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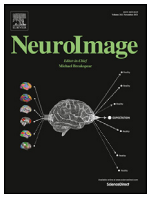

Mental fatigue correlates with depression of task-related network and augmented DMN activity but spares the reward circuit

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ABSTRACT

Long-lasting and demanding cognitive activity typically leads to mental fatigue (MF). Indirect evidence suggests that MF may be caused by altered motivational processes. Here, we hypothesized that if MF consists in an alteration of motivational states, brain functional changes induced by MF could specifically affect the brain motivation circuit. In order to test this hypothesis, we devised a functional neuroimaging protocol to detect altered brain activity in reward-related brain regions in relation to cognitively induced mental fatigue.

Twenty-five healthy participants underwent a FATIGUE and a CONTROL session on different days. In the FATIGUE session, MF was induced by performing a demanding cognitive task (adapted Stroop task) during 90 min, whereas in the CONTROL session, participants were asked to read magazines for the same period of time. We measured the neural consequences of the MF induction during a working memory task (Missing Number task) while modulating extrinsic motivation with block-wise variations in monetary reward. We also tracked participants' momentary fatigue, anxiety state and intrinsic motivation prior to and following the MF inducement and measurement.

Accuracy on the Missing Number Task was lower in the FATIGUE than in the CONTROL condition. Furthermore, subjective MF, but not its behavioral manifestations, was associated with hypoactivity of the task-evoked neural responses. Importantly, activity in regions modulated by reward showed no differences between FATIGUE and CONTROL sessions. In parallel, subjective MF correlated with increased on-task activity and resting-state functional connectivity in the default mode network.

These results indicate that subjective mental fatigue is not associated with altered activity in the brain motivation circuit but rather with hypoactivity in task-specific brain regions as well as relative increases of activity and connectivity in the default mode network during and after the task.

1. Introduction

Prolonged execution of demanding cognitive tasks leads to mental fatigue (MF) which refers primarily to the subjective feeling of a deteriorated ability to initiate and/or maintain mental activities (Chaudhuri and Behan, 2000). MF can also be accompanied, albeit inconsistently, with objective behavioral alterations (van der Linden et al., 2003; DeLuca et al., 2008; Hopstaken et al., 2014; Borragán et al., 2017) and psychophysiological changes (Boksem et al., 2006; Lorist et al., 2009; Hopstaken et al., 2014, 2015, 2016; Gergelyfi et al., 2015). Theories of MF can be classified in two major groups that assume either: (a) alterations of motivational processes leading to restrictions on the recruitment of cognitive resources for the task at hand (Hockey,1997; Meijman and Mulder, 1998; Hockey, 2011; Chaudhuri and Behan, 2000; Boksem and Tops, 2008; Westbrook and Braver, 2016; Kurzban et al., 2013), or b) progressive functional alteration of cognitive processes through metabolic mechanisms (Gailliot and Baumeister, 2007; Christie and Schrater, 2015; Holroyd, 2015; Hopstaken et al., 2015; Blain et al., 2016; Gergelyfi et al., 2015).

Theories from the first group, which propose that MF depends on motivational alterations, usually assume that behavioral changes induced by prolonged task execution rely on the brain circuits involved in reward valuation and motivation, i.e. dopaminergic midbrain and ventral prefrontal cortex (Meijman and Mulder, 1998; Hockey, 2011; Kurzban et al., 2013; Chaudhuri and Behan, 2000; Boksem and Tops, 2008; McGuire and Botvinick, 2010). However, while several studies have consistently reported alterations in task-related activations in

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relation to MF (Lim et al., 2010; Hedgcock et al., 2012; Persson et al., 2013; Blain et al., 2016; Breckel et al., 2011), findings have been less conclusive regarding the implication of the motivation circuits. Whereas Nakagawa and colleagues have reported a hypoactivity in the dopaminergic midbrain following fatigue (Nakagawa et al., 2013) and a larger mean diffusivity (*i.e.* reduced white matter structural integrity) in the right putamen of healthy subjects with high subjective trait fatigue (Nakagawa et al., 2016), MF has also been shown to increase activity in dopaminergic midbrain (Moeller et al., 2012).

In addition to changes in the activity of task-specific networks, some studies have reported changes in default mode network (DMN) connectivity after fatigue induction procedure (Waites et al., 2005; Gordon et al., 2012; Barnes et al., 2009; Esposito et al., 2014; Gui et al., 2015; Qi et al., 2019). DMN activations are typically anti-correlated to goal-directed behavior (Raichle and Snyder, 2007; Yeo et al., 2011; Fox et al., 2005; Harrison et al., 2008), leading the long-lasting changes in DMN connectivity in relation to MF to be interpreted as compensatory mechanisms redirecting cognitive resources to the task (Esposito et al., 2014).

The aim of the present study was to provide a detailed investigation of the neural circuits involved in MF and motivation. We relied on performance-contingent monetary rewards to manipulate the motivational state during the evaluation of MF while fMRI scans were carried out. We hypothesized that if MF relies on altered motivational states, the regions involved in the brain reward system should be hypoactive in the MF group compared to the controls. Finally, we examined changes in resting-state brain activity pattern after MF induction in task-correlated and anti-correlated brain areas.

2. Materials and methods

2.1. Participants

Twenty-six healthy subjects (14 females; age = 23.81 ± 3.17, mean±sd) participated in this study. The participants had to meet the following criteria for participation: absence of contraindication for MRI, age between 20 and 35, right-handedness, normal or corrected-to-normal visual acuity, no current medical treatment. Participants were assessed for absence of contraindication to MR prior to the experiment and provided written informed consent. All the subjects were naive regarding the aim of the study, and were financially compensated for their participation (75–135 €).

All procedures were approved by the local ethics committee (Comité d' Ethique hospital-facultaire de l'UCL), and were in accordance with the Helsinki Declaration.

2.2. Experimental tasks

In order to limit the confounding effect of boredom, we used different visual tasks to induce and measure MF.

In the FATIGUE session, MF was induced by performing a modified Stroop task for at least 90 min (see Fig. 1A). The CONTROL session consisted in reading magazines for 90 min. Then the neural effects of MF were assessed by measuring the participant's blood-oxygen-level dependent responses while they were engaged in the Missing Number task (see Fig. 1B). Prior to and after the different tasks, questionnaires [Multidimensional Fatigue Inventory (MFI), State-Trait Anxiety Inventory (STAI) and Intrinsic Motivation Inventory (IMI)] were used to evaluate the participants' cognitively induced fatigue, anxiety state and task interest/enjoyment (see Fig. 1C).

2.2.1. Mental fatigue (MF) induction: stroop task

In accordance with earlier studies, we used a modified version of the Stroop task, including interleaved "number" and "arrow" Stroop trials, to induce MF (Barwick et al., 2012; Moeller et al., 2012; Wang et al., 2014, 2016). In the "number" Stroop, pairs of digits (ranging from 1 to 9) were presented in the middle of the computer screen. After a delay, a cue then indicated whether the participants had to report the larger digit in terms of "value" or in terms of "size" (see Fig. 1A; left or right key on the numeric keypad). In the "arrow" Stroop, arrows were displayed at the top or bottom of the screen and following the instruction cues, participants had to report either the "location" or "direction" of the arrow (up or down key). The blocks included 92 trials per condition (value, size, location and direction). Additionally, the trials were equally divided into congruent (*e.g.* large/small digit with large/small value, upward/downward pointing arrow with corresponding up/down location) and incongruent trials (*e.g.* large/small digit with small/large value, upward/downward pointing arrow with down/up location). Finally, the number of consecutive trials with the same condition followed a geometric distribution. Subjects were instructed to be as fast and accurate as possible in every trial.

2.2.2. Control of mental fatigue (MF): magazine reading

The CONTROL session consisted in reading magazines for 90 min. The issues of a magazine, called Science & Santé, were downloaded from the website of Institut national de la santé et de la recherche médicale (Inserm: http://www.inserm.fr/actualites/rubriques/magazine-science-sante) from the year of 2014/2015. This magazine illustrates discoveries, debates and issues of biomedical research. The participants were free to choose their favored issue(s).

2.2.3. Mental fatigue (MF) evaluation: missing number task

The Missing Number task contained three conditions: number series 7 (including numbers from 1 to 7), 8 (numbers from 1 to 8) and 9 (numbers from 1 to 9). The number of digits shown was always inferior to the range of possible values (*i.e.* 6 numbers were shown in number series 7 (see Fig. 1B); 7 numbers in number series 8, and 8 numbers in number series 9) and the participants were asked to report the digit that was missing from the series. In addition, four distractor digits, whose color differed from the target color, were interleaved with the target digits (see Fig. 1B). Participants were instructed to perform the task as fast and accurately as possible by using an MRI-compatible numeric keypad, developed in-house.

The performance-contingent monetary rewards were color-coded (see Fig. 1B) and the subject-specific arbitrary rule linking the color cue to the reward value was reminded to the participant at the beginning of each block. Then, the reward color for the block was shown in order to inform the participant about the reward they would receive for each correct response in the upcoming trials. Participants did not receive any performance feedback till the end of the experiment.

