded. A total of 35 patients started the assessment (15 females, 20 males) and therefore were included. Before their assessment, all patients were orally informed that these data could be used for clinical research. They were also informed that the monetary earnings in the behavioural tasks were purely fictive, as were healthy participants. Other clinical data were retrieved from the electronic medical files. The study was conducted with our institution's ethical standards for a retrospective study.

Control group

Healthy participants (15 females, 15 males) were tested in the PRISME facility of the Paris Brain Institute. Each control participant was chosen to match one patient' demographics (age, gender, education level). Inclusion criteria were: French-speaking participants, normal or corrected-to-normal vision. Non-inclusion criteria were: colour-blindness, medical history of sleep disease (insomnia, hypersomnia, narcolepsy…), psychiatry medical history (depression, hyperactivity disorder…), neurological medical history (epilepsy, traumatic brain injury, stroke…), psychotropic substance use, alcohol use 24 hours before the assessment.

Participants signed informed consent prior to taking part in the study, which was approved by the Pitié-Salpêtrière Hospital (Paris) local ethics committee. They received a financial compensation for their participation (30 €) that was independent from their monetary earnings in the behavioural tasks.

Missing data and outliers

Among the 35 cases that were retrospectively reviewed, 4 patients did not complete the full assessment and were therefore excluded, as data were missing for the last run. All control participants completed the entire assessment. However, some participants in both groups (2 controls and 3 patients) made the same kind of choice (either smaller-sooner or larger-later), irrespective of the reward / delay combinations, in more than 90% of trials over the entire assessment. These outliers were also excluded from data analysis, as their behaviour was not comparable to that observed in the rest of participants (their choices did not reflect their preferences).

Population description

Controls (n=27) and patients (n=29) had a similar sex ratio (48 and 41% female, respectively) and age distribution (mean of 44.7 and 42.5 years, respectively). Tumoral brain tissue (for

each patient assessed before surgery) and resected brain tissue (for each patient assessed after surgery) were delineated to localise lesions on their structural MRI normalized to the Montreal Neurological Institute (MNI) space (see Fig. 1).

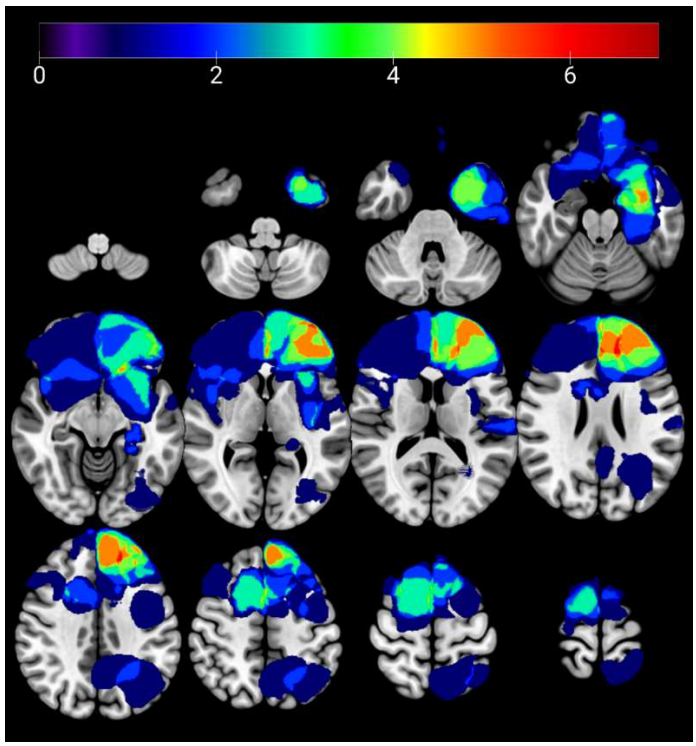

Figure 1. Overlap of lesions. *Both glioma for pre-surgery and resection for post-surgery patients were delineated and superimposed on a normalized T1 scan in the Montreal Neurological Institute (MNI) space. Colour code indicates for each voxel the number of patients with a lesion at this location. Per radiological convention, right hemisphere appears on the left side.*

The gliomas were located in the frontal lobe for 69% of patients and in the left hemisphere for 75% of patients (Table S2). Almost half of the patients (n=14) was assessed prior to surgery, and the other half (n=15) was assessed at various delays post-surgery. Most patients (n=18) were under antiepileptic treatment at the time of the assessment. In most cases (n=14), the treatment was Levetiracetam (Keppra) twice a day (morning and evening) with doses varying from 250mg to 1250mg. Alternative treatments were Lamotrigine (Lamictal), Oxcarbazépine (Trileptal) or Lacosamide (Vimpat), or a combination of two antiepileptic medications.

Patients were also evaluated by a speech therapist, either before the surgery or 4 months after the surgery (hence sometimes remotely from the behavioural assessment reported hereafter). We retrieved the normalized scores on the seven tests systematically administered to all patients: naming test, semantic test, phonological and categorical fluency test, trail making test, forward and backward digit span (see Table S3). These evaluations demonstrated that patients had no significant language, short-term memory, or cognitive flexibility disorders.

Fatigability assessment

The overall neuropsychological assessment lasted approximatively four hours. The same neuropsychologist (VF) conducted the assessment of patients and healthy controls.

First, participants filled in clinical questionnaires for psychometric evaluation (see next paragraph for details). Afterwards, they performed a series of computerized tasks targeting different functions, including cognitive control (task-switching), and high-order cognition (HOC) tasks assessing creativity through divergent, convergent, and relational thinking and reasoning [29]. Note that the selected HOC tasks are also demanding in cognitive control and require the integrity of the cognitive control system [30–32]. Inter-temporal choice tasks were interleaved with high-order cognition and switch tasks (see Fig. 2) and grouped into runs (Calib, HOC, Switch). Participants rated on visual analog scales their perceived level of fatigue, stress and hunger before the Calib run and at the end of the HOC and Switch runs.

