Neural fatigue by passive induction

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Abstract:
Theories of mental fatigue disagree on whether performance decrement is caused by motivational or functional alterations. We tested the assumption that keeping neural networks active for an extensive period of time entrains consequences at the subjective, objective and neurophysiological level – the defining characteristics of fatigue – when confounds such as motivation, boredom and level of skill are controlled. We reveal that passive visual stimulation affects visual gamma activity and the performance of a subsequent task when carried out in the same portion of visual space. This outcome was influenced by participants' level of arousal, manipulated through variations in the difficulty of concurrent auditory tasks. Thus, repeated stimulation of neural networks leads to their altered functional performance and this mechanism seems to play a role in the development of mental fatigue.

Introduction

Prolonged mental activity leads to a sensation of discomfort with well-known adverse consequences on overall quality of life (Åkerstedt et al., 2007; Raslear et al., 2011), productivity (Ricci et al., 2007), emotional regulation (Grillon et al., 2015), workplace accidents (Goode, 2003; Swaen et al., 2003), comorbidity with medical conditions such as insomnia (Fortier-Brochu et al., 2010), Parkinson's disease (Havlikova et al., 2008) and multiple sclerosis (Pittion-Vouyovitch et al., 2006), all regrouped under the umbrella term of Mental Fatigue (MF). MF manifests itself in two empirically measurable components: the *subjective* feeling of tiredness and the *objective* decrease in performance (DeLuca, 2007). To this day, the neural origin of MF remains elusive, and this lack of understanding stems in part from MF's dependence on the duration and difficulty of the task (Hockey, 2013), as well as on the motivation (Boksem et al., 2006), level of fatiguability and skills of the agent performing it (Borragán et al., 2017).

Theories of mental fatigue generally concur on its role in disengaging individuals from cognitive tasks to seek rest. Yet, the underlying cause of this need to withdraw from effortful tasks continues to be debated by two schools of thought. Functional theories assume that fatigue arises as a consequence of alterations in the neural circuitry (e.g. depletion of finite resources or accumulation of metabolites), or as an outcome of mechanisms that prevent such alterations (Dongen et al., 2011; Schellekens et al., 2000; Zénon et al., 2019). Despite their intuitive appeal, these accounts have suffered from a lack of evidence (Hockey, 2013). In response, motivational theories view fatigue as a cognitive strategy, responsible for the reallocation of effort when the cost-benefit ratio of ongoing behaviour is disadvantageous (Boksem & Tops, 2008; Hopstaken et al., 2015; Kurzban et al., 2013). However, this motivational view of fatigue has also been challenged (Benoit et al., 2019; Gergelyfi et al., 2015).

From a neuroscientific perspective, the fact that fatigue may arise from any type of task complicates the process of pinpointing it to specific brain areas (Harrington, 2012), due to the risk of conflating fatigue-specific effects with unrelated activity across brain regions. We reasoned that rigorous exploration of fatigue should first contemplate its functioning at the lowest degrees of complexity, to rule out as many confounds as possible. A prediction of the functional paradigm is that repeated stimulation of specific neural networks should lead to their altered performance over time.
We coin as *neural fatigue* this putative specific functional deterioration, which we tested by drawing inspiration from a line of research on sleep that found a decrease in performance due to repetitions of a visual task, the texture discrimination task (TDT), where participants are required to identify the orientation of briefly presented peripheral targets (Mednick et al., 2002). Remarkably, in this study, participants' performance was restored when perceptual characteristics of the targets (orientation and location) were changed, but not when they were offered money to manipulate motivation. Additionally, a follow-up neuroimaging study found this perceptual deterioration to correlate with functional changes in the visual cortex (Mednick et al., 2008).
More recent work has found performance in this task to correlate with measures of local resource depletion (Jubera-Garcia et al., 2020). Here, we sought to determine if prolonged passive stimulation with flashing stimuli (hereon referred to as saturation) of specific portions of the visual field (referred to as quadrant) could induce a degradation in the performance of the TDT, measured at different timepoints of the experimental procedure, namely BASELINE, MIDDLE and CONCLUSION (see Figure 1).

Given gain theories of arousal (Aston-Jones & Cohen, 2005; Mather et al., 2016), we predicted that being engaged in concomitant auditory tasks of varying difficulty (EASY or HARD) during saturation would modulate its impact on behaviour. Three tasks were employed with distinct demands (the n-back task, a pitch-sequence task and the side task; see methods), and participants were randomly assigned to perform either the EASY or the HARD version of these tasks during their saturation sessions.

Our initial hypothesis was to expect a stronger effect in agents performing tasks with harder demands, given the stimulating effects of arousal on cortical activity (Jones, 2003; Mather et al., 2016). Diverging levels of arousal between difficulty conditions were assessed through pupillometry, a well-established marker for this construct (McGinley et al., 2015; Wang et al., 2018).

Furthermore, electroencephalography (EEG) was used to record cerebral activity to assess neurophysiological alterations induced by the experimental procedure. Since we were expecting to disrupt low-level bottom-up visual processing, we focused on the steady-state response at stimulation frequency (~7.5 hertz), and the visual gamma spectrum (60-80 hertz; (Michalareas et al., 2016)). Lastly, we investigated the relationship between the consequences of saturation on behaviour and on the subjective evaluation of fatigue and sleepiness, as assessed by the Multidimensional Fatigue Inventory (Gentile et al., 2003) and the Karolinska Sleepiness Scale (Shahid et al., 2011).