2.2.4. Control of reward effect: simple reaction time task

The impact of monetary reward on extrinsic motivation was evaluated by means of a Simple Reaction Time task in which subjects had to press the left mouse button as fast as possible whenever a red triangle appeared on the screen following a fixation cross. This fixation cross was presented for a variable duration (from 500 ms to 3000 ms) following a geometric distribution. During a block, the sum of the response times was fixed to a total of 6000 ms. Thus, the faster the participants responded, the more trials they could perform and the more points they could gain. The reward condition was instructed in the same form as in the Missing Number task, with the same color code (see Fig. 1B).

The Stroop, Missing Number and Simple Reaction Time tasks were implemented in MATLAB 7.5 (The MathWorks, Natick, Massachusetts, USA) and were displayed by means of the psychophysics toolbox (Brainard, 1997) and an in-house graphics toolbox (CosyGraphics).

2.3. Subjective measures

2.3.1. Multidimensional fatigue inventory (MFI): general fatigue subscale

In both sessions, a modified version of the MFI (Gentile et al., 2003) was used to assess the participants' subjective feeling of fatigue at base-

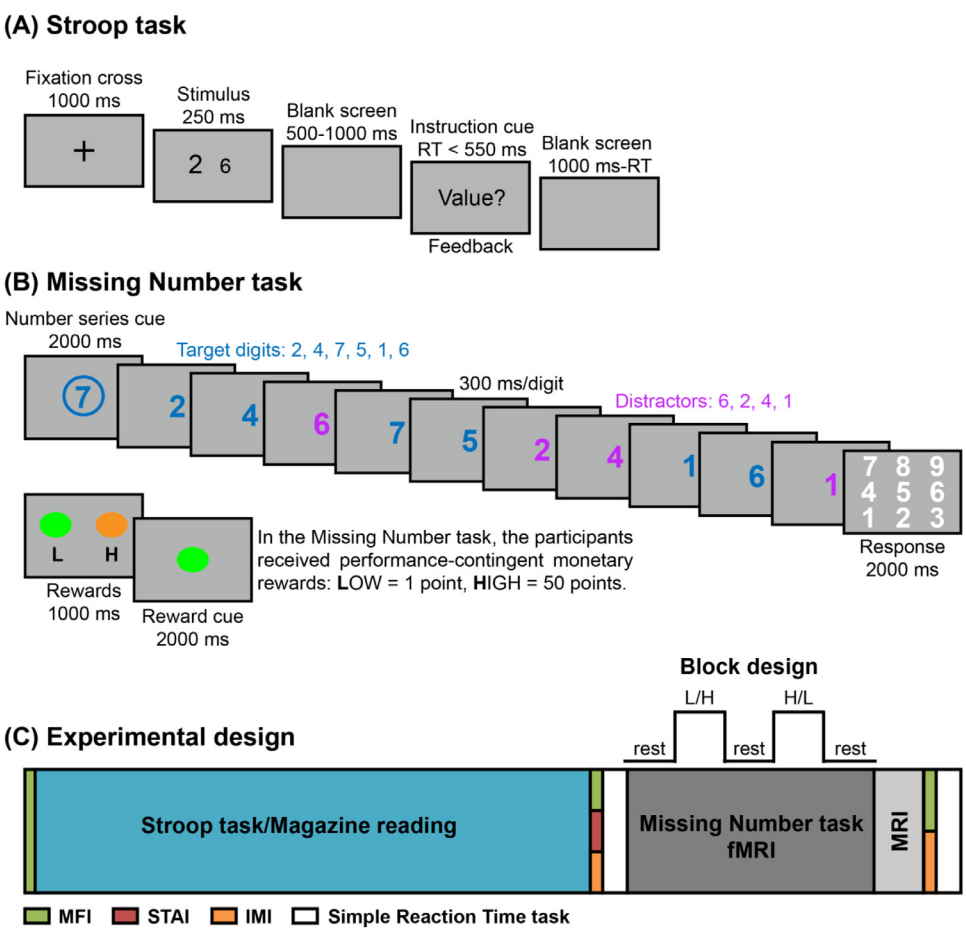

Fig. 1. Experimental design.
(**A**) In the Stroop task, the stimulus appeared for 250 ms following a fixation cross (1000 ms). After a 500–1000 ms delay (blank screen), the instruction cue ("value" or "size" in this example) was presented for 550 ms. Participants had to respond before the end of the cue presentation, and were given an auditory feedback afterwards. The delay between the cue onset and the beginning of the next trial was fixed at 1000 ms, independently of the participants' RT. After the participants' response, the screen remained blank until the beginning of the next trial. (**B**) At the beginning of every trial of the Missing Number task, a 2000 ms cue informed the participant on the number series condition for the next trial (7 in the present example) and on the color defining the target digits (blue or magenta, indicated by the color of the cue). Each digit in the series (target digits or distractors) was presented for 300 ms. The missing element of the number series had to be selected by pressing the corresponding number on a numeric keypad which was also shown on the screen for 2000 ms. The display (2000 ms) of the reward condition (1 or 50 point(s) per correct response) was preceded by a reward information display of 1000 ms, which reminded the color-reward association rule to participants. (**C**) Prior to and following the FATIGUE induction (Stroop task) or CONTROL condition (magazine reading), and after the MF evaluation (Missing Number task), questionnaires were used to assess the participants' subjective fatigue (MFI) and anxiety (STAI) states and their interest/enjoyment in the task (IMI). The effect of reward on extrinsic motivation was controlled by means of the Simple Reaction Time task, performed before and after the Missing Number task (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

line, after Stroop task/magazine reading and a third time after the Missing Number task. Due to the time constraints, we included only the "global fatigue" subscale from the inventory. This subscale was shown to track mental fatigue reliably in our previous study (Gergelyfi et al., 2015). Every statement has to be rated on a Likert scale ranging from 1 to 5 (with anchors of "Yes, that is true" and "No, that is not true"). The lower the MFI score, the higher the level of subjective fatigue.

2.3.2. Post-experimental intrinsic motivation inventory (IMI): task interest/enjoyment subscale

Participants' intrinsic motivational state was evaluated by The Post-experimental IMI (http://selfdeterminationtheory.org/intrinsic-motivation-inventory/) in both sessions after the Stroop task/magazine reading and a second time after the Missing Number task. The IMI consists of 45 items. We used only the items from the inventory that are relevant to assess the subjects' intrinsic motivation in our experimental tasks, namely the interest/enjoyment subscale. In this inventory, the subjects have to rate each item on a 7-point Likert scale (from "Not at all true" to "Very true") depending on their current feeling. The higher the score, the higher the participant's task interest/enjoyment.

2.3.3. State-trait anxiety inventory: state anxiety

The STAI (Spielberger, 1983) involves two 20-item subscales describing trait and state anxiety, respectively. Only the latter subscale was used in this study after the Stroop task/magazine reading, just before the scanning session. A score between 1 and 4 (from "Not at all" to "Very much so") has to be provided on every item. The higher the score, the more severe the state anxiety.

2.4. Design and experimental procedure

The experiment included three sessions (TRAINING, FATIGUE and CONTROL), performed on different days. The purpose of the TRAINING session (70–80 min) was to familiarize the participants with the numeric keypad and the reward system used during the experiment and to help participants approach asymptotic performance in the tasks, so as to minimize order effects. After being informed about the general experimental procedure and completing the informed consent and MR contraindication forms, participants practiced a total of 184 trials of the Stroop task (see above), 180 trials of the Missing Number task (see above) and 4 blocks (88 trials on average) of the Simple Reaction Time task (see above). In all tasks, participants received feedback about their performance.

Within 1 week after the TRAINING session, participants underwent the CONTROL and FATIGUE sessions, in a counterbalanced order, and with a time interval of 3,4 days between the two (except 2 participants for whom delay was 5 days and one for whom it was 17 days). For a given participant, the experimental sessions were always performed during the same time of the day in order to avoid circadian confounds.

