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► **To cite this version:**

Valentine Facque, Antonius Wiehler, Emmanuelle Volle, Emmanuel Mandonnet, Mathias Pessiglione. Present bias in economic choice demonstrates increased cognitive fatigability of glioma patients. *Cortex*, 2022, 151, pp.281-293. 10.1016/j.cortex.2022.02.015 . hal-04575692

HAL Id: hal-04575692

<https://hal.sorbonne-universite.fr/hal-04575692>

Submitted on 15 May 2024

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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

1 **Abstract**

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

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

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

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

24

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

27

28 **Abbreviations:** IDH = Isocitrate Dehydrogenase

29

30 **Introduction**

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

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

61 variety of treatments: partial or complete surgery (80% of cases), followed by radiotherapy
62 (68%), chemotherapy (11%) or a combination.

63 To better understand the still unexplained and untreated fatigability of patients with IDH-
64 mutated glioma, we turned to specific objective tests. Our assumption was that these patients
65 suffer from an increased fatigability of the cognitive control brain system. Indeed, previous
66 studies have suggested that cognitive control abilities, investigated with mental flexibility,
67 problem solving or working memory tasks, are particularly vulnerable to fatigue¹³⁻¹⁶.
68 Cognitive control can be defined as the regulation of automatic routines responding to the
69 present environment, in a manner that enables achieving goals more distant in the future. It is
70 operated by a large-scale brain system that chiefly includes the lateral prefrontal cortex, with
71 the addition of midfrontal, parietal and temporal regions^{17,18}. As many everyday activities
72 involve cognitive control, patients would be maintained in a permanent state of fatigue, unless
73 they just rest or limit their activity to habitual behaviour.

74 A typical challenge for cognitive control is switching between tasks that require different
75 responses to the same stimuli, such that stimulus-response mapping cannot be made automatic
76^{19,20}. Measuring performance decrement with time on task during this sort of cognitive control
77 tests has been classically employed as a way to assess fatigability. However, performance
78 measures, such as response time or accuracy, have been criticized as being elusive markers of
79 fatigue, showing deterioration with time on task in some studies, but stability or even
80 improvement in others (see²¹ for an overview). These inconsistencies may relate to possible
81 confounds, as performance decrement can be compensated by training and/or aggravated by
82 boredom or sleepiness. They may also relate to how much effort participants invest in the
83 task, which can explain why performance decreases with time on task in some individuals but
84 not others, for instance young adults but not older people^{22,23}. Critically, performance
85 decrement can be counteracted by motivation, when the benefits of good performance in a
86 task overcomes the costs²⁴. Thus, choice tasks probing the current cost of exerting cognitive
87 control can be expected to provide better markers of cognitive fatigability than performance
88 decrement.

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

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

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

109 **Methods**

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

113 **Participants**

114 **Patient group**

115 In the neurosurgery department of Lariboisière Hospital (Paris), low-grade glioma patients
116 undergo neuropsychological evaluations on a regular basis, both before and after surgery, as a
117 standard of care. Starting from June 2018, we decided to include high-level cognitive tasks in
118 our standard neuropsychological evaluation, intermingled with intertemporal choices which
119 were previously shown to provide a good fatigability marker in healthy controls ²⁵. We thus
120 retrospectively reviewed the data collected during neuropsychological assessments between
121 1st of June 2018 and 1st of March 2021 in IDH-mutated glioma patients. Patients with
122 progressive disease or ongoing adjuvant therapy at the time of their assessment were