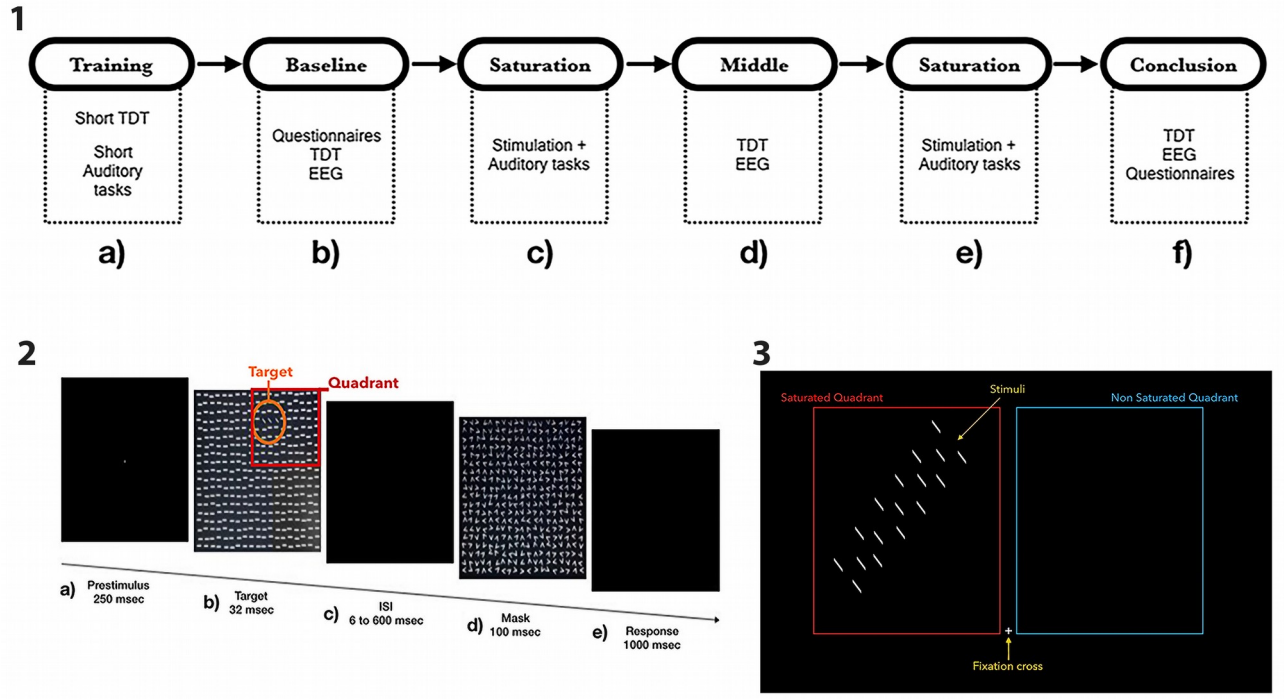

Figure 1: : Panel 1: Flowchart of the experimental design. Panel 2: Visual representation of the Texture Discrimination Task (TDT). Please note that across the whole trial a fixation cross stayed in the centre in order to help participants maintain their gaze fixated. Panel 3: Visual representation of saturation and EEG sessions. While fixating the centre a participant would be presented with stimuli identical to the targets of the TDT, appearing in all possible target locations within a quadrant at 7.5 Hz. During EEG sessions the quadrants alternated, while during saturation sessions the stimuli flashed in a single quadrant (the saturated quadrant), and participants were engaged in concurrent auditory tasks, the difficulty of which depended upon their experimental group

Results

Behaviour

We ran a Generalized Linear Mixed Model (GLMM) on response accuracy in the TDT task (see Figure 2), with Session (BASELINE, MIDDLE and CONCLUSION), Inter-stimulus interval (ISI), Saturation (SATURATED or NON-SATURATED) and the Difficulty of the auditory tasks performed during saturation (EASY or HARD) as independent variables. In the TDT task, the ISI between stimulus and mask determines the difficulty of the task and was varied adaptively to optimize inference of participants' ability (see Methods). We found the quadruple effect of ISI, Saturation, Difficulty and Session to be strongly significant ($X^2_{(2, 46080)} = 21.96$, $p < 0.0001$; together with Session: $X^2_{(2, 46080)} = 28.18$, $p < 0.0001$; ISI: $X^2_{(1, 46080)} = 95.56$, $p < 0.0001$; ISI and Session interaction: $X^2_{(2, 46080)} = 29.43$, $p < 0.0001$; Saturation, Difficulty and Session interaction: $X^2_{(2, 46080)} = 12.68$, $p = 0.002$; ISI, Difficulty and Session interaction: $X^2_{(2, 46080)} = 51.89$, $p < 0.0001$; and ISI, Saturation and Session interaction: $X^2_{(2,46080)} = 6.88$, $p = 0.032$).

In order to investigate this four-way interaction, we performed separate GLMMs for the two difficulty groups and for the first and second half of the experiment, applying Holm-Bonferroni correction for multiple comparisons. For the EASY group, in the SATURATED quadrant, performance largely improved between BASELINE and MIDDLE sessions ($Z = 3.67$, $p_{corrected} = 0.001$, $\exp(\beta) = 18.5$) and fairly decreased between MIDDLE and CONCLUSION sessions ($Z = -2.47$, $p_{corrected} = 0.039$, $\exp(\beta) = 6.9$). However, there wasn't a significant change between BASELINE and CONCLUSION ($Z = 1.06$, $p_{corrected} = 0.287$).

On the other hand, the HARD group displayed a major loss of performance in the SATURATED quadrant, between BASELINE and MIDDLE sessions ($Z = -4.168$, $p_{corrected} = 0.0002$, $\exp(\beta) = 24.4$) and BASELINE and CONCLUSION ($Z = -3.93$, $p_{corrected} = 0.0004$, $\exp(\beta) = 15.3$), but not between MIDDLE and CONCLUSION ($Z = 1.13$, $p_{corrected} = 0.518$), as between these sessions their performance decreased also in the NON-SATURATED quadrant.