Both the CONTROL and FATIGUE sessions started with participants receiving instructions and filling the Multidimensional Fatigue Inventory (MFI) questionnaire (see above), assessing their subjective feeling of fatigue (see Fig. 1C). Then, they performed either the Stroop task (FATIGUE) or magazine reading (CONTROL) for 90 min (see Fig. 1C). The Stroop task normally included 4 blocks, but its actual duration depended on the fMRI scanner availability, in order to prevent the participants from recovering between the end of the Stroop task execution and

the beginning of the neuroimaging acquisition. Consequently, 8 participants performed 5 blocks and 1 participant performed 6 blocks whereas 3 participants did not fully complete the 4th block. Each block consisted of 368 trials and lasted around 22,5 min. Participants received trial-wise auditory feedback on their performance and block-wise feedback on the number of trials performed correctly. In the CONTROL session, participants read magazines of their choice, displayed on the computer screen, for 90 min without being granted access to the Internet or their phone. Following either the Stroop task (FATIGUE) or magazine reading session (CONTROL), the subjects' cognitively induced fatigue, motivational and anxiety state were assessed by means of the MFI, IMI and STAI questionnaires, respectively (see above and Fig. 1C). Following these questionnaires, participants performed 4 blocks of Simple Reaction Time task (see above; 4 min) and then entered the MR scanner to perform the Missing Number task (see above and Fig. 1C). The average time delay between the end of the Stroop task or magazine reading and the beginning of the fMRI recording was 26.3 (SD = 9.51) and 31.2 (SD = 6.79) min respectively. In both FATIGUE and CONTROL sessions, the Missing Number task included 4 runs. Every run included ten blocks of 6 trials (46,8 s per block). The reward condition varied block-wise, with 5 blocks (thus 30 trials) in each reward condition (1 point or 50 points). The maximum number of points earned in the run was 1530, which translated to a maximum of 12€ per run (about 127 points per €). Every run started and finished with a 4.5 s blank screen. An additional 11.7 s blank screen was also shown at the end of each block. The total duration per run was around 10 min. After the 2nd run, a 6 min resting-state block was performed, during which the participants were instructed to close their eyes and let their mind wander without falling asleep. The total scan duration of the Missing number task, including the intervening RS was 46 min. Following the last run of the Missing Number task, an 8 min structural scan was performed. After the completion of the scanning session, the Simple Reaction Time task and the questionnaires (MFI and IMI) were performed again (see Fig. 1C). The total duration of either FATIGUE or CONTROL sessions was approximately 3 h. Only after the completion of the entire experimental protocol the participants were informed about the total amount of monetary reward gained at the Missing number task.

2.5. Data and statistical analysis

One participant was excluded from the data analysis because she had participated in another experiment right before. Thus, analyses were performed on a group of 25 participants. Furthermore, 4 runs, from different participants, were excluded due to technical problems related to the MR scanner (1 run from the CONTROL and 3 runs from the FATIGUE session). These runs were not included in either the neuroimaging or behavioral data analysis.

2.5.1. Behavioral data

Statistical analyses were performed with SAS Enterprise Guide software, Version 5.1 (Copyright © 2012 SAS Institute Inc., Cary, NC, USA) and with MATLAB 7.5 (The MathWorks, Natick, MA, USA).

Generalized Linear Mixed Models (GLMMs) were performed in the SAS software. In all models, all fixed effects were allowed to vary between subjects in the random part of the model. In the modified version of the Stroop task, the number of blocks varied between participants due to the availability of the MR scanner as mentioned above (see Design and experimental procedure). In order to analyze the effect of time-on-task on accuracy and log-transformed RT, we grouped the data in 5 successive bins, from beginning to the end of the task. The GLMM analysis was performed on both accuracy and RT where the main factors (time bins, congruency) and their interactions were modeled as fixed effects. In the Missing Number task, the model included the session condition (FATIGUE, CONTROL), reward cue (1, 50), number series (7, 8, 9) and their interactions as fixed effects. In the Simple Reaction Time task, the GLMM was performed on log-transformed RT with session condition (FATIGUE, CONTROL), time of performance (before, after MR scan), reward (1, 50) and their interactions as fixed effects.

2.5.2. fMRI data

2.5.2.1. Imaging acquisition parameters. Functional, resting-state and anatomical scans were performed with a Achieva 3T scanner (Philips Healthcare, Eindhoven, The Netherlands) equipped with a 32-channel phased array head coil. Functional and resting-state scans T2-weighted echo-planar images were acquired with the following parameters: echo time (TE) = 27 ms, repetition time (TR) = 2250 ms, flip angle (FA) = 85 °, 41 slices acquired in an ascending order, slice thickness = 3 mm, field of view (FOV) = 123 × 123 mm^2, acquisition matrix = 80 × 80 (reconstruction 80^2). Each functional scan (lasting 2 runs of the task respectively) included 280 vol (acquisition time 10 min and 30 s) while the resting-state scan consisted of 164 vol (acquisition time 6 min and 9 s). A 3D heavily T1-weighted structural image was also recorded at the end of the MRI session. This sequence consisted of a gradient echo sequence with an inversion prepulse (turbo field echo) acquired in the sagittal plane using the following parameters: TR = 9.1 ms, TE = 4.6 ms, FA = 8 °, 150 slices, slice thickness = 1 mm, in-plane resolution = 0.81 × 0.96 mm^2 (acquisition) reconstructed in 0.75 × 0.75 mm^2, FOV = 240 × 240 mm^2, acquisition matrix = 296 × 251 (reconstruction 320^2), SENSE (parallel imaging) factor = 1.5.

2.5.2.2. fMRI preprocessing and analysis. BrainVoyager QX 2.8. (Brain Innovation BV, Maastricht, Netherlands) was used to preprocess and analyze the functional neuroimaging data acquired during the Missing Number task (see Fig. 1B). The preprocessing of the functional data consisted of the following steps: slice time correction, temporal filtering (high-pass, cutoff: 2 cycles; analysis was also performed with 4 cycles, leading to identical GLM results) and motion correction. Since the structural image was acquired in the end of the experiment, motion correction was performed by aligning volumes from all runs to the first volume of the last run in a given session. Co-registration parameters were calculated only between the last functional run and structural image. Prior to the motion correction procedure we first confirmed that the participants' in-scanner motion did not differ between experimental conditions. To this end, we used a Generalized Linear Mixed Model (GLMM), considering either translation or rotation as dependent variable (derived as the root mean square of the temporal derivative of all 3 axes) and reward and fatigue conditions as binary predictors. None of the main effects or interactions were significant (all $p > 0.08$; see Supplementary Fig. 2A). Then, motion parameters per subject (detrended motion variables, their temporal derivative and spikes in the motion pattern) and the global signal (average of brain-wise BOLD signal) were regressed out from the signal in each voxel using a GLM with these variables as predictors (Power et al., 2014). The spikes corresponded to volumes in which root mean square displacement from the previous volume exceeded 0.25 mm (Satterthwaite et al., 2013). Finally, all images were spatially normalized into Talairach space (TaSpatial smoothing was performed with a Gaussian kernel with a full-width at half-maximum (FWHM) of 5 mm, in order to account for anatomical variability between subjects.

Separate statistical analyses on group data ($n = 25$) were performed for the on-task and the ensuing post-task resting state conditions. On-task fMRI analyses include: (1) second-level block- and event-related General Linear Models (GLM) for the contrasts reward, fatigued (session), task and reward-fatigue interaction; (2) correlation analysis between subjective measurements (anxiety, motivation and increased fatigue) and behavioral performance data and the significant clusters from the session- and task-effect; (3) spatial overlap analysis between fatigue contrast correlated with cognitive and behavioral data, and the reward and task contrasts. For the post-task resting state fMRI analysis, whole-brain connectivity matrices were computed per subject and a second-level fatigue (session) GLM contrast was conducted.

First level analyses included two regressors per run, one for each reward level, while the fatigue conditions differed across runs. We used

two different regressors: the block regressors were boxcars encompassing each 48-second task block of corresponding reward level, while the cue-related regressors were 2 s boxcars that encompassed the reward cue presentation period. Random effects GLM analyses were computed separately on the block and cue-related regressors, including four main contrasts: reward ([(HIGH FATIGUE + HIGH CONTROL) – (LOW FATIGUE + LOW CONTROL)], $\Delta BOLD_{REWARD}$); fatigue ([(HIGH FATIGUE + LOW FATIGUE) – (HIGH CONTROL+ LOW CONTROL)], $\Delta BOLD_{SESSION}$); reward-fatigue interaction ([(HIGH FATIGUE – LOW FATIGUE) – (HIGH CONTROL– LOW CONTROL)], $\Delta BOLD_{INTERACTION}$), and task ([(HIGH FATIGUE + LOW FATIGUE) + (HIGH CONTROL+ LOW CONTROL)]-rest, $\Delta BOLD_{TASK}$). Statistical maps (t-statistics) computed according to the contrasts of interest were displayed on the average of the participants' T1-weighted scans and corrected for multiple comparisons using cluster-size thresholding (1000 permutations; (Forman et al., 1995; Goebel et al., 2006)). Unless otherwise specified, the voxel-level threshold was set to 0.001, uncorrected, while the cluster-level threshold was set to 0.05. Clusters surviving multiple comparisons correction were labeled.

Brain-behavior correlations (Spearman's r-statistics) were performed between the participants' change in task-related BOLD responses between sessions ($\Delta BOLD_{SESSION}$, beta weights) on the one hand and changes in questionnaire scores ($\Delta MFI_{CTR\text{-}FAT}$, $STAI_{FAT\text{-}CTR}$ and $IMI\text{-}MissingNumber_{FAT\text{-}CTR}$, see below) or behavioral performance ($MissingNumber_{CTR\text{-}FAT}$, $Stroop_{FAT}$, see below) on the other hand.

Finally, significant correlation maps ($\Delta BOLD_{SESSION}$ x questionnaires/performance Pearson's r-statistics group maps) were then compared with the reward statistical map ($\Delta BOLD_{REWARD}$, [(HIGH FATIGUE + HIGH CONTROL) – (LOW FATIGUE + LOW CONTROL)]) and task activation maps ([(HIGH FATIGUE + LOW FATIGUE) + (HIGH CONTROL+ LOW CONTROL)]-rest, $\Delta BOLD_{TASK}$).