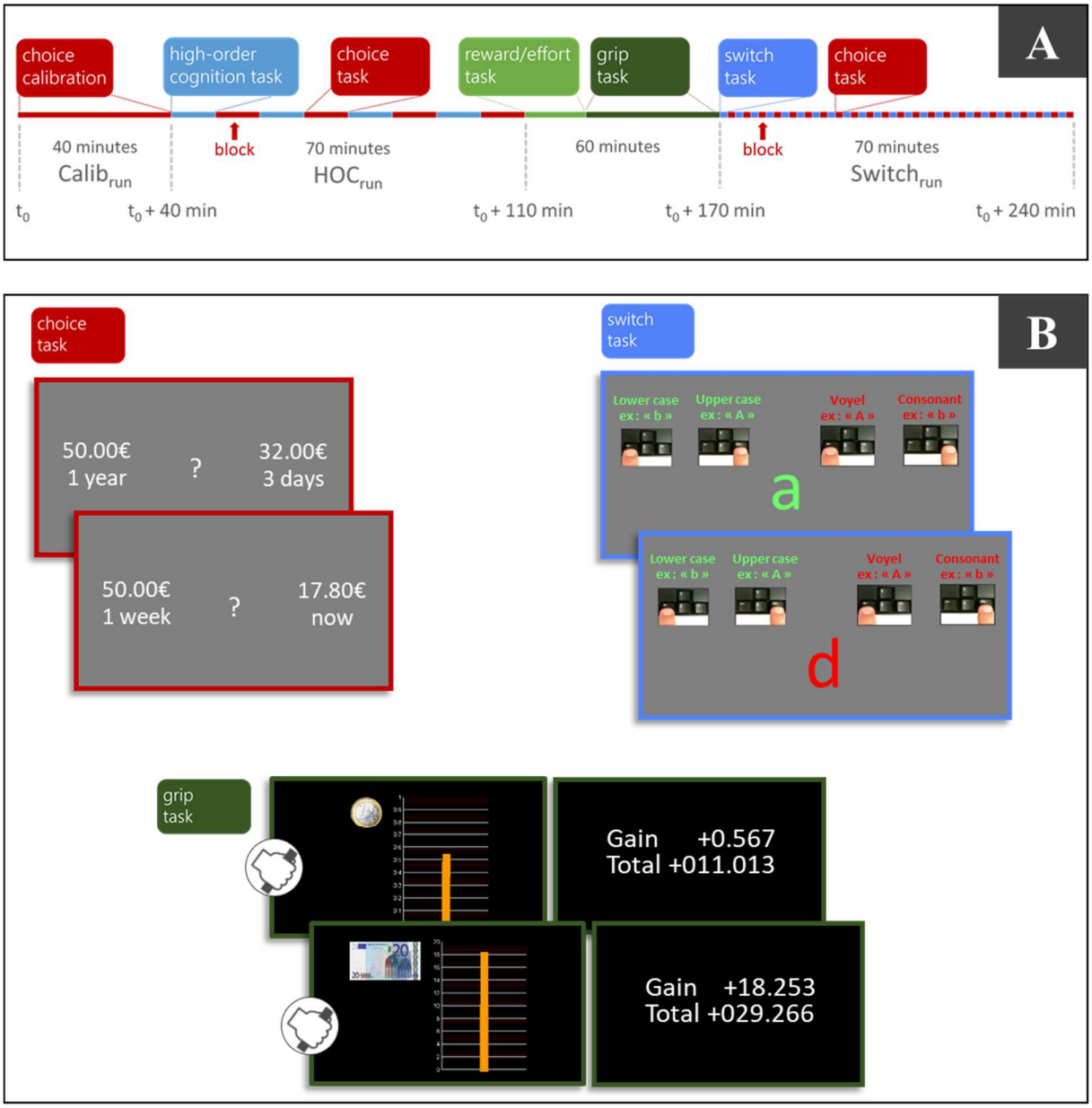

Figure 2. A, Time schedule of neuropsychological and fatigability assessment. *The main proxy for mental fatigue (choice impulsivity) was assessed in the inter-temporal choice tasks interleaved with high-order cognition tasks (HOC run) and switch tasks (Switch run). Between the two runs, patients performed tasks meant to assess their sensitivity to reward and effort (with subjective ratings) and their susceptibility to physical fatigue (with repeated handgrip squeezes). The calibration made before the first run served to tailor choice options around individual indifference points in all subsequent runs of inter-temporal choice tasks. See methods for details about the tasks.* ***B, Illustrations of behavioural tasks analysed to assess fatigability.*** *Screenshots of example trials are shown from top left to bottom right. In the choice task, two options combining reward and delay are displayed on screen (top: delayed vs. delayed rewards, bottom: immediate vs. delayed rewards) and participants indicate their preference by pressing one of two keys. In the switch task, participants categorize the letter as vowel vs. consonant or lower vs. upper case, depending on its colour (according to the rule displayed on screen). In the grip task, participants squeeze a handgrip to earn as much money as possible, knowing that payoff is proportional to both the monetary incentive (displayed as a coin or note image) and their peak force. The feedback screen indicates the gain for the ongoing trial and the cumulative total.*

Psychometric scales

Participants completed the French versions of the four following scales: 1) to assess fatigue, we used the 9-item questionnaire of the Fatigue Severity Scale (FSS), originally developed for patients with multiple sclerosis [3], 2) to assess anxiety and depression, we used the 14-item questionnaire of the Hospital Anxiety and Depression Scale (HADS) [33], 3) to assess apathy, we used the 14-item questionnaire of the Starkstein Apathy Scale (STARK), originally developed for patients with Parkinson's disease [34], 4) to assess impulsiveness, we used the 30-item questionnaire of the Barratt Impulsiveness Scale (BIS), which targets six factors: attention, motor impulsivity, self-control, cognitive complexity, perseverance, and cognitive instability [35].