To further confirm this finding, we explored its session-wise evolution. The absence of a significant interaction between ISI and Saturation in the BASELINE session was confirmed, for the EASY group ($X^2_{(1, 7680)} = 0.99$, $p = 0.32$), and the HARD group ($X^2_{(1, 7680)} = 3.3$, $p = 0.07$). In the MIDDLE session, this interaction became significant for both EASY ($X^2_{(1, 7680)} = 4.95$, $p = 0.026$) and HARD groups ($X^2_{(1, 7680)} = 4.63$, $p = 0.031$) and similarly so in the CONCLUSION session, for EASY ($X^2_{(1, 7680)} = 4.87$, $p = 0.027$), and HARD ($X^2_{(1, 7680)} = 6.19$, $p = 0.013$).

Thus, repeated visual stimulation led to drop of performance in the SATURATED quadrant when participants were engaged in HARD concurrent auditory tasks, particularly in the first half of the experiment. In contrast, participants performing the EASY version of the auditory tasks initially exhibited an improvement in performance, which disappeared following the second saturation session.

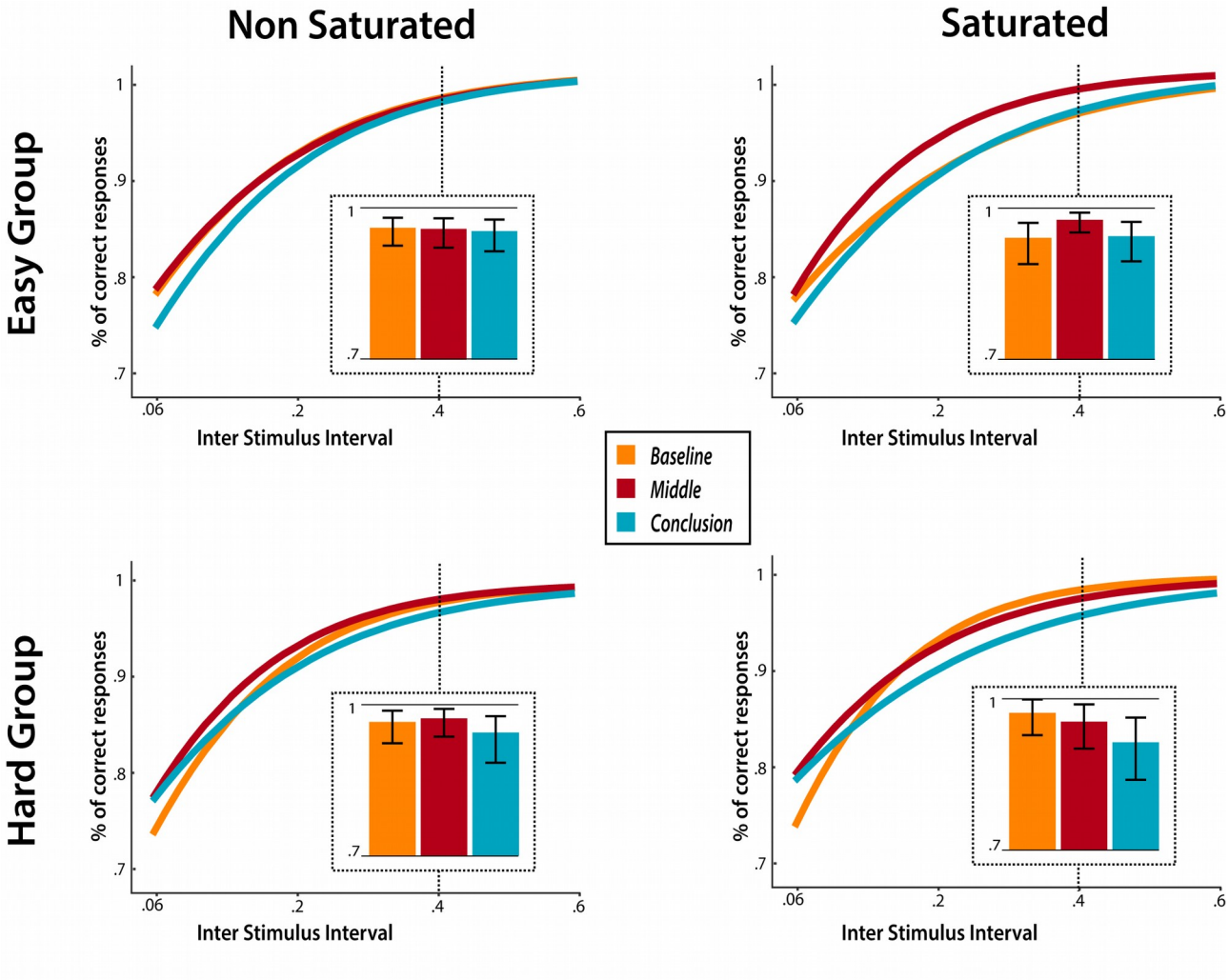

Figure 2: Percent correct responses (y axis), predicted by the GLMM for ISI values ranging from 0.06 to 0.6 (x axis) as a function of saturation condition (left and right columns) and experimental group (top and bottom rows). Error bars depict 95% confidence intervals. Insets: detailed representation for ISI = 400ms.

Electrophysiology

We analysed electrophysiological activity by means of cluster-based permutation methods (Maris & Oostenveld, 2007). We first compared EEG signal between blocks with stimulation of left and right portion of the visual field in the BASELINE session for both frequency ranges (stimulation frequency: 7.5 hertz; and visual gamma range: from 60 to 80 hertz) and across groups (EASY, HARD). No clusters were found in either range. We concluded that the side of stimulation did not induce significant differences and grouped left and right stimulation blocks for further analyses.