The degree of overlap, between the maps was computed at different thresholds as

$$o_{t_x,t_y} = 100\left(\frac{\sum x_{t_x} y_{t_y}}{N} - \left(\sum \frac{x_{t_x}}{N} \sum \frac{y_{t_y}}{N}\right)\right)$$

with N being the number of voxels, x_{t_x} and y_{t_y} being Boolean vectors of length N indicating whether each given voxel statistic is beyond the considered thresholds t_x and t_y, respectively. This formula computes the percent difference between the actual proportion overlap and the one that would be expected by chance. For each threshold the statistical significance of the overlap was also computed by shuffling the questionnaires a thousand times and computing the 95th (i.e. alpha = 0.05) or 99.9th percentile (alpha = 0.001) of the distribution of the chi^2 statistic of the overlap with the other map (either reward or task effect). We then determined, for each threshold combination, whether the chi^2 obtained with the non-shuffled map was above this value or not.

The correlation between average reward ($\Delta BOLD_{REWARD}$) or task ($\Delta BOLD_{Task}$) t-values and each brain-behavior correlation coefficients (fatigue map) was computed across voxels (see for example Fig. 8). To avoid the effect of correlations between neighboring voxels we also used a bootstrap approach to determine statistical significance by computing the distribution of correlation coefficients on a thousand shuffled versions of the questionnaire scores. P-value was computed as: $\frac{(1+\sum C_{sh} \geq C)}{N+1}$, with C_{sh} corresponding to the vector of shuffled correlation coefficients and C to the actual correlation coefficient obtained on non-shuffled data.

Since the reward contrast ($\Delta BOLD_{REWARD}$) highlighted not only motivation-related regions but also the task-related ($\Delta BOLD_{Task}$) areas that were modulated by reward, we identified a set of regions-of-interest (ROI) that have been classically associated to reward and motivation processing (Neurosynth.org meta-analyses for terms "reward" and "motivation", including 922 and 189 published datasets respectively; see Supplementary Fig. 2B): dorsal ACC (dACC) = [± 5 6 40], ventromedial prefrontal cortex (vmPFC) = [± 7 48 2], anterior insula (aIns) = [± 36 14 13], nAc = [± 8 8 -2], ventral pallidum (VP) = [± 11 -2 -1], VTA = [± 3 -19 -10], SN = [± 10 -16 -9] and amygdala (Amg) = [± 22, -16, -13]. The coordinates of these ROIs (Talairach coordinates; Mai et al., 2008) were taken as the center of a 5 mm radius sphere per ROI using the Talairach coordinate-to-spherical VOI plugin in BrainVoyager QX 2.8. (Brain Innovation BV, Maastricht, Netherlands).

The functional sequence acquired during the post-task resting-state condition was processed using the CONN toolbox (Whitfield-Gabrieli and Nieto-Castanon, 2012), based on SPM8 (Wellcome Department of Imaging Neuroscience, London, UK; www.fil.ion.ucl.ac.uk/spm). Images were slice-time corrected, realigned, coregistered to MNI-normalized anatomical images, and spatially smoothed using a Gaussian kernel of 8 mm full-width at half-maximum. Time-series were temporally filtered using 0.008-0.09 Hz band-pass filter. Anatomical aCompCor noise correction strategy (Behzadi et al., 2007) was used to regress the noise estimated as the first 5 principal components separately for white matter and cerebrospinal fluid masks. We also regressed the realignment parameters (three translations and three rotations) and their first-order temporal derivatives. Regions of interest (ROIs) were defined using the Harvard-Oxford atlas of cortical and subcortical areas combined with the AAL atlas of cerebellar areas. We computed the ROI-to-ROI connectivity matrices by correlating averaged BOLD time series between each pair of ROIs. These correlation coefficients were Fisher-transformed and submitted to a second-level GLM. The model included a between-subject factor SESSION, indicating whether the functional data corresponded to the FATIGUE or CONTROL session and a within-subject factor $\Delta MFI_{CTR\text{-}FAT}$.

3. Results

3.1. Psychometric and behavioral results

3.1.1. Questionnaire data

The FATIGUE induction led to increased subjective feeling of fatigue [$\Delta MFI_{CTR\text{-}FAT}$: $t_{(48)}$ = 3.91, p = 0.00029; ΔMFI refers to the CONTROL-FATIGUE difference of the difference between the post- and pre-task measurements, ΔMFI_{FAT} = -6.84 ± 6.96; ΔMFI_{CTR} = -0.4 ± 4.4, mean±SD], but also to increased anxiety prior to the Missing Numbers task ($STAI_{FAT\text{-}CTR}$: $t_{(48)}$ = 2.20, p = 0.0324; $STAI_{FAT}$ = 37.92 ± 6.99; $STAI_{CTR}$ = 33.76 ± 6.34, mean±SD). Participants' task interest/enjoyment was significantly lower for the FATIGUE than the CONTROL task (Stroop versus magazine reading: $IMI_{FAT\text{-}CTR}$: $t_{(24)}$ = -3.28, p = 0.0019; IMI_{FAT} = 3.27 ± 1.41; IMI_{CTR} = 4.49 ± 1.20; mean±SD). But importantly, the participants' interest/enjoyment in the Missing Number task did not differ between sessions ($IMI\text{-}MissingNumber_{FAT\text{-}CTR}$: $t_{(24)}$ = -0.58, p = 0.5662; $IMI\text{-}MissingNumber_{FAT}$ = 3.83 ± 1.23; $IMI\text{-}MissingNumber_{CTR}$ = 4.03 ± 1.29; mean±SD). None of these psychometric measures correlated between each other (all $p > 0.15$). Supportive evidence for fatigue was also found in the Stroop task performance where the congruency effect was found to increase with time-on-task (see Supplementary Material).

3.1.2. Missing number task

In the Missing Number task, we found a small but significant effect of SESSION on accuracy (GLMM with REWARD, SESSION and SERIESLENGTH as within-subject factors and MFI as between-subject factors; SESSION: $F(1,11744)$ = 4.00, p = 0.046; mean and SE of the accuracy difference: -0.0168 ± 0.0108; confidence interval of the odds ratio: 0.901–1.0; see Fig. 2A), with participants performing worse in the FATIGUE than in the CONTROL session. We also found a significant main effect of REWARD and SERIESLENGTH on Missing Number accuracy (REWARD: $F(1,11744)$ = 4.26, p = 0.039; SERIESLENGTH: $F(1,11744) = 67.13$, $p < 0.0001$; see Fig. 2A), with participants performing better in the easy than in the difficult conditions and when the REWARD was large. Importantly, none of the interactions were significant (all $p > 0.4$, see Fig. 2A), in particular the REWARD-FATIGUE interaction ($F(1,11744)$ = 0.36, p = 0.546), indicating that the effect of reward on accuracy did not change between sessions.

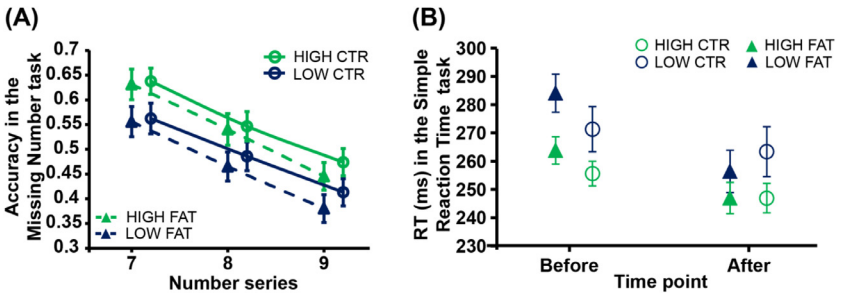

Fig. 2. Behavioral evidence for MF in the Missing Number task and for the absence of relation between MF and motivation. Error bars illustrate the standard error of the mean. CTR: CONTROL condition; FAT: FATIGUE condition. **(A)** Mean accuracy in the Missing Number task as a function of session (CTR, FAT), reward (HIGH, LOW) and difficulty (series length: 7, 8, 9). There was no interaction between the reward and session factors, indicating that the effect of rewards on performance did not differ between sessions. **(B)** In the Simple Reaction Time task, participants' RT as a function of the reward and session conditions is shown before and after fatigue-evaluation (Missing Number task).

There was no correlation between the effect of fatigue on the Missing Number task performance (accuracy: $MissingNumber_{CTR\text{-}FAT}$) and $Stroop_{FAT}$ on the one hand (Spearman $r = 0.11$, $p = 0.612$) and between $MissingNumber_{CTR\text{-}FAT}$ and questionnaire scores on the other hand ($\Delta MFI_{CTR\text{-}FAT}$, $STAI_{FAT\text{-}CTR}$ and $IMI\text{-}MissingNumber_{FAT\text{-}CTR}$; all $p > 0.2$).

