



Exploring of the the neural mechanisms of fatigue by passive induction

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TO OBTAIN THE QUALIFICATION OF

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NEUROSCIENCE

BY STEFANO IOANNUCCI

**EXPLORATION OF THE NEURAL MECHANISMS OF FATIGUE BY
PASSIVE INDUCTION**

Under the supervision of **dr. Alexandre Zénon**

14th of March 2022

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Exploration of the neural mechanisms of fatigue by passive induction

Abstract

Demanding cognitive activity is aversive, requires effort, and, when prolonged, leads to mental fatigue. However, the origin of the aversive aspect of cognition and the neural mechanisms that lead to fatigue still remain enigmas for neuroscience.

The aim of this thesis was to test the hypothesis that fatigue originates from local alterations in neuronal activity caused by prolonged recruitment of brain networks. Moreover, this work sought to address a specific prediction derived from the functional view of mental fatigue: neuronal assemblies that are engaged in activity, even if passive, are bound to saturate and reach the point of failure.

Drawing inspiration from converging yet separate lines of research, a novel experimental approach was devised in order to test our hypothesis while controlling as much as possible for the confounds which are pervasive in the pertaining literature, namely, differences in motivation, level of skill in the task and boredom. Across several experiments, specific behavioural performance deficits were induced in the participants, allowing us to confirm and characterize the posited passive fatigue effect. Indeed, in the first experiment, we unveiled a surprising interaction between the degree of specific performance alteration induced by prolonged stimulation and arousal caused by cross-sensory cognitive load. Additionally, we found a lack of support for sensory habituation being involved in the described process, as the analysis of electrophysiological data from the participants proved to be unfruitful.

We then replicated the results on the decrement of performance in two successive studies, introducing additional psychophysiological manipulations to provide indirect, behavioural evidence for its localisation in visual cortex. More so, several indicators of effort and arousal, such as questionnaires and pupil size, were related to the behavioural changes we observed.

In the final experiment, we confirmed once again the specific performance decrement caused by saturation, attesting to its robustness. Furthermore, we used neuroimaging techniques to show disruption of brain activity of the participants that paralleled the behavioral deterioration, thus providing evidence for neural fatigue by passive induction.

Keywords: cognitive fatigue, mental effort, cross-sensory cognitive load, MVPA, EEG

Exploration des mécanismes neuraux de la fatigue par induction passive

Résumé

L'activité cognitive intense est aversive, nécessite un effort et, lorsqu'elle est prolongée, entraîne de la fatigue mentale. Cependant, l'origine de l'aspect aversif de la cognition et les mécanismes neuronaux qui conduisent à la fatigue restent encore des énigmes pour les neurosciences.

L'objectif de cette thèse était de tester l'hypothèse selon laquelle la fatigue trouve son origine dans des altérations locales de l'activité neuronale causées par un recrutement prolongé des réseaux cérébraux. De plus, ce travail a cherché à répondre à une prédiction spécifique dérivée de la vision fonctionnelle de la fatigue mentale : les assemblées neuronales qui sont engagées dans une activité, même passive, sont vouées à saturer et à atteindre le point de défaillance.

En s'inspirant de lignes de recherche convergentes mais distinctes, une nouvelle approche expérimentale a été conçue afin de tester notre hypothèse tout en contrôlant autant que possible les facteurs de confusion qui sont omniprésents dans la littérature existante, comme les différences de motivation, le niveau de compétence dans la tâche et l'ennui. À travers plusieurs expériences, des déficits de performance comportementale spécifiques ont été induits chez les participants, ce qui nous a permis de confirmer et de caractériser l'effet supposé de la fatigue passive. En effet, dans la première expérience, nous avons dévoilé une interaction surprenante entre le degré d'altération de la performance spécifique induite par une stimulation prolongée et l'excitation causée par la charge cognitive intersensorielle. De plus, nous avons constaté que l'habituation sensorielle n'était pas impliquée dans le processus décrit, car l'analyse des données électrophysiologiques des participants s'est avérée infructueuse. Nous avons ensuite reproduit les résultats sur la diminution de la performance dans deux études successives, en introduisant des manipulations psychophysiologiques supplémentaires afin de fournir des preuves comportementales indirectes de sa localisation dans le cortex visuel. De plus, plusieurs indicateurs de l'effort et de l'excitation, tels que les questionnaires et la taille de la pupille, étaient liés aux changements comportementaux que nous avons observés.

Dans la dernière expérience, nous avons confirmé une fois de plus la diminution spécifique de la performance causée par la saturation, attestant de sa robustesse. De plus, nous avons utilisé des techniques de neuro-imagerie pour montrer une perturbation de l'activité cérébrale des participants parallèle à la détérioration comportementale, apportant ainsi la preuve d'une fatigue neuronale par induction passive.

Mots-clés: fatigue cognitive, effort mental, charge cognitive multisensorielle, MVPA, EEG

Summary of the thesis in French / Sommaire de la thèse en français

L'objectif de la présente thèse était de contribuer à la compréhension de la fatigue cognitive et, plus particulièrement, de ses fondements neuronaux. Malgré des décennies d'études et d'une quantité considérable de travaux expérimentaux réalisés dans ce domaine, il reste encore des points de discordance importants à aborder, notamment en ce qui concerne les perspectives fonctionnelles et motivationnelles sur la nature de la fatigue.

L'un de ces points consiste en la nécessité d'une tâche qui puisse être utilisée de manière fiable pour évaluer l'impact de la fatigue sur sa performance, tout en offrant la possibilité d'être adaptée au niveau de compétence des agents qui y sont engagés, et de contrôler les facteurs de confusion les plus courants liés à la fatigue, notamment ceux liés à la motivation. Comme l'ont attesté plusieurs évaluateurs, une solution élégante à cette nécessité a été trouvée, en s'appuyant sur des méthodes précédemment employées dans des domaines de recherche similaires. En effet, l'utilisation de la tâche de discrimination de texture a permis de répondre aux questions susmentionnées et a fourni un cadre propre à utiliser comme base dans la recherche des bases neuronales de la fatigue induite passivement dans des assemblées neuronales spécialisées, étant donné la spécificité bien connue des neurones visuels en réponse à la stimulation. Dans tous les cas, il faut garder à l'esprit que ce qui suit est une interprétation personnelle, bien que rigoureuse, de résultats qui n'ont pas encore été sanctionnés par un examen par les pairs, et qui sont donc susceptibles d'être modifiés.

Dans la première étude décrite au chapitre 2, le plan expérimental conçu a été validé, révélant qu'une fatigue visuelle spécifique pouvait être induite par une stimulation passive. Nous avons également confirmé la conjecture selon laquelle cet effet serait influencé par l'éveil, manipulé en faisant varier la difficulté des tâches dans une autre modalité sensorielle. Ainsi, nous avons apporté la preuve d'une interaction inter-sensorielle remarquable où des stimuli visuels identiques peuvent susciter des modèles différents de réponse comportementale (et, vraisemblablement, corticale), en fonction de la charge cognitive auditive.

Cette constatation a été corroborée par la relation observée, dans les trois échantillons, entre la taille de la pupille des participants - qui sert de marqueur d'éveil - et la baisse de leur performance comportementale. Parallèlement aux manifestations locales, spécifiques et induites passivement de la fatigue objective, les participants ont signalé une augmentation importante de leurs niveaux perçus de fatigue subjective et de somnolence. Cela montre, une fois de plus, comment ces deux concepts sont associés dans l'expérience. De plus, une corrélation significative a été observée entre les composantes objectives et subjectives de la fatigue, d'autant plus remarquable qu'elle est rarement observée dans la littérature (DeLuca, 2007). Cependant,, distinguer clairement ce qui est mesuré par les questionnaires employés, par exemple en quantifiant l'influence de l'ennui dans leur réponse, est au-delà des possibilités de nos outils actuels.

À la lumière de ce qui précède, il est intéressant de noter que les participants qui ont subi les versions plus faciles des tâches auditives et qui n'ont pas manifesté de fatigue objective spécifique, améliorant plutôt temporairement leurs performances dans la partie saturée du champ visuel, ont tout de même signalé des niveaux accrus de fatigue et de somnolence tout au long de l'expérience. Néanmoins, l'activité corticale enregistrée par EEG en réponse aux stimuli saturés ne différait pas de celle enregistrée en réponse à la stimulation dans la partie non saturée du champ visuel. Ce résultat décevant contraste fortement avec les travaux antérieurs dans le domaine de l'habituation (Grandstaff & Pribram, 1972) et de l'adaptation (Vergeer et al., 2017), qui prédisent une diminution de l'activité électrophysiologique enregistrée des neurones en réponse aux stimuli présentés de manière répétée. Cette absence de résultats a mis en évidence la nécessité de reconsidérer le choix de l'outil de neuro-imagerie pour évaluer les bases neurales de la fatigue visuelle induite passivement. Par conséquent, une version actualisée du plan expérimental a dû être élaborée. Il a été possible de le faire tout en testant d'autres propriétés de l'effet observé. Notamment, sa spécificité aux propriétés de la stimulation saturante, comme l'œil et l'orientation, comme cela a été fait dans la littérature sur l'apprentissage perceptif (Karni & Sagi, 1991 ; Schwartz

et al., 2002) et la détérioration (Mednick et al., 2005 ; Mednick & Boynton, 2004). Ainsi, les deux expériences supplémentaires du chapitre 2 ont été préparées et réalisées.

Étant donné que l'effet de fatigue spécifique était prédominant dans la première moitié de l'expérience dans le groupe soumis à la version la plus difficile des tâches auditives, tout en ayant tendance à être estompé par une perte de performance plus généralisée dans la deuxième moitié, les expériences additionnelles ont été limitées à cette partie du plan. Les résultats de ces expériences supplémentaires, de plus petite taille, ont non seulement confirmé la constatation initiale d'une fatigue visuelle spécifiquement induite dans un échantillon total de 78 participants, mais ont également précisé qu'elle était limitée à l'œil stimulé et à l'orientation des stimuli. Des résultats partiellement similaires dans les publications susmentionnées ont été interprétés en termes d'implication des cortex visuels précoces (Karni & Sagi, 1991 ; Mednick et al., 2005).

En outre, la tendance à la corrélation entre les composantes objectives et subjectives de la fatigue dans le paradigme adopté a été confirmée. Cependant, bien que ces expériences se soient avérées, au moins partiellement, fructueuses, une question fondamentale est restée sans réponse : existe-t-il des altérations observables induites par la fatigue dans les réseaux neuronaux liés à la tâche ? En effet, étant donné l'absence de résultats EEG dans l'expérience 1 et la spécificité oculaire constatée dans l'expérience 2, on pourrait supposer que les effets observés pourraient avoir lieu dans la rétine des participants, indépendamment de la divergence des résultats influencés par l'éveil inter-sensoriel et la charge cognitive. Afin d'éclaircir cette question, dans le chapitre 3, le modèle précédemment utilisé a été adapté pour répondre aux exigences d'une expérience d'imagerie par résonance magnétique fonctionnelle. Une approche moderne à plusieurs variables a été privilégiée en raison de ses propriétés qui permettent de s'adapter au modèle unique d'activité cérébrale de l'individu et d'imiter sa production comportementale, par le biais de la précision de classification. Grâce à cette dernière expérience, les résultats comportementaux de la fatigue spécifique objective

ont été une fois de plus reproduits, portant à 102 participants l'échantillon total sur lequel cet effet a été induit expérimentalement, indépendamment des variations méthodologiques.

Cependant, dans ce cas, aucune corrélation n'a été trouvée entre les estimations objectives et subjectives de la fatigue, conformément à la plupart des publications sur le sujet (DeLuca, 2007).

Néanmoins, une corrélation a été trouvée avec l'évolution de la somnolence auto-déclarée, qui, comme cela a été souligné dans le présent travail, peut être considérée comme le phénomène le plus étroitement liée à la fatigue.

Il est important de noter que l'on a constaté des changements dans l'activité cérébrale en réponse aux stimuli saturés découlant de la procédure expérimentale. De plus, ces changements survenant dans les réseaux neuronaux spécifiques au sujet et responsables du traitement des stimuli étaient directement corrélés à la manifestation objective de la fatigue visuelle spécifique.

Enfin, une similitude frappante a été mise en évidence entre les résultats de précision des participants humains et d'un algorithme de classification exploitant leur activité neuronale.

S'appuyant sur ces résultats issus de méthodes multi-variées, une approche univariée plus classique a révélé que les zones les plus perturbées par la saturation se trouvaient dans les cortex visuels extra-striés des participants, conformément à certaines parties de la littérature qui ont exploité la même tâche pour étudier l'apprentissage perceptif (Raiguel et al., 2006 ; Yang & Maunsell, 2004).

Dans l'ensemble, les résultats de l'expérience du chapitre 3 fournissent une base neuronale pour les effets observés dans les travaux empiriques présentés dans cette thèse, ainsi qu'un soutien fort pour la notion que la fatigue modifie l'activité des assemblées neuronales locales, liées à la tâche, en raison d'un épuisement prolongé. Cela est compatible avec les résultats d'altérations métaboliques des concentrations de lactate, de glucose et de glutamate dans le cortex visuel après stimulation (Bednařík et al., 2015), et avec les rapports d'altérations induites par la fatigue dans les zones du cerveau liées à la tâche (Blain et al., 2016 ; Gergelyfi et al., 2021 ; Mednick et al., 2008 ;

Vyazovskiy et al., 2011). Cela justifie donc un regain d'intérêt pour les comptes fonctionnels de la fatigue présentés dans la section 1.5.

En résumé, tout au long de ce travail académique, un plan expérimental a été préparé afin d'induire et de mesurer les effets de la fatigue spécifique, en résistant aux influences des phénomènes étroitement liées. En guise de remarque générale, on peut conclure des résultats complets que, toutes choses égales par ailleurs, le surmenage prolongé des assemblages cellulaires entraîne une altération de leur fonction et que les effets de la fatigue spécifique peuvent être observés lorsque la motivation et d'autres facteurs de biais sont contrôlés. Ces effets spécifiques de la fatigue se sont révélés être présents de manière fiable dans un laps de temps considérablement plus court que la plupart des recherches dans la littérature connexe. Ces résultats sont compatibles avec la plupart des perspectives fonctionnelles de la fatigue et résonnent avec l'interprétation originale de la détérioration perceptive comme dépendant de réseaux neuronaux locaux surutilisés (Mednick et al., 2002). De plus, on pourrait s'attendre à ce que la taille de l'effet de ce phénomène soit raisonnablement importante, étant donné le taux de réplication non trivial entre les échantillons. Une grande partie de ces résultats est due, de toute évidence, au fait que la notion d'altération de la réponse comportementale à la suite d'une stimulation ou d'un exercice intensif est sans doute aussi ancienne que le domaine des sciences cognitives lui-même. Pourtant, la méthode mise en œuvre et les conclusions tirées dans le présent travail sont toujours novatrices et, espérons-le, contribuent au débat général sur la fatigue cognitive. Dans tous les cas, l'impact des résultats rapportés bénéficierait de leur reproduction dans un domaine différent du domaine visuel.

Pour conclure, les aspects les plus saillants de la recherche présentée consistent probablement en sa contribution à la distinction entre la motivation et la fatigue, qui pourrait éventuellement devenir une possibilité dans les activités quotidiennes. Une compréhension plus approfondie du phénomène de la fatigue pourrait atténuer le risque de syndromes de fatigue, comme le burn-out, et contribuer à la prévention des accidents liés à l'épuisement.



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LIST OF ABBREVIATIONS

ACC:	Anterior Cingulate Cortex
ANOVA:	Analysis Of Variance
BOLD:	Blood Oxygen Level Dependent
CF:	Cognitive Fatigue
EEG:	Electroencephalography
ERP:	Event-Related Potential
GLMM:	Generalized Linear Mixed Model
ISI:	Inter Stimulus Interval
ITI:	Inter Trial Interval
KL:	Kullback-Leibler
LGN:	Lateral Geniculate Nucleus
LQ:	Left Quadrant
MRI:	Magnetic Resonance Imaging
MVPA:	Multi Variate Pattern Analysis
PFC:	Prefrontal Cortex
PVT:	Psycho-Vigilance Task
ROI:	Region Of Interest
RQ:	Right Quadrant
TDT:	Texture Discrimination Task

LIST OF FIGURES, TABLES AND BOXES

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Figure 1.2: Growth of the scientific fatigue literature between 2000 and 2021

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PREFACE

The empirical works contained in the present doctoral dissertation combine both behavioral and neuroimaging techniques to investigate cognitive fatigue and its neural underpinnings. The first, introductory, chapter of this manuscript is designed to offer the reader a broad view on the research topic, and features 7 subsections. The first subsection focuses on the definition of cognitive fatigue, along with its role and justification for academic consideration. The second subsection further describes the phenomenon of interest by showcasing the main dichotomies identified in the study of fatigue. The third subsection covers the relationship of fatigue with other closely related psychological constructs, drawing upon experimental works when relevant. The fourth subsection presents the scientific methods and caveats found in the study of cognitive fatigue, while the fifth subsection briefly describes the workings of the neuroscience of this field. The sixth subsection encompasses a review of the main theories regarding cognitive fatigue. The final subsection of the chapter describes the theoretical bases of the empirical research project, distributed over the 2 subsequent chapters (chapters 2 to 3). Finally, in chapter 4, a general overview of the experimental results is discussed.

CHAPTER 1 – INTRODUCTION

1.1 Definition of fatigue

What is fatigue?

Although 110 years have passed since the discussion of first modern doctoral thesis dedicated to the study of mental fatigue (Arai, 1912), the most comprehensive works to date on the topic begin by stating the difficulty of establishing a univocal definition of this construct (Ackerman, 2011; DeLuca, 2007; Hockey, 2013). Despite this, throughout history the term fatigue has been regularly employed to indicate a situation of unpleasantness, whether physical and/or mental, thus being perceived as an adverse condition. Coincidentally, an example from linguistics provides empirical proof for this statement.

According to the most accredited theory on the topic (J. C. Davis, 1977), the Latin word *tripalium*, originally referring to a torture method akin to crucifixion, has evolved into the modern day word for work, which is the main cause of fatigue in everyday life, in several Romance languages (i.e. languages derived from Latin) such as: French (i.e. *travail*), Spanish (i.e. *trabajo*) and Portuguese (i.e. *trabalho*), among others. In another contemporary Romance language, the modern iteration of the same word has less subtly become equated to an intensely fatiguing and stressful event, as it is usually, but not exclusively, reserved for the process of child-birth (i.e. Italian; *travaglio*).

Curiously, the Latin word for work (i.e. *labor*), is the term commonly used in anglophone countries for child-birth.

Etymological trivia aside, in light of the above it should be quite straightforward to grasp how work, fatigue and negative states are intrinsically associated in our everyday vocabulary since the very origin of contemporary languages, even if unbeknownst to us. Perhaps awareness of this fact might have prevented, in an otherwise brilliant academic work on the topic, an established researcher to assert (R. Hockey, 2013; p. 25) that:

“Our present-day understanding of fatigue as a property of our mental life is usually framed in terms of a depletion of energy resources from work (or overwork); but it may not always have been so. The Oxford English Dictionary defines fatigue as ‘weariness resulting from bodily or mental exertion’. We say that we feel ‘tired’ or ‘weary’; or, if the feeling is stronger, ‘worn out’, ‘drained’ or ‘exhausted’; we complain of overwork and lack of energy. What is the origin of these expressions? And what do they say about what we understand our state to be when we use them? I argue in this chapter that such ideas evolved out of the changing experiences of work during the Industrial Revolution, in particular, the erosion of much of the control over work that was evident in pre-modern times. By the end of the nineteenth century, fatigue had changed from a generally benign (and rarely complained of) natural state to the negative condition we recognize today.”

Indeed, even if the parallel between the feeling of fatigue and the depletion of some finite energetic resource is thought to have become predominant during the industrial revolution (Rabinbach, 1992), given the above-mentioned linguistic facts it seems implausible that the concept of fatigue itself, which is the main outcome of work in daily life, was considered as benign in pre-modern times.

In any case, one may find an exhaustive description of the present-day meaning of the word ‘fatigue’ in the Merriam-Webster dictionary, where it is defined as:

- a) ‘labor’; weariness or exhaustion from labor, exertion, or stress.
- b) the temporary loss of power to respond that is induced in a sensory receptor or motor end organ by continued stimulation.
- c) a state or attitude of indifference or apathy brought on by overexposure (as to a repeated series of similar events or appeals).
- d) the tendency of a material to break under repeated stress.

Combining these interpretations one may determine that the layman definition of fatigue, which is not too far from the scientific one, implies the disruption of the volitional processes of an agent and their incapacity to perform further activities, possibly due to their extended, and effortful, repetition.

Every reader should be to some degree familiar with the feeling of exhaustion that arises after a day of hard work. It is also likely that he or she has experienced some occasion in which they underperformed due to prolonged engagement in some act.

The aggregate of these repercussions is what we call fatigue. Granted, such occurrence is an essential part of life shared by all beings throughout their existence, in strict relation with other experiential cornerstones such as learning and motivation.

It follows from reasoning that we categorize the aforementioned consequences of effort as mental, or cognitive, fatigue when they are elicited by cognitive activities, as opposed to stemming from physical, or manual, labor. Scholars have generally conceptualized cognitive fatigue as a sensation of mental and bodily discomfort that hinders the capacity to concentrate (Boksem & Tops, 2008; Hockey, 1997; Kurzban et al., 2013; Shen et al., 2006; Thorndike, 1900).

Several investigations have sought to link this generalized description with quantifiable alterations in specific mental acts, such as planning (Lorist, 2008; Lorist et al., 2000; van der Linden et al., 2003), attention (Boksem et al., 2005; Dorrian et al., 2006; Holtzer et al., 2011; Lim et al., 2010; Mackworth, 1948), memory (Arai, 1912; Benoit et al., 2019; Massar et al., 2010; Tyagi et al., 2009; van der Linden et al., 2003), task-switching (Borragán et al., 2017) and inter-temporal choices (Blain et al., 2016).

Yet, the presence or absence of quantifiable performance decrements as a hallmark of mental fatigue remains a point of contention in the literature, due to contradictory results (Ackerman, 2011). Since the earliest works in modern science on mental fatigue, some authors have favored the study of its consequences on behavioral outputs, believing the phenomenon to be “a condition caused by activity in which the capacity for repeating the activity that caused it is diminished” (Muscio, 1921; p. 35), while other authors have placed the sensation of weariness in primacy over the decrements in behavioral output (Bartley & Chute, 1947).

A view shared by Robert Hockey, who wrote that “the essence of fatigue (as of effort, anxiety and pain) is not its physiology or its effect on performance, but its undeniable subjective quality; the feeling of mental tiredness is one that is universally recognized and understood.” (R. Hockey, 2013; p.13). Moreover, the dissociation between the performance decrements and the feelings of tiredness is reinforced by the fact that correlations between one and the other are rarely directly tested and witnessed in experimental works (DeLuca, 2007). Inevitably, the choice of weighting more either aspect of mental fatigue influences the entire production chain of the interested researcher: from the conceptualization and design of an experiment, to the inferences made on the gathered data and their subsequent generalizations.

Nevertheless, most, if not all, investigators agree that the final outcome of mental fatigue is the withdrawal from, and aversion to engage in, further cognitive activities.

What is the role of fatigue?

Fatigue may then be considered as an adaptive mechanism, responsible for the preservation of the organism’s well-being despite the fact that the precise reasons underlying its activation remain elusive. By inducing disengagement and signaling the urge to rest to the acting entities, fatigue actively participates in determining the choice of actions that allow them to recover from the expenditure of effort that preceded its onset, whenever it is not chronically and pathologically ever-present.

An apt description for fatigue’s purpose was provided by physiologist Angelo Mosso in an influential work of the early 20th century, where he wrote: “what at first sight might appear an imperfection of our body, is on the contrary one of its most marvelous perfections. The fatigue increasing more rapidly than the amount of work done saves us from the injury which less sensibility would involve for the organism.” (Mosso, 1891; p. 156)

In light of its putative adaptive nature, distinctively recognizable manifestation common across individuals and consequences on a wide range of processes such as attention, mood, motivation and behavior, fatigue has been categorized by some as a “highly generalized emotion” (Hockey, 2013), or more specifically as a “stop-emotion” (Ackerman, 2011). However, the underlying cause for its activation is debated.