In order to mitigate the issue of multiple comparisons, subsequent group-specific tests were carried out on the basis of the behavioural results. Specifically, contrasts were performed for the EASY group between BASELINE and MIDDLE sessions and between MIDDLE and CONCLUSION sessions, whereas for the HARD group, comparisons were performed between BASELINE and MIDDLE and BASELINE and CONCLUSION.

For the EASY group, the tests at stimulation frequency revealed no significant clusters ($p > 0.05$). In the gamma range, a negative significant cluster was found in the comparison between BASELINE and MIDDLE ($T_{(23)} = -47.29$, $p = 0.006$, $d = 0.86$; see Figure 3, left panel), but not between MIDDLE and CONCLUSION ($p > 0.05$). Therefore, EEG response to stimulation in the SATURATED quadrant increased with respect to the NON-SATURATED one in the first half of the experiment.

For the HARD group, the tests at stimulation frequency revealed no significant clusters.

In the gamma range, a positive significant cluster was found in the comparison between BASELINE and CONCLUSION ($T_{(23)} = 12.61$, $p = 0.036$, $d = 0.62$; see Figure 3, right panel), indicating a significant decrease in the brain response to stimulation in the SATURATED quadrant, with respect to the NON-SATURATED quadrant. No clusters were found for the comparison between BASELINE and MIDDLE.

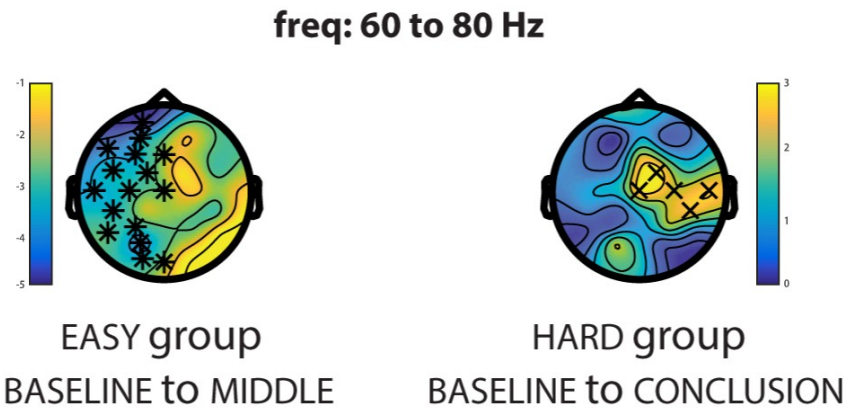

Figure 3: graphical depiction of the clusters displaying significant differences in activity between saturated and non saturated conditions, for the easy group (left) between baseline and middle session, and for the hard group (right) between baseline and conclusion sessions

Pupillometry

The analysis on the average pupil size recorded while participants were engaged in auditory tasks revealed that those assigned to the hard condition had significantly larger pupil size both in the *side* ($Z = 2.11$, $p = 0.0346$, $r = 0.3$) and *n-back* task ($Z = 2.94$, $p = 0.0033$, $r = 0.42$), while no significant group level difference was found for the *pitch-sequence* task ($Z = -0.67$, $p = 0.5$).

Self-reported measures of fatigue and sleepiness

The Multidimensional Fatigue Inventory scores increased importantly over the course of the experiment ($T_{(47)} = 14.9$, $p < 0.0001$, $d = 1.4$). Similarly, the Karolinska Sleepiness Scale scores highlighted a strongly significant increase in perceived sleepiness ($Z = 6.08$, $p < 0.0001$, $r = 0.88$). The two experimental groups did not diverge neither in their evaluation of fatigue ($T_{(23)} = -0.35$, $p = 0.728$), nor in the sensation of sleepiness arising from the experimental procedure ($Z = 0.55$, $p = 0.579$).

Additionally, the increase in subjective fatigue displayed a moderate negative correlation with the change in the behavioural performance ($R_{(46)} = -0.29$, $p = 0.043$; see Figure 4). This indicates that larger perceived fatigue related to greater loss in performance, as indexed by behavioural difference between SATURATED and NON-SATURATED scores across the beginning and conclusion of the experiment. On the other hand, no significant correlation was observed between changes in behaviour and perceived sleepiness ($R_{S(46)} = -0.1$, $p = 0.5$).