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

129 **Control group**

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

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

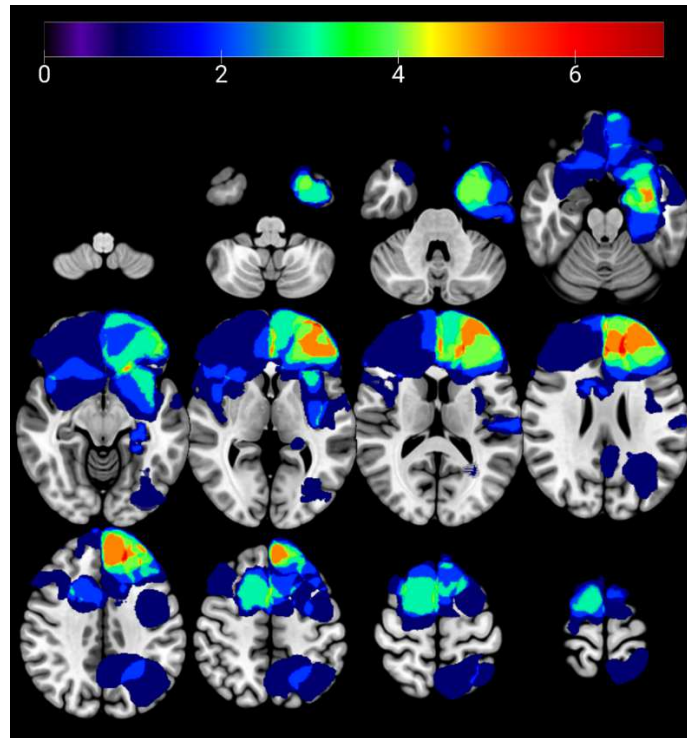
141 **Missing data and outliers**

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

150 **Population description**

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

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



156

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

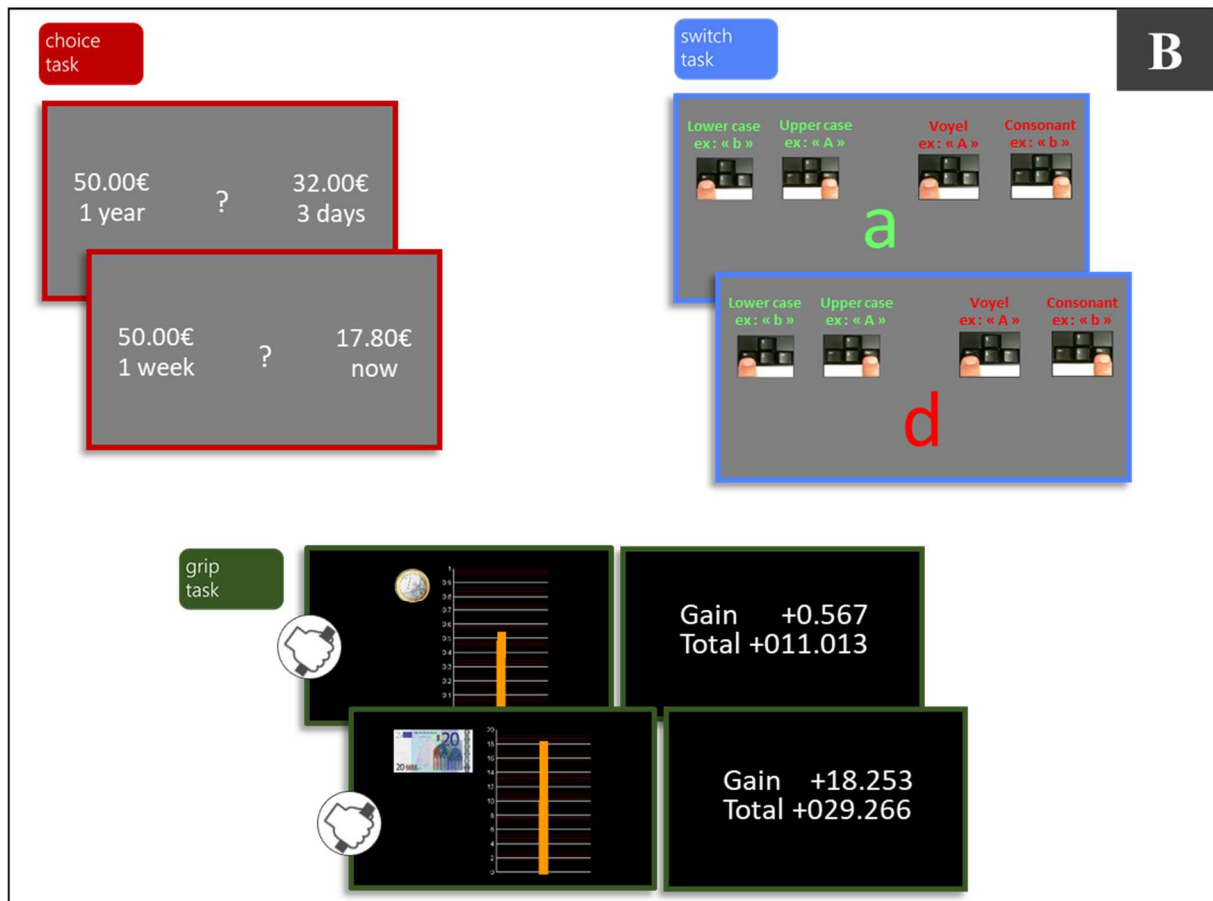
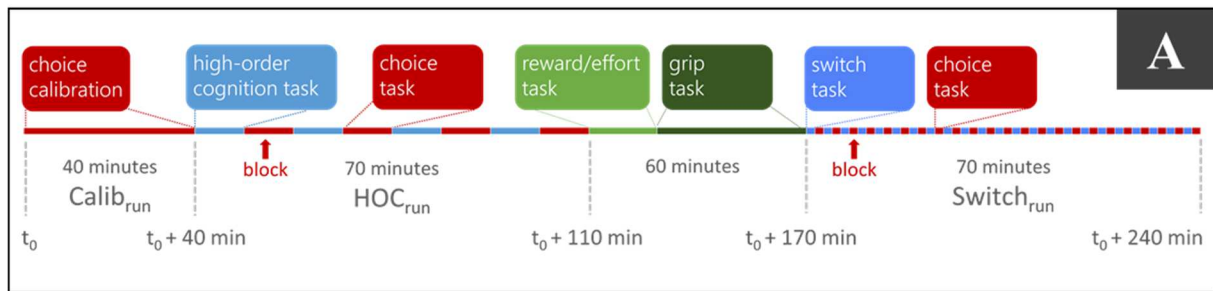
161 The gliomas were located in the frontal lobe for 69% of patients and in the left hemisphere for
162 75% of patients (Table S2). Almost half of the patients (n=14) was assessed prior to surgery,
163 and the other half (n=15) was assessed at various delays post-surgery. Most patients (n=18)
164 were under antiepileptic treatment at the time of the assessment. In most cases (n=14), the
165 treatment was Levetiracetam (Keppra) twice a day (morning and evening) with doses varying
166 from 250mg to 1250mg. Alternative treatments were Lamotrigine (Lamictal), Oxcarbazépine
167 (Trileptal) or Lacosamide (Vimpat), or a combination of two antiepileptic medications.

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

174 **Fatigability assessment**

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

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



187

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

202 **Psychometric scales**

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

212 **Cognitive control tasks**

213 **High-order cognition tasks**

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

228 The high-order cognition tasks were programmed using MeyeParadigm [e(ye)Brain Inc.,
229 2009], while all subsequent tasks (grip, switch and choice) were programmed using the
230 Psychtoolbox of MATLAB version R2017b [MathWorks, 2017]. The conditions of our ethics
231 approval do not permit public archiving of anonymised study data. Readers seeking access to
232 the data should contact the principal investigator Pr. Emmanuel Mandonnet. Access will be

233 granted to named individuals in accordance with ethical procedures governing the reuse of
234 sensitive data. Specifically, requestors must meet the following conditions to obtain the data :
235 completion of a formal data sharing agreement. Study materials is archived and publicly
236 accessible - when feasible - on Github¹. Legal copyright restrictions prevent public archiving
237 of the psychometric scales used in this study, which can be obtained from the copyright
238 holders in the cited references.