In accordance with the above-reported definition d) of the Merriam-Webster dictionary of fatigue, a sizable amount of scientists considers this phenomenon to be triggered in situations where the energetic resources that must be entailed by the expenditure of effort are virtually all but exhausted (Baumeister et al., 2007; Dongen et al., 2011; Ioteyko, 1919; Schellekens et al., 2000; Shirom et al., 2005), coming to the point of failure.

An alternative account in line with this paradigm upholds the explanation of fatigue as a protective mechanism that interrupts on-going activity when the task-relevant physiological mechanisms reach the point of near-damage due to their prolonged use (Benoit et al., 2019; Blain et al., 2016; Kato et al., 1999; McFarland, 1971).

On the other hand, some authors have described the energy-depletion approach as a source of distraction in the search for a theory of fatigue (Bartley & Chute, 1947). Accordingly, authors sharing this point of view argue that fatigue is prompted to prevent fixation on costly, low-reward, activities that are not useful to the organism for its long-term goals (Boksem & Tops, 2008; Hockey, 2013; Kool et al., 2010; Kurzban et al., 2013; Thorndike, 1900).

It is possible to broadly frame these two paradigms into a “functional” school of thought and a “motivational” perspective, as the first focuses on alterations in the biological circuitry that underlies the fatiguing activity, while the second champions the cognitive and motivational processes that subserve the volitional expenditure of effort. A more detailed description of these is the topic of section 1.6.

Why is fatigue worth studying?

Following the definition of the topic of this thesis and its role in our lives, it is pertinent to discuss why its in-depth study is appropriate. First of all, a phenomenon so fundamental to everyday experience and pervasive in the various stages of life is in itself a subject deserving of careful investigation, both of theoretical and of empirical nature.

Presumably, this is the reason why fatigue has attracted the attention of behavioral scientists from the earliest times of modern science in the first place. In addition to academic curiosity, however, the many implications that this phenomenon has on individuals and, importantly, on society have certainly driven the growing literature on the topic (see figures 1 and 2).

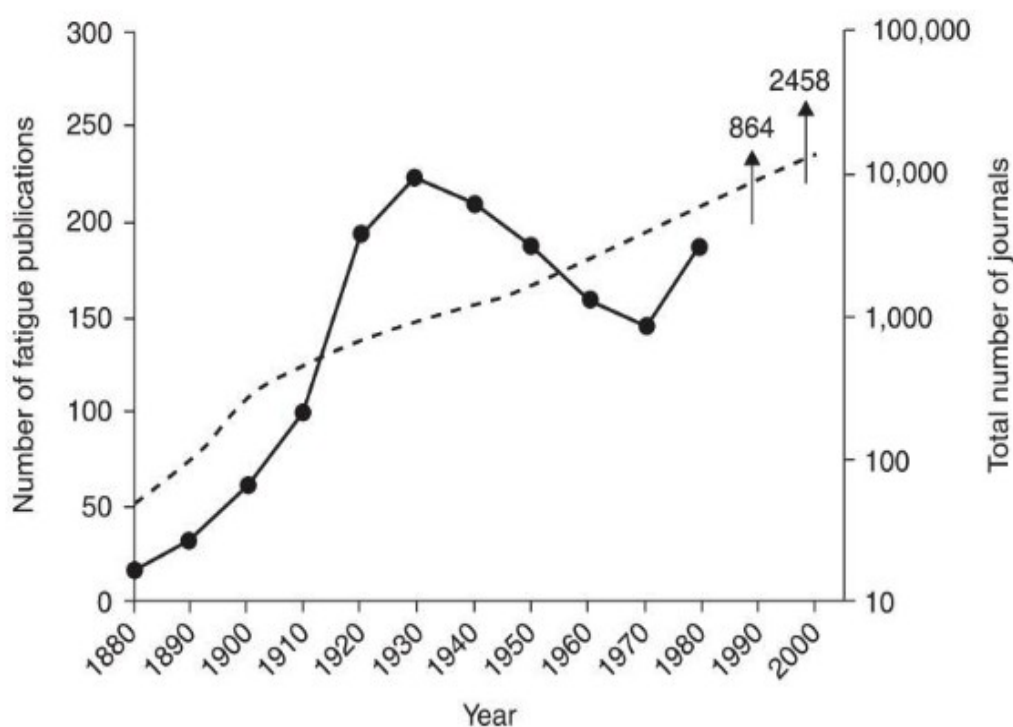


Figure 1: Growth of of fatigue publications per decade from 1880 to 2000, obtained through a query with the word “fatigue” in the title on PSYARTICLES. From “The psychology of fatigue” by R. Hockey, 2013, p.3.

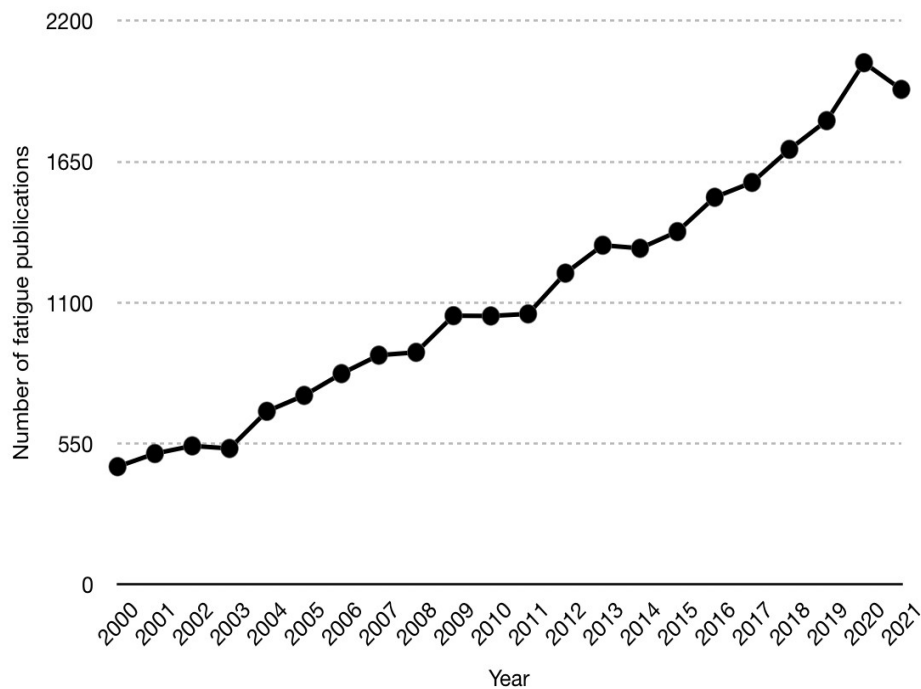


Figure 2: Complementary to above, number of publications per year between 2000 and 2021 in neuroscience, psychology and related fields with "fatigue" in the title, obtained by a query on Web of Science

Indeed, at an individual level, fatigue is linked with an overall poorer quality of life (Åkerstedt et al., 2007; Raslear et al., 2011), and academic performance (Mizuno, Tanaka, Fukuda, et al., 2011; Sievertsen et al., 2016), stress (Doerr et al., 2015), negative consequences on emotional regulation (Grillon et al., 2015) and comorbidity with several debilitating medical conditions such as Parkinson's disease, multiple sclerosis and depression (Havlikova et al., 2008; Lavidor et al., 2002; Pittion-Vouyovitch et al., 2006). At the societal level, it is evident that fatigue has an impact on the productivity of large swathes of the working population across countries (Kajimoto, 2008; Loeppke et al., 2009; Ricci et al., 2007; Setyawati, 1995; van't Leven et al., 2010). However, defining this as an economic burden for society – as is often done in these investigations – seems unjustified if one takes into account the fact that the productivity of workers in industrially developed countries has steadily increased through time (Brem, 2013; Ceccobelli et al., 2012; OECD, 2021), and may implicitly disavow the right to rest of the working population.

Of more salience is, instead, the tangible cost in human lives that fatigue has every year. From the smaller scale, but not less tragic, of car or aviation crashes (Arnold & Hartley, 2001; Goode, 2003; Patel et al., 2011; Saxby et al., 2007) to larger scale workplace risks (Baker et al., 1994; Fletcher et al., 2015) and accidents (Mitchell et al., 2004; Petz, 1994), which tend to happen near the end of shifts or/and at night, when workers are likely to be more exhausted and thus error-prone due to poorer performance (Baker et al., 1994; Schellekens et al., 2000).

In sum, what is mental, or cognitive, fatigue? First and foremost it is an umbrella term, encompassing all the changes that arise from the investment of mental effort in any given cognitive activity, i.e. the fatiguing task(s). These changes that interfere with ongoing and subsequent actions tend to be transient in nature, since a period of rest or, sometimes, a shift of task, restore the individual's baseline levels of perceived tiredness and/or performance.

At its core, mental fatigue consists in an unpleasant bodily state that manifests itself in the growing unwillingness to pursue exertion, translating into an unfocused mental status and the urge to withdraw. As stated, such condition is often accompanied by an amount of failure in the task at hand. Non-pathological fatigue serves the function of signaling to the agent when he must disengage from further effort and activity to seek rest. Thus, serving a protective role, and its overlook may entail grave consequences.

With such premise, it should be clear how mental fatigue is intertwined with other psychological constructs such as motivation, which is formalized as the set of factors that orient an individual towards a goal, determining his behavior (Atkinson, 1964), and with other constructs related to fatigue and motivation, such as: sleepiness, arousal, learning, boredom, stress and even pain. It is thus beneficial to define each of these constructs in relation to mental fatigue, in order to understand the latter optimally. Consequently, this is the topic of the third section of this monograph. However, ahead of exploring fatigue with respect to its associated psychological constructs, it is useful to describe the categoric dichotomies that have been postulated by fatigue scientists.

1.2 Dichotomies in the scientific study of fatigue

The practice of organizing complex thought into contradictory processes and viewpoints has been a hallmark of contemplative sciences and philosophy since their origin. A well-known case is Plato's choice of presenting his philosophical arguments as discussions between his mentor Socrates and opposing interlocutors (Kraut, 2017). In the 19th century, it was the German philosopher G.W.F. Hegel who further developed and formalized this concept as 'dialectical thought', casting his philosophical works into clear-cut dichotomies (Maybee, 2020).

Intuitively, formulating topics in opposition favors a clear description of the main characteristics of the processes being investigated and, accordingly, has been a staple of modern science ever afterwards. In line with this reasoning, a few categorizations have been proposed and discussed also in the domain of fatigue. Namely, these consists in: objective versus subjective fatigue, physical versus mental fatigue and acute versus chronic fatigue. These are not the only dichotomies to have been brought forth in the literature, however the additional ones (i.e. central versus peripheral, trait versus state and primary versus secondary) appear to be mostly redundant with the former.

Objective versus subjective fatigue

The main categorization of fatigue stems directly from the nature of its consequences, a distinction which has implications on how one considers the phenomenon itself. As mentioned in the previous section, fatigue is accompanied by a decrement in performance of some act and a sensation of exhaustion. The former, given its quantifiable essence, has been dubbed as the objective component of fatigue. Indeed, one may quantify the performance in most mental acts, such as number of elements recalled in a memory exercise, and therefore gauge empirically the consequences of fatigue by measuring alterations of this baseline quantity of recalled elements. This possibility has caught the interest of behavioral scientists since the dawn of modern science, with many works

dedicated to describing the “work-curve” of performance in mental tasks, from the initial learning improvement to the subsequent fatigue decay (Kraepelin, E., 1902; Oehrle, 1889).

Another aspect of objective fatigue comprises all the measurable psychophysiological changes that take place in the fatigued individual, such as alterations in heart or blink rate, muscle strength or neural activity (DeLuca, 2007). On the other hand, given the volatility of subjective states, the personal sensation of fatigue has always proved bothersome to empirically measure with respect to the objective performance drops. Nevertheless, this universal feeling is a characterizing element of fatigue and, as previously mentioned, is thought to be its sole marker by some. It must be noted that the objective and subjective aspects of fatigue may take place independently from each other, and that the two have been rarely observed to correlate (DeLuca, 2007; Hockey, 1997; Thorndike, 1900); see however (Benoit et al., 2019; Borragán et al., 2017).

Acute versus chronic fatigue

A further key contrast in the types of fatigue, beyond its repercussions, comes from its onset and/or duration. In fact, one may characterize as acute, or primary, the manifestations of fatigue that happen when an individual is carrying out a precise action, or multiple concurrent tasks, as a consequence of the invested effort. Coherently, this acute manifestation of fatigue would go into remission once the fatiguing and following acts are interrupted in order to restore the agent’s well-being. This type of fatigue is the one treated in the present work.

By contrast, one may classify as chronic, or secondary, any type of fatigue that does not arise from the engagement in some specific activity, instead being pervasively present in the individual regardless of the investment of effort, while being accompanied by an increased susceptibility to it. This type of fatigue is most often present in co-morbidity with other pathological conditions, being for example one of the most common symptoms experienced by individuals with neurological disorders (Chaudhuri & Behan, 2004).

It is not the aim of the present work to investigate fatigue as a symptom, as it should be considered by all means an aspect of the accompanying pathologies, if not a medical condition in itself when uncoupled from other pathologies.

Indeed, such is the case for ‘chronic fatigue syndrome’, which is defined as an intense fatigue state persisting for at least 6 months with substantial disruption for the individual’s social, occupational and personal activities incapable of being relieved by rest (Fukuda et al., 1994; van’t Leven et al., 2010).

Furthermore, for a formal diagnosis, at least four specific symptoms need to be present, among impaired memory or concentration, uninvigorating sleep, muscle or joint pain, drastic post-exertional fatigue, sore throat, cephalgia or tender lymph nodes (Fukuda et al., 1994).

Physical versus mental fatigue

An additional distinction in the domain of fatigue may be drawn on the basis of the nature of the fatiguing act, where it may be classified as mental when arising from cognitive actions, and physical when manifesting itself in reaction to muscular labor. In both cases the characteristics of fatigue stay similar; that is a progressive incapacitation to exert effort accompanied by a mounting sensation of weariness that disincentives further activity.

A key aspect that differentiates the two is our innate ability to perceive distinctly between different subtypes of physical fatigue, based on how they involve whole-body exercises (i.e. endurance training like cycling) or specific single-muscle activities (hand-gripping, finger tapping, etc..). In comparison, mental fatigue appears to us as a mysterious puzzle. Indeed, an equivalent notion of whole-brain or single-joint activity hasn’t been developed in this domain. Extensive research has been carried out investigating the interaction between mental and physical fatigue to probe their similarities and divergences, particularly on the influence of cognitive effort on physical output.

The aforementioned pioneer physiologist Angelo Mosso undertook the earliest modern inquiries into this topic. As part of his scientific endeavors he invented the ergograph, a machine capable of recording and quantifying the contractions performed by the flexor muscles of the index finger (Di Giulio et al., 2006).

By measuring the muscular output in several conditions, notably after a day of high mental effort of lecturing, he reached the conclusion that “fatigue of brain reduces the strength of the muscles” (Mosso, 1891). This result of mental strain negatively affecting motor performance was confirmed over a century later in multiple experiments, without any alteration induced by mental fatigue in physiological markers of effort, such as heart and respiratory rate (Marcora et al., 2009; Pageaux et al., 2013; Van Cutsem et al., 2017).

In partial disagreement with these results, a recent meta-analysis on the topic argued that the effect sizes of the reported results are small-to-medium, and may have been inflated by publication bias. Reaching, therefore, the conclusion that there is not compelling support for the claim that mental fatigue has a negative influence on exercise performance (Holgado et al., 2020).

In line with this, there have been some reports of mental activity as having an enhancing effect on muscular exertion, possibly through the allocation of attentional resources to optimize neuromuscular cooperation (Saidane et al., 2021). It must be noted, however, that the type of mental task used in this series of experiments to manipulate effort varies considerably, from a cue-probe letter sequence task (Marcora et al., 2009) to sustained concentration pre-movement (Saidane et al., 2021).

Whatever may be the case for the interaction between these two types of fatigue, its mechanisms in the physical domain have been more thoroughly described (see box 1) than those in the mental domain, which remain elusive. Thereby, the focus of the present work is on fatigue arising from mental activities and its neural bases.

Lastly, it must be mentioned that some researchers, especially in the earliest works on the topic, refused the notion of considering physical and mental fatigue as separate (Arai, 1912; Thorndike, 1900).

Box 1. “How does muscular fatigue work?”

Muscle fatigue is defined as a decrease in maximal force in response to contractile activity. In order to sustain power production in the involved muscles, there is a sizeable increase in the blood supply to the interested area, and metabolites such as adenosine triphosphate and glycogen are consumed by the local cells, while heat and other by-products such as lactate and IL-6 cytokine are released, altering the state of the tissue involved in the exertion of effort. If the local reserves of metabolic fuel are threatened by their prolonged use, the body recurs to depleting energy reserves stocked elsewhere.

Concurrently to these local alterations (defined as ‘peripheral’ fatigue), a decreased drive is thought to modulate the action potentials stemming from the motor cortex (defined as ‘central’ fatigue), reducing the output of the spinal motor neurons that subtend the muscular contractions (Wan et al., 2017).

Having described the main dichotomies in the field, we may now illustrate the topic of the present thesis as non-pathological, acute, cognitive (or mental) fatigue, both in its objective and subjective dimension.

1.3 Fatigue and its related constructs

Psychological latent constructs consist in complex, abstract, concepts that are observed through a collection of related events. Or, more precisely, a construct is some theorized attribute of people, generally assumed to be indirectly measurable (Cronbach & Meehl, 1955). The workings of psychological formalization, that can also be applied in the case of constructs, have been wittily described by P. Smaldino when he wrote (Smaldino, 2017; p.7):

“As many a late-night dorm room conversation can attest, humans are capable of very elaborate theories about the nature of reality. The problem is that, as scientists, we need to clearly communicate those theories so that we can use them to make testable predictions. In the social and behavioral sciences, the search for clarity can present a problem for verbal models, and can lead to a depressing recursive avalanche of definitions. What is a preference? A preference is a tendency for certain behaviors. What are those behaviors? It depends on the context. What is a context? This can go on for a while.”

Regardless of the ephemeral nature of constructs, the majority of psychological models rely on the assumption of their existence, and strive to measure them. A common pitfall in their postulation is the degree of overlap with similar speculated processes, hence why, among other reasons, the concept of “construct validity theory” was introduced to assess the precision of measuring a proposed construct (Cronbach & Meehl, 1955). For the purpose of the present work, it is thus indispensable to elaborate its construct of interest – that is cognitive fatigue – in regards to its most closely associated phenomena, a commonality likely due to their shared underlying components.

Sleepiness

Possibly, the construct most similar to cognitive fatigue is sleepiness, as we conflate these two processes in our daily experiences. Alike to the case of fatigue, no clear consensus has been found among scientists as to what is exactly implied by the universal experience of sleepiness (Shen et al., 2006). An individual who has spent several hours engaged in some activity is, at the end of the day, sleepy or – mentally and/or physically – fatigued? There are multiple facets from where to address this question, but as a premise one must ascertain his degree of belief in the fact that sleepiness and fatigue are discrete and separable.

Indeed, the two concepts are often used interchangeably, or merged under the more general lay term of 'tired', which has contributed to the murkiness in their distinction, even in the scientific literature (Shen et al., 2006).

A binding characteristic of these two constructs is their similar progressive accumulation during wakefulness as a mounting drive to disengage from activity, which is the probable cause for the blurring between the two states. However, in the manner through which these circumstances appear to us, we subjectively feel – to some degree – a qualitative difference between the two, as the feeling of sleepiness is discrepant to that of weariness. For instance, one can distinguish fatigue and sleepiness based on their causes, as sleepiness arises from the lack of sleep, which depends on factors such as the internal biological clock of the organism, the circadian rhythm (Balkin & Wesensten, 2011), while non-pathological fatigue arises exclusively from the prolonged investment of effort.

Another distinction comes from how we recover from these instances of the body. In the case of sleepiness, there is a clear, impelling, need to sleep, which is defined as “a reversible condition of reduced responsiveness, usually associated with immobility” (Cirelli & Tononi, 2008). This unique state is marked by various definite cycles (Feinberg & Floyd, 1979) and dreams (M. Walker, 2017). Sleepiness may then be described as an intense state of drowsiness, where the urge to sleep becomes gradually preponderant, often overriding ongoing thoughts and activities until the individual finally succumbs to the relieving embrace of Morpheus¹.

On the other hand, in the case of fatigue, often a short, sleepless, rest is sufficient to recover (Ackerman, 2011), since it is dependent on effort and its demands, not sleep deprivation nor circadian rhythm. So far, only the subjective feelings of fatigue and sleepiness have been considered, though there is considerable intersection also in their behavioral, and thus experimental, manifestation.

1 *Roman deity of sleep and dreams*

Indubitably, both have meaningful impact on the performance of the action one is involved in, as sleepiness and/or fatigue increase. These phenomena deter the optimal performance of ongoing behavior and such loss is often used as the dependent variable whenever they are empirically investigated. Yet, they can be separately assessed.

An oft cited example for this dissociation of performance decrement due either to sleepiness or to mental exertion comes from a study (Wesensten et al., 2004) which focused onto the extent to which caffeine and a psychostimulant drug (Modafinil) were able to reverse “fatigue effects” (i.e. the performance decrement) arising from task repetitions during prolonged sleep deprivation. In this experiment, a sample of participants was put in a condition of progressive sleep deprivation for 54.5 hours and their performance on the Psychomotor Vigilance Task (PVT) was assessed every 2 hours. This task consists in a 10-minute attentional exercise that requires participants to respond as quickly as possible to a stimulus appearing at random intervals (within 2 to 10 seconds). The results show an interaction between the accumulation of sleep deprivation and the performance drops due to repetition reappearing at every iteration of the PVT, which were exacerbated by the number of hours spent awake (see figure 3), while Caffeine and Modafinil were able to partially reverse this effect. Therefore, providing evidence for the notion that the decline in behavioral performance witnessed due to fatigue may be distinguished from the one provoked by sleep deprivation.

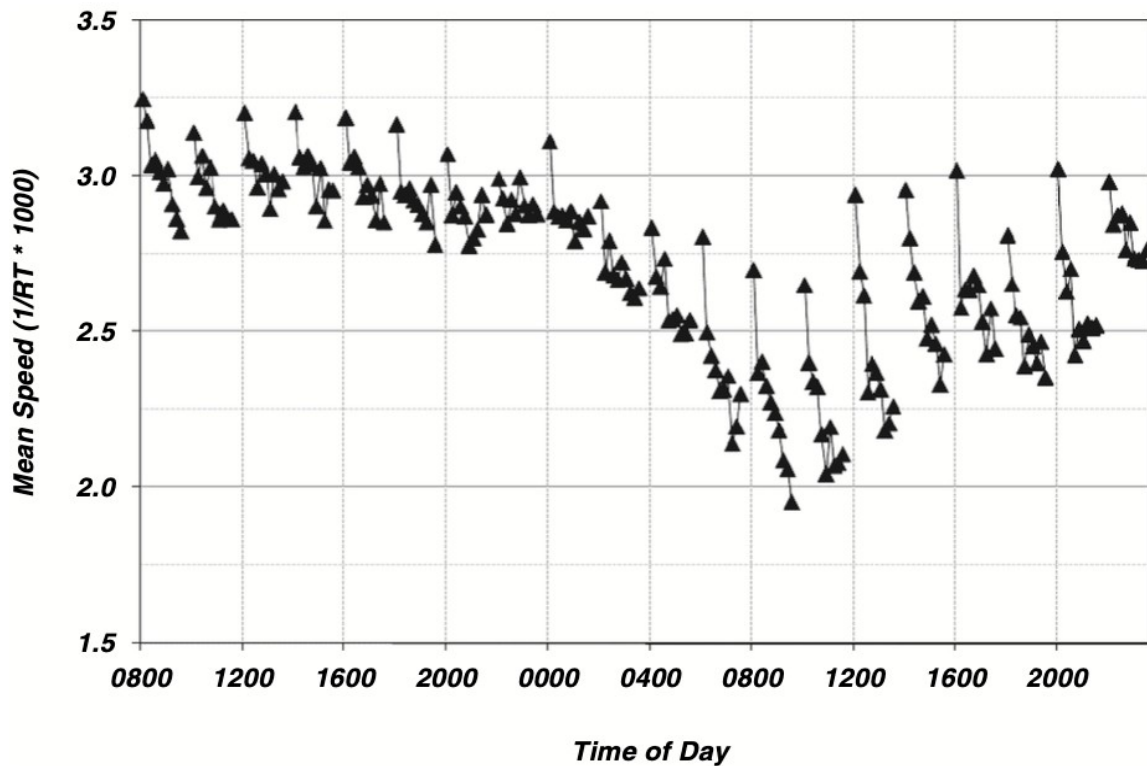


Figure 3: Interaction between fatigue and sleepiness effects. From this figure, one may appreciate how performance (y axis) deteriorates as a function of task-repetition within testing hour [fatigue] and concurrently as a function of time (x axis) spent in a sleep-deprived condition [sleepiness]. From “Modafinil Versus Caffeine: Effects on Fatigue During Sleep Deprivation,” by N. J. Wesensten et al., 2004, *Aviation, Space, and Environmental Medicine*, RT = reaction time.