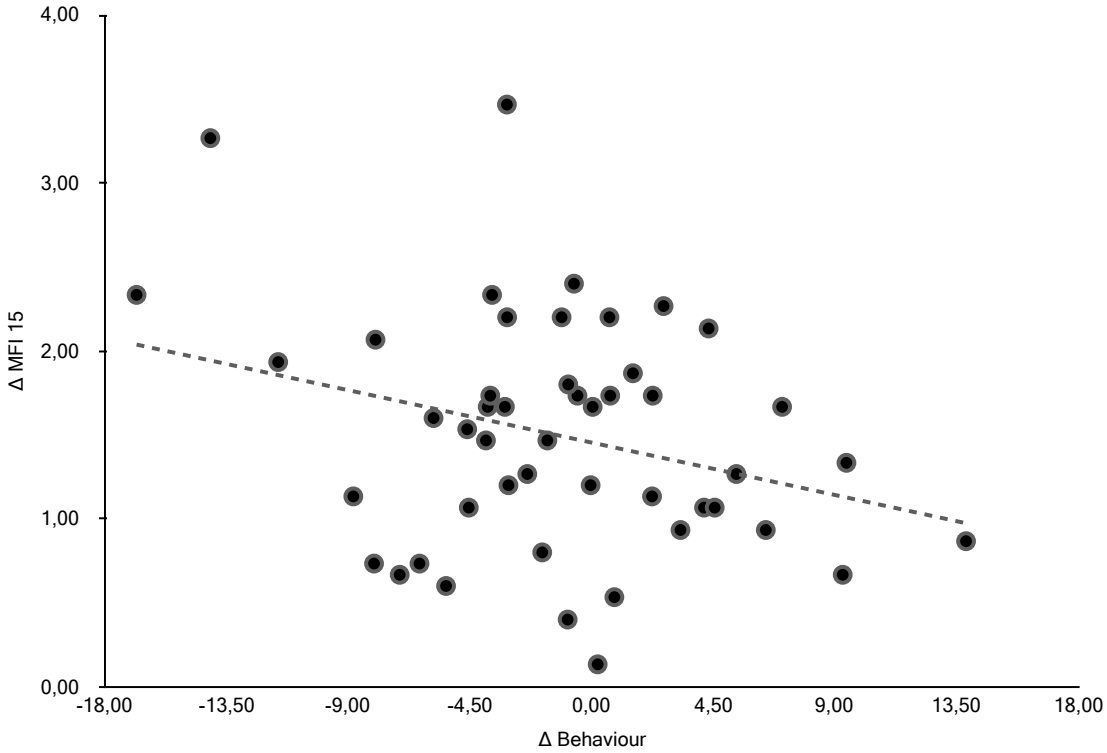

Figure 4: Scatterplot depicting the change in reported fatigue (y axis) in relation to the change in behavioural performance between beginning and conclusion of the experiment (x axis)

Discussion

In the present study, we found that prolonged stimulation of a portion of the visual field led to specific deterioration of participants' performance in that portion of visual space, proving that neural fatigue can be locally and passively induced. Because of its spatial specificity, this neural fatigue phenomenon cannot be explained solely by motivational theories of fatigue. On the contrary, such progressive functional alteration generated by repeated recruitment could constitute one of the mechanisms involved in general fatigue, as suggested by the correlation we observed between the feeling of fatigue and the specific behavioural consequences, which is rarely found in the pertaining literature (DeLuca, 2007).

As predicted, perceptual deterioration was accelerated by concurrent performance of difficult auditory tasks. We argue that increased arousal provoked by the challenging version of the tasks and physiologically indexed by pupil size, led to stronger activations of the simultaneously stimulated visual neurons (Mather et al., 2016; Zhang et al., 2020), which in turn caused faster and greater degradation of performance.

Interestingly, on top of perceptual deterioration, we also observed improvement of perceptual performance induced by passive stimulation. This result was restricted to the participants whom underwent the easy versions of the auditory tasks, and faded following the second session of passive stimulation. This observation evokes the passive learning literature, where repeated, passive presentation of visual stimuli leads to ameliorations in subsequent discrimination performance (Watanabe et al., 2001). However, classical passive learning is usually measured on the days following training while, since our experiment was not designed to investigate learning, we did not measure behavioural performance on different days. Therefore, this observation relates better to the older and more general concept of perceptual priming, than to perceptual learning literature (Wiggs & Martin, 1998). Strikingly, volunteers who were engaged in hard auditory tasks while being visually stimulated failed to show this stimulation-induced enhancement in performance, suggesting that increased neural fatigue induced by their arousal state counteracted perceptual priming. Alternatively, this result may indicate that arousal inhibits perceptual priming processes (though in contradiction of previous accounts; (Thomas & LaBar, 2005)) or that difficult auditory tasks induced diversion of attention away from the visual stimulus (also not in accordance with previous findings (Mulligan, 2003)).

Our results also stand out from previous findings termed as visual fatigue or visual adaptation. In this body of literature, repeated stimulation affects subsequent behaviour on the timescale of seconds (Carandini, 2000), whereas our findings extend over dozens of minutes. Determining with precision how these mechanisms interact would require studying the time course of the effect with better resolution than the one provided in the present study.

From the neurophysiological perspective, we found that repeated visual stimulation altered visual gamma brain waves. In fact this electrophysiological signal, proven to subserve the feedforward processing of basic visual features from occipital to frontal regions in humans (Michalareas et al., 2016) and primates (Bastos et al., 2015), was found to be altered in both groups and in opposite direction, in accordance with the behavioural changes. Such finding, together with the fact that the behavioural consequences were influenced by the difficulty of concurrent auditory tasks, argues in favour of a cortical, as opposed to retinal origin of the effect.

This is in line with previous perceptual deterioration results, caused by prolonged TDT performance, where decreased primary visual cortex activations were observed (Mednick et al., 2008). However, further neuroimaging experiments will have to be performed to definitely confirm the neural nature of the present saturation effect.

All participants reported an increase in fatigue and sleepiness scores at the end of the experiment, providing evidence for the success of the experimental procedure in impacting the *objective* and *subjective* manifestations of fatigue. In fact, the Multidimensional Fatigue Index results were significantly correlated to the change in saturation-specific behavioural performance. Such correlation cannot be attributable to the behavioural difference between easy and hard groups, since the self-reported measures of fatigue did not significantly differ between them. However, the current design does not allow us to make inferences on the causal direction of this relation.

The presented design is immune to confounds such as boredom, motivation and level of skill in the fatiguing task (Gergelyfi et al., 2015). Indeed, since all participants carried out the task in the saturated and non-saturated portion of their visual field, any difference in performance or brain activity between the two, can be solely explained as the by-product of saturation – which was an artifice to keep specific neuronal assemblies active all along. Nonetheless, the current study is subject to limitations.

First, the localisation of the clusters of significant changes in gamma activity between saturation conditions appears to be lateralised despite saturation localisation being balanced between left and right visual hemifields across participants. However, this result must be interpreted with caution due to the nature of EEG data and cluster-based permutation analyses, which do not permit claims on the localisation of the reported effects (Sassenhagen & Draschkow, 2019). The use of more spatially sensitive instruments (e.i. fMRI) is warranted to shed light on the brain localisation of the observed behavioural phenomenon, which might be explained by a different factor than electrophysiological magnitude of cortical brain response. For instance, the behavioural changes may be reflected in the neural encoding of the saturating stimuli, and thereby be more aptly investigated by multi-variate pattern analyses (Haxby et al., 2014).