3.1.3. Simple reaction time task

The absence of changes between sessions in the behavioral signature of motivation was also confirmed with the Simple Reaction Time task, whose objective was to assess the possible alteration of motivation mechanisms in a task that has very little demand in cognitive control. There was a significant main effect of REWARD on participants' RT ($F(1,24) = 8.10$, $p = 0.0089$; see Fig. 2B) but there was no main effect of FATIGUE ($F(1,24) = 1.31$, $p = 0.2631$; see Fig. 2B) or REWARD-FATIGUE interaction ($F(1,24) = 0.04$, $p = 0.8383$; Fig. 2B). The participants' RT was faster after than before the Missing Number task (effect of TIME POINT: $F(1,24) = 31.28$, $p < 0.0001$; Fig. 2B). This is similar to our earlier findings (Gergelyfi et al., 2015), and probably reflects general effect of training on the task. Furthermore, the effect of TIME POINT on participants' RT changed between sessions ($F(1,24) = 4.36$, $p = 0.0475$; Fig. 2B), with the change in RT following the Missing Number task being larger in the FATIGUE ($t(1,24) = 5.42$, $p < 0.0001$) than the CONTROL session ($t(1,24) = 2.48$, $p = 0.0888$). There was no difference in performance in the Simple Reaction Time task between the CONTROL and FATIGUE sessions when performed either before ($t(1,24) = -2.23$, $p = 0.1449$) or after the Missing Number task ($t(1,24) = 0.51$, $p = 0.9559$; see Fig. 2B). Finally, there was neither significant TIME POINT-REWARD ($F(1,24) = 1.03$, $p = 0.3197$; see Fig. 2B) nor triple, TIME POINT-REWARD-FATIGUE interaction ($F(1,24) = 1.84$, $p = 0.1872$; see Fig. 4B). These results confirm that reward had similar impact on the performance in the Simple Reaction Time task following cognitive fatigue induction or control manipulations.

3.2. Whole-brain fMRI analysis

3.2.1. Fatigue modulation of brain activity: ventral visual processing stream deactivations

The block-based analysis of the fatigue (session) contrast, modeling the effect of the fatigue condition across reward conditions ([(HIGH FATIGUE + LOW FATIGUE) –(HIGH CONTROL + LOW CONTROL)]), resulted in no significant effect at voxel-$p < 0.001$, uncorrected; cluster-level corrected $p < 0.05$.

We also performed an event-related analysis of the response to the cue presentation in the same fatigue (session) contrast, which highlighted significant changes between conditions (see left image in Fig. 3 and Supplementary Table S5). We found that the FFG (Brodmann area 37 or fusiform gyrus) and the visual areas (Brodmann areas: 18, 19) were hypoactivated with cognitively induced fatigue. These same regions, part of the ventral processing stream, associated with form/object recognition, were highly active during the task (peak activity level t-values for event-related task condition: BA18: 10.83; BA19: 10.63; BA37: 10.72; see Fig. 4B and Supplementary Table S4).

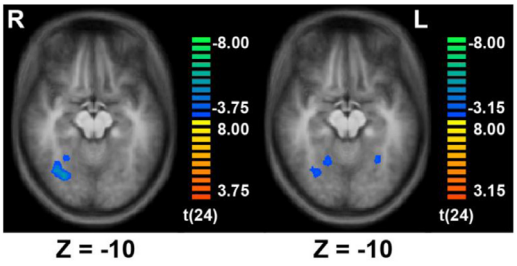

Fig. 3. Contrast between control and fatigue sessions ($\Delta BOLD_{SESSION}$). Cue-related (left) and block-based (right) session contrast ([(HIGH FATIGUE + LOW FATIGUE) – (HIGH CONTROL + LOW CONTROL)]). Event-related map is thresholded at voxel-$p < 0.001$, uncorrected and $p < 0.05$, cluster-level corrected. Block-based map was computed with more liberal threshold ($p < 0.005$). In both maps, ventral visual processing stream / FFG activity is decreased in fatigue compared to control condition. Unthresholded data is available from NeuroVault at https://identifiers.org/neurovault.image:512326 (cue-related) and https://identifiers.org/neurovault.image:512327 (block design).

In order to confirm the results of the cue-related analysis we revisited the block-based analysis under a more liberal threshold (voxel-$p < 0.005$), finding the same fatigue-induced hypoactivity of the ventral visual stream (see right image in Fig. 3).

These findings suggest that regions most affected by cognitively induced fatigue are amongst those most active during the task and also during the fatigue-inducing STROOP task (Neurosynth.org meta-analysis for "stroop task", including 139 published datasets).

3.2.2. Reward modulation of brain activity: task-and reward-related regions

We compared brain activations in high and low reward conditions in the block design ([(HIGH FATIGUE + HIGH CONTROL) – (LOW FATIGUE + LOW CONTROL)], $\Delta BOLD_{REWARD}$, random-effects group GLM analysis, voxel-$p < 0.001$, uncorrected; cluster-level corrected < 0.05). This analysis demonstrated brain activity changes in motor cortex, ventral visual processing stream, precuneus, basal ganglia and thalamus but showed no effect in other components of the classical reward circuit [see Fig. 4A and Supplementary Table S1].

We also performed an event-related analysis of the BOLD response to the presentation of the reward cue ([(HIGH FATIGUE + HIGH CONTROL) – (LOW FATIGUE + LOW CONTROL)], random-effects group GLM analysis, voxel-$p < 0.001$, uncorrected; cluster-level corrected < 0.05). Similarly to the block-based analysis, this analysis revealed an ample pattern of modulations of brain activity including motor cortex, visual areas along the ventral visual processing stream including Brodmann areas BA17, BA18 and BA19 and fusiform gyrus (FFG), and also precuneus, basal ganglia and thalamus. Importantly the event-related approach revealed also the involvement of the main regions of the reward circuit, in particular ACC, anterior insula, caudate, putament and nAc (see Supplementary Table S2).

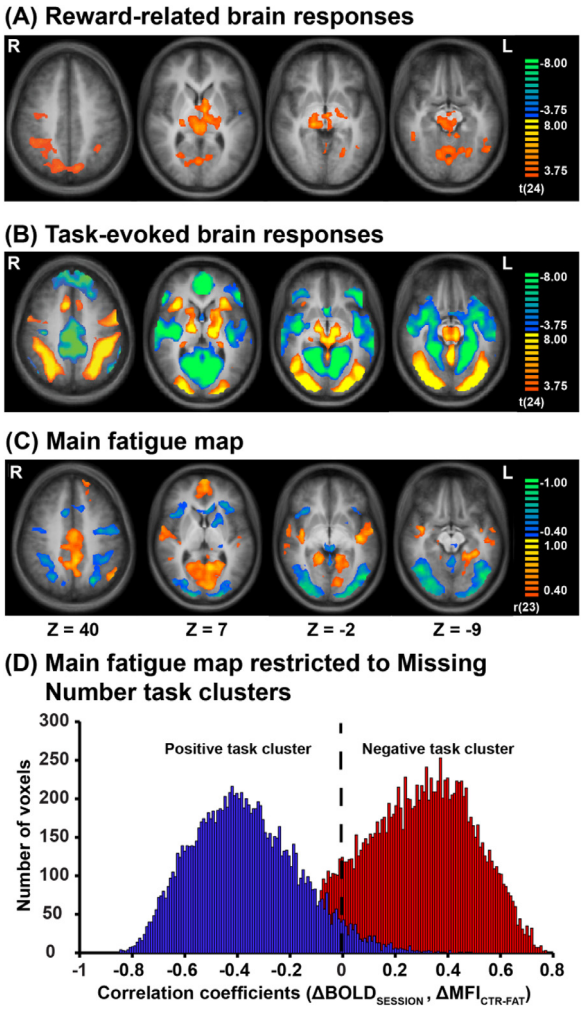

Fig. 4. The effect of the reward and fatigue manipulations on brain responses (**A**) Block-based reward contrast ([(HIGH FATIGUE + HIGH CONTROL) – (LOW FATIGUE + LOW CONTROL)], $\Delta BOLD_{REWARD}$). Z coordinates are in Talairach space. (**B**) Task execution evoked positive BOLD responses ([(HIGH FATIGUE + LOW FATIGUE) + (HIGH CONTROL + LOW CONTROL)] - rest, $\Delta BOLD_{TASK}$) in motor and visual areas (Brodmann areas: 17, 18, 19), ACC, FFG, thalamus and dorsal striatum while task-evoked signal decrease was observed mostly in the default mode network (DMN). (**C**) Correlation maps between the participants' subjective feeling of fatigue ($\Delta MFI_{CTR-FAT}$) and the averaged session-related changes in BOLD responses ([(HIGH FATIGUE + LOW FATIGUE) - (HIGH CONTROL + LOW CONTROL)], $\Delta BOLD_{SESSION}$). (**D**) Negative and positive correlations were found between the participants' subjective feeling of fatigue and their brain responses in the positive and negative Missing Number task clusters, respectively. Unthresholded data is available from NeuroVault at https://identifiers.org/neurovault.image:512325 (reward contrast), at https://identifiers.org/neurovault.image:512329 (task contrast) and https://identifiers.org/neurovault.image:512332 (main fatigue map).