Still, some researchers interpret similar results as indicating an overlap in the neural underpinnings of the two processes (Satterfield et al., 2017).

In fact, performance decrements arising from sleepiness or task repetition may share the same neurobiological bases, as posited by the ‘local sleep’ theory, a model described in the section of this manuscript dedicated to the functional and motivational paradigms of mental fatigue.

Boredom

Consistently with the constructs treated so far, there is no universally shared definition of boredom.

Nevertheless, its main manifestation has been scientifically described as “a specific mental state that people find unpleasant—a lack of stimulation that leaves them craving relief, with a host of

behavioral, medical and social consequences” (Koerth-Baker, 2016). Or also as “a state of relatively low arousal and dissatisfaction, which is attributed to an inadequately stimulating situation” (Mikulas & Vodanovich, 1993).

Similarly to sleepiness, we may distinguish boredom from fatigue by two key aspects: origin and recovery. In fact, boredom may appear specifically because the agent isn’t engaged in any type of task, or alternatively it may arise from being engaged in a situation he would rather not be engaged in. This causes in the individual a need to actively seek some other, subjectively more gratifying, activity, even if effortful. On the other hand, in the case of fatigue, as mentioned, generally there should be a need for some type of rest before switching to a new activity, and if it is present when the agent hasn’t been involved in some kind of exertion, it is a symptom of some underlying medical condition. Yet, the distinction between cognitive fatigue and boredom remains a challenging problem.

Indeed, if fatigue is framed as the progressive need to change on-going repeated activity, coupled with a loss of optimal performance in said activity, how can we distinguish it from boredom, which manifests itself in a similar fashion? This is particularly true in experimental settings, which largely consist of participants recruited from the student or general population for the purpose of spending a few hours in a laboratory to provide data to the researcher via repetitions of rarely entertaining tasks.

Thus, these experimental tasks are of intrinsically low-value and likely to provoke boredom in the person carrying it out, even more so given that said activity is rarely conceived with the “end-user” perspective in mind. A hallmark example for this is the case of Colleen Merrifield, a researcher in cognitive science who purposely developed a dull video to induce boredom in participants, in order to test its effects on a subsequent sustained vigilance task. Eventually, she was forced to change her design, since the task itself bored participants more than the video (Koerth-Baker, 2016).

This is a dilemma without an apparent solution also in the domain of fatigue research, as there are no tools that discern with what degree of “true fatigue” a participant responds to the items in a fatigue questionnaire or to the demands of some task, while actually under the influence of boredom. Awaiting such elaborate tools, every researcher is left to his own intuition in designing an experiment that may account for this unavoidable phenomenon, doing his best to control for it and address such potential limitation, as fatigue, sleepiness and boredom are routinely intertwined in our daily lives, and even more so in experimental settings.

Motivation

If one considers the three above-mentioned constructs, fatigue, sleepiness and boredom, it is fairly plain to recognize that they all share a common factor: their dependence and impact on the drive to conduct, or not, actions. Thereby, since motivation consists in the force that causes an agent to partake in some goal-directed action (Atkinson, 1964), it is safe to conjecture that these processes are influenced by it. In fact, a sizable part of fatigue researchers believes motivation and the usefulness of activity to be the main factors at the origin of tiredness (Boksem & Tops, 2008; Herlambang et al., 2019; Hockey, 2011; Kurzban et al., 2013), an argument that will be addressed in section 1.6 of this monograph.

An indicative example of how different levels of motivation influence task performance comes from a recent work on mice, where neurons in the anterior insula – which influence the brain’s motivation circuit through the activation of a specific gene² – were directly manipulated by experimenters (Deng et al., 2021).

Coherently with the type of manipulation conducted on these neurons (i.e. excitation or inhibition), mice would increase or decrease their behavioral output to obtain sugar rewards in a range of tasks in which they were trained, such as licking a water bottle spout or running on a wheel.

Thus, designing experiments that probe the alterations of performance due to fatigue while controlling for variations in the levels of motivation to engage in the laboratory task represents a challenge for researchers. Attempts to experimentally manipulate motivation in fatigue conditions, usually by increasing the monetary reward associated with task efficiency, have yielded conflicting results: either successfully restoring performance (Boksem et al., 2006; Hopstaken, van der Linden, et al., 2015; Hopstaken et al., 2016; Lorist et al., 2009) or failing to do so (Esterman et al., 2014; Gergelyfi et al., 2015, 2021; Mednick et al., 2002).

Arousal

Arousal can be broadly defined as a state of physiological and/or psychological excitation, driving the responsiveness of individuals to sensory stimuli (McGinley et al., 2015). It also influences, albeit non-linearly, behavioral output. Therefore, it is strictly related to motivation, with which it has been shown to co-vary (Kahneman & Peavler, 1969), boredom, sleepiness and its opposite, alertness. Nevertheless, the link between arousal and fatigue has been scarcely explored, except for a study which failed to observe any relation between the two (Benoit et al., 2019).

Notably, given its dependence on the norepinephrine released in the midbrain, pupil size is a valid physiological marker of this construct, providing a quantifiable proxy measure of it (Berridge, 2008; Reimer et al., 2016), unlike the constructs treated so far.

Activities may be placed along a continuum from low to high arousal, and perhaps the best way to convey its sense is with an example: we may indicate an engaging puzzle-solving game as a high arousal activity, and we may assume proof reading some extremely tedious text (hopefully not this manuscript) as the opposite³.

3 *Clearly, this is dependent on a number of factors, such as the personality of the individual performing the act. Some, although not many, may find proof-reading more salient than solving a puzzle*

It has been theorized that the fundamental reason of existence for arousal is to coordinate the agent's response to events in a manner that amplifies attentional focus to the most salient or goal-relevant information while suppressing the rest (Mather et al., 2016).

One may then speculate the involvement of arousal levels in influencing the outcome of fatigue. Accordingly, it has been proposed that fatigue occurs as a consequence of excessive arousal, increasing neural noise under the continued stimulation of challenging tasks (Welford, 1968).

Learning

Considering how fatigue determines the temporary loss of performance in some activity, learning may be placed at the opposing side of a putative skill acquisition spectrum.

Coherently, several studies have been conducted in the earliest attempts to investigate human performance in mental tasks, from improvement to deterioration. Such studies (Kraepelin, E., 1902; Oehrn, 1889) meticulously observed how participants oscillated between these states across time in a plethora of mental activities, such as reading, writing from dictation, addition, counting letters one by one or three by three and learning numbers or nonsense syllables, dubbing it as a “work-curve”. Interest over this fascinating subject hasn't faded in time, as computational models on the subject have been put forth relatively recently (Gonzalez et al., 2011).

Importantly, paradigms developed to probe learning may be adapted to investigate fatigue, as is the case for the works in this thesis.

Stress

Stress has many aspects in common with fatigue. In the first place, it lacks a clear-cut definition. Then, it is defined by its behavioral or physiological responses, yet these have been observed to be discordant in terms of magnitude and direction of effect (Levine, 1985).

One may succinctly posit stress as “the perception of threat with resulting anxiety discomfort, emotional tension and difficulty in adjusting” (Selye, 2013).

Similarly to fatigue, stress consists in an unpleasant bodily state, marked by the subjective feeling of strain and performance decrement (Matthews et al., 2000). Nevertheless, an important distinction lies in the fact that the conceptualization of stress has always emphasized reaction to stressors, that is, factors capable of threatening the organism’s homeostasis (or perceived to be so) and changes in the endocrine system (Levine, 1985). Any uncontrollable stimulus or condition capable of eliciting a ‘fight or flight’ reaction via intense sympathetic activation may be categorized as stressor (Chrousos, 2009).

Thereby, unwilling expenditure of effort in a low-reward, low-control, task has been posited by Hockey to act as a stressor, which causes the subjective state of strain in the attempt to maintain low utility goals (Hockey, 1997). However, even if a link was found between self-reported measures of stress and fatigue, no evidence supported a causal relationship between cortisol, the main neuroendocrine marker of stress, and subjectively evaluated fatigue (Doerr et al., 2015; Klaassen et al., 2013).

Pain

As several English words in current use, the word pain derives from a Latin word: *pæna*, which essentially described the price to pay for some crime (and its modern versions still do in Romance languages). Eventually, one of the evolutions of this term – that is pain in English – has evolved to indicate exclusively the unpleasant bodily sensation that used to be linked with receiving a punishment. If one bears in mind this broader concept of pain as the negative price to pay for some action, then one could make a parallel with the notion of fatigue arising from effort.

This is by all means an unusual comparison, yet some would argue that whenever the subjective sensation of mental tiredness reaches its zenith, then its aversiveness may be compared to a state of such discomfort to cause headache.

Furthermore, we can identify a key feature of both pain and effort investiture: the general proclivity of individuals to avoid both, whenever possible.

Such is the premise for a recent investigation exploring the similarities between cognitive effort and pain. In their design, Vogel et al. offered participants a choice between varying degrees of cognitive effort, in the form of the n-back task, and of physical pain, in the form of intense heat.

The main finding was that at higher levels of cognitive demand participants significantly tended to prefer a physically painful stimulus, effectively demonstrating that mental effort can be traded off for physical pain (see figure 4; Vogel et al., 2020).

Thus, this study provides compelling proof that one may go to great lengths in order to avoid mental effort. Indirectly, and unawarely⁴ to the authors, providing support for the “law of least effort” postulated by Guglielmo Ferrero in 1894, which stated that in the mental realm, just as in the physical realm, individuals seek to minimize exertion as much as possible.

In his seminal paper, this author stated that (Ferrero, 1894; p. 9):

“Man instinctively proves aversion towards all forms of mental effort. [...] when the necessities of existence force him to work with the brain, man always seeks to accomplish the smallest effort, to use the psychological processes which cost him the least fatigue and which therefore are not painful.”

4 *As far as can be told by reading their manuscript*

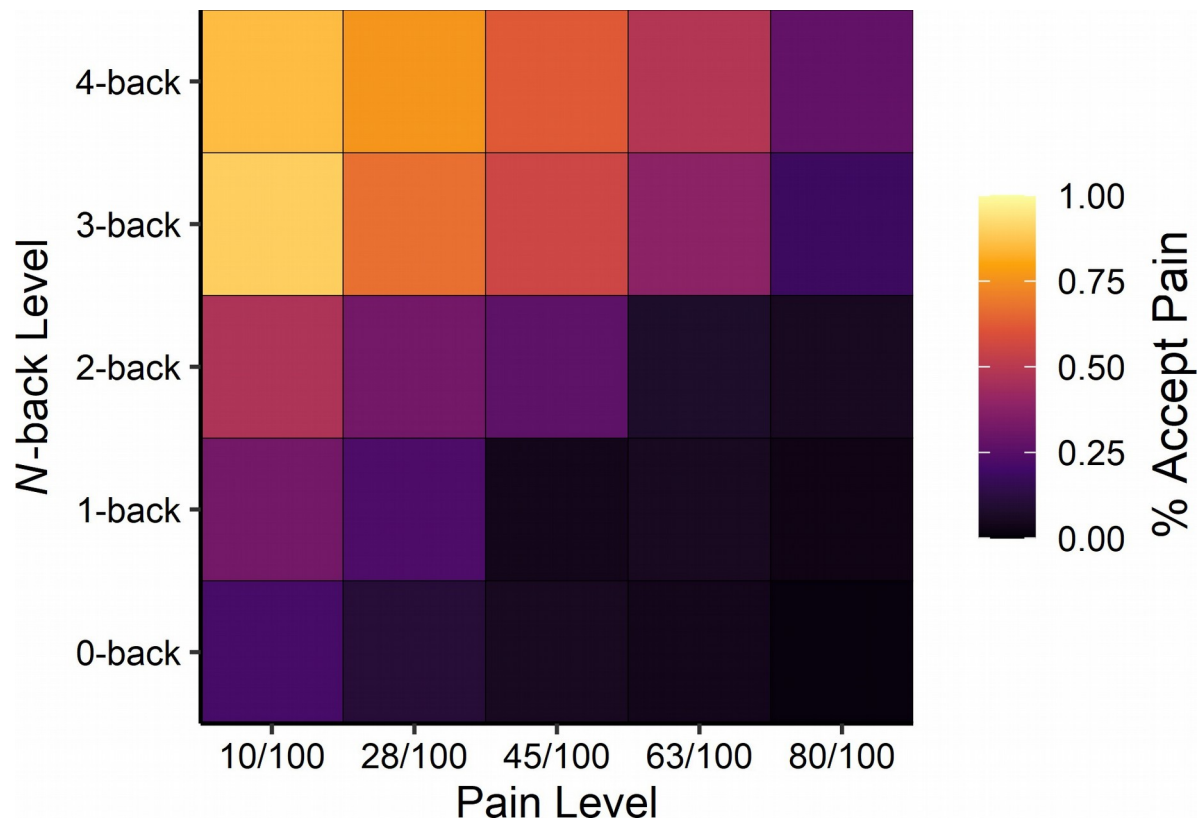


Figure 4: Averaged heatmap of choice behaviour across participants as a function of pain stimulus level (horizontal axis) and N-back difficulty level (vertical axis). From "Forced choices reveal a trade-off between cognitive effort and physical pain" by T. A. Vogel et al. 2020, *eLife*.

1.4 Methods and caveats in the scientific study of fatigue

Given the nuance that separates mental fatigue from other constructs, an interested researcher must develop sound methodology that seeks to control as best as possible for their influences.

Nonetheless, the nature of these pitfalls or confounds does not exclusively stem from other theoretical constructs, as there are other additional factors that one should, ideally, keep present when inducing fatigue. The next paragraphs aim at providing a succinct description of the most commonly found and known confounds. However, before doing so, it is best practice to discuss the methodological techniques by which fatigue is manipulated in experimental settings.

Continuous work and probe methods

As mentioned beforehand in the relevant part of this manuscript, the performance decrements that are witnessed as a product of fatigue have been categorized as its objective manifestation, due to their comparatively ease of measuring with respect to the subjective components.

In light of this, it may appear straightforward that most methodological approaches have focused on this aspect of fatigue, while the subjective component is generally measured by means of self-reported questionnaires (DeLuca, 2007), with the most onerous methodological decision lying on the specific questionnaire choice.

Considering task-related performance decrements, usually consisting in reduced accuracy and/or longer reaction times, there have been generally two types of techniques employed, which test either the time course of mental fatigue or its generalizability. These have been named the ‘continuous work’ and ‘probe’ methods respectively (Hockey, 2013).

In fact, as we have previously defined the objective component of fatigue to be the performance decrement arising during the execution of a task and hindering successive activity, these are the two facets onto which research has focused.

A considerable portion of studies on fatigue have made use of markedly lengthy designs to induce the observable decrements (the so called ‘time on task’ effect; (Bills, 1937; Blain et al., 2016; Boksem et al., 2005, 2006; Hopstaken, Linden, et al., 2015; Lorist, 2008; Trejo et al., 2005; van der Linden et al., 2003; C. Wang et al., 2016)), or in alternative shorter designs with harder demands (Borragán et al., 2017). This method provides the advantage of characterizing the evolution of fatigue in time, though concurrently limiting its scope to the impact on the employed task. By contrast, the probe method seeks to assess the transferring effects of mental fatigue, that is its widespread, unspecific, aftermath following its triggering in the fatiguing task (Blanco et al., 2006; Klaassen et al., 2013; Massar et al., 2010; Plukaard et al., 2015; Posner & Boies, 1971). Such approach affords testing the common substrates shared by the different processes. On the other hand, there is a tendency to overlook fatigue’s evolution in the primary task in these types of designs, potentially fostering misinterpretations on the actual evolution of performance decrements.

Choice of task and level of skill

As mental effort may be expended in any type of task requiring thought, one may expect a considerable disparateness in the range of tasks employed by researchers. Accordingly, a non-exhaustive audit of the relevant literature confirms this, with tasks ranging from classic psychological tasks such as the n-back (Hopstaken, Linden, et al., 2015; Ishii et al., 2013) and stroop task (Smolders & de Kort, 2014), to digit span and advanced progressive matrices task (van der Linden et al., 2003), action monitoring (Boksem et al., 2006), cognitive control tasks (C. Wang et al., 2016), various types of psycho-vigilance tasks (Gui et al., 2015; Haubert et al., 2018; Lim et al., 2010; Mackworth, 1948; Tyagi et al., 2009; Xiao et al., 2015), sudoku (Gergelyfi et al., 2015), mental arithmetics (Thorndike, 1900; Trejo et al., 2005), flanker tasks (Faber et al., 2012; Lorist et al., 2005), switch tasks (Lorist et al., 2000; Plukaard et al., 2015), memorizing tasks (Meijman, 1997; Roy et al., 2013), cue-probe sequence tasks (Marcora et al., 2009; Pageaux et al., 2013),

advanced trail making test (Kajimoto, 2008; Tanaka et al., 2009), simon task (Arnau et al., 2021; Möckel et al., 2015) or a combination of a number of cognitively demanding tasks (Arai, 1912; Blain et al., 2016; Mizuno, Tanaka, Yamaguti, et al., 2011).

At a glance, this variety of tasks renders the conundrum of unveiling the neural underpinnings of fatigue rather problematic. Indeed, in most of these tasks the precise underlying neuronal processes are poorly known, if at all. Therefore, how could one verify if they are impacted by exertion, and thus reflect fatigue? Coherently with this, few studies have accurately sought to measure this phenomenon, rather preferring to focus on the electric activity of the brain as a whole, by means of electroencephalography (EEG), likely due to its compatibility with long experimental runs (Barwick et al., 2012; Boksem et al., 2005; Borghini et al., 2014; Chen et al., 2021; Craig et al., 2012; Klimesch, 1999; Lorist et al., 2009; Roy et al., 2013; Trejo et al., 2007), or integrating in theoretical models findings from empirical neuroscientific studies devised to directly probe other psychological constructs, such as reward and motivation (Boksem & Tops, 2008; Hockey, 2013; Kool et al., 2010; Kurzban et al., 2013). Unsurprisingly, reviews on the topic of the neuroscience of mental fatigue are inconclusive, with a recent meta-analysis arguing that subjective cognitive fatigue in the healthy population has a recognizable cerebral electrophysiological signature, consisting in an increase in theta activity in frontal, central and posterior portions of the brain (Tran et al., 2020).

Such conclusion is in fact in partial disagreement with other accounts that had found: a main involvement of the alpha rhythm (Trejo et al., 2015), no involvement of specific frequency bands (Lorist et al., 2009), or that different types of mental fatigue produce different kinds of alterations in the various EEG bands (Tanaka et al., 2012).

It must also be noted that the theta rhythm is thought to reflect decreased alertness during drowsiness (Schacter, 1977), hence it is unclear to what extent these conclusions regard the neural mechanisms of mental fatigue, rather than reflect the state of drowsiness that is likely to be induced by the monotonous, hour-spanning, experiments that have been generally employed.

More narrow, and thereby accurate, research has been carried out on the event-related potentials (ERP) measured by EEG, finding changes in the error-related negativity and P300 signals (Boksem et al., 2006; Lorist et al., 2005). As these signals are believed to underlie respectively performance monitoring in the anterior cingulate cortex (Yeung et al., 2004) and information processing (Polich & Kok, 1995), these results provide neurophysiological markers for the errors that are observed under cognitive fatigue, yet do not provide sufficient insight into potential changes taking place into the task-relevant networks. A further relatively recent review on the topic of the neuroscience of fatigue (Ishii et al., 2014) argues for the existence of ‘facilitation’ and ‘inhibition’ systems which partake in the onset of cognitive fatigue, in addition to the changes within the task-related neural networks. These systems, inspired by the biology of physical fatigue, would encompass most of the cerebrum and regulate the activity of task-related networks during cognitive task performance. Proof for the existence of the theorized systems is limited, and it seems more plausible that the main fatigue-induced alterations in the neural circuitry take place in the neuronal assemblies directly involved in the task (Gergelyfi et al., 2021).

An additional key factor to account for is the level of skill of participants in the fatiguing task. It is well-known in fact, since the earliest work on the previously mentioned ‘work-curve’, that performance is actively mediated by expertise in the task itself. For example, already in 1912 Tsuru Arai (see box 2) observed that individuals more competent in the task were usually less impacted by fatigue (Arai, 1912). The absolute level of skill is not the sole factor to account for, since prior practice with the fatiguing task itself is essential to rule out, as much as possible, the improvement due to initial learning. Thus, the ideal task to investigate the neuroscience of fatigue would need both reasonably clear neural bases and directly manipulable demands, in order to be adapted to the skill of agents engaged in it.

Box 2. “Tsuru Arai’s seminal thesis on mental fatigue”

A pioneer woman in science, Tsuru Arai was awarded with a PhD in experimental psychology in 1912, being the first Japanese woman to ever receive one.

Her work focused on the impact of prolonged mental exertion on performance of a range of tasks (arithmetics, memorizing nonsense syllables, translating across languages) and physiological variables, such as pulse rate and body temperature.

She was among the first to report the transferability of mental exhaustion over different tasks and the relationship between subjective feelings of fatigue, decreased efficiency in mental functions and heart rate variability.

Furthermore, she presented evidence for interindividual differences in the susceptibility to mental fatigue, as participants who were more competent displayed a different evolution with respect to participants with less familiarity with the task (Arai, 1912).

Physical factors

So far only caveats depending on internal elements have been considered. However, several external variables that may influence the progression of mental fatigue have been identified.

The time of day, and its interaction with the circadian rhythm, has been shown to significantly impact the triggering of mental fatigue (Powell et al., 2007).

Another case of time of day influence involves the post lunch drop in alertness, which is not due solely to digestion, but is also dependent on the circadian rhythm of humans (Monk, 2005).

Additionally, it is known that during digestion there is a decrease in activity in the sympathetic nervous system with a concurrent increase in parasympathetic activity, reducing norepinephrine in the system (Bray, 2000), resulting in a decrease in arousal which leads to observable repercussions on task performance. Changes due to food intake are visible also on the brain’s activity, as the signal characteristics (amplitude, latency) of several event-related components have been found to be modulated by food assimilation (Geisler & Polich, 1992).

Likewise, the consumption of psychoactive drugs can greatly impact the onset of mental fatigue. From largely diffused molecules, such as caffeine and nicotine, to prescription drugs such as Modafinil or illegal drugs such as amphetamines, a wealth of substances is capable of deterring and slowing the time course of fatigue (Griesar et al., 2002; van Duinen et al., 2005; Weiss & Laties, 1962; Wesensten et al., 2004).

Ambient temperature is another circumstance that must be controlled in experimental settings that seek to study mental fatigue, as its impact on the onset of this phenomenon has been thoroughly proved in the physical domain (González-Alonso et al., 1999; Nybo et al., 2014) and some proof has been found also in the mental domain (Qian et al., 2015).

Lastly, the posture of participants is a factor to keep in mind when studying mental fatigue, especially in the case of experiments involving Magnetic Resonance Imaging (MRI) scan sessions, as these require the volunteer to be lying down, which has been shown to decrease arousal and induce sleepiness (Kräuchi et al., 1997).

1.5 Synopsis of the neuroscience of fatigue

Generally, the neuroscience of cognitive fatigue has, apart from the aforementioned investigations on alterations in the EEG bands, focused on the role of two cerebral regions: the prefrontal cortex (PFC) and the anterior cingulate cortex (ACC).

The PFC consists in the anteriormost region of the brain, usually identified with a portion of neocortex in the frontal lobe that contains a distinct granular layer unique to primates, while it is agranular in other species such as rodents (Carlén, 2017). This region is a hub for converging information as it receives and sends signals to all cortical sensory and motor systems.

It plays a critical role in goal-directed behavior that requires attention, flexibility, memory and adaptation to rapidly changing associations between sensory inputs, actions and internal states.

In other words, it has been identified as the cerebral region responsible for executive functions and top-down processing (Miller & Cohen, 2001). Coherently, lesions to this area lead to deficits in working memory, rule-learning, planning, attention, and motivation (Szczepanski & Knight, 2014).