239 **Switch task**

240 To assess cognitive control directly, we used the switch task that was employed to induce
241 fatigue in a previous study²⁵, which itself was adapted from tasks shown to activate cognitive
242 control brain regions in the lateral prefrontal cortex¹⁹. In each trial of this task, a letter
243 appears on screen, either red or green. The colour of the letter determines the relevant
244 dimension for the classification that participants must perform (either lower vs. upper case or
245 vowel vs. consonant). Thus, a change of colour corresponds to a switch between classification
246 tasks. Colour-task associations were counterbalanced across participants. To maintain the
247 demand on cognitive control, there were here 8 switches in each block of 24 trials, over a total
248 of 23 blocks. For each classification task, the two categories are associated with left and right
249 arrows on the keyboard. Responses that are either incorrect or too slow are followed by a
250 negative auditory feedback. Before the assessment, participants are trained first with one rule,
251 then with the other, and last mixing both rules. During this training session, there was a large
252 response time window (20 seconds) to allow self-paced rule acquisition. The training session
253 loops until participants reach a correct response rate of 90%. The response time window is
254 continually adjusted to response time measured in the preceding block (maximum RT for the
255 new block is set to three times the mean RT in the previous block), both to accommodate
256 inter-subject variability in cognitive speed and to maintain time pressure throughout task
257 completion.

258 **Motor control task**

259 To assess the trade-off between physical effort and monetary reward, we relied on an
260 incentive force task previously used to assess motivation deficit in patients with apathy due to
261 stroke or Parkinson's disease^{39,40}. The aim for the participant is to win as much money as
262 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/>

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

274 **Choice-tasks**

275 **Reward/effort trade-off task**

276 Participants are first presented with reward and effort items presented one by one on screen
277 and asked to rate on a visual analog scale how pleased they would be if they were given the
278 reward or displeased if they were to exert the effort. We used 24 rewards items (e.g.: a 100g
279 chocolate bar) and 24 efforts items (e.g.: sort 100 words in alphabetic order). Then
280 participants are shown options combining a given effort to obtain a given reward (e.g.: sort
281 100 words in alphabetic order to earn a 100g chocolate bar). As they are not assessing
282 fatigability, results of this task will be reported in another paper.

283 **Intertemporal choice task**

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

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

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

314 **Computational modelling**

315 Inter-temporal choices were fitted with the same computational model as used in a previous
316 study to capture the effect of fatigue on choice impulsivity^{25,26}, itself inspired by the
317 ‘exponential plus bias’ model⁴¹. The model compares the values of the two options with a
318 standard softmax function to generate choice probability:

$$319 \quad P_{ss} = \frac{1}{1 + \exp(-\beta (V_{ss} - V_{ll}))}$$

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

324
$$V = R \times \exp(-k \cdot D) + \textit{bias} \text{ (if } D = 0)$$

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

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

333 **Statistical methods**

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

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

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

345 $DV \sim 1 + \textit{group} + \textit{HOC} + \textit{Switch} + \textit{group} * \textit{HOC} + \textit{group} * \textit{Switch}.$