Cognitive control tasks

High-order cognition tasks

Participants performed the four following tasks (in this order) assessing insight problem solving, semantic flexibility, idea generation, and abstract relational reasoning : 1) the Combination of Associates Task [30,36], which requires finding a word associated with three presented unrelated cue words (40 trials; e.g., the word 'link' for 'bridge – social – to tie'), 2) the Free Generation of Associates Task [30], which requires generating first a word obviously associated with a presented cue word and then an unusual associate (58 trials each) (e.g., 'back' → 'front' and then 'back' → 'future'), 3) the Alternative Uses Task [37], which requires finding a maximum of alternative and original uses for three day-to-day-life objects in 3 minutes each (e.g., a brick is usually used to build walls but can also be used as a paperweight), 4) the Analogy Task [31,38], which requires finding abstract, relational similarities between sets of dissimilar visuospatial stimuli (42 trials; e.g., sets composed of stimuli of different shape, colour, or size but sharing a similar organization, for instance symmetry). As high-level cognitive tasks were not themselves assessing fatigability, performances in these tasks will be studied in another paper.

The high-order cognition tasks were programmed using MeyeParadigm [e(ye)Brain Inc., 2009], while all subsequent tasks (grip, switch and choice) were programmed using the Psychtoolbox of MATLAB version R2017b [MathWorks, 2017]. The conditions of our ethics approval do not permit public archiving of anonymised study data. Readers seeking access to the data should contact the principal investigator Pr. Emmanuel Mandonnet. Access will be

granted to named individuals in accordance with ethical procedures governing the reuse of sensitive data. Specifically, requestors must meet the following conditions to obtain the data : completion of a formal data sharing agreement. Study materials is archived and publicly accessible - when feasible - on Github[1]. Legal copyright restrictions prevent public archiving of the psychometric scales used in this study, which can be obtained from the copyright holders in the cited references.

Switch task

To assess cognitive control directly, we used the switch task that was employed to induce fatigue in a previous study [25], which itself was adapted from tasks shown to activate cognitive control brain regions in the lateral prefrontal cortex [19]. In each trial of this task, a letter appears on screen, either red or green. The colour of the letter determines the relevant dimension for the classification that participants must perform (either lower vs. upper case or vowel vs. consonant). Thus, a change of colour corresponds to a switch between classification tasks. Colour-task associations were counterbalanced across participants. To maintain the demand on cognitive control, there were here 8 switches in each block of 24 trials, over a total of 23 blocks. For each classification task, the two categories are associated with left and right arrows on the keyboard. Responses that are either incorrect or too slow are followed by a negative auditory feedback. Before the assessment, participants are trained first with one rule, then with the other, and last mixing both rules. During this training session, there was a large response time window (20 seconds) to allow self-paced rule acquisition. The training session loops until participants reach a correct response rate of 90%. The response time window is continually adjusted to response time measured in the preceding block (maximum RT for the new block is set to three times the mean RT in the previous block), both to accommodate inter-subject variability in cognitive speed and to maintain time pressure throughout task completion.

Motor control task

To assess the trade-off between physical effort and monetary reward, we relied on an incentive force task previously used to assess motivation deficit in patients with apathy due to stroke or Parkinson's disease [39,40]. The aim for the participant is to win as much money as possible by squeezing a handgrip. In each trial, the payoff is proportional to both peak force

[1] https://github.com/ValentineFa/gliomafatigue/ and https://mbb-team.github.io/VBA-toolbox/

and monetary incentive. Peak force is expressed as a percentage of maximal force, which is measured before starting the task by asking participants to squeeze the grip as hard as they can (without explaining that the maximum they reach will be used to normalize their monetary payoff). The monetary incentive is varied on a trial-by-trial basis, between six possible values (0.01€, 0.20€, 0.50€, 1€, 5€, 20€), presented as a coin or banknote picture. The six incentives are presented twice in each block (of 12 trials), following a randomised order, and 20 times in total (over 10 blocks). On a given trial, participants receive the fraction of the incentive corresponding to the percentage of the maximal force they produce (e.g., participants would win 7€ if producing 70% of their maximal force for a 10€ incentive). Feedback about the force produced and the monetary payoff are both indicated on screen to the participant at the end of every trial.

Choice-tasks

Reward/effort trade-off task

Participants are first presented with reward and effort items presented one by one on screen and asked to rate on a visual analog scale how pleased they would be if they were given the reward or displeased if they were to exert the effort. We used 24 rewards items (e.g.: a 100g chocolate bar) and 24 efforts items (e.g.: sort 100 words in alphabetic order). Then participants are shown options combining a given effort to obtain a given reward (e.g.: sort 100 words in alphabetic order to earn a 100g chocolate bar). As they are not assessing fatigability, results of this task will be reported in another paper.

Intertemporal choice task

Inter-temporal choice trials were interleaved with tasks involving cognitive control (HOC and switch tasks). In each trial of the choice task, participants indicate their preference between the two options displayed side-by-side on screen (their position being counterbalanced over trials), by pressing left or right arrow. Each option combines a monetary reward (0.20 to 50 €) and a delay of delivery (0 to 365 days). The smaller-sooner option offers a variable reward associated with one of two possible delays: either 0 (in the immediate vs. delayed trials, IvD) or 3 days (in the delayed vs. delayed trials, Dvd). These two delays are implemented to distinguish between the present bias (i.e., the tendency to favour all immediate rewards) and the discount factor (i.e., the weight of delay in the devaluation of reward). The larger-later option offers a fixed reward (50€) associated with one among four possible delays (1 week, 1

month, 3 months, 1 year) in DvD trials and one among five possible delays in IvD trials (3 days, 1 week, 1 month, 3 months, 1 year). Thus, there are nine possible trial types (four DvD plus five IvD), for which the smaller-sooner reward could vary.