It appears straightforward then to see how alterations in the performance of tasks that require any of these processes should be reflected by changes in the activity of this cerebral area. Indeed, such is the case for studies employing attentional paradigms in fatigue conditions, across neuroimaging methods (Lim et al., 2010; Lorist et al., 2000).

Moreover, it has been shown that recruiting the lateral PFC over prolonged time with challenging executive control tasks decreased the blood-oxygen-level-dependent (BOLD) activity within this area across the work day (>6h). This coincided with an increase in impulsive behavior, a sign of diminished top-down regulation, when compared to a control group undergoing easier tasks (Blain et al., 2016).

The ACC consists in the anterior section of the innermost and archaic portion of the human cortex, the cingulate gyrus, developed around the corpus callosum. The role of this region in the management of conflicting information, for example in the context of the stroop task, is amply documented (Barch et al., 2001; MacLeod & MacDonald, 2000; Yeung et al., 2004), along with its function in monitoring performance, characterized by a distinct electrophysiological signature; the error-related negativity, which was found to be attenuated by cognitive fatigue, unlike other ERP components (Lorist et al., 2005).

It has been proposed that the ACC serves to detect internal states and events that indicate a need to strengthen top-down processing or shift the focus of attention by evaluating conflicts between required and actual actions and threats to their outcome (M. M. Botvinick et al., 2004).

Additionally, it has also been posited as the brain's key region for effortful engagement with task goals, due to its localization between motivation and motor areas of the brain (Paus, 2001). In line with this, the joint activity of the PFC and the ACC has been observed to have a coordinated nature (Milham et al., 2003) and the two are anatomically linked by dopaminergic connections (Aarts et al., 2011), which is consistent with the well-known role of dopamine in determining behavior motivated by reward (Baik, 2013; Schultz, 2002; Taber et al., 2012).

Along with the PFC and ACC also the basal ganglia, which consist in a subcortical set of six interconnected nuclei, have received attention from cognitive scientists interested in fatigue due to their relaying function between the two aforementioned areas and the role they play in the preparation and execution of movements and in dopamine-reward signaling (Chaudhuri & Behan, 2000).

On the other hand, there are fewer works focusing on fatigue-induced alterations in task-relevant networks other than the PFC, or more broad frontal areas, and ACC. Yet, compelling evidence for their existence has been brought forth in several experiments.

For example, one work employing visual search trials found that healthy participants displayed a fatigue induced decrease in BOLD activity exclusively in the visual cortex, as opposed to patients with chronic fatigue syndrome, where it was found that this proxy measure of brain activity decreased also in the task-unrelated auditory cortex (Tanaka et al., 2006). Similarly, and of particular salience for the following section of the thesis, a recent experiment ascertained the impact of fatigue on the task-relevant networks following 90 minutes of cognitive effort, while at the same time failing to observe any alteration taking place in the brain areas involved in motivation (Gergelyfi et al., 2021).

1.6 Functional and motivational accounts of cognitive fatigue

In these paragraphs a tentative framing of some of the main models on cognitive fatigue, with a focus on its neuroscience, is presented. One may broadly distinguish between a functional perspective, concerned with the posited changes taking place in the circuitry directly subtending the effortful action, and a motivational paradigm focused on the drive to partake in actions according to their intrinsic reward value and utility for the long-term objectives of the organism.

Functional perspective

As aptly noted by Hockey (Hockey, 2013), historically several authors in the cognitive sciences have referred to an abstract “energy” underlying disparate mental states and processes: from Freud’s ‘psychic energy’ (Strachey, 1964) to modern day publications (Baumeister et al., 2007; Deci & Ryan, 2008; Lieberman, 2007; Shirom, 2003; Zohar et al., 2005). Notwithstanding, what this mental energy may actually consist in is often left opaque, as it is seldom precised in these texts. With the notable exception of ego-depletion theory, which clearly hypothesized brain concentrations of glucose to be involved in effortful self control (Gailliot & Baumeister, 2007), however this research was shown to be confounded by the participant’s beliefs (Job et al., 2013) and to ignore baseline levels of glucose (Kurzban, 2010). Further, given the extent of recent controversies over this line of empirical work (Blázquez et al., 2017; Carter & McCullough, 2014; Hagger et al., 2016; Schimmack, 2018), it will not be discussed further in detail in the present text.

In section 1.1 we have mentioned how the parallel between fuel-driven machine and humans, particularly with regard to the triggering of fatigue as a signal that our internal fuel needed for the task is running out, has emerged during the industrial revolution (Rabinbach, 1992). While in section 1.2, there has also been mention of how in the physical domain actions have a metabolic cost, as muscles contract thanks to the consumption of metabolites, such as adenosine triphosphate (Wan et al., 2017).

Depletion of energy

Thus, the body has material energetic constraints on the expenditure of effort, and accordingly stores molecules from which additional energy may be synthesized, in order to always have the necessary means to carry out actions. Thereby, several investigators have posited the manifestation of mental fatigue to stem from the depletion of some crucial resource (Ackerman, 2011; Kahneman, 1973).

Similarly to muscles, the brain depends on metabolic molecules to run its activity, the lion's share of which consist in glucose (Mergenthaler et al., 2013), whose precursor, glycogen, is stored in the astrocytes: neurons' support cells (see figure 5; Brown & Ransom, 2007).

As a consequence, many research works have sought to assess if the dynamics of supply and consumption of glucose may reflect the empirical manifestation of mental effort and fatigue. For example, non-central nervous system (i.e. 'peripheral'), glucose levels have been found to be sensitive to the degree of mental exertion, albeit in the absence of noticeable performance drops (Fairclough & Houston, 2004). However, many researchers challenge the notion that these task-induced changes reflect actual brain glucose dynamics (Gibson, 2007; Kurzban, 2010; Messier, 2004).

On the other hand, glucose's cycle in the central nervous system has been shown to react to stimulation (Bednařík et al., 2015; Díaz-García et al., 2017), to have a central role in memory processing (Newman et al., 2011), and its perturbation has been theorized to progressively impair sustained attention and cognition (Killeen et al., 2016). Coherently, elaborate computational models for a 'sophisticated controller' of resource allocation have been put forth to bridge between glycogen metabolic dynamics, motivational processes and behavioral output in conditions of mental effort (Christie & Schrater, 2015).

It comes as no surprise then that ~30% of the body's glucose is employed within the central nervous system (Clarke & Sokoloff, 1999), as the brain's well-being and energetic provision are favored at the expense of other organs (what is known as the “selfish brain mechanism”, Peters et al., 2004).

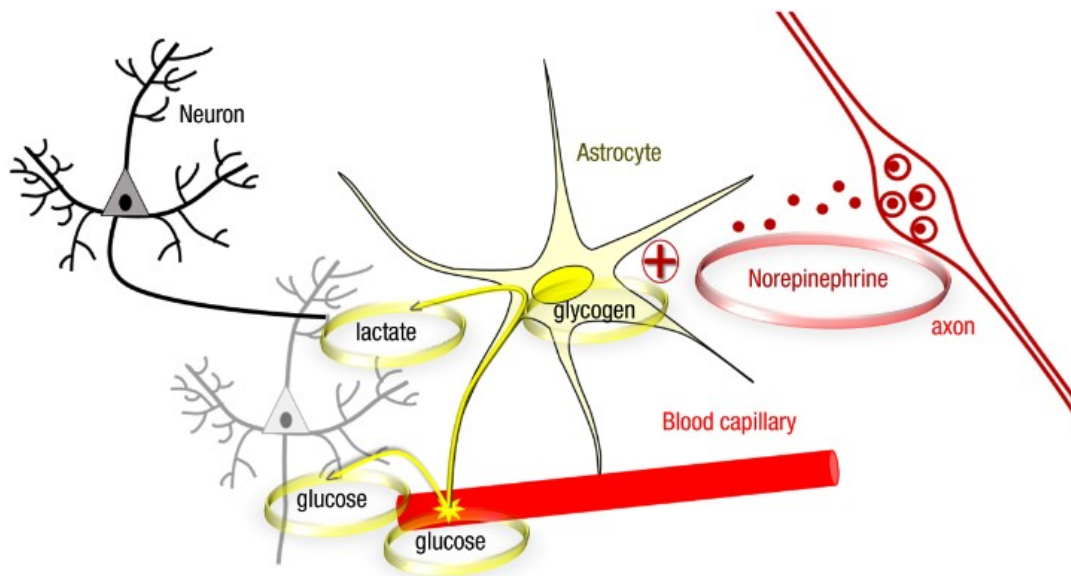


Figure 5: Graphic depiction of neuronal energetic supply. Neurons receive their metabolic fuel in the form of glucose (that gets broken down into lactate), either via the glycogen stored in the surrounding astrocytes or by a slower process of intake from the blood flow coming from outside the central nervous system. Norepinephrine regulates the rate of conversion and release. From "Neuroenergetics" by Killeen et al., 2016, Current Directions in Psychological Science

Yet, insofar no definitive evidence has been found that mental operations have detectable impact upon glucose/energy levels in the brain, which are already generously taxed during idle wakeful states (Raichle & Mintun, 2006; Shulman et al., 2014). Coherently, no change was noticed in fluctuations in brain glucose and oxygen consumption between morning and evening, when people are expected to be more wearied after a day of work (Shannon et al., 2013). In any case, despite the fact that the global energy supply to the brain appears to be constant, the distribution of blood and resources among the different areas of the brain varies over time as a function of their use (this is the very principle of the BOLD effect observed in functional MRI).

Accumulation of metabolites

Instead, or in addition to the actual near-depletion of finite resources, the waste inherently implied by the metabolic processes at play during labor may explain the progressive mounting sensation of fatigue in a functional perspective.

Such mechanism would thus be similar to the accumulation of specific proteins in brain degenerations, such as the buildup of amyloid beta peptide in the hippocampus in Alzheimer's patients, which relates to greater memory decline (Sperling et al., 2019).

This metabolite serves the purpose of enhancing learning and retention (Morley & Farr, 2014), and has been proposed to be released during the exertion of cognitive control (Holroyd, 2016), which is defined as the “set of superordinate functions that encode and maintain a representation of the current task—i.e., contextually relevant stimulus-response associations, action-outcome contingencies, and target states or goals—marshaling to that task subordinate functions including working, semantic, and episodic memory; perceptual attention; and action selection and inhibition” (M. Botvinick & Braver, 2015), a definition remarkably complementary to mental effort.

Another case worth mentioning here consists in the cellular mechanisms that underlie physical effort and induce sleepiness. In fact, during the consumption of adenosine triphosphate in the cells, there is a progressive accumulation of waste in the form of pure adenosine (Moritz et al., 2017). This molecule has a crucial role in the promotion and regulation of sleep (Benington & Craig Heller, 1995), along with the molecules that adjust alertness.

A telltale sign is that a powerful antagonist of adenosine is perhaps the most common substance consumed by humans to fight sleepiness and weariness – that is caffeine (J. M. Davis et al., 2003). Indeed, adenosine has an inhibitory effect on neural activity, and has been shown to increase in the central nervous system as a function of brain metabolism (Porkka-Heiskanen et al., 1997), as glycogen levels fall due to mental activity (Kong et al., 2002) inducing somnolence in the agent.

This is because during sleep the brain restocks on glycogen and removes excess adenosine (Basheer et al., 2004; Wigren et al., 2007).

In general, it doesn't seem far fetched to expect fundamentally similar metabolic processes between physical and mental fatigue, as argued by some (Hancock et al., 2012; Martin et al., 2018).

One may even speculate that the overlap between feelings of sleepiness and fatigue may originate from the release of adenosine during exertion and extended wakefulness.

Local sleep

Support for an ulterior possible account of mental fatigue in the functional perspective comes from the local sleep theory. In this view, fatigue is the outcome of use-dependent sleep regulatory processes, induced by neuronal use-enhanced metabolism (Krueger et al., 2008, 2019). In other words, prolonged periods of stimulation during wakefulness affect the activity of portions of the relevant neuronal populations. Specifically, these neural subassemblies would crave rest, in the form of local sleep, in response to protracted activity without the need for the entirety of the organism to enter a general sleep state. Through this mechanism, the individual is able to remain engaged in the task while sheltering its cells from damage due to overexertion, although resulting in the loss of performance and mounting sensation of weariness.

Indeed, since performance is dependent on the output of the task-relevant brain assemblies, whenever parts of these gradually slip into local sleep the ability to carry out the activity is bound to deteriorate, and the build-up of these exhausted assemblies would eventually generate the pervasive need for general sleep (P.A. Van Dongen et al., 2011). Evidence of this account has been found on rats (see box 3), on which direct measuring of electrophysiological activity is possible with high precision (Rector et al., 2009; Vyazovskiy et al., 2008, 2009, 2011).

Box 3. “Local sleep in awake rats”

In a series of studies on rats, Vyazovskiy et al. showed that sleep-like slow wave firing patterns occur in local cortical networks during wakefulness and that these correlate with behavioral performance drops.

Their *in situ* recordings of both local field potentials and local multi-unit activity in the frontal motor cortex of sleep-deprived rats displayed scattered and unsynchronized EEG sleep-like activity that increased in amplitude and frequency as a function of time, quantifying the mounting pressure of sleep and effectively showing how sub-circuits of cortical neurons can suddenly turn “OFF” as others remain “ON”.

These experiments were carried out both during spontaneous or imposed sleep deprivation, as well as upon natural, unprovoked waking.

Although no physical manifestation corresponded to these OFF periods in the awake rats, performance in an assigned reach test was hindered by the concurrent presence of at least one OFF period, or if OFF periods occurred repeatedly, in the moments preceding the action (Krueger et al. 2019).

Motivational perspective

Given the mentioned inconsistencies of effort-induced energetic deficiency in the brain and general lack of definitive evidence for alterations in the neural circuitry subtending mental activity, a great deal of scientists dismiss the notion of energy costs of single mental actions, and therefore of a metabolic origin of mental fatigue. The key idea of these different motivational theories of fatigue is that as the time spent exerting mental effort increases, so does the perception of the cost of that effort. This would not be due to the fact that the capacity for mental effort is limited by physiological resources, but to the fact that the resource being spent would be time itself.

Thus, a long time spent using cognitive resources without obtaining a congruent reward would be perceived as an increasing subjective cost and eventually trigger fatigue.

These models share the tendency to interpret fatigue in relation to other mental aspects of the agent, such as their attention, motivation, control over the task and the prioritization of objectives.

Motivation control theory

Mental fatigue may then be posited as a goal-directing instrument that keeps motivation priorities in check with regards to the flow of control between conflicting action plans, rather than an unwelcome by-product of effort or the result of energy exhaustion (Hockey, 2013). Fatigue permits a reassessment of motivational priorities with a bias towards preferred or personally significant objectives by disrupting attention to ongoing tasks. Thus, it works as a brake on present actions, allowing for a re-evaluation of motivating priorities that have shifted, disrupting the performance in the low priority task by means of degraded engagement (Hockey, 1997). However, it must be noted that in this view the distinction with the sensation of effort is rather unclear.

In situations where unwanted activity goals must be retained, an effortful task maintenance strategy is then required as a compensatory mechanism in order to overcome increasing resistance generated by the fatigue process, until the agent eventually concedes to the mounting sensation of tiredness. The neural bases for such model have been identified in the brain mechanisms that are involved in the regulation of tasks goals, monitoring, interruption and effort (Hockey, 2013). Of paramount importance would be the role of the PFC in managing goals, from their selection to maintenance, and its dopaminergic connections to the ACC, responsible of regulating effort while monitoring errors and performance.

Equivalently crucial would be the role of the basal ganglia and its cortical-subcortical control loops in associating motor outputs with rewarding outcomes. Evidence for the involvement of this cerebral structure in fatigue is recognized by the proponents in the fact that its malfunctioning is implicated in chronic fatigue syndrome (Chaudhuri & Behan, 2004).

Overall, some evidence for the existence of a compensatory mechanism capable of temporarily reverting, or compensate, the progressive decline in behavioral performance and brain activity, was found in the anterior frontal region during an extensive cognitive control task (C. Wang et al., 2016).

Opportunity cost model

The concept of fatigue depending on the falling utility of current activities in conflict to other possible options was further developed by the opportunity cost model of Kurzban et al. (Kurzban et al., 2013). This opportunity cost would consist in the aversive sensation caused by the prolonged use of executive functions, which translates into pressure from the brain to favor shorter term rewards (Inzlicht et al., 2014; Kurzban, 2016; Kurzban et al., 2013).

As the time engaged in cognitively effortful tasks passes without obtaining rewards, the aversive sense of cost increases to drive the agent to partake in another, competing, activity that would be more profitable in the short term, such as rest. Therefore, agents would be continuously evaluating and comparing the costs and benefits of the effort being invested in relation to alternative possible choices, in order to prioritize the utility of spent exertion.

This cost/benefit ratio would be encoded in the ventromedial prefrontal – ventral striatal network, with the lateral prefrontal network involved in action monitoring in relay to the ACC (Kurzban et al., 2013).

Behavioral economic theories of cognitive control

A branch of literature on mental effort has focused on the neuroeconomic aspect of the mechanisms that determine the choice of effortful (i.e. fatiguing) actions of individuals. Also in this literature there has been a shift from depletion-based accounts towards motivational models that regard it as a reward-based decision making process, within which actions are chosen based on decision

mechanisms akin to those involved in other forms of reward-based selection (M. Botvinick & Braver, 2015).

Similarly to above, the dopaminergic projections between the basal ganglia, ventromedial and lateral PFC and the ACC are thought to determine the amounts of effort an agent is willing to expend and therefore be impacted by prolonged work. Yet, the subjective intrinsic costs of mental exertion is recognized and interpreted as an evolutionary heuristic that encourages careful allocation of cognitive control, while sparing the organism the otherwise computationally demanding chore of actually calculating the cost/benefit ratio of each specific mental act (Kool & Botvinick, 2018).

Recent support for this concept was found in an artificial intelligence study showing that in order to have a system that optimizes the automation of its behaviors, it was beneficial to attach a cost to "top-down" processes that seek to readapt behavior continuously instead of relying on hard-coded optimal fixed strategies (Teh et al., 2017). Although this work did not pertain to human psychology nor neuroscience, it raises a novel interpretation regarding the cost of mental effort, by demonstrating that it may be sound to provide an intrinsic price for top-down cognitive exertion, specifically because it spurs the development of optimal habits. Coherently with such findings, models positing similar costs of cognition and mental effort in humans have been put forth (Zénon et al., 2019).

Rewards and costs framework

Boksem and Tops proposed a middle-ground model in which the evaluation of expected rewards and the energetic costs associated with prolonged performance are integrated (Boksem & Tops, 2008). In line with motivational accounts, fatigue would stem from an imbalance in the amount of effort invested and the perceived utility of the expected reward, however this model factors-in also the theoretical price in terms of 'energy' (with little specification in regard to what this energy may consist in) that the on-going action has. Thus, fatigue is posited as the outcome of inconveniently repeated behavior that requires effort even after a significant amount of energy has already been

expended and the objective has yet to be achieved, or has diminishing intrinsic value as a function of the energy consumed. In this case, the desire to rest after prolonged work is interpreted as a signal aimed at prioritizing the achievement of long-term goals, which are more appealing to the organism.

The cerebral structures of the dopamine reward system are included in the model, as they subtend motivated behavior and are posited to explain the proposed mechanism. Specifically, the basal ganglia, orbitofrontal cortex (a subdivision of the PFC), insula and ACC.

Conclusion on the motivational and functional accounts of fatigue

It is this author's belief that, as is oft the case in science, the truth lies likely in-between the functional and motivational models elaborated by a plethora of bright researchers.

Indeed, many of the neural elements mentioned by motivational models undoubtedly are involved in the generation and maintenance of motivated behavior, error detection and action monitoring. Such as dopamine, PFC and ACC. Therefore, it is certain that they have a key role in the experience of fatigue. Yet, at a fundamental level, there must be changes taking place in the task-relevant regions as a consequence of prolonged or intense activation.

One may suppose that the objective component of fatigue can be explained both by diminished cortical processing of the regions responsible for top-down control, hindering the ability to partake in goal-directed behavior efficiently, with a concomitant decay of bottom-up signals in task-related regions due to metabolic constraints on prolonged activity. The subjective component would be a manifestation of these integrated processes, possibly with a distinct time-course, which would explain why they are rarely observed to correlate.

In such perspective, the two schools of thought of mental fatigue can be seen not as mutually exclusive, but explaining different aspects of this phenomenon, which is transversally recognized as multidimensional (Ackerman, 2011; DeLuca, 2007; Hockey, 2013).

1.7 Premise for empirical works

If the content so far treated in this work has attained its purpose, the need for a means to assess putative alterations taking place in the task-relevant neural circuitry subtending on-going mental effort should have emerged. To do so, an interested researcher is required, in the first place, to identify a task that implicates specific neuronal populations. Further, this task should ideally be fairly resistant to previously considered psychological confounds, such as variations in motivation, boredom, sleepiness, level of skill and physiological factors such as temperature, intake of food, psychoactive substance use and posture. It follows then that such behavioral task should afford the comparison of the evolution in performance (starting from a trained level) within participants, possibly so that only the fatiguing of exact cellular assemblies may justify any observed differences. Opportunely, as shall be described in the following manuscripts, such a task may be recognized when exploring the literature on visual perception. Albeit some have outright negated, in the form of a straw-man argument, the possibility of existence of fatigue in the visual domain (Kurzban et al., 2013), it should be the case that keeping specific visual neurons active for a long time – which are rather selective as to which stimuli they respond to – will alter their behavioral output, thus producing the objective aspect of fatigue, while accompanied by mounting sensations of subjective weariness.

Such is the premise for the series of empirical works presented in the following section. Indeed, if one looks back to the definitions b, c and d of fatigue from the Merriam-Webster dictionary, being:

- b) the temporary loss of power to respond that is induced in a sensory receptor or motor end organ by continued stimulation.
- c) a state or attitude of indifference or apathy brought on by overexposure (as to a repeated series of similar events or appeals).
- d) the tendency of a material to break under repeated stress.

One may then intuitively suppose that continuously stimulating distinct neurons implies wearing them down, thus triggering protective fatigue mechanisms at a cellular level due to over-work. If proof of such mechanism is found, regardless of motivation levels, then it would be reasonable to suppose that the same would apply also in the case of more complex tasks for which the exact neural underpinnings are more resistant to localization, as they are likely to involve less specialized, higher order, neurons that partake in a wealth of cognitive actions.

In fact, the idea of stimulating specific visual neurons and assess alterations in their behavioral and neurophysiological outputs is not a ground-breaking nor entirely novel concept, and draws inspiration from related literatures that share this hypothesis, namely habituation/adaptation and perceptual deterioration.

Habituation or adaptation

Several empirical works have focused on the decline in responsiveness of cellular assemblies following repeated stimulation and subsequent behavioral decreases, eventually converging on naming such phenomenon ‘habituation’ (Thompson, 2009).

At a glance, its manifestation largely coincides with definition b) of fatigue from the Merriam-Webster dictionary. Indeed, early theorists of habituation tended to describe its effects explicitly in terms of fatigue (Humphrey, 1933; Sherrington, 1906), a custom that seems to have faded as the literature on the topic specialized and ruled out the involvement of “sensory and motor fatigue”, justified by the fact that habituation effects can be reversed and that they are specific to the employed stimuli rather than capable of generalization (Rankin et al., 2009). Yet, none of these reasons seem to conclusively rule out fatigue of specific cellular assemblies, except for when the behavioral manifestation does not consist in a deterioration of some kind.

Therefore, there is no fundamental reason to distinguish firmly between the two processes, except perhaps for the timescale at which they take place or have been investigated so far.

Habituation has been shown to take place in a range of diverse cases, from the startle response (Prosser & Hunter, 1936), to arousal estimated by EEG (Jasper & Sharpless, 1956), without generally being discussed in regards to mental fatigue nor its related constructs and confounds, as the field has tended to focus more on behavioral reflexes and hard physiological measures, rather than behavioral alterations and subjective sensations (Rankin et al., 2009; Thompson, 2009).

Somewhat similarly to habituation, adaptation is typically defined as “a brief and temporary change in sensitivity or perception when exposed to a new stimulus, as well as the lingering aftereffects when the stimulus is removed. [...] A hallmark of these changes is that they are selective, reducing sensitivity for stimuli similar to the adaptor but not for sufficiently different patterns” (Webster, 2015). Thus, in this case the main distinction with habituation, and tangentially with fatigue, appears to be the possibility that the posited after-effects of stimulation may be positive, or enhancing, in lieu of decreasing. Coherently, in an early work on the topic of habituation, this phenomenon was referred to as “negative adaptation” (Harris, 1943). Nevertheless, also this concept has been occasionally explained in terms of fatigue, for example in the visual domain (Carandini, 2000).