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

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

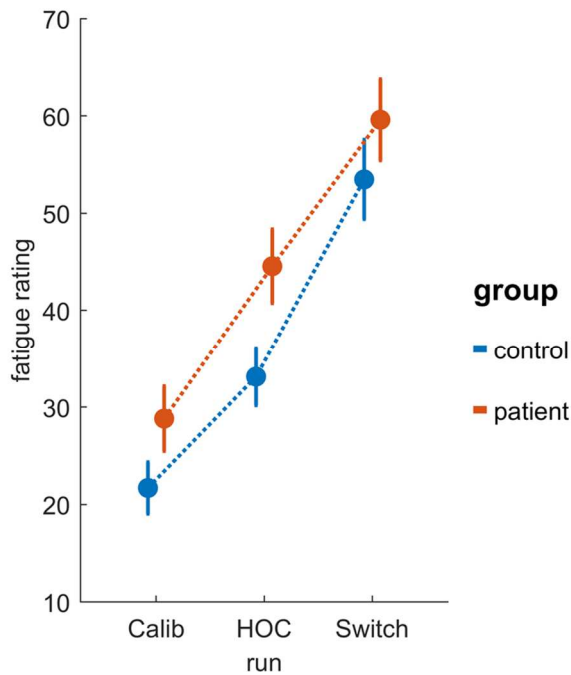
- 360 - psychosocial factors including scores on clinical questionnaires and also age, sex and
361 education level: $DV \sim 1 + age + sex + education + FSS + HAD_anxiety +$
362 $HAD_depression + STARK + BIS$
- 363 - cognitive efficiency factors including performance in cognitive tasks during
364 neuropsychological assessment (Combination of Associate, Analogy and Switch tasks)
365 : $DV \sim 1 + combination\ of\ associate + analogy + switch$
- 366 - lesion factors including volume, side (left or right), frontal localisation (yes or no): DV
367 $\sim 1 + lesion\ volume + frontal + hemisphere$
- 368 - treatment factors including surgery (pre or post), antiepileptic treatment (yes or no),
369 experience of chemotherapy or radiotherapy : $DV \sim 1 + surgery + chemotherapy +$
370 $radiotherapy + antiepileptic$

371

372 Results

373 Subjective questionnaires and ratings

374 Psychometric scores on clinical questionnaires were compared between controls and patients
375 using two-tailed t-tests (Table S4). There were significant differences in fatigue severity (FSS
376 score: $t(54) = 3.481$, $p = 0.001$) and depression symptoms (HAD depression score: $t(54) =$
377 3.016 , $p = 0.004$), plus a borderline trend in anxiety symptoms (HAD anxiety score: $t(54) =$
378 1.974 , $p = 0.053$). However, there were no significant difference in apathy (STARK score:
379 $t(54) = 0.611$, $p = 0.544$) nor in impulsiveness (BIS score: $t(44) = 0.490$, $p = 0.626$). These
380 results strengthen the idea that fatigue is a most prominent complaint in patients with low-
381 grade glioma.