3.2.3. Reward-fatigue interaction

The reward-fatigue interaction contrast ([(HIGH FATIGUE – LOW FATIGUE) – (HIGH CONTROL – LOW CONTROL)], $\Delta BOLD_{INTERACTION}$) resulted in no significant effect in either event-related or block-based GLM designs at threshold voxel-$p < 0.001$, uncorrected; cluster-level corrected $p < 0.05$.

3.2.4. Task modulation of brain activity

In both the block-based and cue-related designs, task execution evoked positive BOLD responses ([(HIGH FATIGUE + LOW FATIGUE) + (HIGH CONTROL + LOW CONTROL)] - rest, $\Delta BOLD_{TASK}$, random-effects group GLM analysis, voxel-$p < 0.001$, uncorrected; cluster-level corrected < 0.05) in motor and visual areas (Brodmann areas: 17, 18, 19, 20), FFG, intraparietal sulcus and frontal eye fields, cingulate cortex, anterior insula, thalamus and dorsal striatum (see Fig. 4B and Supplementary Table S4) while task-evoked signal decrease was observed mostly in areas related to the default mode network (DMN; see Fig. 4B and Supplementary Tables S3 and S4 for comparison).

We further reproduced all the analyses above using the original raw data in order to control for the influence of the motion correction procedure (see Panels A & B in Supplementary Fig. 3). These motion uncorrected analyses led to results highly consistent with those obtained with motion corrected data (see Figs. 4A and 4B for comparison).

3.2.5. The neural correlates of subjective increased fatigue, intrinsic motivation and anxiety state

The effect of cognitively induced fatigue on the brain was further evaluated by correlating the behavioral fatigue indices ($MissingNumber_{CTR-FAT,}$ $Stroop_{FAT}$, $\Delta MFI_{CTR-FAT}$) with the between-session difference in brain activity ([(HIGH FATIGUE + LOW FATIGUE) – (HIGH CONTROL + LOW CONTROL)], $\Delta BOLD_{SESSION,}$). In addition, we also performed similar correlations with the stress and motivation indices ($STAI_{FAT-CTR}$ and $IMI\text{-}MissingNumber_{FAT-CTR}$).

In the block-based analysis, we found that across the brain, changes in the task-positive and task-negative regions (see Fig. 4B and Supplementary Table S3) correlated negatively and positively with the change in MFI score respectively (see Panels C & D in Fig. 4 and Supplementary Table S6). This correlation map will be hereafter referred to as the main fatigue map. When averaging the BOLD responses within the whole task-positive cluster, we found that the between-session change in activation in this cluster correlated strongly with the change in the subjective fatigue score (Spearman correlation with $\Delta MFI_{CTR-FAT}$: r = -0.70, p = 0.00011; see Fig. 5A), while it failed to correlate with any of the other measures ($SStroop_{FAT}$: $r = 0.31$, $p = 0.1266$; $MissingNumber_{CTR-FAT}$: $r = -0.18$, $p = 0.4024$; $STAI_{FAT-CTR}$: $r = -0.1112$, $p = 0.5968$; $IMI\text{-}MissingNumber_{FAT-CTR}$: $r = -0.052$, $p = 0.8066$; see Fig. 5A). Likewise, the average between-session decrease of BOLD responses in the task-negative network also correlated, albeit positively, with $\Delta MFI_{CTR-FAT}$ (Spearman correlation: $r = 0.54$, $p = 0.0055$; see Fig. 5B), while it also failed to show any correlation with the other indices ($STAI_{FAT-CTR}$: $r = 0.28$, $p = 0.1786$; $IMI\text{-}MissingNumber_{FAT-CTR}$: $r = -0.22$, $p = 0.2896$; see Fig. 5B) even though some correlations approached significance ($Stroop_{FAT}$: $r = -0.39$, $p = 0.0529$; $MissingNumber_{CTR-FAT}$: $r = 0.39$, $p = 0.0530$). In other words, subjective fatigue induced a global decrease in task-related activations/deactivations throughout the brain. Similar results were obtained with the event-related design for the same contrast, which also varied in proportion to the MFI score (Spearman correlation for task-positive cluster and $\Delta MFI_{CTR-FAT}$: $r = -0.4758$, $p = 0.0162$; all other correlations: $p > 0.1$, see Panel *C* in Fig. 5 and Supplementary Table S7; Spearman correlation for task-negative cluster: $\Delta MFI_{CTR-FAT}$: $r = 0.4411$, $p = 0.0273$; $STAI_{FAT-CTR}$: $r = 0.4956$, $p = 0.0118$, all other Spearman correlations: $p > 0.1$., see Panel *D* in Fig. 5). To summarize, while we found no relationship between fatigue-versus-control task-related brain activity and motivation or anxiety, increased subjective fatigue correlates with decreased average activity of the task-positive cluster and a parallel activity increase of the task-negative cluster.

3.2.6. No evidence for a causal link between MF and motivation

We then investigated the topographical relation between the reward-related brain activations ($\Delta BOLD_{REWARD}$, t-values, see Fig. 4A) and the main fatigue map (correlation between $\Delta BOLD_{TASK}$ and $\Delta MFI_{CTR-FAT}$, see Fig. 4C). The proportion of overlap between the maps was compared, at different thresholds, with the one expected by chance (see Methods). We found that the reward contrast maps failed to show significant overlap with the main fatigue map, whereas we observed a strong overlap between the main fatigue and the task-related maps. This was true both for task-positive and task-negative regions and with both block-related

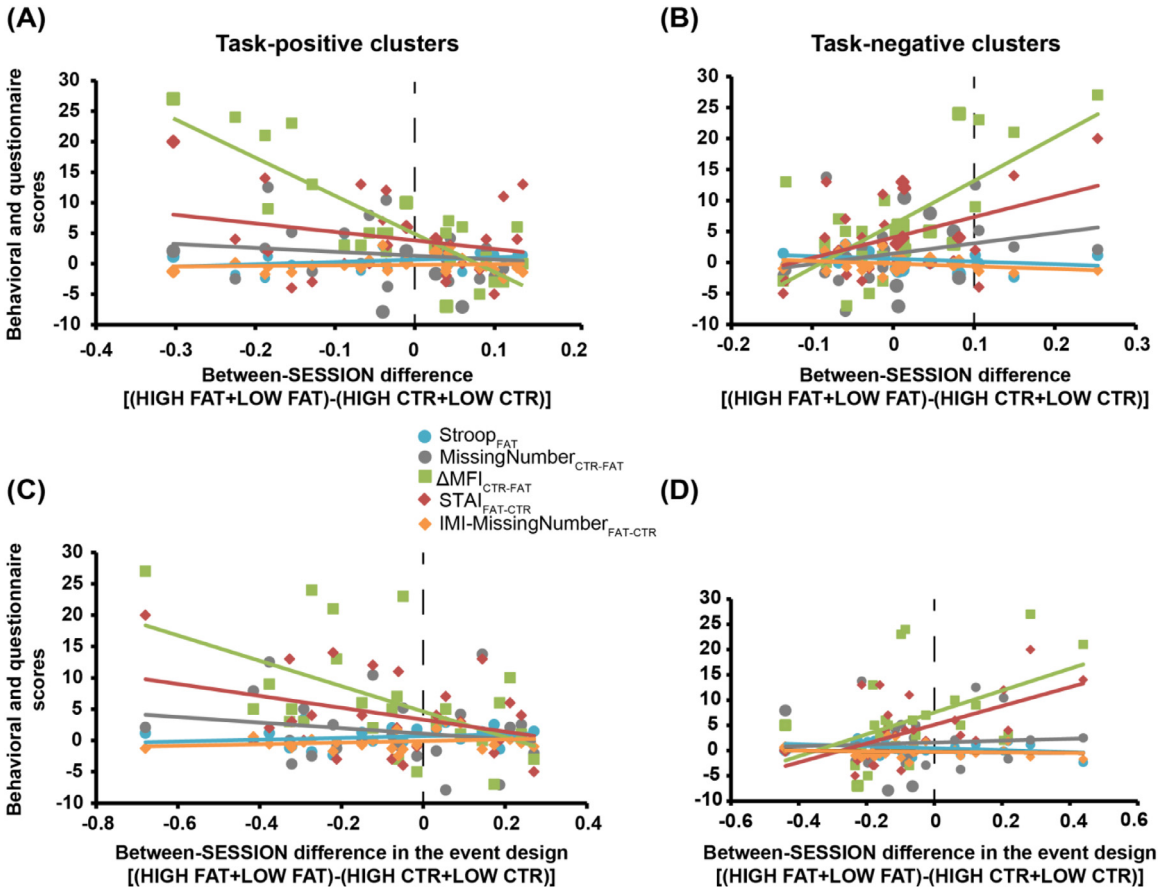

Fig. 5. Modulation of brain responses by subjective MF.
CTR: CONTROL condition; FAT: FATIGUE condition. **(A-B)** Block-based analysis: In the positive/negative Missing Number task clusters, the average between-session change in activation/deactivation was correlated with the change in the subjective feeling of fatigue ($\Delta MFI_{CTR\text{-}FAT}$). **(C,D)** Event-based analysis: In the positive/negative Missing Number task clusters, the average between-session change in activation/deactivation was also correlated with the change in the subjective feeling of fatigue ($\Delta MFI_{CTR\text{-}FAT}$).