In sum, there is an undeniable overlap between the concepts of fatigue, habituation and adaptation as they all posit behavioral and physiological alterations stemming from repeated work/stimulation. A testament to this is the persistent confusion over their use, which generates amusingly intricate science riddles, such as “taken together, the results challenge the account of habituation of adapter in repeated adaptation, while leaving the account of habituation of adaptation mechanism to be tested.” (Dong et al., 2020).

The nomenclature here preferred is in line with the one adopted in a recent publication which defined habituation as “decreased behavioral response” and adaptation as consisting in the neural processes underlying this decrease (Pellegrino et al., 2017), a definition shared by other researchers

interested in these topics (Censor et al., 2016), although with less emphasis on the distinction between behavioral and neural phenomena.

In any case, findings from these literatures provide a conspicuous body of evidence of the presence of cell-specific alterations elicited by protracted activity, a hypothesis that was sought to be assessed also by the works in the next chapter of this monograph.

Perceptual deterioration

Likewise, further proof of specific fatigue comes from a line of research on sleep, specifically naps, where perceptual deterioration was observed. This phenomenon consisted in a progressive and mounting failure to carry out a perceptual task in extended periods of repetition (four 1 hour long sessions, from 9 am to 7 pm). Importantly, this deterioration was restricted to the repeatedly presented stimuli's location (Mednick et al., 2002) and orientation (Mednick & Boynton, 2004). Furthermore, neither monetary rewards nor a decrease in difficulty were capable of re-establishing baseline levels of performance, displaying a resistance to motivation and difficulty levels (Mednick et al., 2002). Thus, this series of experiments directly provided tangible and assessable examples of specific neural fatigue. Additionally, alterations of activity in the primary visual cortex concurrent to perceptual deterioration were demonstrated (Mednick et al., 2008). From these results, one may hypothesize that if prolonged involvement in a visual task fatigues visual neurons, then perhaps a perceptual deterioration effect should be witnessed just by means of passive extended stimulation, possibly on a shorter timescale. Additionally, one could measure subjective evaluations of tiredness, physiological measures of manipulated arousal levels and take advantage of relatively recent neuroimaging techniques to further characterize this phenomenon. Such are the hypotheses tested in the following pages.

CHAPTER 2 – FIRST STUDY

Passive visual stimulation induces fatigue under conditions of high arousal induced by auditory tasks

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Abstract

Theories of mental fatigue disagree on whether performance decrement is caused by motivational or functional alterations. Here, drawing inspiration from the habituation and visual adaptation literature, we tested the assumption that keeping neural networks active for an extensive period of time entails consequences at the subjective and objective level – the defining characteristics of fatigue – when confounds such as motivation, boredom and level of skill are controlled. In experiment 1, we revealed that passive visual stimulation affected the performance of a subsequent task that was carried out in the same portion of visual space. While under conditions of low cognitive load and arousal, participants improved their performance in the stimulated quadrant, the reverse was observed under high arousal conditions. This latter performance decrement correlated also with the reported subjective level of fatigue and occurred while neural responses to the saturating stimulus remained constant, as assessed through steady-state EEG. In subsequent experiments, we replicated and further characterized this performance deterioration effect, revealing its specificity to the stimulated eye and stimulus orientation. Across the three experiments, the decrease in performance was correlated with pupil-linked arousal, suggesting its mediating effect in this phenomenon. In sum, we show that repeated stimulation of neural networks under high-arousal conditions leads to their altered functional performance, a mechanism which may play a role in the development of global 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), impulsivity (Blain et al., 2016), emotional regulation (Grillon et al., 2015) and workplace accidents (Goode, 2003; Swaen et al., 2003), all regrouped under the umbrella term of Cognitive Fatigue (CF). CF 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 CF remains elusive, and this lack of understanding stems in part from CF's dependence on the duration and difficulty of the task (Hockey, 2013), as well as on the motivation (Boksem et al., 2006), fatigability and skills of the agent performing it (Borragán et al., 2017).

Theories of cognitive 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, accumulation of metabolites), or as an outcome of mechanisms that prevent such alterations (Blain et al., 2016; 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; Kurzban et al., 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, Linden, 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. Thus, 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, which is consistent with the literature on habituation, originally defined as a behavioural response decrement that results from repeated stimulation (Thompson, 2009). In contrast to that line of research, where generally bare reactions to stimulation are measured (e.g. pupillary, neuronal or muscular responses; (Rankin et al., 2009; Thompson, 2009), the objective component of cognitive fatigue consists in a performance decrement during a behavioral task (Gergelyfi et al., 2015). In the visual domain, on which we focus the present work, such performance deterioration may be considered also the product of visual adaptation (Blakemore & Campbell, 1969; Greenlee et al., 1991; Webster, 2015), originating from a decrease in sensitivity due to repetitions of a visual stimulus. Indeed, this hypothesis has been tested, among other methods, by means of the texture discrimination task (TDT), where participants are required to identify the orientation of briefly presented peripheral targets (Censor et al., 2016; Mednick et al., 2002, 2005; Ofen et al., 2007). Remarkably, performance can be restored when perceptual characteristics of the targets (orientation and location) are changed, but not when participants are offered money to manipulate motivation (Mednick et al., 2002).

Here, we sought to determine if this perceptual deterioration in the TDT could be passively induced by prolonged stimulation of specific portions of the visual field, rather than repetitions of the task itself, and if it would be accompanied by a concurrent increase in the subjective feeling of fatigue. We refer to this prolonged stimulation as saturation, as we hypothesise that taxing the relevant neurons with activations over prolonged periods of time progressively saturates them to the point of failure. We tested this paradigm across a series of three experiments, in which, in agreement with the habituation (Thompson, 2009), visual adaptation and perceptual deterioration literature (Censor

et al., 2016; Mednick et al., 2002, 2005; Ofen et al., 2007), we assessed the evolution of the electrophysiological response to passive stimulation (Exp. 1), and studied the level of specificity of the effect in terms of stimulated eye (Exp. 2) and line orientation (Exp. 3).

Experiment 1

Habituation consists of a decrease in the response to repeated stimulation. Therefore, in experiment 1, on top of assessing the behavioral consequence of saturation, we also assessed the occurrence of habituation by measuring neural responses via electroencephalography (EEG). Moreover, given that the magnitude of the saturation effect should depend on the level of activation of the stimulated neurons, variations in arousal should also influence its impact, as they are thought to act as a modulator of the gain of sensory responses (Aston-Jones & Cohen, 2005; Lin et al., 2019; Mather et al., 2016; McGinley et al., 2015). We thus predicted that being engaged in concomitant auditory tasks of varying difficulty during stimulation would induce variations in arousal level (Kahneman & Beatty, 1966; Shi et al., 2007), thereby modulating the intensity of the saturation effect: agents performing tasks with harder demands should exhibit greater consequences, given the enhancing effects of arousal on their cortical response to stimulation.

Methods

Forty-eight participants took part voluntarily in the experiment (24m and f, $M_{\text{age}} = 22.1 \pm 2.24$). 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 enough participants for the various experimental conditions and randomizations.

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 behavioral 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).

Experimental design

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. Fixation ruptures were indicated by a change in the color of the fixation cross and by oral feedback from the experimenter. 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).

The experimental design was divided into different phases, which will be detailed in the following sections. First, a brief training with reduced number of trials of the various tasks was carried out in order to have the participants familiarize with their procedures (see Figure 1 panel 1a).

Behavioral and physiological measures were taken at multiple timepoints of the experiment, namely: BASELINE, MIDDLE and CONCLUSION (see Figure 1 panel 1b,d,f). In-between these measurements, subjects underwent continuous stimulation, ('saturation') of a specific portion of their visual field ('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, M_{age} : 22.37 ± 2.7) or “HARD” (N=24, 12m and f, M_{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. Therefore 3 different tasks were adopted, based on the fact that their complexity could be manipulated and that they provided variety in demands (working memory, executive functions, attention). These tasks were

randomly cycled across a saturation session, until its pre-scripted duration of 41 minutes had passed. Specifically, the following 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

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)

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.

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 signaled 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.

Behavioral index of fatigue

As a behavioral 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 and 5 possible positions per quadrant. 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 250 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 is 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 the 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.

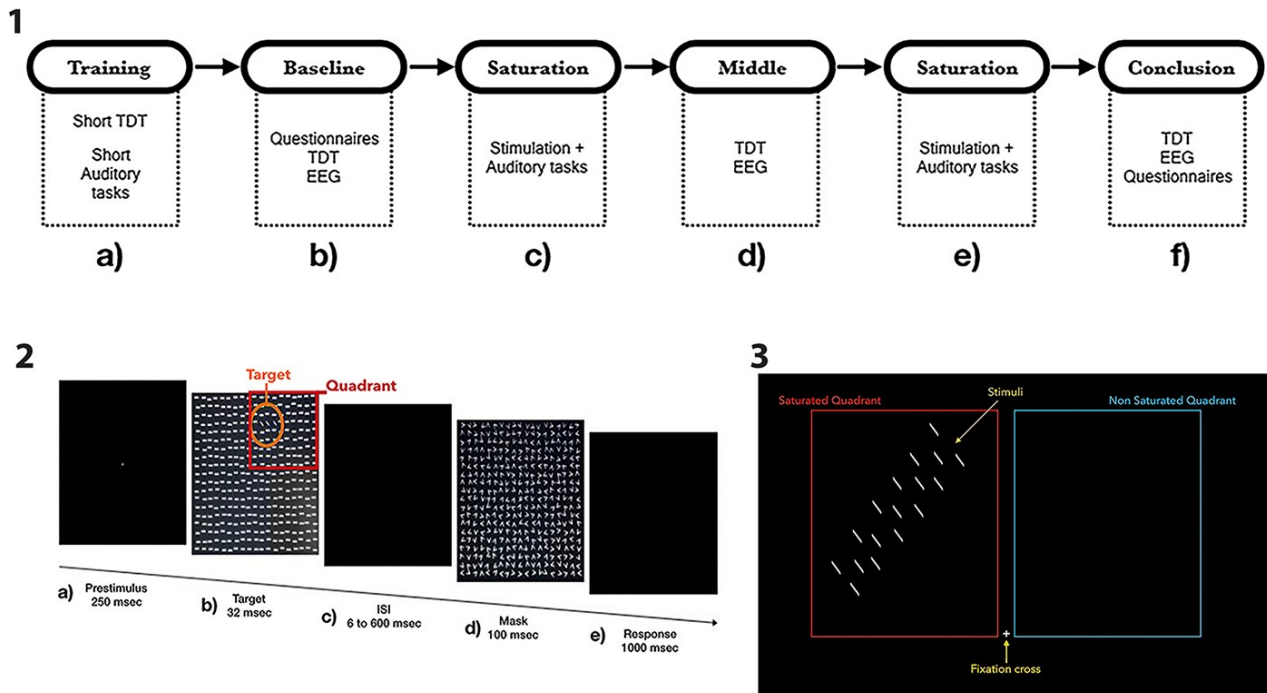


Figure 1: : Panel 1: Flowchart of the experimental design. Panel 2: Visual representation of the Texture Discrimination Task (TDT). Please note that across the whole trial a fixation cross stayed in the centre in order to help participants maintain their gaze fixated. Panel 3: Visual representation of saturation and EEG sessions. While fixating the centre a participant would be presented with stimuli identical to the targets of the TDT (here they appear larger due to representation), appearing in all possible target locations within a quadrant at 7.5 Hz. During EEG sessions the quadrants alternated (see EEG methods for details), 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

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 regression, $y_{1:n}$ 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 Kullback-Leibler (KL) divergence between current and future estimates, representing how much information one would expect to gain about the parameter estimates, was computed for each ISI and possible response according to the following formula:

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

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:

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

These KL values 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 behavioral (TDT) response would differ between SATURATED and NON-SATURATED quadrants.

EEG

EEG recordings of whole brain activity in response to the presentation of the saturation stimulus (See Figure 1 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 between blocks, 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.

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, artifacts 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 neighboring 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), and this noise-subtracted 7.5hz was then used in subsequent analyses.

Pupil

We also recorded the pupil size of participants as a physiological index of arousal, as it is a well-established physiological marker of this construct (McGinley et al., 2015; C.-A. Wang et al., 2018). Variations in pupil size were tracked during saturation sessions, while participants were engaged in

the concurrent auditory tasks, the difficulty of which varied according to the experimental group they were assigned to. Specifically, after linear interpolation of blinks, filtering (high-pass with 0.01Hz cutoff frequency) and baseline correction, the pupil responses between the onset of the first stimulus of trial n and the onset of the first stimulus in trial $n+1$ were averaged.

These estimates of trial-wise average pupil responses were then averaged by auditory task and session, thus resulting in one data point for each subject and task in both saturation sessions.

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 Generalized Linear Mixed Model (GLMM) on response accuracy in the TDT task. Correct response in the task was modeled 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, averaged across trials, was computed for each of the three sessions, for each participant.

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

These values were then analyzed in dependent sample two-tailed t-tests to assess changes across sessions. 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, the participants' performance in each of the auditory tasks was evaluated by means of a mixed model on the ratio of correct responses, by saturation session and difficulty condition, for each of the tasks. This approach was preferred to a repeated measures ANOVA due to missing data points at a subject-wise level (3 on average across tasks).

Fourth, we assessed the efficacy of the auditory tasks in inducing different cognitive load and arousal levels based on their difficulty. Again, given the missing data points, a mixed model was performed with the pupil data of each task as dependent variable. As above, group and session were set as explanatory variables.

Fifth, 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. Separate repeated measures ANOVAs were carried out for the responses in the two

questionnaires, with pre-post experiment as within-subjects factor and difficulty as between-subjects factor.

Sixth, estimates of behavioral performance change (conclusion-baseline) between BASELINE and CONCLUSION session obtained by the psychometric function, and the unfiltered, non baseline corrected, average pupil size recorded during the auditory tasks were correlated.

In a last step, we explored the correlation between the same estimates of behavioral performance change and the change in both questionnaire scores (conclusion-baseline).

Open code and data policy

Source code is available at [<https://github.com/ste-ioan/TDT21>], all data is available freely for download at [<https://zenodo.org/record/5575767>](Ioannucci, 2021).

Results

Texture Discrimination Task

The GLMM revealed the quadruple effect of ISI, Saturation, Difficulty and Session to be strongly significant (see Figure 2; $X^2_{(2, 46080)} = 21.96$, $p < 0.0001$; 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 [$\beta = 2.92$, CI = 1.36, 4.48, $Z = 3.67$, $p_{\text{corrected}} = 0.001$, $\exp(\beta) = 18.5$] and moderately decreased between MIDDLE and CONCLUSION sessions [$\beta = -1.94$, CI = -3.47, -0.41, $Z = -2.47$, $p_{\text{corrected}} = 0.039$, $\exp(\text{abs}(\beta)) = 6.9$]. However, there wasn't a significant change between BASELINE and CONCLUSION [$\beta = 0.75$, CI = -0.62, 2.12, $Z = 1.06$, $p_{\text{corrected}} = 0.287$].

On the other hand, the HARD group displayed a major loss of performance in the SATURATED quadrant, between BASELINE and MIDDLE sessions [$\beta = -3.19$, CI = -4.7, -1.68, $Z = -4.15$, $p_{\text{corrected}} = 0.0002$, $\exp(\text{abs}(\beta)) = 24.4$] and BASELINE and CONCLUSION [$\beta = -2.73$, CI = -4.08, -1.38, $Z = -3.95$, $p_{\text{corrected}} = 0.0004$, $\exp(\text{abs}(\beta)) = 15.3$], but not between MIDDLE and CONCLUSION [$\beta = 0.71$, CI = -0.53, 1.95, $Z = 1.13$, $p_{\text{corrected}} = 0.518$], as between these sessions their performance decreased also in the NON-SATURATED quadrant.

To further confirm this finding, we explored its session-wise evolution, by performing the same statistical procedure, per group, session-by-session. 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 changes in performance within the SATURATED quadrant, depending on the difficulty condition. Specifically, participants assigned to the HARD condition saw their performance drop, particularly in the first half of the experiment. In contrast, participants in

the EASY group initially exhibited an improvement in their TDT performance, which disappeared following the second saturation session.

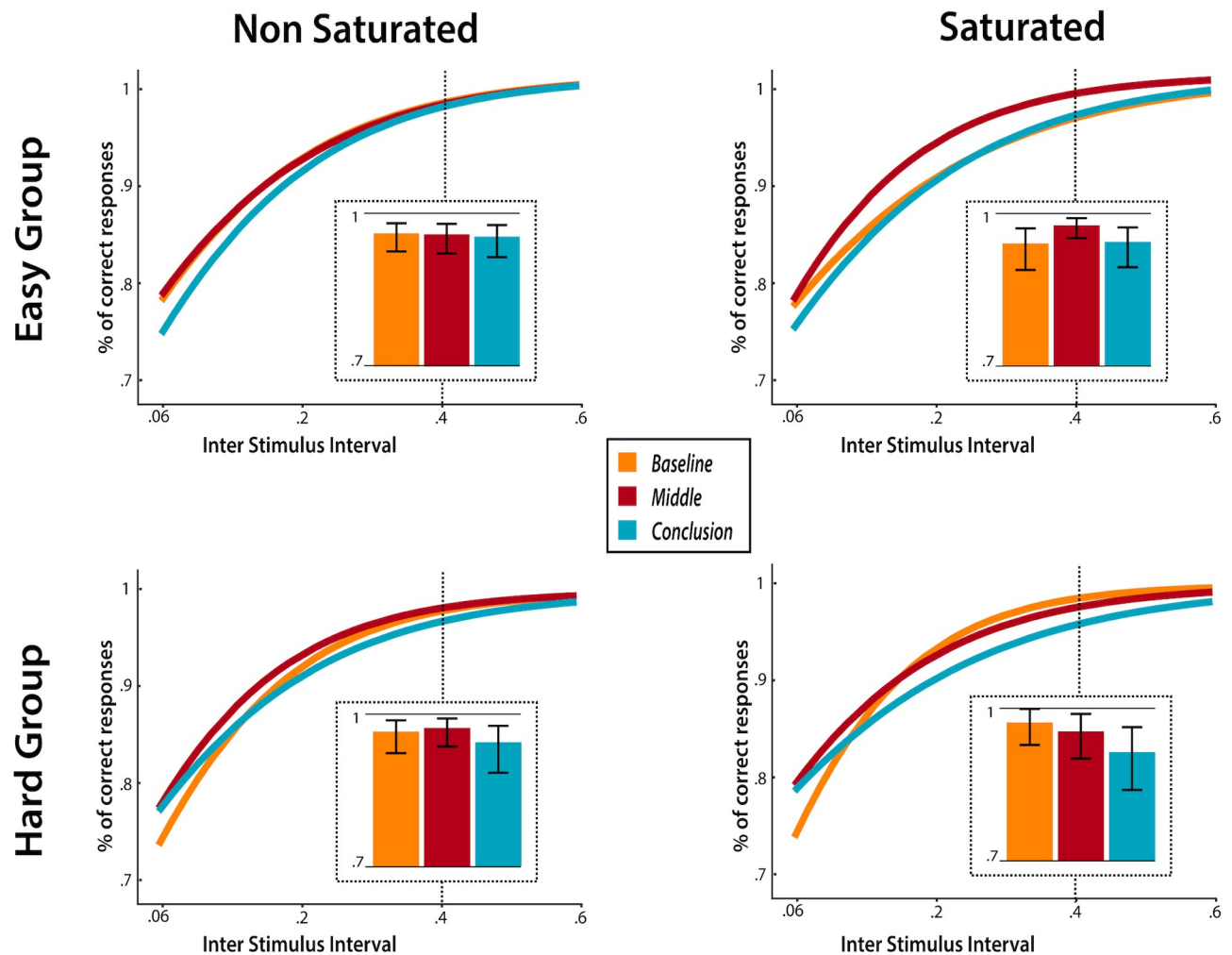


Figure 2: Percent correct responses (y axis), predicted by the GLMM for ISI values ranging from 0.06 to 0.6 (x axis) as a function of saturation condition (left and right columns) and experimental group (top and bottom rows). Error bars depict 95% confidence intervals. Insets: detailed representation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

Electrophysiology

We analyzed electrophysiological activity by means of cluster-based permutation methods (Maris & Oostenveld, 2007). We first compared EEG steady-state responses between blocks with stimulation of left and right portion of the visual field in the BASELINE session across groups (EASY, HARD). As no clusters were found, we concluded that the side of stimulation did not induce significant differences and grouped left and right stimulation blocks for further analyses. Comparisons of the amplitude of

the steady-state response to 7.5Hz stimulation were performed separately for both groups, between BASELINE and MIDDLE, MIDDLE and CONCLUSION and between BASELINE and CONCLUSION. No significant clusters were found.

Audio task performance

Concerning the performance of the auditory tasks carried out during saturation, the EASY group outperformed the HARD group in each task. Specifically, in the n-back task the overall mean accuracy of the EASY group was 93.3% versus 62.1% of the HARD group ($\beta = 31.5$, CI = 25.34, 37.65, $t_{(45)} = 10$, $p < 0.0001$). In the side task, the EASY group had on average 99.2 % of correct responses, whilst the HARD group had an accuracy of 89.1% ($\beta = 10.1$, CI = 5.12, 15.01, $t_{(46)} = 3.99$, $p = 0.0002$). Finally, in the pitch-sequence task, the EASY group displayed 73.5% average accuracy, while the HARD group only reached 49.1% ($\beta = 24.97$, CI = 17.22, 32.71, $t_{(46)} = 6.31$, $p < 0.0001$).

Pupillometry

The analysis of the average pupil size recorded while participants were engaged in the auditory tasks revealed a significant effect of the group condition, in each task (see Figure 3). On top of this, also the effect of session was found to meaningfully impact the pupil size of participants in each task. In the case of the side task, participants in the HARD condition had a larger pupil than those in the EASY condition ($\beta = 0.01$, CI = 0.005, 0.01, $t_{(46)} = 3.94$, $p = 0.0003$) and the whole sample's pupil size decreased between the first and second saturation sessions ($\beta = -0.004$, CI = -0.006, -0.002, $t_{(45)} = -3.58$, $p = 0.0008$). The same result was found also in the n-back task, both in the group-wise effect ($\beta = 0.005$, CI = 0.00001, 0.01, $t_{(46)} = 2.02$, $p = 0.049$) and in the session-wise effect ($\beta = -0.002$, CI = -0.004, -0.00002, $t_{(45)} = -2.16$, $p = 0.036$).

On the other hand, in the case of the pitch-sequence task, the pupil averages in the EASY condition were found to be larger than those in the HARD condition ($\beta = -0.02$, CI = -0.03, -0.01, $t_{(43)} = -4.18$, p

= 0.0001), while the pupil responses decreased in the second session, similarly to the other tasks (β = -0.04, CI = -0.08, -0.01, $t_{(40)} = -2.62$, $p = 0.012$).

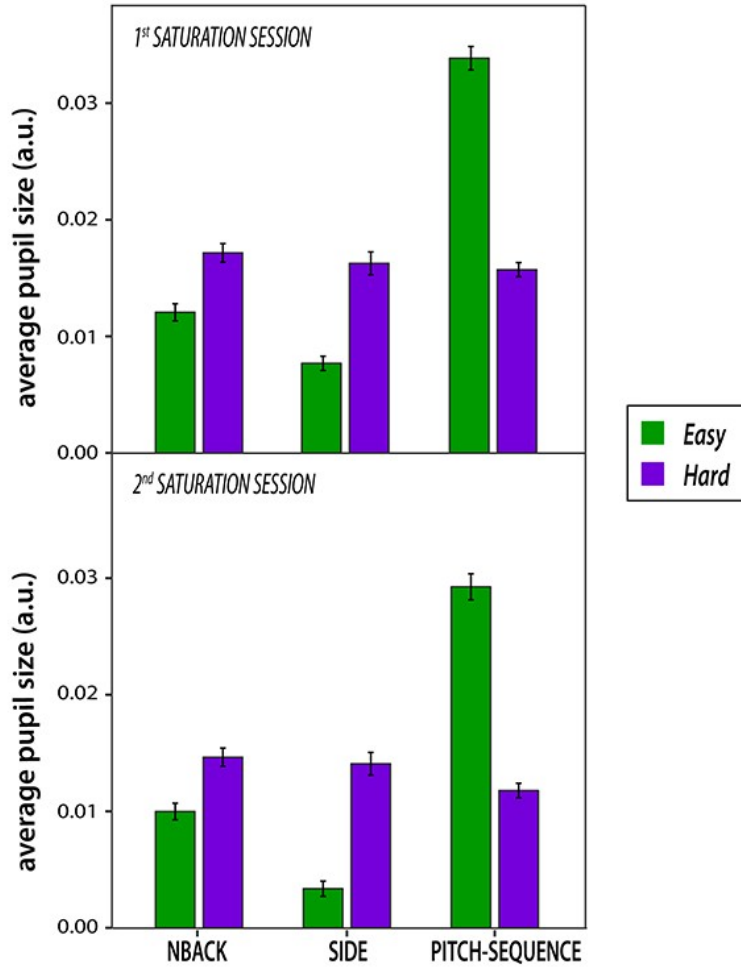


Figure 3: Average pupil size in each auditory task per saturation session, by experimental group

TDT performance and pupil size correlation

The correlation between the raw pupil-size of participants during the execution of the auditory tasks and the change in their performance in the TDT was not significant ($R_{(46)} = -0.20$, CI = -0.45, 0.18, $p = 0.18$).