In order to have choices sensitive to any change in preference, the immediate reward was adjusted to individual specific indifference points, determined for each of the nine possible trial types during calibration. The calibration procedure, conducted during the Calib run at the beginning of the assessment, included three cycles of convergence using bisection to narrow down the difference between accepted and rejected smaller-sooner options to less than 4€. The midpoints between the lower accepted and the higher rejected reward were then averaged over the three cycles to generate indifference points. For the choice task, five sorts of smaller-sooner options were generated for each of the nine trial types: three neighbouring the indifference point (for choices to be sensitive), plus one largely above and one largely below the indifference point (for choices to inform computational modelling). The precise amount was slightly randomised to avoid repeating the exact same choice. We also added one catch trial in which the sooner option offered a larger reward than the delayed option. This makes a total of 46 choices, which we doubled to obtain a sufficient dataset. We then pseudo-randomly assigned the 92 choices to blocks intermingled with other cognitive tasks, such that the different trial types were regularly sampled in successive time periods. The 92 choices were split into four blocks of 23 choices performed just after each block of HOC tasks, and 23 blocks of four choices performed just after each block of the switch task.

Computational modelling

Inter-temporal choices were fitted with the same computational model as used in a previous study to capture the effect of fatigue on choice impulsivity [25,26], itself inspired by the 'exponential plus bias' model [41]. The model compares the values of the two options with a standard softmax function to generate choice probability:

$$P_{ss} = \frac{1}{1 + \exp(-\beta\ (V_{ss} - V_{ll}))}$$

With V_{ss} and V_{ll} being the value of smaller-sooner and larger-later options and β an inverse temperature parameter that adjusts choice consistency. Option value was calculated as the offered reward magnitude weighted by an exponential decay with reward delivery, plus a bias only applied in case of immediate reward:

$$V = R \times \exp(-k.D) + bias\ (if\ D = 0)$$

With R and D being the reward and delay associated to the considered option, k a discount parameter that adjusts the weight of delay on reward devaluation and *bias* an additive bonus added to all immediate rewards. Thus, when D=0 (for immediate reward), the value is simply the reward plus the bias (because the exponential weight is 1). Note that the smaller-sooner option can be either an immediate or delayed reward, while by definition the larger-later option is always a delayed reward.

The model was inverted using the VBA toolbox [42], which provides a posteriori distributions of fitted parameters.

Statistical methods

All analyses were run using MATLAB version R2017b [MathWorks, 2017].

The two main dependent variables were impulsive choice rate (percentage of trials in which the sooner option was selected) and fatigue subjective rating (on the visual analog scale). To analyse impulsive choice rate, the data collected during calibration (Calib run) were resampled to a set of options that was comparable to those presented in the HOC and Switch runs. Indeed, the calibration was meant to establish a baseline around 50% of impulsive choices, for options symmetrically distributed over and above indifference points. Once the options made equivalent across runs, we conducted the regression analyses.

We used a generalized linear regression model to test the main effects of group (control vs patient) and run (HOC and Switch, using Calib as a baseline), as well as their interactions, on the two main dependent variables. The regression model was the following:

*DV ~ 1 + group + HOC + Switch + group*HOC + group*Switch.*

A similar regression model was used to analyse DV that were assessing motor and cognitive fatigability as performance decrement within the grip and switch tasks. For the grip task, DV were peak force (expressed in percentage of maximal force) and response time (latency of force onset after the go cue). For the switch task, DVs were accuracy (correct response rate), response time (from stimulus onset to button press) and switch cost (difference in response time between switch and non-switch trials). In all cases, we used a generalized linear regression model to test the main effects of group and trial number, as well as their interaction: *DV ~ 1 + group + trial + group*trial.*

We performed post-hoc analyses for the fatigability measures that showed an interaction between group and run (in practice: the impulsive choice rate). First, we performed a two-tailed Student's t-test to assess significance of the group difference (patients vs controls) at the end of the assessment (during the Switch run). Then we applied separately four generalized linear regression model to account for the preference shift observed in patients, with:

- psychosocial factors including scores on clinical questionnaires and also age, sex and education level: *DV ~ 1 + age + sex + education + FSS + HAD_anxiety + HAD_depression + STARK + BIS*
- cognitive efficiency factors including performance in cognitive tasks during neuropsychological assessment (Combination of Associate, Analogy and Switch tasks) : *DV ~ 1 + combination of associate + analogy + switch*
- lesion factors including volume, side (left or right), frontal localisation (yes or no): *DV ~ 1 + lesion volume + frontal + hemisphere*
- treatment factors including surgery (pre or post), antiepileptic treatment (yes or no), experience of chemotherapy or radiotherapy : *DV ~ 1 + surgery + chemotherapy + radiotherapy + antiepileptic*

Results

Subjective questionnaires and ratings

Psychometric scores on clinical questionnaires were compared between controls and patients using two-tailed t-tests (Table S4). There were significant differences in fatigue severity (FSS score: $t(54) = 3.481$, $p = 0.001$) and depression symptoms (HAD depression score: $t(54) = 3.016$, $p = 0.004$), plus a borderline trend in anxiety symptoms (HAD anxiety score: $t(54) = 1.974$, $p = 0.053$). However, there were no significant difference in apathy (STARK score: $t(54) = 0.611$, $p = 0.544$) nor in impulsiveness (BIS score: $t(44) = 0.490$, $p = 0.626$). These results strengthen the idea that fatigue is a most prominent complaint in patients with low-grade glioma.