(see Panels A–D in Fig. 6) and cue-related designs (see Panels E–H in Fig. 6). We then looked at the voxel-by-voxel correlations between these maps (reward-related responses vs fatigue map, task-related responses vs fatigue map, in both designs, and for task-positive and task-negative regions). The fatigue map failed to show any significant correlation with the reward contrast map obtained from the block-based analysis (positive task regions: bootstrap significance test: $p = 0.4096$, negative task regions: $p = 0.2707$) but a strong correlation with the task-related map (globally: $p < 0.0001$; positive task regions only: $p < 0.0001$, negative task regions only: $p < 0.0001$; see Panels *A* & *B* in Fig. 9). We also found similar results when looking at the cue-related reward contrast (all $p > 0.1$; see Panels *C* & *D* in Fig. 7).

3.2.7. Between-session brain activity differences in resting state and relationship to subjective increased fatigue

Finally, in the resting-state data, we found that the between-session change in connectivity correlated with $\Delta MFI_{CTR\text{-}FAT}$, especially in the DMN (see Fig. 8 and Supplementary Table S8), such that connectivity increased between the seed regions of the DMN proportionally to the level of subjective fatigue. Increased inter-connectivity between brain regions include dorso-lateral frontal cortex, anterior and posterior cingulate cortices, posterior temporal and lateral parietal cortices (Supplementary Table S8). This finding is of particular interest in the light of the aforementioned increased activity of the task-negative regions, including the components of the DMN, with increased subjective fatigue (see Figs. 4B–C and 5, panels *B* and *D*). Thus, the components of the DMN, whose activity pattern is anti-correlated to the task, show a fatigue-related increase of activity during the task coupled with increased resting state connectivity.

4. Discussion

In the present study, we investigated the relationship between the neural underpinnings of MF and motivation to find out whether the buildup of MF involves a disruption of the motivational circuits. To this end, we assessed the neural effects of induced MF on BOLD brain signal during the execution of a challenging visual working memory task wherein participants' extrinsic motivation was manipulated by different levels of monetary reward. We further accounted for behavioral and cognitive changes including cognitively induced mental fatigue, extrinsic and intrinsic motivation, and anxiety.

From a behavioral point of view, if MF had been caused by an alteration of motivational processes, high reward conditions should have restored at least partly the worsened performance caused by cognitively induced fatigue (Boksem et al., 2006; Lorist et al., 2009; Hopstaken et al., 2014, 2015, 2016) and a significant reward-session interaction should have been observed. However, in agreement with earlier findings (Esterman et al., 2014) as well as our own previous study (Gergelyfi et al., 2015), we found no evidence for a reward-session interaction in either the Missing Number or the Simple Reaction Time task. In addition, it is also important to note that the participants' intrinsic motivation in the Missing Number task, assessed with the IMI questionnaire, remained unchanged between sessions and failed to show any correla-

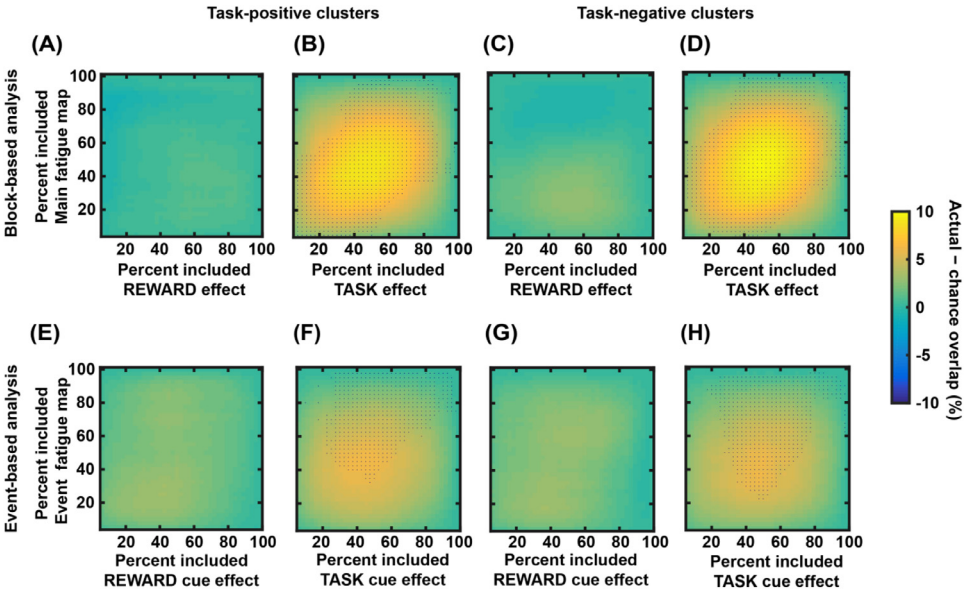

Fig. 6. Lack of overlap between reward and main fatigue map in the block- and event-based analysis

(**A–D**): **Block-based analysis: (A)** Degree of overlap between the **main fatigue map and the reward effect** on the brain in the task-positive clusters, as a function of the threshold used in both maps. The *X*-axis represents the percent voxels included from the reward-related brain activations, whereas the *Y*-axis illustrates the percent voxels included from the main fatigue map. The percentage of overlap is indexed by the difference with respect to what would be expected by chance and is illustrated by the color in the heatmap. The dots indicate significant overlap. **(B)** Overlap between the **main fatigue map and the task effect** on the brain in the positive Missing Number task clusters. Same convention is used as in Panel A. **(C-D)** Overlap between the **main fatigue map and the reward effect (C)** or the **task-evoked responses (D)** in the negative Missing Number task clusters. **(E–H): Cue-based analysis: (E,F)** Overlap between the **cue-related fatigue map and the reward cue effect (E)** or task cue responses **(F)** in the positive Missing Number task clusters. Same convention as in Panel A. **(G,H)** Overlap between the **cue-related fatigue map and the reward cue effect (G)** or **the task cue effect (H)** in the negative Missing Number task clusters.

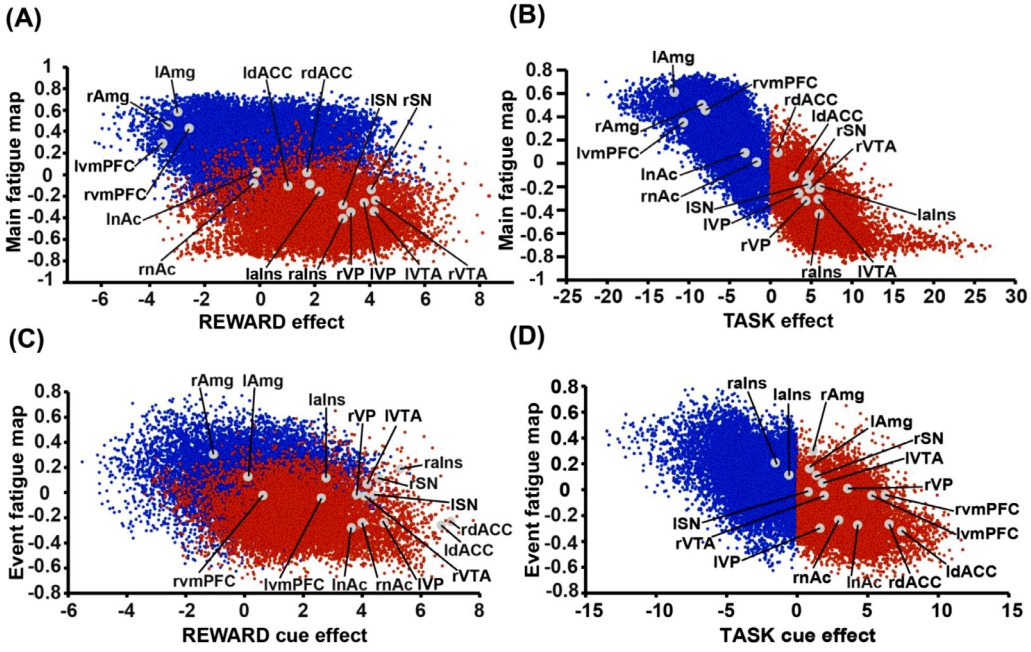

Fig. 7. Lack of correlation between reward and fatigue effects across voxels.

(**A,B**): **Block-based analysis: (A)** Voxel-by-voxel correlations between the main fatigue map (correlation coefficients are plotted on the y-axis) and the reward-related responses (t-values are plotted on the x-axis) in the positive (in red) and the negative (in blue) Missing Number task clusters. The classical reward-motivational ROIs are shown as gray circles. **(B)** Voxel-by-voxel correlation between the main fatigue map and the task-related responses (t-values on the x-axis). **(C,D) Cue-related analysis: (C,D)** Voxel-by-voxel correlations between the fatigue map (correlation coefficients are plotted on the y-axis) and the reward-related responses (*t*-values are plotted on the *x*-axis) on the one hand **(C)** and between the fatigue map and the task-related responses on the other hand **(D)** in the positive and the negative Missing Number task clusters (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

tion with the other behavioral and neural markers, further confirming that motivation and fatigue were independent.