Self-reported measures of fatigue and sleepiness

The rANOVA on the Multidimensional Fatigue Inventory scores revealed an important increase over the course of the experiment, as highlighted by the significance of the pre-post experiment factor ($F_{(1, 46)} = 255.9$, $p < 0.0001$, $\eta^2_p = 0.85$), while neither the main effect of group, nor their interaction reached significance. Similarly, the Karolinska Sleepiness Scale scores highlighted a strongly significant increase in perceived sleepiness across sessions ($F_{(1, 46)} = 176$, $p < 0.0001$, $\eta^2_p = 0.77$), while no effect was found for the group condition nor its interaction with session.

Additionally, the increase in subjective fatigue displayed a moderate negative correlation with the change in the behavioral performance (performed across groups given lack of difference shown above; $R_{(46)} = -0.29$, $CI = -0.55, -0.02$, $p = 0.041$; see Figure 4). On the other hand, no significant correlation was observed between changes in behavior and perceived sleepiness ($R_{S(46)} = -0.1$, $p = 0.5$).

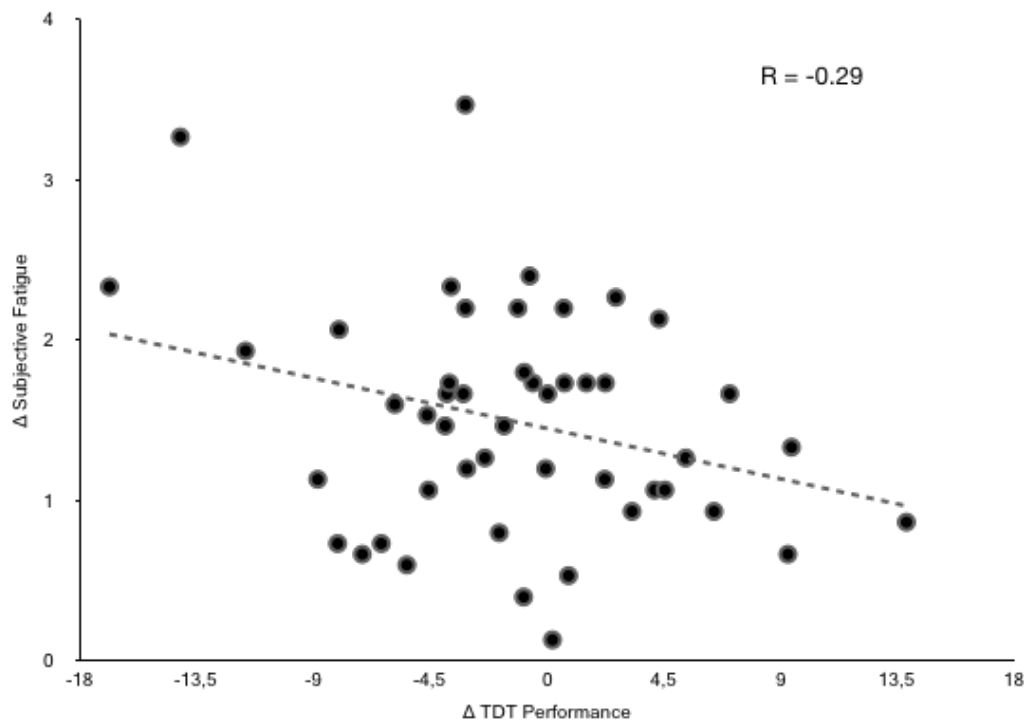


Figure 4: Scatterplot depicting on the y axis the change in reported fatigue (i.e. the delta in the Multidimensional Fatigue Inventory scores between baseline and conclusion) in relation to the change in visual discrimination performance on the x-axis (i.e. the delta between conclusion and baseline in the individual slopes of the participant's psychometric curves)

Discussion

In the present experiment, we found that protracted stimulation of a specific portion of the visual field affected subsequent behavioral performance in a visual discrimination task when targets were within the saturated quadrant. This effect interacted with arousal and cross-sensory cognitive load, as participants engaged in the easy versions of the auditory tasks during saturation initially displayed an improvement in their ability to discriminate targets in the saturated quadrant. This finding evokes the early accounts of perceptual learning (Karni & Sagi, 1991, 1993). However, in the present case, this improvement faded following the second session of passive stimulation, thus not displaying any consolidation, unlike previous reports. Therefore, this observation of temporary improvement relates better to the more general concept of perceptual priming (Wiggs & Martin, 1998), than to the perceptual learning literature.

On the other hand, volunteers who underwent the hard version of the 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, it 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 result also stands out from previous publications in the field of visual fatigue, which generally rely on self-reported measures of eye discomfort, or other physiological markers such as dry eyes and binocular vision stress (Sheppard & Wolffsohn, 2018). Albeit we did not record these variables, there is no reason to suppose there would be a difference between the experimental groups in any of these measures, as they were exposed exactly to the same visual stimuli under identical conditions and recruited from a homogeneous sample.

Furthermore, in the few attempts where this body of literature has sought to assess behavioral effects, it has failed to detect any (Chi & Lin, 1998).

From the neurophysiological perspective, we failed to observe significant differences in the amplitude of the electrophysiological brain response to the 7.5 Hz flashing of the stimuli.

This lack of change in neural response, concomitant with clear behavioral alterations, clearly sets these results apart from the phenomenon of habituation (Carandini, 2000; Thompson, 2009), which would have consisted of a progressive decrease in the magnitude of the response to stimulation. It also suggests that the observed neural fatigue originates from decreased signal-to-noise ratio rather than simple decrease in activation magnitude.

The use of more spatially sensitive instruments (e.i. fMRI) is warranted to shed light on the brain localization of the observed behavioral phenomenon, which might be explained by a different factor than electrophysiological magnitude of cortical brain response. For instance, the behavioral 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).

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 behavioral performance. Such correlation cannot be attributable to the behavioral 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.

Analysis of the arousal-related pupil response showed increased dilation in the hard version of the n-back and side tasks, confirming the increased demand associated with these task conditions (van der Wel & van Steenbergen, 2018; Zénon, 2019). However, surprisingly, we found the opposite effect in the pitch-sequence task, with the easier group displaying larger average pupil size.

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, a phenomenon known to reduce pupil size (Hopstaken, Linden, et al., 2015). Indeed, the pitch-sequence task had the lowest performance across tasks and conditions (49% of correct responses overall) and several participants spontaneously reported that this task was the most challenging of the three.

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; McGinley et al., 2015; Zhang et al., 2020) which in turn caused

faster and greater degradation of performance. Alternatively, it could be argued that the difference in the impact of passive stimulation on performance across groups could be due to cognitive load per se, rather than to the related changes in arousal. Indeed, it cannot be excluded that the effect observed here would require taxing of the cognitive control network (Asplund & Chee, 2013; Blain et al., 2016; Braver, 2012; Mandrick et al., 2013; Niendam et al., 2012) on top of the saturation of the local visual processes.

In sum, we find evidence that passive, repeated neuronal activation induces progressive functional alteration under the modulatory influence of cross-sensory cognitive load and arousal. Under low cognitive load, we observed an initial perceptual priming effect followed by a decrease to baseline performance, while no changes were detected in the unstimulated portion of visual field. In contrast, participants under higher cognitive load displayed an early, specific, loss of performance which then generalized to the non-saturated quadrant.

Experiment 2

Conflicting reports are present in the perceptual learning literature concerning the eye-specificity of the enhancing effects of prolonged TDT repetitions (Karni & Sagi, 1991, 1993; Ofen et al., 2007; M. P. Walker et al., 2005). On the other hand, the perceptual deterioration phenomenon has been univocally reported to generalize to the eye that is spared the protracted task-involvement (Mednick et al., 2005).

Therefore, in this follow-up experiment our objective was four-fold. First, we wanted to confirm the findings from experiment 1 that prolonged passive stimulation under conditions of high arousal/cognitive load induces perceptual deterioration, with a simplified, shortened, experimental design. Second, we assessed whether this effect stayed within the stimulated eye or generalized to the other.

Third, we aimed at confirming that participants would report increased fatigue between the beginning and the conclusion of the experiment, and that this increase would correlate with the behavioral changes. And finally, we slightly adjusted the difficulty of the auditory tasks, seeking to highlight the correlation between individual levels of arousal as indexed by pupil size and the magnitude of the performance decrement.

Methods

16 participants were originally recruited to participate, however 2 dropped out, thereby bringing the total number of participants to 14 (13f, $M_{\text{age}} = 21.3 \pm 1.5$). All were naive to the experimental procedure, with no history of mental or visual conditions and normal or corrected-to-normal vision. They provided written informed consent to participate and were compensated 20€. This study was approved by the Ethical Review Board.

Experimental design

The stimuli and procedure were similar to the ones used in experiment 1, except for the following. Here, each experimental run was carried out in two separate days. In the first day, participants underwent training on the main task (TDT) and their performance determined the ISI (and thus the difficulty) of the task on the second day, when they would undergo the test session (25.4 ± 7.5 hours average distance between training and test). On test day, participants were asked to perform the TDT before and after a 41-minute saturation session, thereby reducing our design to the first half of experiment 1 (see figure 1, panel 1 b,c,d).

Auditory tasks

The auditory tasks performed concurrently to visual stimulation corresponded to the ones used in the hard group condition used in experiment 1.

The only differences were a reduced range of possible number of sounds in the pitch-sequence task (4 to 6 instead of 5 to 8) and a harder version of the n-back task: 3-back instead of 2-back. These changes were brought to increase the pupillary response to the n-back task with respect to experiment 1 and to reduce the difficulty of the pitch-sequence task in order to avoid task disengagement.

TDT

Similarly to experiment 1, the Texture Discrimination Task (TDT) was the main behavioral task (Karni & Sagi, 1991). However, in this version, we restricted target locations to one per quadrant, and had the participants undergo the task with a single eye exposed to the stimuli, which would alternate between blocks. Monocular viewing was assured by means of a patch.

Trials were composed of a pre-stimulus fixation cross, followed by a brief presentation of the target stimuli (32ms), an Inter Stimulus Interval, a mask (100ms) and finally a 1 second window to indicate the perceived alignment of the target.

On training day, the task comprised 6 blocks. The first 2 blocks had a reduced number of trials (40) and extended durations of ISI and target display to allow the participants to familiarize with the procedure. In the remaining 4 blocks, similarly to experiment 1, a Bayesian staircase procedure was used to determine the ISI depending on the participants' online performance, varying within the range of 0.02 to 0.6s. On test day, the subject-specific, fixed ISI corresponded to the value that had an 80% ratio of correct responses on the basis of the psychometric curve obtained from the block with the best performance in the training day. However, the participants' extracted ISI could not surpass a 0.6 seconds threshold, which was set as the maximum. Therefore, even if a participants' predicted ISI for an 80% correct performance was larger than this value, it was enforced to be 0.6s.

To prevent the predictability of target onset given the fixed ISI, a random Inter Trial Interval was introduced, varying within the range of 200 to 800 ms, uniformly distributed across trials and conditions. A single TDT trial lasted on average 2.5 seconds and 80 trials composed a block. A complete TDT test session consisted of 4 blocks, with equal numbers of trials per quadrant, target alignment, lasting 13 minutes on average.

Saturation

In between the baseline and conclusion TDT runs, participants underwent a saturation session that lasted for 41 minutes and consisted of prolonged visual stimulation, during which they had to maintain their gaze on a central fixation point while stimuli were continuously flashed at 7.5Hz. The visual characteristics of saturation were kept equal to those of experiment 1, such that here, beside the possible target line locations, the saturating stimuli also included lines that were never targets (see figure 1, panel 3 for reference). Each participant would undergo saturation with a single eye exposed to the stimuli. The assignment of saturated eye and quadrant was counterbalanced across participants.

Questionnaires

To confirm the findings of experiment 1 concerning subjective fatigue, the Multidimensional Fatigue Inventory (Gentile et al., 2003) was given at the beginning and end of the experiment.

Open code and data policy

Source code is available at [<https://github.com/ste-ioan/TDT21>], data is available freely for download at [<https://zenodo.org/record/5575767>](Ioannucci, 2021).

Statistical analysis

Behavioral effects were assessed by means of a Generalized Linear Mixed Model (GLMM) on response accuracy in the TDT. Correct response in the task was modeled as a logistic dependent variable, with SESSION, EYE and QUADRANT as explanatory variables, clustered by participant and also included in the random part of the model.

Repercussions on the subjective evaluation of fatigue were assessed by comparing the values reported before and after the experiment in the Multidimensional Fatigue Inventory via a paired samples t-test. Also, the performance change between beginning and conclusion of the experiment, in the saturated quadrant and saturated eye, was correlated to the change in the fatigue questionnaire scores.

Lastly, the participants' unfiltered, non baseline corrected pupil size recorded during the execution of the auditory tasks was correlated to the drop in performance in TDT in the saturated eye and saturated quadrant.

Results

The average test-day ISI estimated from training across participants was of 0.36 ± 0.18 sec.

The GLMM highlighted the fixed effects of SESSION ($X^2_{(1, 8960)} = 4.18$, $p = 0.041$) and the interaction of EYE and SESSION ($X^2_{(1, 8960)} = 6.52$, $p = 0.011$) as significant, while the triple interaction of EYE, SESSION and QUADRANT was only on the edge of significance ($X^2_{(1, 8960)} = 3.29$, $p = 0.07$). The post-hoc tests revealed that there was a significant loss of performance effect only in the saturated eye ($[\beta = 0.36$, $CI = 0.01, 0.73$, $Z = 2.91$, $p_{\text{corrected}} = 0.022$, $\exp(\beta) = 1.45$]).

Thus, revealing that the saturated eye condition was prominent in determining the behavioral effect (see figure 5).

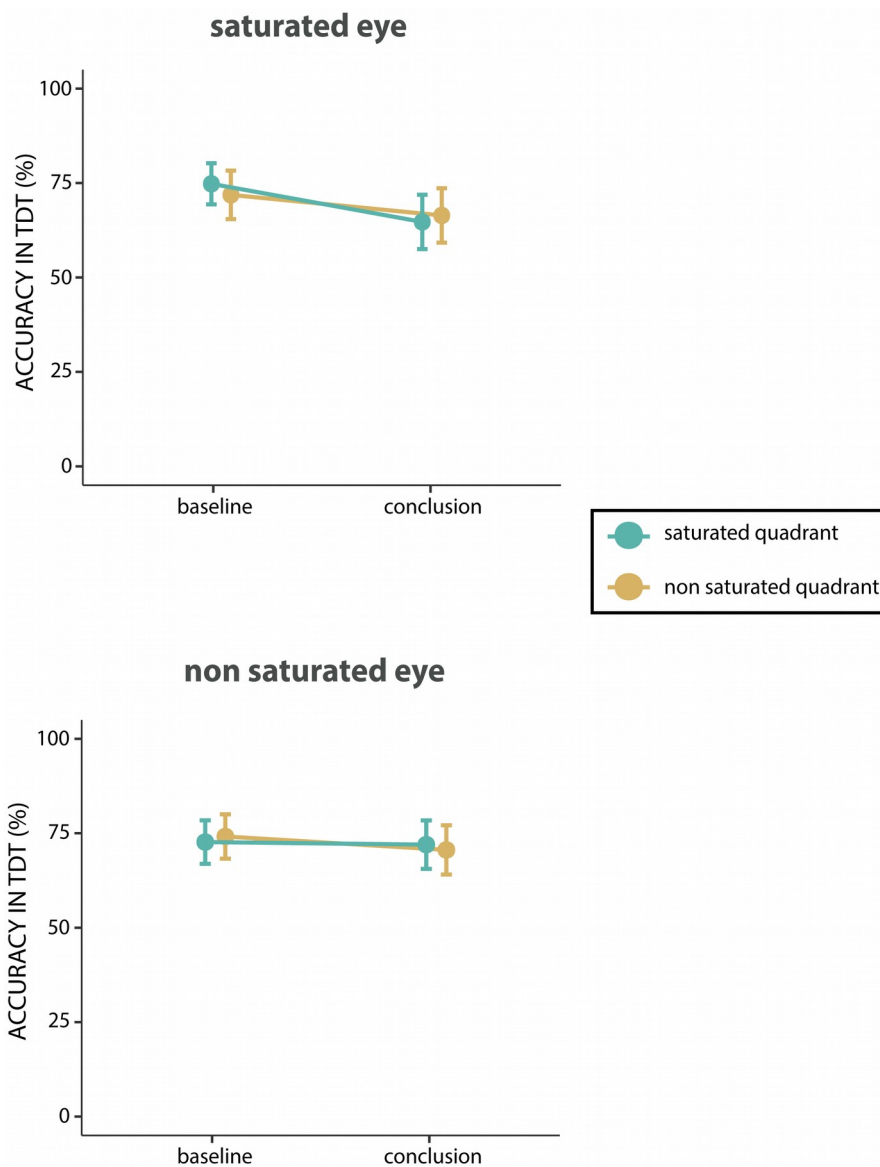


Figure 5: Percent of correct responses on the y axis as a function of session on the x axis, for both the saturated and non saturated quadrant and eye. Error bars depict the standard error of the mean.

Concerning the subjective feeling of fatigue, the paired samples t-test confirmed that the participants overwhelmingly reported increased fatigue at the end of the experimental manipulation ($T_{(13)} = -7.91$, $p < 0.0001$, $d = 2.1$).

Moreover, this change was found to be negatively correlated [$R_{(12)} = -0.56$, $CI = -0.84, -0.05$, $p = 0.035$; (see Figure 6a)] with the performance drop in the saturated eye & saturated quadrant

condition, such that a larger amount of perceived fatigue by the end of the experiment was significantly related to greater specific performance loss.

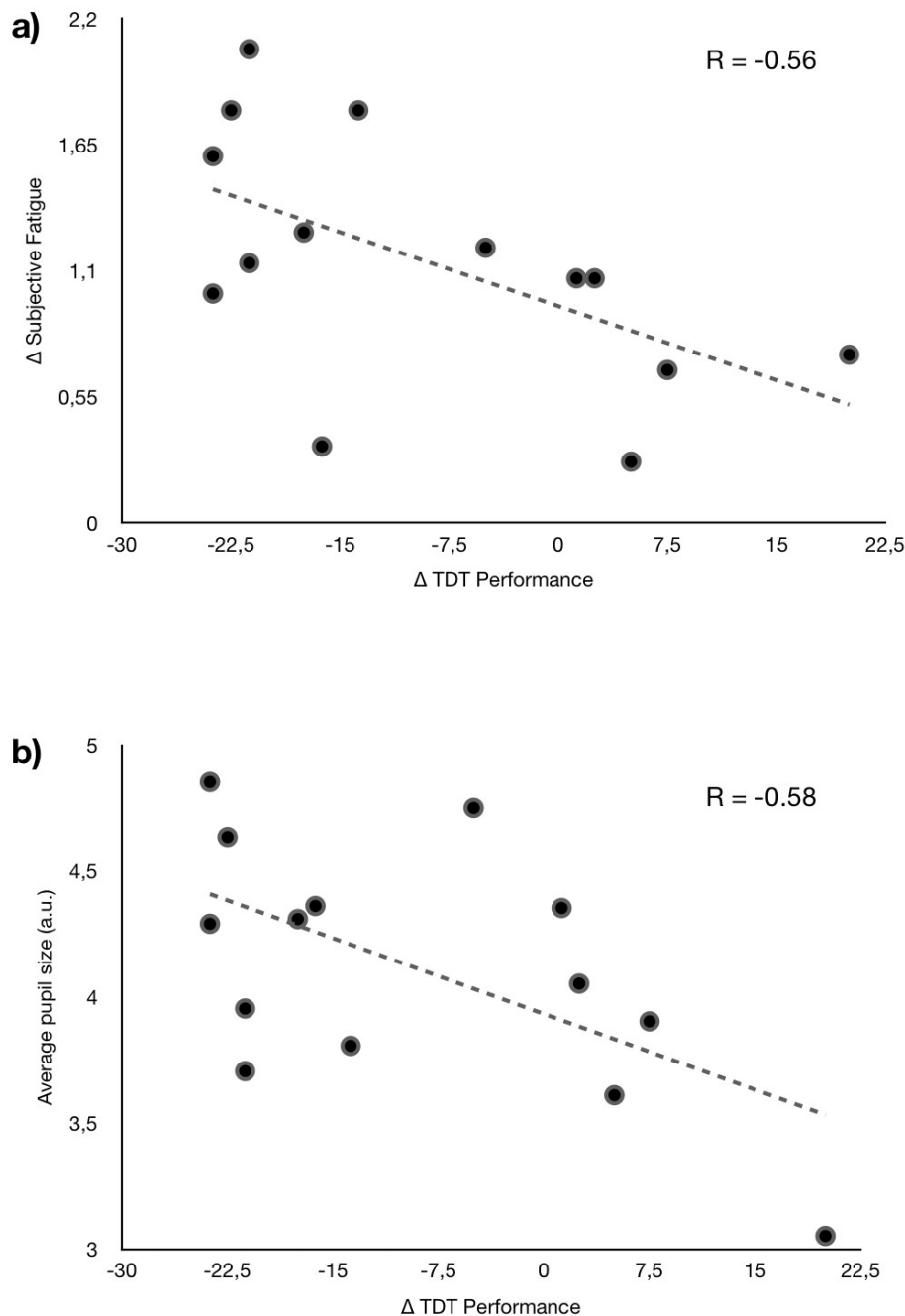


Figure 6: a) Scatterplot depicting on the y-axis the change in reported fatigue (i.e. the delta in the Multidimensional Fatigue Inventory scores between baseline and conclusion) in relation to the change in visual discrimination performance in the saturated eye and quadrant on the x-axis (i.e. the delta between conclusion and baseline percentage of accurate responses) b) Scatterplot depicting on the y-axis the average unfiltered pupil size during the auditory tasks in relation to the change in visual discrimination performance in the saturated eye and quadrant on the x-axis.

Additionally, the change in performance in the saturated eye and saturated quadrant conditions of the TDT was found to significantly correlate also with the average unfiltered, non baseline-corrected, pupil size of participants during the execution of the auditory tasks [$R_{(12)} = -0.58$, $CI = -0.85, -0.07$, $p = 0.029$; (see Figure 6b)]. Thus, larger average pupil sizes were related to stronger specific loss of performance.

Discussion

In this study, we replicated the finding from experiment 1, where participants displayed a specific loss of performance following 40 minutes of prolonged stimulation, regardless of minor changes to the experimental design. This effect was eye-specific rather than quadrant-specific, meaning that the eye that was exposed to said stimulation had a significant loss of performance compared to the unstimulated eye, with no significant difference between the sides of visual field where the targets were displayed. It cannot be ignored, however, that this eye-specific loss of performance was on average the double in the saturated quadrant than in the non-saturated one.

The present results are in discordance with previous accounts of lack of eye specificity of perceptual deterioration following prolonged task execution (Mednick et al., 2005) and suggests that the neural correlates of this deterioration must include regions of the brain that exhibit ocular specificity, such as V1, V2 or Lateral Geniculate Nucleus (LGN) (Hubel & Wiesel, 1968; Shatz, 1996), as posited by previous accounts on perceptual learning that found the effect to be eye-specific (Karni & Sagi, 1991).

Furthermore, we found that participants reported increased fatigue due to the experimental manipulation, and that their performance drop in the saturated eye and quadrant condition correlated with this accrued fatigue, thus replicating another result from experiment 1.