Second, contrary to our initial hypotheses, we did not find a significant impact of the experimental procedure in the EEG steady-state response at the frequency of stimulation (7.5 Hz). Furthermore, we did not observe significant differences in the gamma visual peak for the hard group between the baseline and middle sessions. This may indicate that perceptual deterioration may originate from decreased signal-to-noise ratio rather than simple decrease in activation magnitude. Alternatively, this lack of effect may be caused by the relatively low sensitivity of our approach, caused by limited efficacy of peripheral visual stimulation, given the under-representation of the peripheral visual fields in the retinotopic map (Azzopardi & Cowey, 1993). Future designs could be devised with central saturating stimuli, in order to ensure higher responses in the visual cortex, due to the cortical over-representation of the fovea.

Third, we did not find evidence of group level differences in the average pupil sizes of participants in the pitch-sequence task. This may be due to the excessive demands of this task for those assigned to the hard condition, potentially leading to their disengagement from the task. Indeed, the pitch-sequence task had the lowest performance across tasks and conditions (49% of correct responses overall) and several participants reported that this task was the most challenging of the three. Alternatively, the lack of difference in pupil dilation between easy and hard versions of the pitch-sequence task could be due to the different timing of the task across difficulty conditions, leading to more overlap between stimulus- and response-aligned pupil dilation in the case of the easy group, showing as an artificially larger peak in this condition relative to the harder task version.

In sum, we bring new evidence that passive, repeated neuronal activation induces progressive functional alteration under the modulatory influence of arousal: in low arousal conditions, we observed an initial perceptual priming effect followed by a decrease to baseline performance, while participants engaging in harder tasks displayed an early, specific loss of performance. This neural fatigue phenomenon could justify renewed interest in metabolic accounts of fatigue.

Indeed, while the neural mechanism underlying this recruitment-related performance deterioration remains to be investigated, one may speculate the involvement of depletion or accumulation of metabolites (Dalsgaard & Secher, 2007; Dienel & Hertz, 2001; Fairclough & Houston, 2004). The detailed characterisation of such process is matter for subsequent studies, which may disentangle how exactly the phenomena brought forward by the present results, to our best knowledge previously unreported, act and interact with each other.

Methods

Forty-eight participants took part voluntarily in the experiment (24m and f, age = 22.1 ± 2.24). All of them were naive to the experimental procedure, with no history of mental or visual conditions. Participants had normal or corrected-to-normal vision and provided written informed consent to participate. They received 10€ per hour in compensation for their participation. The study was approved by the Ethical Review Board. Due to the lack of literature on the effect we sought to test, the sample size was arbitrarily preplanned to have a balanced and sufficient number of participants for the various experimental conditions and randomisations.

In total, 56 participants were recruited, given that 7 participants were excluded; 4 due to failure to respond to an adequate number of trials in the behavioural task (less than half the trials in two or more blocks of the first session), 2 spontaneously dropped out during the experiment and 1 for being an outlier (performance > 4 std).

Source code is available at [https://github.com/ste-ioan/TDT2019], data is available upon request to the corresponding author.

All aspects of the experiment, except the questionnaires, were implemented through Matlab 2019a (The MathWorks, Inc., Natick, Massachusetts, United States), using Psychtoolbox (Brainard, 1997; Pelli, 1997) and displayed on a computer screen with 1280 by 1024 resolution. Participants sat in front of the screen at a distance of 60 cm and accommodated their heads on a chin-rest. A keyboard was used to respond across the various tasks. Below the screen there was an Eyetracker 1000 (SR Research Ltd., Mississauga, Canada), which was employed to ensure central fixation of the participants' gaze while tracking variations in the size of their pupils. A 32-channel Active Two Biosemi system (Biosemi, Amsterdam, Netherlands) EEG headset was mounted on their heads. Lastly, a pair of in-ear headphones was provided (Cellularline spa., Reggio Emilia, Italy).

Experimental design

The experimental design was divided into different phases, which will be detailed in the following sections. First of all, a brief training with shorter versions of the tasks was carried out in order to have the participants familiarise with their procedures (see Figure 1 panel 1a). Behavioural and physiological measures were taken at different timepoints of the experiment, namely: BASELINE, MIDDLE and CONCLUSION (see Figure 1 panel 1b,d,f). In-between these measurements, subjects underwent continuous stimulation (referred to as 'saturation') of a specific portion of their visual field (referred to as 'quadrant') (see Figure 1 panel 1c,e). During saturation, volunteers were engaged in auditory tasks, the difficulty of which differed based on the experimental group to which they were randomly assigned, being either in an "EASY" (n=24, 12m and f, age: 22.37 ± 2.7) or "HARD" (n=24, 12 m and f, age: 21.92 ± 1.69) condition. The assignment of SATURATED quadrant and group was counter-balanced across participants. Overall, an experimental run lasted approximately 2h and 30 minutes, depending on the time spent to install the EEG headset.

Auditory tasks

As outlined, during each saturation session participants were engaged in auditory tasks, the demands of which varied according to the experimental group to which they were assigned for the duration of the whole experiment, being either EASY or HARD. This experimental condition was introduced to evaluate potential effects of differing cognitive loads, and resulting arousal levels, on the time course of fatigue.

These tasks were randomly cycled across a saturation session, until its pre-scripted duration of 41 minutes had passed. Specifically, 3 different tasks were used: the n-back task, a pitch-sequence reproduction task, and a switch task which we named the side task (Table 1). All tasks of the experiment employed the same response keys (F and J), except for the pitch-sequence task where 2 additional keys were added (D and K).