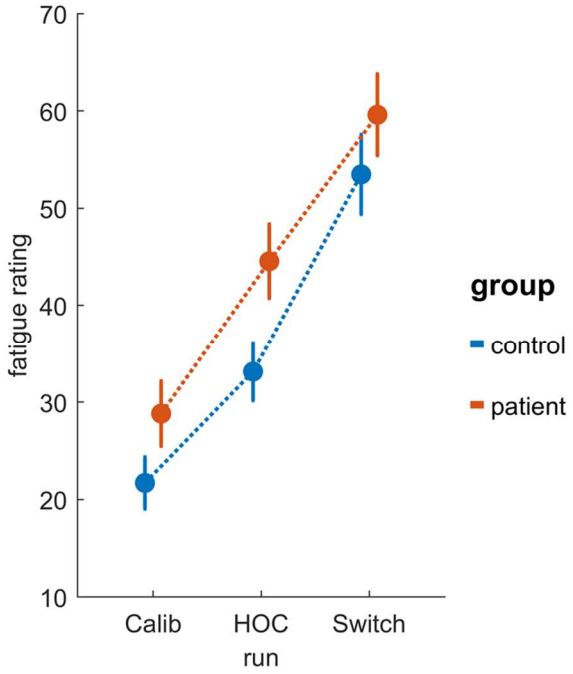

Figure 3. Subjective ratings. *All participants indicated their fatigue level on a visual analog scale after each run of the neuropsychological assessment. Dots show inter-participant means and error bars show standard errors of the mean.*

As a first possible marker of fatigability, self-reports (subjective ratings on a visual analog scale) were compared between groups and runs. Subjective ratings of fatigue increased with runs, in both controls and patients (Fig. 3). Linear regression analyses showed that, relative to calibration, only the switch run had a significant impact on fatigue rating ($\beta = 31.79$, $p<0.0001$). Although ratings tended to be higher in patients, there was no significant group

effect (β = 7.12, p = 0.32) nor significant interaction between group and run. The same analyses were also performed on subjective ratings of hunger but yielded no significant main effect or interaction.

These results indicate that subjective ratings provide no evidence of increased fatigability in patients compared to controls.

Task performance

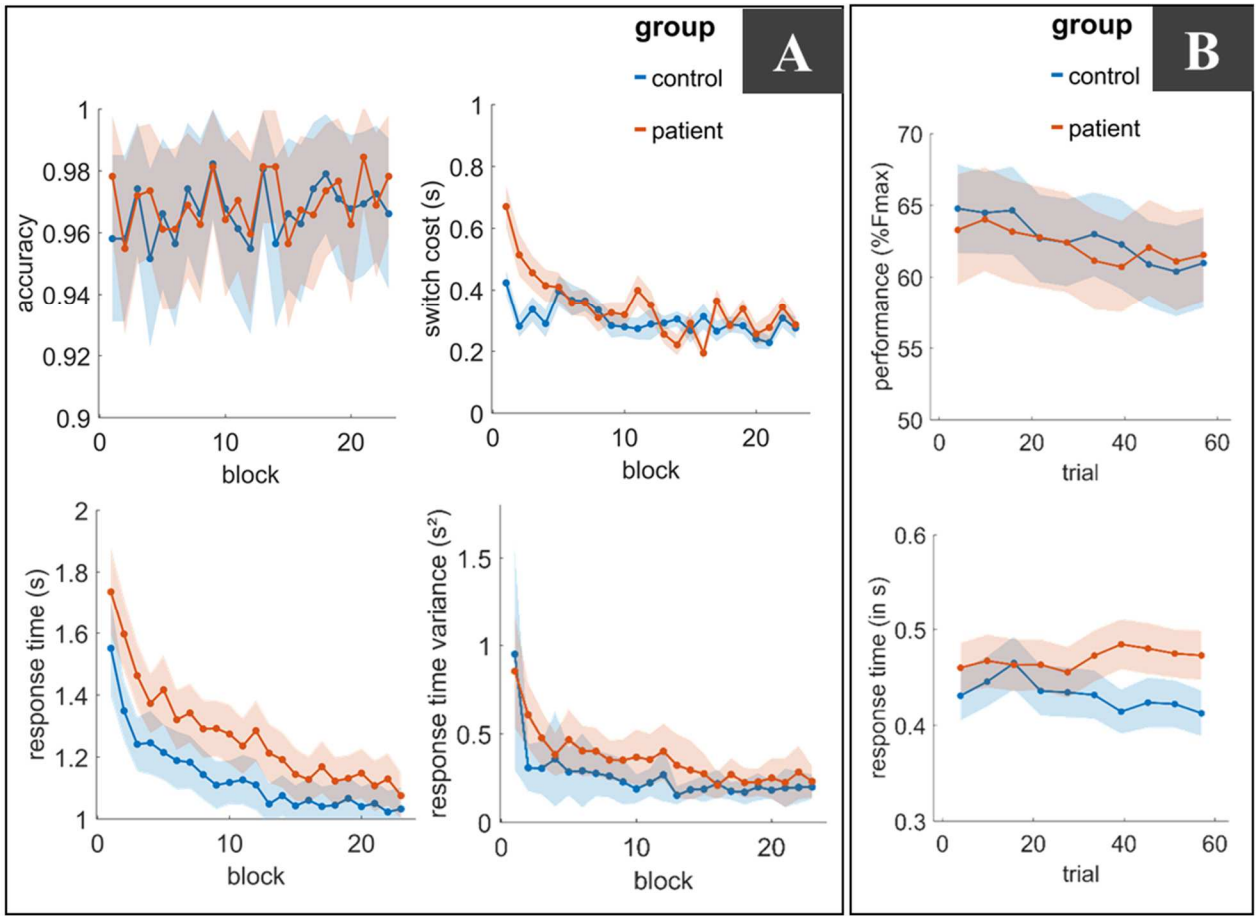

Figure 4. Cognitive and motor performance. A, Performance in the switch task. *Plots show accuracy (correct response rate), switch cost (difference in response time between switch and non-switch trials), response time and response time variance (across trials within a block) along the 23 blocks of task trials.* ***B, Performance in the grip task.*** *Plots show force (in percentage of maximal force) and response time along task trials. Dots are means and shaded areas are inter-participants standard errors of the mean.*