Finally, in the present experiment we found evidence of a meaningful relation between the participants' average pupil size and their change in performance in the TDT for the saturated conditions, thus providing empirical evidence for the role of arousal in mediating the perceptual deterioration as induced by saturation.

Experiment 3

Another important feature of the stimulus to which specificity should be assessed is the orientation, also regularly investigated in the fields of perceptual learning (Mayer, 1983; Ramachandran & Braddick, 1973; A. A. Schoups et al., 1995) and deterioration (Mednick & Boynton, 2004).

Similarly to experiment 2, here we sought to assess if we could successfully replicate the behavioral results induced by saturation, while assessing if the effect would be specific to the saturated stimulus orientation, thereby adding strength to the notion that the decrease in performance in the TDT is a by-product of prolonged neuronal activation.

Methods

16 participants were recruited to participate in the second follow-up experiment (9f, $M_{\text{age}} = 21.9 \pm 2.19$). All were naive to the experimental procedure, with no history of mental or visual conditions and normal or corrected-to-normal vision. They provided written informed consent to participate and were compensated 20€. This study was approved by the Ethical Review Board.

Experimental design

The stimuli and procedure were the same as the ones in experiment 2, here the average distance between training and test sessions was of 25.6 ± 4.7 hours.

Auditory tasks

Likewise to the stimuli and procedure, also the auditory tasks were the same as those employed in experiment 2.

TDT

As in the previous experiments, the Texture Discrimination Task (TDT) was the main behavioral task (Karni & Sagi, 1991), with a single target location per quadrant as in experiment 2. However, here, two orientations of the target lines were introduced, being either 45 degrees or 135 degrees. All the other aspects of the task were kept the same as in experiment 2, except for a larger number of trials per block (128), to have an equal number of trials per combination of conditions to the previous experiments.

Saturation

The visual characteristics of saturation were kept equal to those of experiment 1 and 2. The assignment of saturated quadrant was counterbalanced across participants, while the saturated orientation (45°) was kept constant.

Questionnaires

Questionnaires were not collected for this experiment, as it was originally designed to acquire pilot data for another experiment.

Open code and data policy

Source code is available at [<https://github.com/ste-ioan/TDT21>], data is available freely for download at [<https://zenodo.org/record/5575767>](Ioannucci, 2021).

Statistical analysis

A generalized linear mixed model was run with accuracy in the TDT as dependent variable.

SESSION, ORIENTATION and QUADRANT were introduced as explanatory variables, clustered by participant and also included in the random part of the model.

As in the two previous experiments, the participants' raw pupil size recorded during the execution of the auditory tasks was correlated to the drop in performance in TDT in the saturated conditions.

Results

The average test-day ISI estimated from training across participants was of 0.34 ± 0.17 sec.

The GLMM highlighted several fixed effects as significant. Other than the SESSION condition ($T_{(20093)} = -3.99$, $p < 0.0001$) and QUADRANT ($T_{(20093)} = 2.03$, $p = 0.042$), along with their interaction ($T_{(20093)} = -3.13$, $p = 0.002$), the triple interaction of QUADRANT, ORIENTATION and SESSION was found to be prominent ($T_{(20093)} = 2.6$, $p = 0.009$).

A post-hoc analysis on this triple interaction revealed that this result relied upon the significant difference between pre and post sessions, for the saturated quadrant and orientations [$\beta = -0.28$, CI = $-0.46, -0.1$, $Z = -3.07$, $p_{\text{corrected}} = 0.01$, $\exp(\text{abs}(\beta)) = 1.32$], while no other contrast reached statistical significance.

Thus, as expected, despite a general trend of reduced performance across sessions, participants displayed a specific deterioration in the saturated quadrant and target orientation (see figure 7).

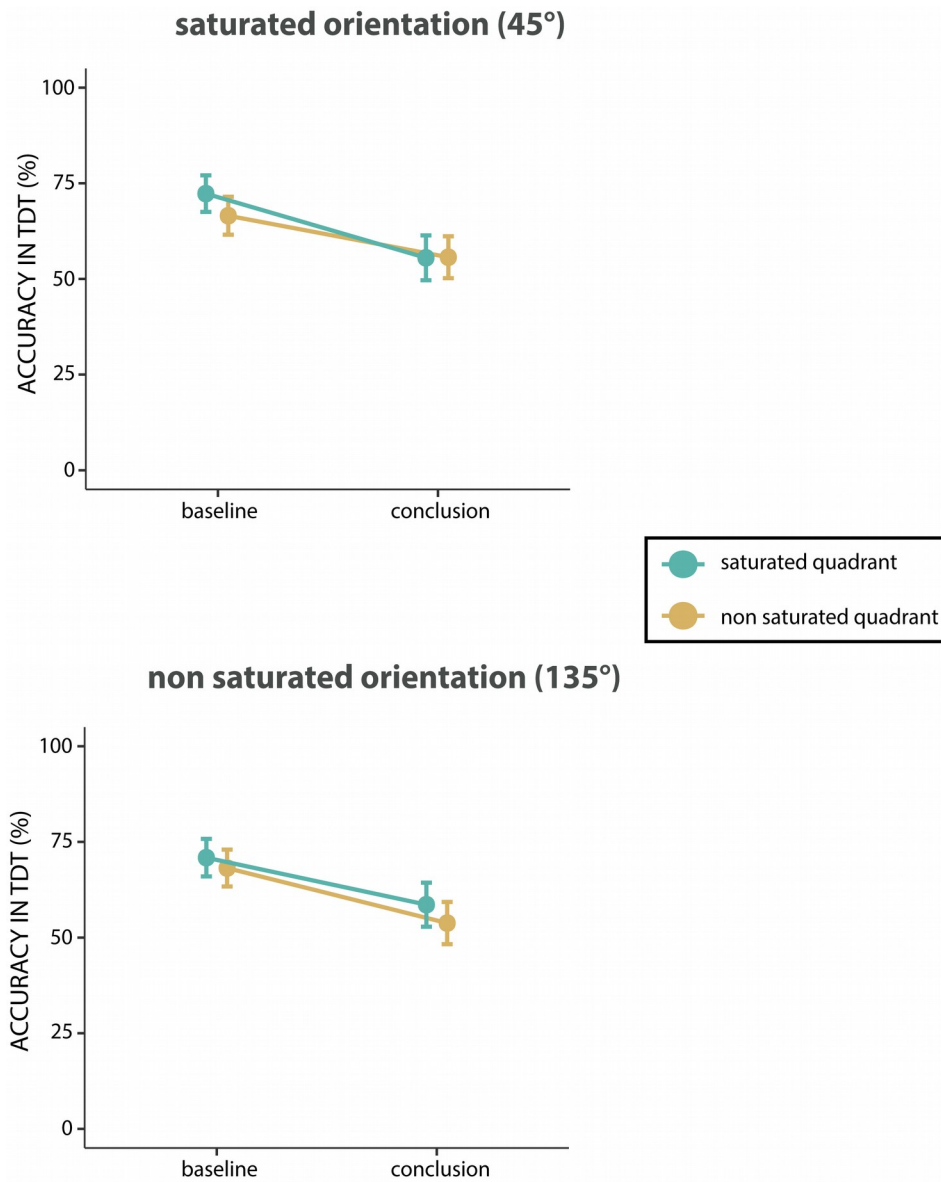


Figure 7: Percent of correct responses on the y axis as a function of session on the x axis, for both the saturated and non saturated quadrant and orientation. Error bars depict the standard error of the mean.

Similarly to experiment 1, the correlation between the average pupil size of participants during the execution of the auditory tasks was not significantly correlated to the change in TDT performance in the saturated conditions ($R_{(14)} = 0.07$, $CI = -0.48, 0.82$, $p = 0.82$).

Analysis of pupillary data from the three experiments

In order to assess if the pupil size of participants during the execution of the auditory task was related to the performance change in the texture discrimination task, we included data from the three experiments in a single linear mixed model, with the delta in TDT performance as dependent variable, average unfiltered pupil size as covariate and experiment as clustering variable.

Indeed, a significant relation between the average pupil size of participants and their performance drop in the TDT was found, where larger pupil size corresponded to greater performance drop ($\beta = -2.52$, CI = -4.56, -0.49, $t_{(26)} = -2.43$, $p = 0.022$).

Discussion

In the case of experiment 3, our results are in line with previous accounts of perceptual deterioration (Mednick & Boynton, 2004). Indeed, we found that the loss of performance induced by the saturation procedure was specific to the orientation of the saturating stimuli. This finding, along with the previous ones, is suggestive of a failure in specialized cellular assemblies that arises from the overextended activity in response to saturation, and their interaction with arousal induced by the auditory tasks.

Candidate specialized assemblies may be found in neurons from orientation selective areas of the visual cortices, either in the primary visual cortex V1 (Fahle, 1994; A. Schoups et al., 2001; Teich & Qian, 2003), but also possibly in higher visual areas involved in orientation detection, i.e. V4 (Raiguel et al., 2006; Yang & Maunsell, 2004). Further neuroimaging studies are needed to investigate the neural correlates of the reported effects. Lastly, while in experiment 3 we failed to replicate the correlation between raw pupil size and behavioral change that we witnessed in experiment 2, we were able to confirm this relation when integrating the data from the three experiments.

General discussion

The possibility of analytically determining the mechanisms by which organisms decline or improve in performance when performing mental actions has been a fascinating ambition of behavioral sciences since their dawn (Kraepelin, E., 1902; Oehrn, 1889). Such ephemeral and intertwined processes have proven arduous to formalize in the scientific *modus operandi*, for they depend on a range of heterogenous factors, both external (i.e. the environment and characteristics of the activity) and internal to the organism (i.e. the individual's personality and motivation), the latter type being particularly challenging to measure. Thus, a recurring strategy in behavioral sciences is the reduction of the general question (i.e. how do organisms learn or become fatigued?) to simpler, more circumstantiated, research objectives (how many repetitions in a given task are necessary for improvement to appear and stabilize? How many for the opposite?), which provide insights into the broader problem. Through similar reasoning, many of those keen to explore how agents ebb and flow between improvement and decay in performance as they carry out operations have been drawn to the domain of perception. Certainly, in such domain the process of conjugating behavioral outputs to specific modalities or quantities of stimulation, while quantifying such outputs, is appreciably more streamlined than in others. Moreover, it may be argued that there can hardly be any learning without previous perception, albeit it may happen unconsciously (Watanabe et al., 2001).

Here, we aimed at bridging the gap between three distinct areas of the literature on progressive performance alteration, namely cognitive fatigue (Gergelyfi et al., 2015), perceptual deterioration (Mednick et al., 2002) and habituation (Thompson, 2009). The fatigue literature is currently dominated by the motivational perspective, according to which no functional deterioration of neural networks would have to take place for cognitive fatigue to develop. This prevailing opinion is caused by the lack of compelling evidence for functional deterioration associated with fatigue. On the other hand, perceptual deterioration, sometimes referred to as visual adaptation (Censor et al.,

2006, 2016; Ofen et al., 2007) has provided such evidence, though in different contexts (Mednick et al., 2002). In particular, an extensive use has been made of the Texture Discrimination Task (Karni & Sagi, 1991), a visual perceptual task that relies on fast stimulus presentations and offers a diverse range of modifiable parameters, depending on the aim of the experimental design.

As a consequence, several studies have been published assessing the impact of the presence of training, duration of inter-stimulus-intervals, number of trials within a session, blocks and/or sessions (Censor et al., 2006, 2016; Censor & Sagi, 2008; Ofen et al., 2007) on the above-mentioned phenomena, particularly in the domain of learning and sleep where the task was initially introduced (Karni & Sagi, 1993; Stickgold et al., 2000). Therefore, by employing the performance in this task as a proxy to measure the underlying neural modifications, throughout the years authors have accumulated several results. Perceptual deterioration is now hypothesized to arise from the saturation of specific neural networks, preventing further processing of information that has not been consolidated yet into memory by sleep (Mednick et al., 2002, 2008). Finally, the habituation literature provides yet another perspective on behavioral alteration following repeated stimulation, being concerned more specifically with the progressive decrease of response amplitude, viewed as an adaptive mechanism to favor learning rather than as a limit to performance (Thompson, 2009).

The hypothesis that cognitive fatigue is caused by gradual, functional alterations in neural networks following their prolonged recruitment, leads to the prediction that even passive stimulation should cause performance decrements. This resonates with the common, day-to-day experience of being immersed in painstaking visual tasks, such as spread-sheet analysis or proofreading a document, which eventually leads to our need to seek temporary relief by looking away. In experiment 1, we confirmed this prediction by showing perceptual deterioration induced by passive stimulation in situations of high arousal and cross-sensory cognitive load.

In experiments 2 and 3, we confirmed that prolonged stimulation of a portion of the visual field led to specific deterioration of participants' performance in that portion of visual space, albeit restricted to the stimulated eye (experiment 2), and specific to the saturation orientation (experiment 3). An undeniable feature of the present design is its efficacy in inducing specific loss of performance, whether to the saturated eye, quadrant, or orientation, following only 40 minutes of passive stimulation. Such timeframe is considerably shorter than previous paradigms employing the same task to induce perceptual deterioration (Mednick et al., 2002, 2005, 2008; Mednick & Boynton, 2004). Across the three experiments, we were also able to show evidence that the magnitude of the performance decrement correlated with pupil size, suggesting that this effect was mediated by arousal as originally hypothesized. The combined findings that the observed neural fatigue phenomenon depends on arousal level and is both orientation- and eye-specific place its brain correlate presumably at the level of early visual cortex (i.e. V1 or V2; Hubel & Wiesel, 1968), though implication of some parts of the extra-striate (i.e. V4; Roe et al., 2012) or lower areas such as the LGN (Xu et al., 2002) can be considered.

We propose, therefore, that such progressive functional alteration generated by repeated recruitment could constitute one of the mechanisms involved in general fatigue, as confirmed by the correlation we observed in experiment 1 and 2 between the feeling of fatigue and the specific behavioral consequences, which is rarely found in the pertaining literature (DeLuca, 2007).

Importantly, our findings are immune to confounds common in the relevant literature such as boredom, motivation and level of skill in the fatiguing task (Gergelyfi et al., 2015). Certainly, since all participants carried out the task in the saturated and non-saturated portion of their visual field or eye, any difference in performance 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.

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 characterization of such process is matter for subsequent studies, which may disentangle how exactly the phenomena brought forward by the present results, act and interact with each other.

Context

The question of the neural origin of mental fatigue remains hotly debated. It remains unknown, in particular, whether mental fatigue is associated with brain functional alterations or occurs as a consequence of motivational redirection. In previous studies we have provided evidence against the motivational hypothesis by showing that extrinsic rewards were not effective in alleviating the impact of mental fatigue on performance, and that the brain motivation circuits did not show preponderant alterations. Here, we set out to test the opposite hypothesis by assessing whether prolonged neuronal activity leads to functional alterations, measured through behavioral performance. We chose a design based on passive visual stimulation in order to free ourselves from important confounding factors such as motivation or boredom. We drew inspiration from the visual adaptation and habituation literature and sought to verify whether the effects could arise just by means of passively stimulating the relevant neuronal populations instead of extensively repeating the manipulating task. Indeed, we confirmed our hypothesis that fatigue was selectively inducible by passive stimulation, across 3 behavioral experiments. Additionally, in conditions of low arousal, performance improved rather than decreased. Thus, we provide the first report of behavioral passive fatigue, show its specificity as well as its dependence on arousal.

CHAPTER 3 – SECOND STUDY

Neural fatigue by passive induction

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Abstract

Cognitive fatigue is characterized by failure to perform in mental tasks. Despite its pervasiveness, its underlying neural mechanisms remain elusive. Specifically, it is unclear whether alterations due to prolonged mental effort take place in over-worked task-relevant neuronal assemblies, or in task-unrelated networks involved in motivation regulation. Here, we tackle this question by means of a paradigm that permits to discern fatigue effects from motivation, level of skill and boredom. Brain changes following fatigue were assessed by means of multivariate neuroimaging techniques (MVPA) that afford a subject-specific approach. We replicated previously observed passively induced performance loss, and observed parallel alterations in the neural functional blueprint of the task. Furthermore, estimated levels of activity in these networks correlated with changes in behavioral performance, and functional areas that responded the most to stimulation were also the most affected by fatigue induction. Finally, by means of univariate analysis, we localized in the visual cortex the clusters that displayed significant disruption following fatigue.

In sum, we show that specific fatigue via repeated stimulation impacts the activity of task-relevant networks and is associated with tangible behavioral repercussions. These results provide evidence for the hypothesis that fatigue issues from local, functional brain alterations induced by repeated recruitment.

Introduction

Cognitive fatigue (CF) is characterized by a pervasive avoidance of mental effort usually triggered by periods of sustained cognitive activity. It is a distinctively recognizable state that is often experienced on a daily basis: without fail, even the most energetic individuals ultimately succumb to CF and feel the urge to seek rest and recovery. Behavioral scientists have so far formalized two key aftermaths of CF. The first, “objective” component of fatigue, is an incapacitation to carry out effortful mental actions with a quantifiable decline in performance (DeLuca, 2007). The second, “subjective” component of fatigue, consists of a sensation of mental exhaustion (DeLuca, 2007), whose method of measurement remains debated due to its murky overlap with other constructs, such as boredom and underlying levels of motivation, which are hardly controllable in experimental settings (Ackerman, 2011; DeLuca, 2007; Hockey, 2011).

Despite its ubiquity, the causes of mental fatigue remain elusive but have been theorized along a functional and a motivational axis. The former focuses on posited alterations taking place in the circuitry directly subtending the effortful action due to overwork (Blain et al., 2016; Gergelyfi et al., 2015, 2021; Krueger et al., 2019), while the latter stresses the importance of the drive to partake in actions according to their intrinsic reward and utility (Boksem & Tops, 2008; Hockey, 2011; Kurzban et al., 2013). As the functional paradigm of CF proposes that fatigue issues from accumulation of metabolites or depletion of resources over repeated recruitment of the same neural networks, this leads to the prediction that even passive neural stimulation should eventually produce fatigue in specific neuronal assemblies. In previous work (Ioannucci et al., 2021), we provided support for this hypothesis by showing, across multiple experiments, that passive visual stimulation had tangible repercussions on tasks that involved stimuli identical to the repeatedly presented ones. These performance drops were mainly present, if not bound within, the portion of visual field that underwent continuous passive stimulation (‘saturation’), observed only under conditions of higher arousal and cognitive load induced by auditory tasks concurrent to the visual stimulation.

These findings, thanks to their striking specificity, provide evidence for fatigue-induced performance drops that are unequivocally dissociated from other confounds, such as boredom, level of skill in the task and motivation.

Such result is in line with reports of metabolic changes taking place in the relevant neural networks during visual stimulation, albeit on a shorter timescale (Bednařík et al., 2015) and reports of fatigue-induced alterations taking place in the task-relevant networks in humans (Blain et al., 2016; Gergelyfi et al., 2021; Mednick et al., 2008) and rats (Vyazovskiy et al., 2011). Still, the neuroimaging literature on the broader topic of cognitive fatigue has yet to reach a clear consensus, as attested by the diverging reviews on the topic (Boksem & Tops, 2008; Ishii et al., 2014; Tran et al., 2020). Indeed, functional paradigms of cognitive fatigue have suffered from contradictory results, particularly in regards to the hypothesis of energy consumption in the central nervous system as related to quantifiable deteriorations in the performance of mental effort (Kurzban, 2010). On the other hand, motivational paradigms have focused onto integrating findings from neuroscientific research on the broader topics of reward and drive to engage in tasks (M. Botvinick & Braver, 2015; Hockey, 2013; Kurzban et al., 2013) to interpret the neural bases of fatigue and effortful behavior.

In the present study, we set out to test the hypothesis that the decline in performance decrement following prolonged passive stimulation (Ioannucci et al., 2021) is caused by altered cortical responses developing in the brain regions that are recruited by the fatiguing condition. Other neuroscientific works sharing parallel hypotheses have so far been carried out assessing the impact of considerably longer active task engagement and by enforcing an *a priori* determined brain area of interest (Blain et al., 2016; Mednick et al., 2008) and/or using mainly univariate methods (Gergelyfi et al., 2021).

Here, instead, we hypothesized that each participant would have their own functional response to the task-relevant stimuli, since cortical response to identical stimuli and tasks varies from subject to subject (Seghier & Price, 2018).

Therefore, we adopted a subject-specific functional approach, instead of a one-fits-all procedure, by using a multivariate neuroimaging method (Haxby et al., 2014) to run a classifier on the brain activity within the subject-specific cluster of voxels that responded to the stimuli, and compared its performance before and after saturation. We also performed a univariate analysis of the pre-post brain scans to identify the cerebral regions where the alteration between sessions was most prominent across participants. Importantly, we expected the regions of the brain that were the most responsive to the stimulation to also show the largest drops in encoding reliability, which we tested by correlating the voxel-wise change in classifier accuracy to the degree of response to passive stimulation.

Methods

The experimental design and main analyses performed in the present study were pre-registered on the Open Science Foundation platform (<https://osf.io/vkrst>).

Participants

Given previous results (Ioannucci, 2021), and the current consensus on functional neuroimaging sample sizes (Szucs & Ioannidis, 2020), we pre-planned the study to have 24 participants.

We eventually ran a total of 25 participants but had to exclude one from the fMRI analysis (because of visible artifacts in MR scans) and another from the behavioral analysis (because of failure to respond in the concluding session). We thus had a total sample of 24 in both the behavioral and neuroimaging analyses. Participants were recruited informally and took part voluntarily in the experiment ($M_{\text{age}} = 21.6 \pm 1.8$, 10 m).

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 50€ in compensation for their participation. The study was approved by the Ethical Review Board.

Design

The experiment was carried out in two separate days (see figure 1a). On the first day, participants would undergo a training on the Texture Discrimination Task (TDT; see figure 1 panel b) to adapt the difficulty of the task to their level of skill, via a Bayesian staircase procedure (Ioannucci, 2021), and to familiarize with the auditory tasks employed during saturation.

On the following day, participants would undergo the test session within the MRI scanner.

Participants were first presented to a localizer task, in order to identify the portions of their brain that responded significantly to the stimuli, which were identical to the targets used in the TDT.

Then, they carried out the TDT at their personalized difficulty. Following the first TDT session, participants underwent neuronal saturation (see below), which was then followed by a second TDT and localizer session. At the beginning and conclusion of the test day, outside the scanner, participants were asked to fill out the Multidimensional Fatigue Inventory (Gentile et al., 2003) and the Karolinska Sleepiness Scale (Shahid et al., 2011) to assess the evolution in their perceived levels of fatigue and sleepiness during the experiment.

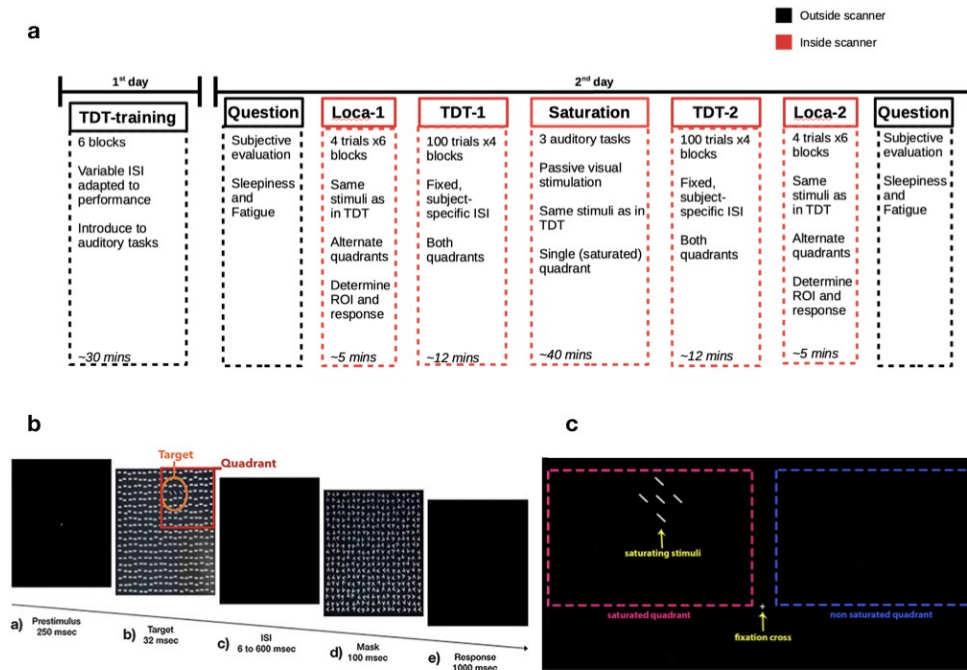


Figure 1: a) Experimental design b) Breakdown of a Texture Discrimination Task trial c) Graphical depiction of a saturation session

Materials

All experimental tasks were coded in Matlab 2019a (The MathWorks, Inc., Natick, Massachusetts, United States), using Psychtoolbox (Brainard, 1997; Pelli, 1997). On training day, participants sat in front of a 1280 by 1024 computer screen at a distance of 60 cm and accommodated their heads on a chin-rest, using a keyboard to respond across the various tasks. On test day, participants lied in the MRI scanner and employed bimanual fiber optic response pads (Current Designs Inc., Philadelphia, USA) to respond during the TDT and auditory tasks. Sounds were presented in the scanner via OptoActive ANC headphones with active noise cancellation (Optoacoustics Ltd., Tel Aviv District, Israel). Heart and respiratory rate were recorded through the Physiologic ECG and Respiratory Unit of the Physiological Measurement Unit (Siemens AG, Bavaria, Germany).