N-back: a trial would consist of a list of 12 letters where participants had to report the occurrence of the target letter. In the EASY group, the target letter was 'X' (0-back), while in the HARD group the target letter was any letter repeated 2 steps before (2-back). A block of N-back was composed of 35 trials for both conditions, each trial lasted 15 seconds for both groups.

Pitch-sequence: In this task, participants were required to replicate a sequence of beeps that was presented to them. Four different beeps (from low-pitch (336hz) to high-pitch (475hz) and in between (377hz, 424hz) were put together in randomly generated sequences. To each beep corresponded a key on the keyboard. For the EASY group these sequences comprised 2 beeps, while for the HARD group they comprised 5 to 8 beeps. A block of pitch-sequence task consisted in 80 trials for both conditions, with longer intervals between beeps for the EASY group and shorter intervals for the HARD group. On average, the duration of stimuli presentation for the EASY group lasted 2.7 seconds, while the mean duration for the HARD group was of 8.9 seconds.

TASK	EASY GROUP	HARD GROUP
N-back	Press key when hearing the letter X	Press key when current letter corresponds to a letter presented 2 steps before in the sequence
Pitch-sequence	Reproduce a sequence of two beeps	Reproduce a sequence of 5 to 8 faster beeps
Side	Indicate if a sound was played through the left or the right headphone	Same as easy, but the response keys could be inverted throughout the block depending on sound category. Inhibit response to an additional category

Table 1: Summary of the demands in the auditory tasks (rows) by difficulty condition (columns)

Side: In this task sounds were presented randomly either to the left or to the right earphone of the participant. These sounds came from different categories, namely: animal sounds or vehicle sounds. For the EASY group, participants only had to indicate if the current sound was played on the left or the right. The HARD group had instead a cue voice indicating, at random points during the block, which category they had to answer coherently to (i.e. if a sound of that category was presented to the left, they had to press the left key and *vice-versa*), this implicitly signalled they had to answer incoherently to the unmentioned category (i.e. if the sound was on the left, they had to press right and *vice-versa*). Furthermore, for this group a third category of sounds was added, the computer/electronics category, to which they were instructed not to respond. A block would be made up of 135 sounds with shorter silences in-between for the HARD group, and 80 sounds with longer distances in-between for the EASY group, subdivided into trials of 5 sounds for both groups. A trial would last on average 30 seconds in the EASY condition, and 18 for the HARD group.

Behavioural index of fatigue

As a behavioural measure of fatigue, we adopted the participants' performance in the Texture Discrimination Task (TDT), based on the task developed by Karni and Sagi (Karni & Sagi, 1991). The task's goal is to discriminate the orientation of a peripheral target, which consists of three diagonal lines aligned either vertically or horizontally, against a background of horizontally oriented bars (see Figure 1 panel 2b). Participants were instructed to maintain their gaze on a central fixation cross and report the perceived orientation of a peripheral target at the end of each trial.

These targets would relocate from trial to trial, within a defined quadrant of the screen. Quadrants would vary depending on the block, either on the upper right or upper left portion of the screen. Each experimental trial comprised a pre-stimulus window of 700 ms (see Figure 1 panel 2a), followed by the target screen for 32 ms (see Figure 1 panel 2b), a blank screen, known as ISI (inter stimulus interval), with variable length between 6 and 600 ms, determined by a Bayesian staircase procedure (see below) (see Figure 1 panel 2c), followed by a mask of 100 ms (see Figure 1 panel 2d). The mask was designed to disrupt the subjects' processing of the peripheral target lines, therefore shorter ISIs translated into harder trials.
Finally, there was a 1000 ms time window where the participant indicated, by pressing on the keyboard, if the target was perceived as horizontal or vertical (see Figure 1 panel 2e).
A single TDT trial lasted on average 2.26 seconds (±0.28 sec) and 80 trials composed a block.
A complete TDT session consisted of 4 blocks, 2 per quadrant, and lasted 12.4 minutes on average (± 37 sec). The order of blocks was random for every session and participant. A block would begin when the participant pressed spacebar, after which he or she was informed on the quadrant within which the target would appear, by means of a message at the centre of the screen.

Adaptive ISI selection procedure
In order to optimize inference of participants' psychometric curve from limited data, we opted for an adaptive procedure to select ISI values (inspired from (Kontsevich & Tyler, 1999)). This procedure was applied following the five first trials (in which ISI was selected randomly). In each trial, a variational Bayesian logistic regression was performed on currently acquired data (Drugowitsch, 2019), resulting in parameter estimates and variance. Then, the expected update in these parameters was computed under the hypotheses of correct or incorrect response in the next trial, and for all possible ISI values:

$$\theta_{n+1}(x_{n+1}, y_{n+1}) = f([x_{1:n}, x_{n+1}], [y_{1:n}, y_{n+1}]),$$

for θ the mean (θ^{μ}) and variance (θ^{Σ}) estimates of the parameters, f the variational logistic function, $y_{1:n}$ the acquired response data and y_{n+1} the expected response, $x_{1:n}$ the past ISI values and x_{n+1} the ISI value for the next trial.
The KL divergence between current and future estimates was computed for each ISI and possible response according to the following formula:

$$KL(\theta_i, \theta_j) = \frac{1}{2} log\left(\frac{|\theta_j^{\Sigma}|}{|\theta_i^{\Sigma}|}\right) - 2 + tr\left((\theta_j^{\Sigma})^{-1}\theta_i^{\Sigma}\right) + (\theta_j^{\mu} - \theta_i^{\mu})^T (\theta_j^{\Sigma})^{-1} (\theta_j^{\mu} - \theta_i^{\mu}) \cdot$$

These KL values for correct and incorrect expected response were then averaged and weighted as a function of the probability of obtaining either correct or incorrect response given current parameter values:

$$V(x_{n+1}) = p(y_{n+1} = 1 | \theta_n) KL(\theta_n, \theta_{n+1}(x_{n+1}, 1)) + p(y_{n+1} = 0 | \theta_n) KL(\theta_n, \theta_{n+1}(x_{n+1}, 0)) \cdot$$

These KL values, representing how much information one would expect to gain about the parameter estimates under each ISI condition, were then softmax-transformed to lead to a probability distribution over all ISI values, which was then sampled randomly to select the value of the ISI for the next trial.