As a second possible marker of fatigability, motor and cognitive performance in the grip and switch tasks were compared between groups and blocks or trials. Results from the generalized linear regression model suggests that regarding accuracy in the switch task, there was no main effect of group or block index, and no interaction between the two (Fig. 4A). Regarding response time (RT), the same regression revealed both a group effect (β = 0.14, p < 0.00001)

and a trial effect (β =0.0025, p = 0.0032) but no interaction (β = -0.00023, p = 0.84). There was no significant interaction either in RT variance (across trials within a block), which has been conceived as an index of concentration on the task. Regarding switch cost (difference in RT between switch and non-switch trials), there was again an impact of trial index (β = -0.05, p = 0.016) but no group effect nor interaction.

Regarding force produced in the grip task (Fig. 4B), we found no main effect nor interaction, whether we examined the impact of trial index (for assessing fatigue) or the impact of monetary incentive (for assessing motivation). However, there was a trial effect on force onset (β =-0.0006, p = 0.036), with an interaction between trial and group (β =0. 0.0009, p = 0.016), but no group effect. The interaction was not related to fatigue but to controls being faster in the end (and not to patients being slower).

Overall, investigation of performance provided no evidence for enhanced fatigability in patients. Motor and cognitive performance was similar between patients and controls, except that patients were slower, particularly in the switch task.