382

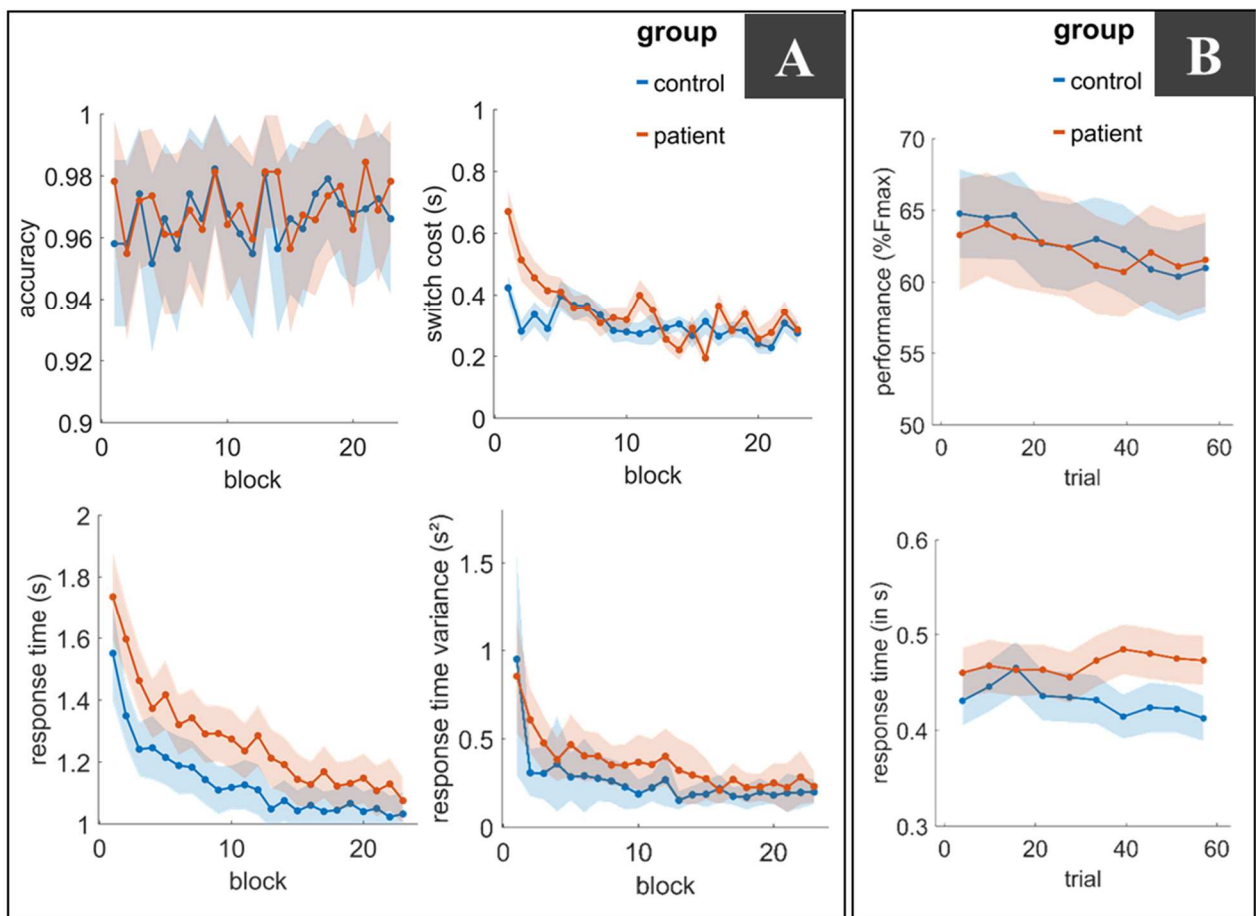
Figure 3. Subjective ratings. All participants indicated their fatigue level on a visual analog scale after each run of the neuropsychological assessment. Dots show inter-participant means and error bars show standard errors of the mean.

383 As a first possible marker of fatigability, self-reports (subjective ratings on a visual analog
384 scale) were compared between groups and runs. Subjective ratings of fatigue increased with
385 runs, in both controls and patients (Fig. 3). Linear regression analyses showed that, relative to
386 calibration, only the switch run had a significant impact on fatigue rating ($\beta = 31.79$,
387 $p < 0.0001$). Although ratings tended to be higher in patients, there was no significant group