Saturation
A saturation session lasted for 41 minutes and consisted of a prolonged visual stimulation, during which participants had to maintain their gaze on a central fixation point while stimuli were continuously flashed at 7.5Hz (see Figure 1 panel 3). Stimuli were composed of all the possible targets within a quadrant in the TDT. The SATURATED quadrant was kept constant for each participant across all saturation sessions. This ensured the entraining of specific neuronal populations across the whole experiment, providing a way to test whether the neural (EEG) and behavioural (TDT) response would differ between SATURATED and NON-SATURATED quadrants.

Physiological measures
EEG recordings of whole brain activity in response to the presentation of the saturation stimulus (fig.4 panel 3) were performed. A complete EEG session comprised four repetitions of 1-minute long stimulations (two per quadrant), with a 5-second pause in between. Visual stimulation during EEG blocks was identical to the one used during saturation blocks, except that the quadrants with stimuli alternated, their order being counterbalanced across participants.

FieldTrip toolbox (Oostenveld et al., 2011) was employed for the analysis of EEG data. Specifically, we focused our analysis on the stimulation frequency (7.5 Hz), reasoning that alterations in bottom-up visual processing should lead to modulation of the steady-state response. For similar reasons, also the higher range of the gamma spectrum (60 to 80 hertz) was included in our analyses as this range includes the peak of the visual gamma response, which subserves feedforward processing of basic visual features (Bastos et al., 2015; Michalareas et al., 2016).

The preprocessing consisted in a low-pass filter at 100 hertz, a high-pass filter at 0.4 hertz and a line-noise filter at 50 and 100 hertz applied to the raw data, which was then re-referenced on the average of all 32 channels. Before segmentation into trials, artefacts were rejected upon visual inspection of the data and then by independent component analysis.
Subsequently, one Fourier transform with a single Hanning taper was applied to extract the power spectrum around stimulation frequency, (7.3 to 7.7 hertz, in steps of 0.1). Signal from neighbouring frequencies (7.3 to 7.4 and 7.6 to 7.7 hz) was subtracted from the 7.5 Hz signal, to highlight the specific response to stimulation (Norcia et al., 2015). For the gamma spectrum analysis, discrete prolate spheroidal sequences were employed as tapers for the spectral estimation between 60 and 80 hertz. The power spectrum within this range was then averaged to obtain a single index of the visual gamma component. The natural log of these values was then computed to improve the normality of their distribution.

As previously mentioned, we also recorded the pupil size of participants as a physiological index of arousal. Variations in pupil size were tracked while participants were undergoing saturation sessions and were engaged in the concurrent auditory tasks, whose difficulty varied according to the experimental group they were assigned to. Specifically, after linear interpolation of blinks and filtering (high-pass with 0.01Hz cutoff frequency), we extracted stimulus-aligned pupil responses and computed their average within the average duration of sound presentations, per task and condition.

Questionnaires
In order to measure the participants' subjective feeling of fatigue and sleepiness, two pen-and-paper questionnaires were administered at the beginning and end of the experiment; the Multidimensional Fatigue Inventory (Gentile et al., 2003) and the Karolinska Sleepiness Scale (Shahid et al., 2011).

Statistical Analysis
First, behavioural effects were assessed by means of a Generalised Linear Mixed Model (GLMM) on the TDT data. Correct response in the task was modelled as a logistic dependent variable, with ISI as a covariate and participants as a random variable. Difficulty group (EASY, HARD), experimental session (BASELINE, MIDDLE, CONCLUSION) and saturated quadrant (YES, NO) were set as explanatory variables, testing their main effects and interactions. This was done on Jamovi (The jamovi project, 2019) through its module GAMLj (Gallucci, 2019). Random effects were included step-by-step as long as the Bayesian Information Criterion and deviance values kept decreasing and no convergence issues were encountered. Specifically, intercept, ISI and Session were included in the random part of the model and were therefore allowed to vary across participants.

Second, effects on brain activity were evaluated by examining changes in the EEG signal.
To evaluate the interaction of session and condition, the difference of EEG activity between SATURATED and NON-SATURATED condition was computed, for each of the three sessions and for each participant.

$$(\Delta EEG_{session}) = (sat_{session} - nonsat_{session})$$

These values were then analysed in dependent sample two-tailed t-tests to assess changes across sessions, according to the behavioural results. Correction for multiple comparisons across electrodes was enforced by means of a non-parametric Monte Carlo cluster-based permutation approach with 1000 randomisations (Maris & Oostenveld, 2007).

Third, we assessed the efficacy of the auditory tasks concurrent to saturation in inducing different arousal levels based on their difficulty. Given the violation of normality of the pupil size averages, this was done by means of independent samples rank-sum tests, on Matlab, between mean pupil sizes of both groups, one for each task.

Fourth, participants' subjective evaluation of fatigue was assessed by comparing the values reported before and after the experiment in the Karolinska Sleepiness Scale and Multidimensional Fatigue Inventory. In the case of the latter questionnaire the mean change across items was calculated for each participant and then evaluated in a t-test against 0. For the Karolinska Sleepiness Scale results, given their non-normal distribution and impossibility to average across several items, a sign-rank test against 0 was conducted. Lastly, estimates of behavioural performance change between BASELINE and CONCLUSION session obtained by the psychometric function, and the change in the both questionnaire scores were correlated. These tests were carried out in Matlab.

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