Choice impulsivity

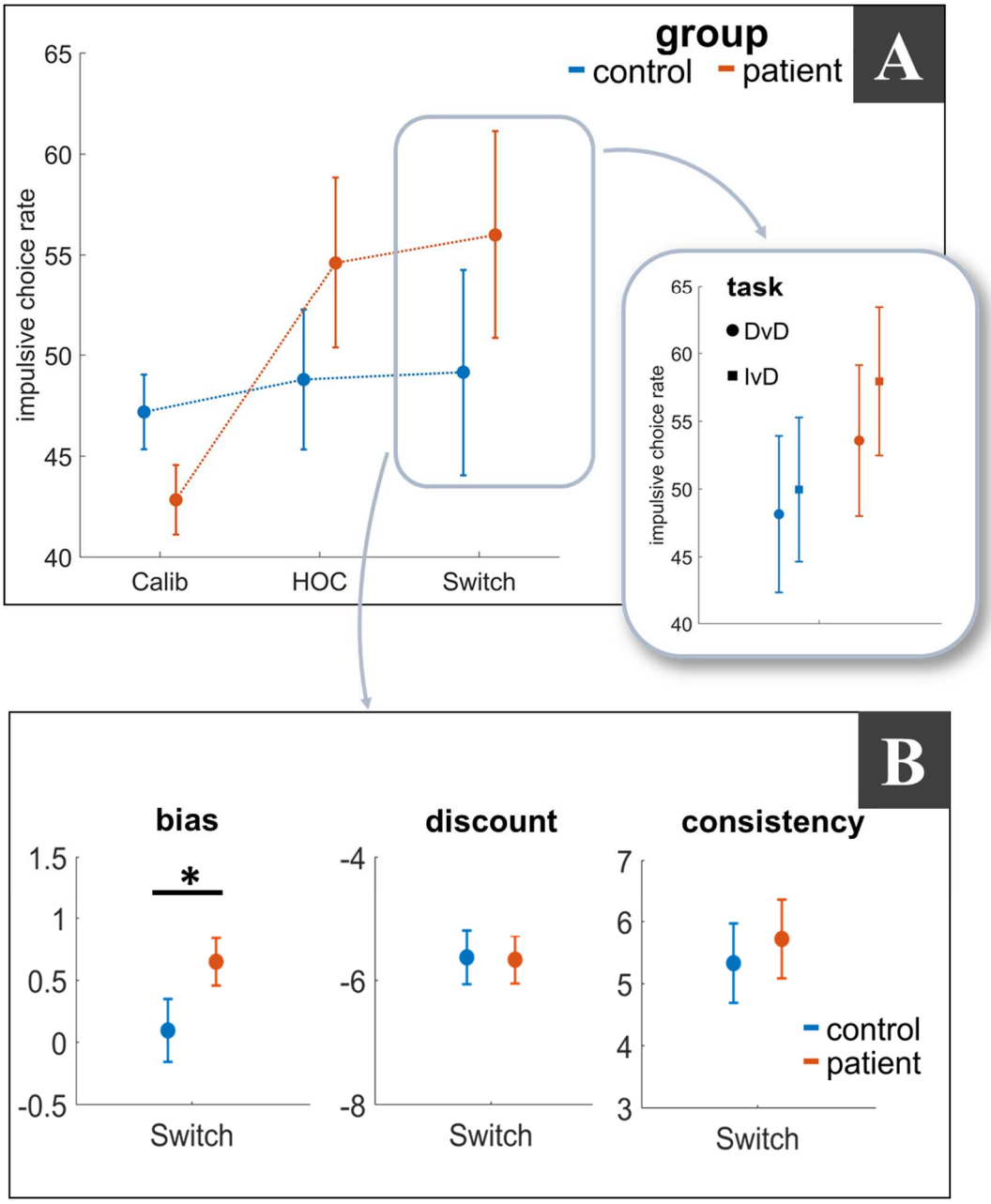

Figure 5. Choice impulsivity. A, Model-free results. *Impulsive choice means that the smaller-sooner reward has been selected. Main panel: impulsive choice rate is shown separately for the two groups (patients and controls), at baseline (Calib run) and during the two runs in which inter-temporal choices were interleaved with high-order cognition and switch tasks. Note that choices were forced near indifference (50%) for the calibration run by selecting options similar to those used in subsequent runs. Insert: impulsive choice rate during the final run (interleaved with switch tasks) is shown separately for choices involving an immediate versus a delayed reward (IvD) or just two delayed rewards (DvD).* ***B, Model-based results.*** *Plots show the parameters of the 'exponential plus bias' model fitted to choices made in the last run. 'Bias' is an additive bonus to the value of immediate rewards, 'discount' is a multiplicative weight on delay in the value function, 'consistency' is the weight on decision value in the choice (softmax) function. In all plots, dots are means and error bars are inter-participant standard errors of the mean.*

We then turned to our new marker of fatigability, the rate of impulsive choice, which was also compared between groups and runs (Fig. 5A). Results showed a significant interaction between group and both the HOC run ($\beta = 0.30$, $p= 0.0001$) and the Switch run ($\beta = 0.34$, $p= 0.00001$). The effect of group alone was not significant ($\beta = -0.07$, $p= 0.21$), and neither were the effects of HOC run ($\beta = 0.08$, $p= 0.12$) nor Switch run ($\beta = 0.10$, $p= 0.08$). The interaction was due to impulsive choice rate increasing more in patients than in controls, thus denoting higher fatigability. At the end of the assessment, in the Switch run, impulsive choice rate was significantly ($t(5150) = 4.926$, $p < 0.0001$) higher in patients (mean = 56,0%) than in controls (mean = 49,2%). Note that the increase in choice impulsivity, in the sense of a preference shifted toward immediate rewards, does not necessarily reflect faster responses. Indeed, even if choice RT decreased in the course of the assessment ($\beta = -1.17$, $p= 0.0014$) and although patients were globally slower than controls ($\beta = 1.10$, $p= 0.0023$), there was no interaction between group and run (Fig. S1). Thus, the pattern observed in impulsive choice rate was not mirrored by variations in choice RT.

Inspection of individual data revealed a diverse picture (Fig. S2). While by construction the patient and control groups were forced toward indifference (50% impulsivity) during calibration, impulsive choice rate covered the full possible range during the switch run, showing both increases and decreases. Note that the strongly significant difference obtained at the group level was not driven by outliers, as the difference between medians was even greater than the difference between means. We intended to leverage this inter-individual variability, as impulsive choice rate was the only dependent variable testifying for a higher fatigability in patients, to test associations between this fatigue index and other factors (Table S5). We did not find any significant association, even at a permissive (uncorrected) statistical threshold. In particular, there was no statistical link between fatigue as indexed by impulsive choice rate and fatigue reported in subjective rating ($\beta = -0.18$, $p = 0.56$).

On closer inspection, we observed that the main difference in impulsive choice rate during the switch run was mostly driven by choices involving an immediate reward (IvD), rather than choices involving two delayed options (DvD). This hints at a specification of fatigue as an increased present bias (preference for immediate rewards). To better formalize this idea, we turned to computational modelling of choices (see Methods for details) and compared fitted parameters in the Switch run between controls and patients. In line with model-free results, we found a significant difference in the bias parameter ($t(59) = 1.905$, $p = 0.031$), but none in the discount ($t(59) = 0.021$, $p = 0.491$) or consistency ($t(59) =0.525$, $p =0.301$) parameters.

Computational results therefore suggest that increased choice impulsivity in patients is due to an additional bonus assigned to immediate reward, and not to a higher discount (which would have predominantly affected delayed rewards) or a higher stochasticity (which would have shifted choice rate toward chance level, i.e. 50%).

Discussion

To our knowledge, this is the first study using model-based analysis of economic choices to assess fatigability in patients with IDH-mutated glioma. While subjective report and performance decrement remained inconclusive, the increase in choice impulsivity provided an objective marker of cognitive fatigability that differentiated patients from their matched controls. At the computational level, cognitive fatigability translated into an increase in the present bias parameter that boosted the attraction of immediate rewards. In previous studies, choice impulsivity and its computational signature have been associated to reduced recruitment of the cognitive control brain system [25,26]. Altogether, these results therefore suggest that fatigability in glioma patients might be specified as a faster (compared to controls) exhaustion of cognitive control exertion when solicited for demanding tasks. In the following, we discuss the potential causes and consequences of such cognitive fatigability.

Note that we use the term cognitive control in a rather specific sense here: we do not claim that choice impulsivity would capture all processes that have been grouped under the umbrella term of cognitive control (or executive functions) and shown to be altered in a variety of neuropsychiatric disorders. In our definition, cognitive control is the function that regulates automatic responses to the immediate environment, with the aim of maintaining the pursuit of longer-term goals. Consistently, recruitment of the lateral prefrontal cortex during intertemporal decision-making has been associated with preference for delayed rewards [27,43]. Conversely, inhibition of cognitive control using transcranial magnetic stimulation of the lateral prefrontal cortex has been shown to favour impulsive choices [28,44]. This shift in preference was specified in our computational analysis as a bonus assigned to immediate rewards, as was shown before in a mild case of burnout syndrome [26]. It was dissociated from alternative behavioural patterns, such as an increase in choice stochasticity, which would have artificially maintained preferences around indifference points (because chance level is 50%). Although this behavioural signature fits well with reduced cognitive control, we fully acknowledge that it is only indirect evidence in need of further confirmation with brain

imaging. While the cognitive control interpretation goes with a shift in the decision process (failure to resist the attraction of immediate rewards), our computational account is mathematically equivalent to a shift in the valuation process (immediate rewards become more attractive) that might involve more ventromedial prefrontal regions. Relatedly, we also acknowledge that our computational account remains descriptive and falls short of specifying the shift in cognitive terms. For instance, it does not tell whether patients in the end continue to weigh the options and regularly fall for the immediate reward, or if they decide at some point to follow a heuristic that would simplify their decision problem (for instance: take the immediate reward every time it is above some threshold, irrespective of the other option).