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

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

393 Task performance



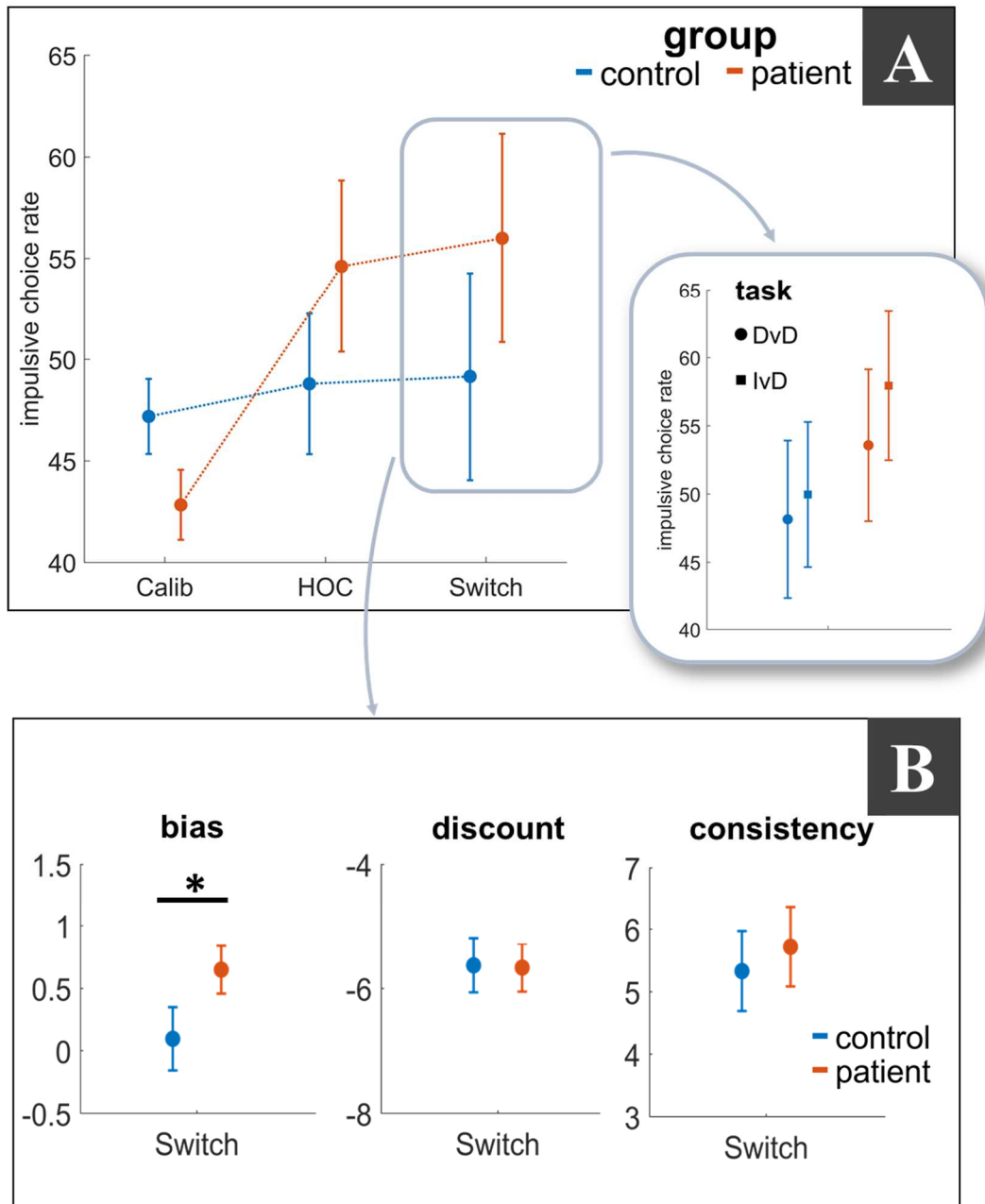
394
395 **Figure 4. Cognitive and motor performance. A, Performance in the switch task.** Plots show accuracy (correct
396 response rate), switch cost (difference in response time between switch and non-switch trials), response time and
397 response time variance (across trials within a block) along the 23 blocks of task trials. **B, Performance in the**
398 **grip task.** Plots show force (in percentage of maximal force) and response time along task trials. Dots are
399 means and shaded areas are inter-participants standard errors of the mean.

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

405 and a trial effect ($\beta = 0.0025$, $p = 0.0032$) but no interaction ($\beta = -0.00023$, $p = 0.84$). There
406 was no significant interaction either in RT variance (across trials within a block), which has
407 been conceived as an index of concentration on the task. Regarding switch cost (difference in
408 RT between switch and non-switch trials), there was again an impact of trial index ($\beta = -0.05$,
409 $p = 0.016$) but no group effect nor interaction.

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

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



420

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.