The motivation hypothesis led to another important prediction: behavioral fatigue should relate to concurrent alterations of the brain motivation circuit. We highlighted this circuit through analysis of the reward effect on brain activity. In agreement with the literature (Knutson and Cooper, 2005), we found that the even-related design was more sensitive than the block design and brought out more of the classical structures of the motivation network. Crucially, and in agreement with the behavioral data, we found no effect of reward-session interaction, thus, no activity changes in reward-modulated regions between fatigue and control sessions. Along the same line, the topographical analysis showed that none of the fatigue maps computed in this study overlapped or correlated with the corresponding reward contrast maps. These findings, together

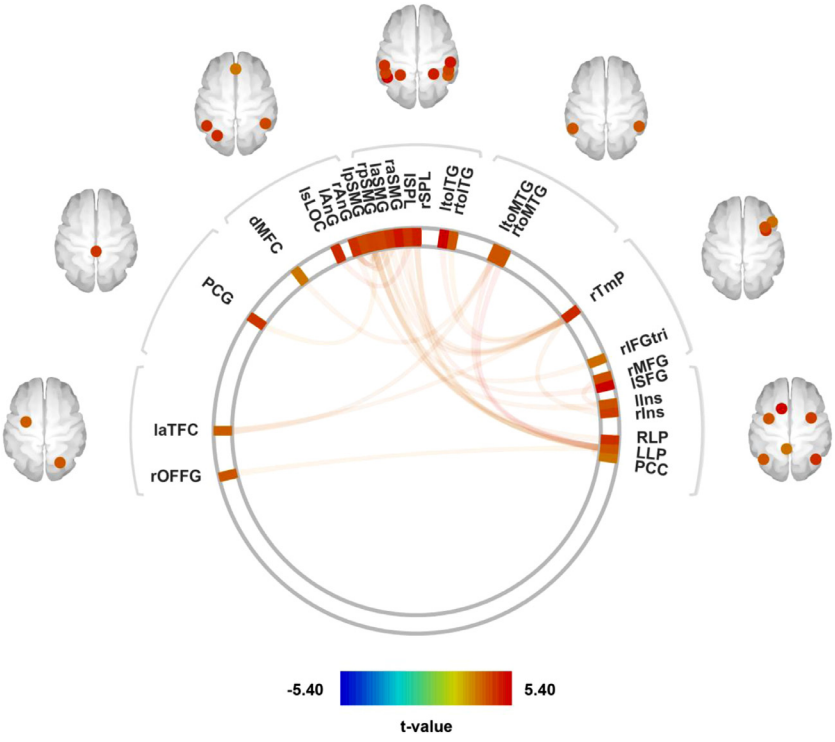

Fig. 8. MF globally increased the connectivity within the DMN.
Regions that survived seed-wise multiple comparison correction at qFDR < 0.05 are shown on the circular diagram and on the MNI atlas. Color-coded connections represent the between-session change in the functional connectivity that covaried with the between-session change in the subjective fatigue score ($\Delta MFI_{CTR\text{-}FAT}$).

with the lack of reward-fatigue interaction, challenges theoretical models proposing that the impact of cognitively induced fatigue on behavior is mediated by the motivation circuit (Hockey, 1997; Meijman and Mulder, 1998; Chaudhuri and Behan, 2000; Boksem and Tops, 2008; Hockey,2011; Westbrook and Braver, 2016; Kurzban et al., 2013). It is important to stress, however, that our findings do not directly contradict the existence of motivation-related fatigue effects. Previous reports have highlighted the importance of motivation in sustaining activation of task-related networks (Esterman et al., 2017) and it could be hypothesized that fatigue leads to task disengagement through mechanisms that are independent from the brain regions associated with reward-related motivational control. Alternatively, alterations in the motivation circuit could take the form of baseline, tonic variations in brain activity, which would not appear in our analysis since it focuses instead on task-induced changes. Therefore, we interpret our findings as showing more specifically that the inducement of fatigue by prolonged performance of a cognitive task is not accompanied by significant alterations in the task-induced activity of brain regions classically involved with motivation.

In contrast, our results show a significant reduction of activity in the brain areas belonging to the specific network supporting task performance routines, in particular along the ventral visual processing stream. This is in agreement with previous studies that reported decreased activations with time-on-task (Coull et al., 1998; Lim et al., 2010; Breckel et al., 2011) or following execution of a fatigue-inducing procedure (Hedgcock et al., 2012; Persson et al., 2013; Blain et al., 2016; Tanaka et al., 2006; Suda et al., 2009) in task-specific brain regions. These findings, together with the ones reported in the present study, could be interpreted as evidence in favor of the hypothesis that sustained task performance leads to progressive functional alteration of task-related brain regions (Christie and Schrater, 2015; Holroyd, 2015; Hopstaken et al., 2015; Blain et al., 2016; Gergelyfi et al., 2015; Cook et al., 2007). Indeed, the fact that both the fatigue-inducing task (Stroop) and the Missing Number task relied on active visual discrimination leads us to speculate that the depression of task-specific regions during the latter could have been induced by their prolonged recruitment during the former (Cook et al., 2007). However, short of controlling the overlap between activations during fatigue-inducing and test tasks, neither previous reports nor the present study can determine whether the level of engagement of the brain regions during the fatigue-inducing procedure determines the level of their disruption during the test task. Testing this hypothesis is an important topic for future research.

In addition to altering activations in task-related regions, cognitively induced fatigue also leads to long-lasting disruption of resting brain activity. Observations of the persistent effects of cognitive fatigue after sustained visual attention have been described in the form of down-regulation of the fronto-parietal network (Lim et al., 2010; Esposito et al., 2014), early visual cortex (Esposito et al., 2014) and as up-regulation of the default mode network (Esposito et al., 2014). The present findings highlighted the existence of a similar correlation between subjective fatigue and increased activity in the DMN, which occurred both during and following task execution. These findings suggest a balancing act between DMN and task-specific regions whereby decreasing activity in the latter would lead to increased activation of the former. The relation of causality of this increased DMN activity on the phenomenology of fatigue remains to be investigated.

We report both subjective and objective consequences following cognitively induced fatigue: participants experienced a higher feeling of fatigue, and performed worse in the Missing Number task. The performance drop induced by fatigue was relatively small, which could be partly explained by the intervening period between the end of the Stroop and the beginning of the scan session. Thus, despite the fact that all participants were kept equally busy during this interval, we cannot discard that these delays could mask to a certain extent the fatigue-induced effect and constitute a potential limitation in our study design.

As in many other published studies (Krupp and Elkins, 2000; Bryant et al., 2004), the subjective and objective dimensions of MF did not correlate with each other, nor did the brain activity change show any relation to task performance. A classical explanation to this lack of correlation is the *compensatory hypothesis*, whose central tenet is that the initial maintenance of performance with time-on-task incurs a cost derived from the recruitment of additional resources (aka, compensatory brain activity), which is manifested phenomenologically as the subjective feeling of fatigue (Hockey, 1997). Therefore, when performance eventually starts to drop, subjective MF is already high. Previous stud-

ies have reported increased frontal EEG activity that could correspond to the brain signature of such compensatory mechanism (Wang et al., 2016). Here, we found no evidence for such compensatory brain activity (*i.e.* increased activation in task-relevant brain regions), though the present study was not primarily designed to tackle this question. Instead, in relation to the increase of fatigue, we found only reductions of activity level in task-related regions and increased activations in brain regions that were anti-correlated with the task. Higher relative levels of activity of the DMN during a task have been previously related to decreased performance (Anticevic et al., 2012 for a review) and thus could not easily account for a compensatory effect.

In conclusion, the present study shows that MF does not disrupt the motivational circuit specifically but that it rather modulates brain activity by (a) reducing the activity task-related brain areas, and (b) increasing the default mode network activity both during and following the task. In agreement with our previous study (Gergelyfi et al., 2015), these new findings support the view that MF alters brain resources, or impairs their recruitment, through mechanisms independent of the motivation circuit in healthy participants.

Declaration of Competing Interest

The authors declare no competing financial interests.

Credit authorship contribution statement

Mónika Gergelyfi: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. **Ernesto J. Sanz-Arigita:** Writing – review & editing. **Oleg Solopchuk:** Data curation, Formal analysis, Visualization. **Laurence Dricot:** Formal analysis, Methodology, Validation, Visualization. **Benvenuto Jacob:** Software. **Alexandre Zénon:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – review & editing.

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Data and code availability statement

Unthresholded images are available on the Neurovault public repository (https://neurovault.org/collections/10479/).

All remaining data as well as the Matlab code used in this work are not documented in their present form but can nevertheless be made freely available upon request. Please write an email to alexandre.zenon@u-bordeaux.fr.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2021.118532.

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