At a meta-decisional level, cognitive control itself can be considered as motivated, meaning that its exertion depends on expected costs and benefits [45]. Under this perspective, fatigue can be interpreted as an elevated cost of cognitive control, preventing its exertion unless an important outcome is at stake. Thus, fatigue may not come with a loss of cognitive control abilities, as would happen for instance with lesions of the lateral prefrontal cortex, but may induce a shift in the cost-benefit arbitration that drives cognitive control exertion. This would explain why performance can be maintained, even in tasks involving cognitive control, while choices become more impulsive. Indeed, intertemporal choices are expressions of personal preferences, as participants are told that there are no right or wrong responses in this task. On the contrary, grip and switch tasks in our design lead to objective feedbacks that participants are willing to maximize, as shown by their near-ceiling correct response rate. Thus, strong motivation to score well might have countered fatigue effects on performance in cognitively demanding task. We also note that performance even tended to improve with time on task, as shown by reduced RT, which may reflect training effects that could also have masked fatigue effects.

One may wonder why patients implicitly express high fatigability in this economic choice task and not when directly asked, as in fatigue ratings. In fact, all participants reported increasing levels of fatigue in their subjective ratings, but contrary to what was observed with impulsive choice rate, there was no interaction between group and time. Interestingly, this result is in line with a previous finding that objective markers of fatigability do not correlate across patients to subjective measures [46]. One explanation is that participants normalize the visual scale to the range of fatigue they experience in their daily life, such that the shift in rating may not reflect the absolute change in subjective fatigue sensation, which may nonetheless differ between patients and controls. A related explanation is that because

patients start with higher fatigue ratings, they have less room to express an increase. In any case, impulsive choice rate proved to be a more sensitive measure of fatigability than both subjective rating of fatigue sensation. This is an important result, given the recurrent observation that existing measurement tools have poor validity and are confounded by various factors such as mood and motivation [4,5,47].

The absence of correlation between choice impulsivity and all other tested factors does show that our measure of fatigue provides additional information, but does not help elucidate the reasons for the fragility of cognitive control in glioma patients. In particular, we did not find any significant link with psychometric scores of mental states such as apathy, depression or anxiety, suggesting that fatigability is an independent symptom. Obviously, our assessment of psychosocial factors was not exhaustive, so it remains possible that our marker of fatigability may be related to unassessed factors. More interestingly, there was no association either between choice impulsivity and lesions or treatments. This could be attributed to the limited sample (n=29) and/or the recruitment bias (20/29 lesions were frontal). However, we would not necessarily expect lesions causing fatigue to damage cognitive control brain regions. Indeed, any consequent lesion inducing a loss of automatic processing would be taxing on cognitive control, explaining the lower processing speed (increased RT) that was observed in most tasks. This excessive recruitment of cognitive control would in turn increase its cost and therefore explain the emergence of fatigue. The absence of surgery effect, meaning that pre-operative patients (n=14) were as fatigable as were post-operative patients (n=15) is also intriguing. If anything, it means that resection was parsimonious and did not significantly worsen the damage caused by the glioma.

While our findings provide insight into the nature of fatigability in glioma patients, they suffer from a number of limitations that may preclude a straightforward application to clinical settings. One obvious limitation is that such assessment would take time, because fatigability has to be measured over a sufficient duration. A related drawback is that a subset of patients (11%) left before completing the entire assessment (because of agenda constraints in most cases). This did not happen in controls, possibly because they were financially compensated for their participation after completion of the full protocol. Removing some tasks from the neuropsychological assessment might shorten the duration, but with the current design we could not identify which task was sufficient to induce fatigue in patients and which was unnecessary. Choice impulsivity was higher in the Switch run, which was likely demanding in cognitive control, but also coming last and hence possibly cumulating the impact of preceding

tasks. Another issue for shortening the assessment is that the choice task requires a high number of trials to elicit preferences. The calibration procedure is not to be skipped, because choice options have to be tailored around individual indifference points. Indeed, baseline impulsivity measures might reflect other factors than fatigue, for instance a different stance over the future in patients with reduced life expectancy. Also, given the high variability of time preferences across patients, using the same options for everyone would certainly occasion ceiling effects that would preclude the observation of increasing choice impulsivity. We note that the increase itself was only observed on average, individual choice impulsivity going both ways. While it can provide strong evidence at the group level, the measure is therefore too noisy to be reliably exploitable at the individual level. Further research is needed for finding ways to reduce measurement time and noise, such that increasing choice impulsivity can become a clinically reliable marker of individual fatigability. Follow-up studies are also needed to assess whether choice impulsivity may represent a good marker of fatigability in other clinical conditions than those investigated so far (brain tumour and overtraining syndrome).

To conclude, model-based analysis of decisions appears as a promising approach to assess the fatigability that plague patients in many diseases. In patients with IDH-mutated glioma, it suggests that fatigability can be understood as a rapid increase in the cost of cognitive control leading to more impulsive choices. This may have clinical consequences, as it has been shown that choice impulsivity, by discarding long-term outcomes, degrades compliance with treatment [48]. It may also orient cognitive rehabilitation toward training impaired processes to rebuild habits and relieve the demand for cognitive control [49]. Another possibility would be to train cognitive control directly: although this could aggravate fatigue on the short term, one may expect that it would, on the long run, alleviate fatigability by enhancing cognitive control resources.

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