393 We then turned to our new marker of fatigability, the rate of impulsive choice, which was also
394 compared between groups and runs (Fig. 5A). Results showed a significant interaction
395 between group and both the HOC run ($\beta = 0.30$, $p = 0.0001$) and the Switch run ($\beta = 0.34$, $p =$
396 0.00001). The effect of group alone was not significant ($\beta = -0.07$, $p = 0.21$), and neither were
397 the effects of HOC run ($\beta = 0.08$, $p = 0.12$) nor Switch run ($\beta = 0.10$, $p = 0.08$). The interaction
398 was due to impulsive choice rate increasing more in patients than in controls, thus denoting
399 higher fatigability. At the end of the assessment, in the Switch run, impulsive choice rate was
400 significantly ($t(5150) = 4.926$, $p < 0.0001$) higher in patients (mean = 56,0%) than in controls
401 (mean = 49,2%). Note that the increase in choice impulsivity, in the sense of a preference
402 shifted toward immediate rewards, does not necessarily reflect faster responses. Indeed, even
403 if choice RT decreased in the course of the assessment ($\beta = -1.17$, $p = 0.0014$) and although
404 patients were globally slower than controls ($\beta = 1.10$, $p = 0.0023$), there was no interaction
405 between group and run (Fig. S1). Thus, the pattern observed in impulsive choice rate was not
406 mirrored by variations in choice RT.

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

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

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

430 **Discussion**

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

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

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

466 At a meta-decisional level, cognitive control itself can be considered as motivated, meaning
467 that its exertion depends on expected costs and benefits⁴⁵. Under this perspective, fatigue can
468 be interpreted as an elevated cost of cognitive control, preventing its exertion unless an
469 important outcome is at stake. Thus, fatigue may not come with a loss of cognitive control
470 abilities, as would happen for instance with lesions of the lateral prefrontal cortex, but may
471 induce a shift in the cost-benefit arbitration that drives cognitive control exertion. This would
472 explain why performance can be maintained, even in tasks involving cognitive control, while
473 choices become more impulsive. Indeed, intertemporal choices are expressions of personal
474 preferences, as participants are told that there are no right or wrong responses in this task. On
475 the contrary, grip and switch tasks in our design lead to objective feedbacks that participants
476 are willing to maximize, as shown by their near-ceiling correct response rate. Thus, strong
477 motivation to score well might have countered fatigue effects on performance in cognitively
478 demanding task. We also note that performance even tended to improve with time on task, as
479 shown by reduced RT, which may reflect training effects that could also have masked fatigue
480 effects.

481 One may wonder why patients implicitly express high fatigability in this economic choice
482 task and not when directly asked, as in fatigue ratings. In fact, all participants reported
483 increasing levels of fatigue in their subjective ratings, but contrary to what was observed with
484 impulsive choice rate, there was no interaction between group and time. Interestingly, this
485 result is in line with a previous finding that objective markers of fatigability do not correlate
486 across patients to subjective measures⁴⁶. One explanation is that participants normalize the
487 visual scale to the range of fatigue they experience in their daily life, such that the shift in
488 rating may not reflect the absolute change in subjective fatigue sensation, which may
489 nonetheless differ between patients and controls. A related explanation is that because

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

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

512 While our findings provide insight into the nature of fatigability in glioma patients, they
513 suffer from a number of limitations that may preclude a straightforward application to clinical
514 settings. One obvious limitation is that such assessment would take time, because fatigability
515 has to be measured over a sufficient duration. A related drawback is that a subset of patients
516 (11%) left before completing the entire assessment (because of agenda constraints in most
517 cases). This did not happen in controls, possibly because they were financially compensated
518 for their participation after completion of the full protocol. Removing some tasks from the
519 neuropsychological assessment might shorten the duration, but with the current design we
520 could not identify which task was sufficient to induce fatigue in patients and which was
521 unnecessary. Choice impulsivity was higher in the Switch run, which was likely demanding in
522 cognitive control, but also coming last and hence possibly cumulating the impact of preceding

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

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

548

549 **Fundings** – VF was supported by a CIFRE PhD fellowship (Industrial Agreement of Training
550 through Research) that funds collaborations between industrial partners (here, Humans
551 Matter) and research institutes (here, Paris Brain Institute).

552 **Conflict of interest** – None.

553 Transparency and Openness Promotion - no part of the study procedures or analyses was pre-
554 registered prior to the research being conducted.

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