On both days, an Eye-tracker (SR Research Ltd., Mississauga, Canada) was employed to ensure compliance of central fixation throughout the tasks, monitored by the experimenter.

Texture discrimination task

The main behavioral task consisted in the TDT, based on the task originally 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 1b).

Participants were instructed to maintain their gaze on a central fixation cross and report the perceived orientation of the peripheral target at the end of each trial, by pressing on the keyboard. These targets would relocate from trial to trial, with 2 possible locations, one for each quadrant of the upper half of the screen. Therefore, there were 4 possible targets: either horizontal or vertical, in either the left or right quadrant. Additionally, to mitigate potential biases in the brain activity data, the response keys would change in each block and their order alternate among participants, who were informed of this.

On training day, the task comprised 6 blocks with a balanced number of targets for each alignment (vertical/horizontal) and quadrant (left/right). The first 2 blocks differed from the rest as they had a reduced number of trials (40) and extended durations of Inter Stimulus Interval (ISI) and target display to allow the participants to familiarize with the routine. In the remaining 4 blocks, composed of 100 trials each, a Bayesian staircase procedure was used to determine the ISI depending on the participants' online performance, varying within the range of 0.02 to 0.6s.

On test day, the subject-specific, fixed ISI corresponded to the value that had an 80% ratio of correct responses on the basis of the psychometric curve obtained from the block with the best performance in the training day. However, the participants' extracted ISI could not surpass a 0.6 seconds threshold, which was set as the maximum. Therefore, even if a participant's predicted ISI for an 80% correct performance was larger than this value, it was enforced to be 0.6s.

To prevent the predictability of target onset given the fixed ISI, a random Inter Trial Interval was introduced at the beginning of each trial, varying within the range of 200 to 800 ms, uniformly distributed across trials and conditions.

A complete TDT test session consisted of 4 blocks, with equal numbers of trials per quadrant and target alignment, lasting ~15 minutes on average (~2 seconds per trial). Across participants, the order of target locations and alignments was predetermined to maximize the blood-oxygen-level-dependent (BOLD) signal to noise ratio via design efficiency analysis (CANlab toolbox).

Localizer

To identify the areas involved in the processing of the task stimuli we devised a localizer task. Here, unique targets (e.g. horizontal alignment of three 45° lines in left quadrant, etc.) were presented to participants inside the scanner as they fixated the central cross. Each unique target alignment and quadrant combination was presented 6 times for 12 seconds, alternating. The total duration of a localizer session was ~5 minutes.

Note that we opted to employ the actual target stimuli for this retinotopic mapping, rather than an unrelated grating checkerboard, as done in other works employing the same behavioral task (Schwartz et al., 2002; Yotsumoto et al., 2008).

Saturation

In between the baseline and conclusion TDT sessions, participants underwent a saturation session that lasted for 41 minutes. This saturation session consisted in prolonged visual stimulation, during which participants had to maintain their gaze on a central fixation point, while the stimuli were continuously flashed fluttering at 7.5Hz, with brief pauses between the end and the beginning of the auditory tasks in which the participants were engaged during saturation.

These stimuli comprised all possible target line locations of one of the quadrants (i.e. the saturated quadrant), which was alternated between participants (see figure 1c).

auditory tasks

During saturation, participants were engaged in 3 different tasks that tax executive functions, short term memory and attention. For a more detailed description we refer the reader to our previous work (Ioannucci, 2021).

MRI acquisition

A 3T Magnetom Prisma scanner (Siemens, Erlangen, Germany) was employed using a 64-channel head coil. Subjects underwent anatomical and functional acquisitions during a single session. 3D T1-weighted MPRAGE anatomical volumes were acquired with the following parameters: Repetition Time/Echo Time = 2400/2.21 msec, Inversion Time = 1000 msec, Field-of-view = 256 mm², Matrix = 256 × 256 × 208, Slice Thickness = 1 mm.

All the functional MRI series were acquired using a 2D simultaneous multi-slice echo gradient echo planar sequence (2 x 2 mm voxels in-plane; 2 mm slice thickness with no gap; 40 transverse slices, 170 x 170 mm field-of-view; matrix 86 x 86; partial-fourier 6/8; repetition time = 1 s; echo time = 31 ms; multiband slice acceleration factor of 4; phase encoding direction Anterior-Posterior; flip angle 71°; bandwidth 1384 hz/pixel). The acquisition was aligned to the calcarine scissure of the participants.

Quality control

A quality control was conducted using mriqc software (Esteban et al., 2017). MRI images were visually inspected in order to remove those which presented major spatial artifacts (deformations and movements). In addition, fMRI series exhibiting a Framewise Displacement value greater than 2mm or a DVARS value greater than 0.4% BOLD change were excluded for excessive motion

according to Power's recommendations (Power et al., 2014). As mentioned, images from a single participant presented major deformations and were therefore rejected.

fMRI Preprocessing

Susceptibility-induced distortions were estimated and corrected for all functional images using the top-up method (Andersson et al., 2003) with FSL6.0.3 (FMRIB, Oxford, UK). In a second step, they were motion-corrected using linear transformation with the automated tool MCFLIRT in FSL and intensity-scaled to 1000. Then, the PhysIO Toolbox with MATLAB v9.7 was used to apply physiological noise correction (Kasper et al., 2017). Both cardiac and respiratory signal were recorded using a finger pulse oximeter and a pneumatic belt during MRI acquisition. Respective physiological regressors were created using the RETROICOR algorithm (Glover et al., 2000) as well as heart rate variability (Chang & Glover, 2009) and respiratory volume per time (Birn et al., 2006) and regressed out of from the functional MRI time series. Due to the short repetition time used, no slice timing correction was applied. Finally, each series was realigned to the first localizer acquisition using rigid transformation with FSL flirt using mean as reference image and normalized to MNI-space using SPM 12 by warping the T1 anatomical scans and applying the linear transformations to the functional scans.

fMRI analysis

During statistical contrasts, all the fMRI scans were high-pass filtered with a cutoff of 128 s/cycle, as per SPM default. For the scans used in the ROI determination contrast, an additional smoothing step was carried out ($8 \times 8 \times 8$ mm), in order to more leniently determine the extent of the clusters, as voxels neighboring the peaks include potentially useful signal. This approach was preferred over directly enforcing a strict anatomical *a priori* region of interest, or choosing voxels from contrasts

that aren't corrected for multiple comparisons which are expected to include more noise and thereby usually restricted *a posteriori* by some anatomical criterion (for an example see Liang et al., 2017).

Subject-wise ROI determination

For each subject, a contrast was carried out on their localizer data in both sessions (baseline and conclusion) between the targets in one quadrant versus the other (e.g. Left Quadrant (LQ) > Right Quadrant (RQ) and viceversa). Then, the clusters surviving Family Wise Error multiple comparison correction ($p_{\text{corrected}} < 0.05$) in both localizer sessions (AND operation) were combined into a single, subject-specific, binarized functional ROI, via the marsbar toolbox (Brett, Anton, Valabregue, Poline, 2002). Therefore, for each subject we obtained two ROIs, one for each side of quadrant stimulation (see figure 3), which were later categorized as saturated or non saturated, depending on which quadrant would display the stimuli during saturation.

Multi variate pattern analysis

MVPA was carried out both on the localizer betas and the TDT betas, with the same LQ vs RQ contrasts mentioned above as regressor. In the case of the localizer, the beta coefficients were derived by means of separate regressors for each single 12-second block of stimulation, while in the case of the TDT, regressors included groups of 10 successive same-condition trials.

MVPA analysis was carried out via The Decoding Toolbox (Hebart et al., 2015), in the baseline and conclusion sessions, separately for the RQ and LQ ROIs. The classifier was asked, with a leave-one-out cross-validation procedure, to label in which quadrant were the stimuli presented, given the observed brain activity. Therefore, for each participant, we derived a data point of classifier accuracy for each quadrant, at baseline and conclusion, for both the localizer and the TDT brain scans.

Additionally, to estimate a voxel-wise measure of classifying accuracy, the above analysis was repeated with a searchlight procedure using a 4 voxel radius within the subject-specific ROIs. Searchlight analyses generate accuracy maps by measuring the variation in activity in multiple, overlapping, group of voxels (“searchlights”) in relation to the experimental conditions (Etzel et al., 2013), thus outputting a measure of classifying accuracy for every voxel in the functional ROIs.

open code and data policy

All the data, scripts and analyses employed in this work can be found at the following links: <https://zenodo.org/record/5907050>, <https://github.com/ste-ioan/nfbpi>

Statistical analysis

Behavioral and MVPA analyses, except correlations which were done in Matlab, were carried out in jamovi (The jamovi project, 2019) including the package gamlj (Gallucci, 2019) for linear models. Contrasts and analyses with neuroimaging data were carried out via SPM 12 (Friston et al., 2007), unless otherwise specified.

Behavioral effects were assessed by means of a Generalized Linear Mixed Model (GLMM) on response accuracy in the TDT. Correct response in the task was modeled as a logistic dependent variable, with Session, Quadrant and their interaction as explanatory variables, clustered by participant and also included in the random part of the model.

Changes in MVPA accuracy were evaluated by repeated measures ANOVAs with session (baseline, conclusion) and quadrant (saturated, not saturated) as within-subject factors, separately on the localizer and TDT estimates of brain activity.

To identify precisely the spatial localization of the alteration induced by the saturation procedure, we proceeded to homogenize brains in relation to their stimulation side (i.e. the brains of

participants who were saturated on the left portion of the visual field were flipped, so that all participants had coherent saturated and non saturated sides of the brain). These beta maps were then contrasted with a classic second-level univariate approach, by means of a repeated-measures analysis with non-parametric cluster-wise bootstrap procedure (SwE toolbox; Guillaume et al., 2014), between conclusion and baseline scans of all the participants.

For this analysis, an explicit mask was restricted to the functionally relevant parieto-occipital portions of the brain, obtained by aggregating each subject-specific functional ROI and excluding any clusters anterior to the central gyrus and/or inferior to the lower bound of the occipital lobe. Most voxels of the single ROIs fell within this mask (91% on average), with the majority of voxels located in the hemisphere contralateral to stimulation. The yielded data-driven mask is available for scrutiny in the data repository (<https://zenodo.org/record/5907050>).

Classifier-behavior correlation was assessed by extracting the random coefficients of the Session-Quadrant interaction in the GLMM on TDT accuracy data (representing individual deviations from the mean effect) and correlating these values to the delta (conclusion – baseline) in classifier accuracy in the saturated ROI, while brain-behavior correlation was assessed by correlating the same random coefficients to the delta (conclusion – baseline) in mean brain activity inside the saturated ROI.

The quantification of voxel-wise deterioration in classifying accuracy in relation to the degree of response to passive stimulation was assessed by a linear mixed model on the baseline brain activity with the delta in voxel-wise accuracy, the saturation condition and their interaction as explanatory variables, clustered by participant and included in the random part, except for their interaction, as including interactions of between and within factors in the random part of a mixed model is not recommended, especially for small to moderate samples (Barr et al., 2013).

The evolution of subjective fatigue was evaluated by a paired-samples t-test on the average change towards fatigued responses in the Multidimensional Fatigue Index (Gentile et al., 2003), and by a sign-rank test between the baseline and conclusion scores in the Karolinska Sleepiness Scale (Shahid et al., 2011). Finally, the correlation between objective and subjective components of fatigue was assessed by correlating the random coefficients of the GLMM and the delta (conclusion – baseline) in questionnaires scores.

Results

Behavior

The average test-day ISI estimated from training across participants was of 0.22 ± 0.13 sec.

The GLMM revealed significant Session ($X^2_{(1, 19200)} = 6.61, p = .01$) and Quadrant ($X^2_{(1, 19200)} = 7.98, p = .005$) main effects as well as significant Session-Quadrant interaction ($X^2_{(1, 19200)} = 23.61, p < .001$). Post-hoc tests, corrected for multiple comparisons by Holm procedure, confirmed a lack of difference at baseline between the saturated and non saturated quadrant ($\beta = 0.24, CI = -0.19, 0.66, Z = 1.4, p_{\text{corrected}} = .48, \exp(\beta) = 1.27$), and between baseline and conclusion for the non saturated quadrant ($\beta = 0.13, CI = -0.21, 0.48, Z = 0.88, p_{\text{corrected}} = .76, \exp(\beta) = 1.14$), while highlighting a significant decrease between sessions in the saturated quadrant ($\beta = 0.64, CI = 0.02, 1.27, Z = 3.85, p_{\text{corrected}} < .001, \exp(\beta) = 1.91$; see figure 2).

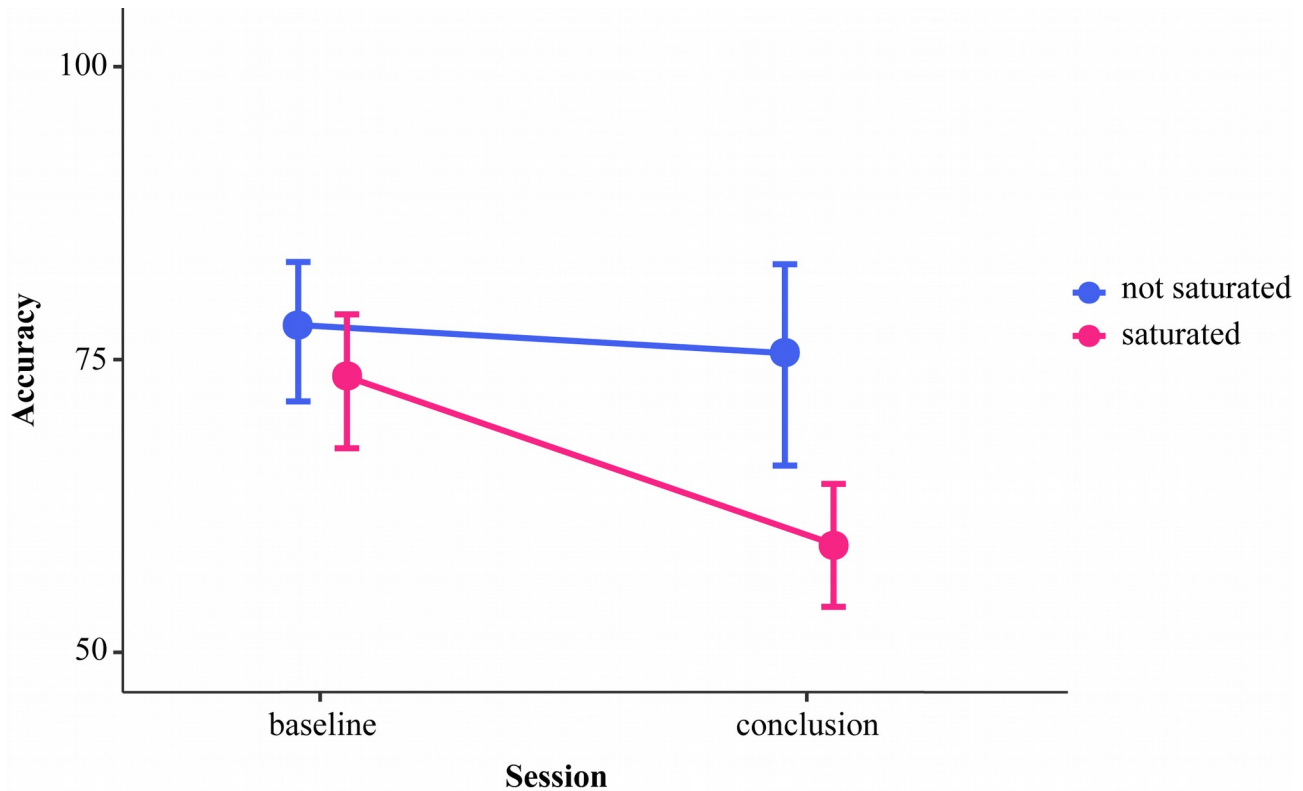


Figure 2: Graphical depiction of the average accuracy in the TDT (y-axis) , between experimental sessions (x-axis) and condition (color).

Thus, we successfully replicated the finding that ~40 minutes of passive visual stimulation hinders the performance in a behavioral task involving the same stimuli, inducing specific, measurable, objective fatigue (Ioannucci et al., 2021).

Subject-wise ROI determination

Concerning the subject-specific ROIs, we found via a paired samples t-test that significantly more voxels responded to RQ than LQ stimulation (mean 1889 vs 636, $p = .025$). However, this significant difference did not carry over when ROIs were divided into saturated and non saturated (mean 1135 vs 1391, $p = .66$).

In any case, an undeniable variability was found in the personal profile of response to stimulation, with the most overlapping area being within the visual cortex, common across at most 18 subjects for the RQ and 12 for the LQ (see Figure 3a).

Mvpa on localizer brain activity

The rANOVA on the classifier accuracy revealed the effect of Session ($F_{(1, 23)} = 12.59$, $p = .002$, $\eta^2_p = 0.35$) and the interaction of Quadrant and Session ($F_{(1, 23)} = 9.79$, $p = .005$, $\eta^2_p = 0.3$) as significant. A post-hoc test on this interaction, corrected for multiple comparisons by Holm procedure, confirmed the absence of any baseline difference between saturation conditions ($T_{(23)} = 0.5$, $p_{\text{corrected}} = .67$), and yielded a significant difference in performance between baseline and conclusion, exclusive to the saturated quadrant (see Figure 4; $T_{(23)} = 4.43$, $p_{\text{corrected}} = .001$), while none was found in the non saturated quadrant ($T_{(23)} = 1.25$, $p_{\text{corrected}} = .67$).

The MVPA findings thus display a remarkable consistency with the behavioral results, with a specific drop between experimental sessions in classifier accuracy, exclusively when exploiting the brain activity within the saturated ROIs (see figure 3b).

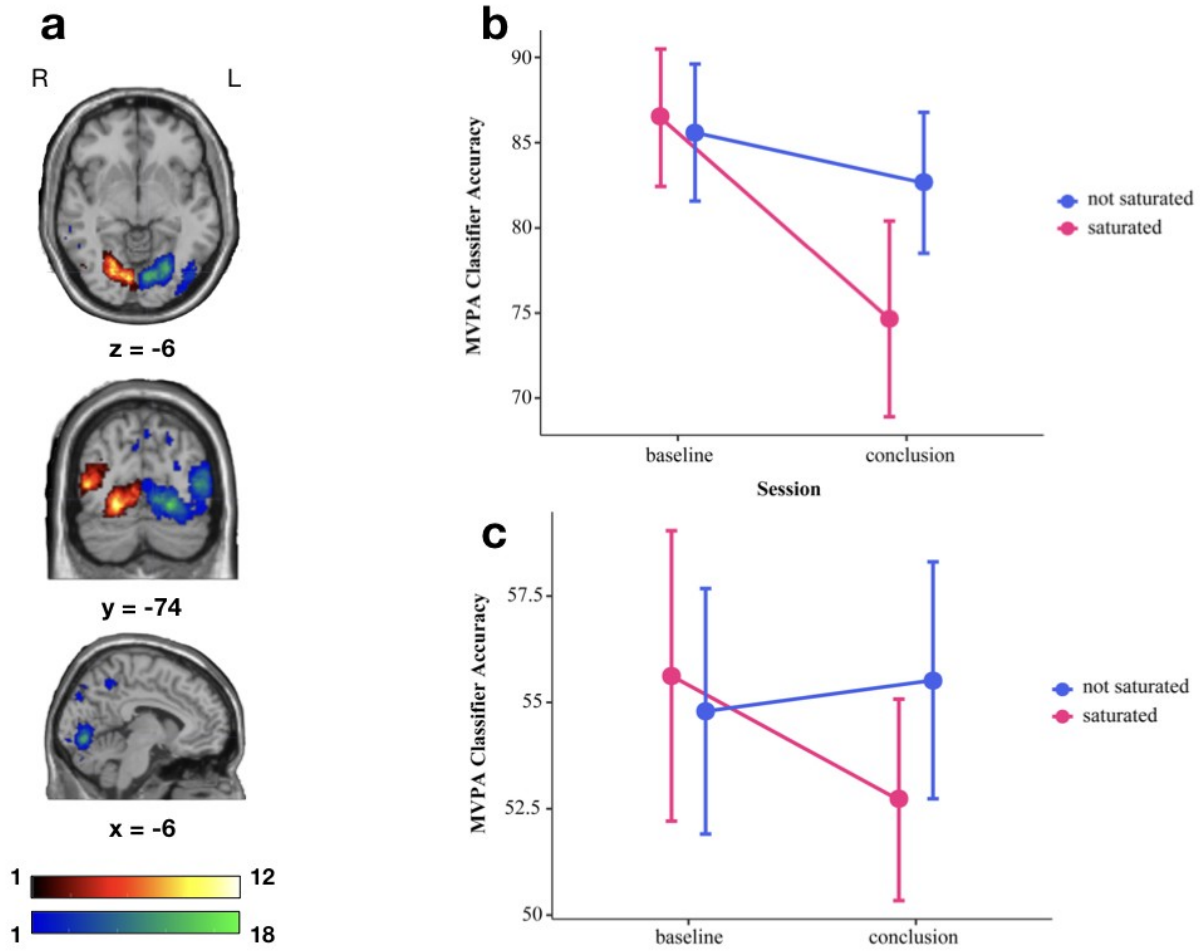


Figure 3: a) Overlapping ROIs across participants obtained from the union of voxels responding to stimuli in the left or right quadrant across pre and post localizer sessions, red-yellow = LQ, blue-green = RQ. b) Graphical depiction of the accuracy of the classifier (y-axis) exploiting the brain activity of participants in response to stimuli during the localizer task, between experimental sessions (x-axis) for both experimental conditions (color), error bars represent the 95% confidence intervals. c) Graphical depiction of the accuracy of the classifier (y-axis) exploiting the brain activity of participants in response to stimuli during the TDT, between experimental sessions (x-axis) for both experimental conditions (color) error bars represent the 95% confidence intervals.

Mvpa on tdt brain activity

No significant effects were found when looking at the MVPA results in the TDT task, though the interaction of Quadrant and Session was not far from statistical significance ($F_{(1, 23)} = 3.24$, $p = .085$, $\eta^2_p = 0.124$; see figure 3c).

Univariate analysis

The repeated-measures cluster-wise univariate analysis revealed two significant clusters showing significant decrease in response to the localizer task following saturation [$K = 139$, $K_z = 1.42$, $p_{fwe} = .017$; $K = 38$, $K_z = 0.97$, $p_{fwe} = .048$], on the side of the brain contro-lateral to the stimulation.

These were anatomically located, by probabilistic cytoarchitectonic mapping via the Julich anatomy toolbox (Eickhoff et al., 2005), in the inferior lateral occipital cortex and lingual gyrus, divided among functional regions V4 and V5 (see figure 4a).

Voxel-wise baseline activity in response to stimuli & change in classifying accuracy

We next looked at the relation between the level of activation of individual voxels and their susceptibility to saturation-induced disruption. We hypothesized that voxels that responded the most to the stimulation would also be the most impacted by the saturation procedure. The mixed linear model highlighted the interaction of saturation condition and baseline beta activation as impacting significantly on the change in voxel-specific classifying accuracy, revealing that the voxels that exhibited the highest beta estimates at baseline in response to stimuli in the saturated quadrant also displayed the largest loss in classifying accuracy between experimental sessions, while the opposite was true when stimuli were present in the non-saturated quadrant ($\beta = -0.005$, $CI = -0.006, -0.004$, $T_{(29575)} = -7.57$, $p < .001$; see figure 4b).

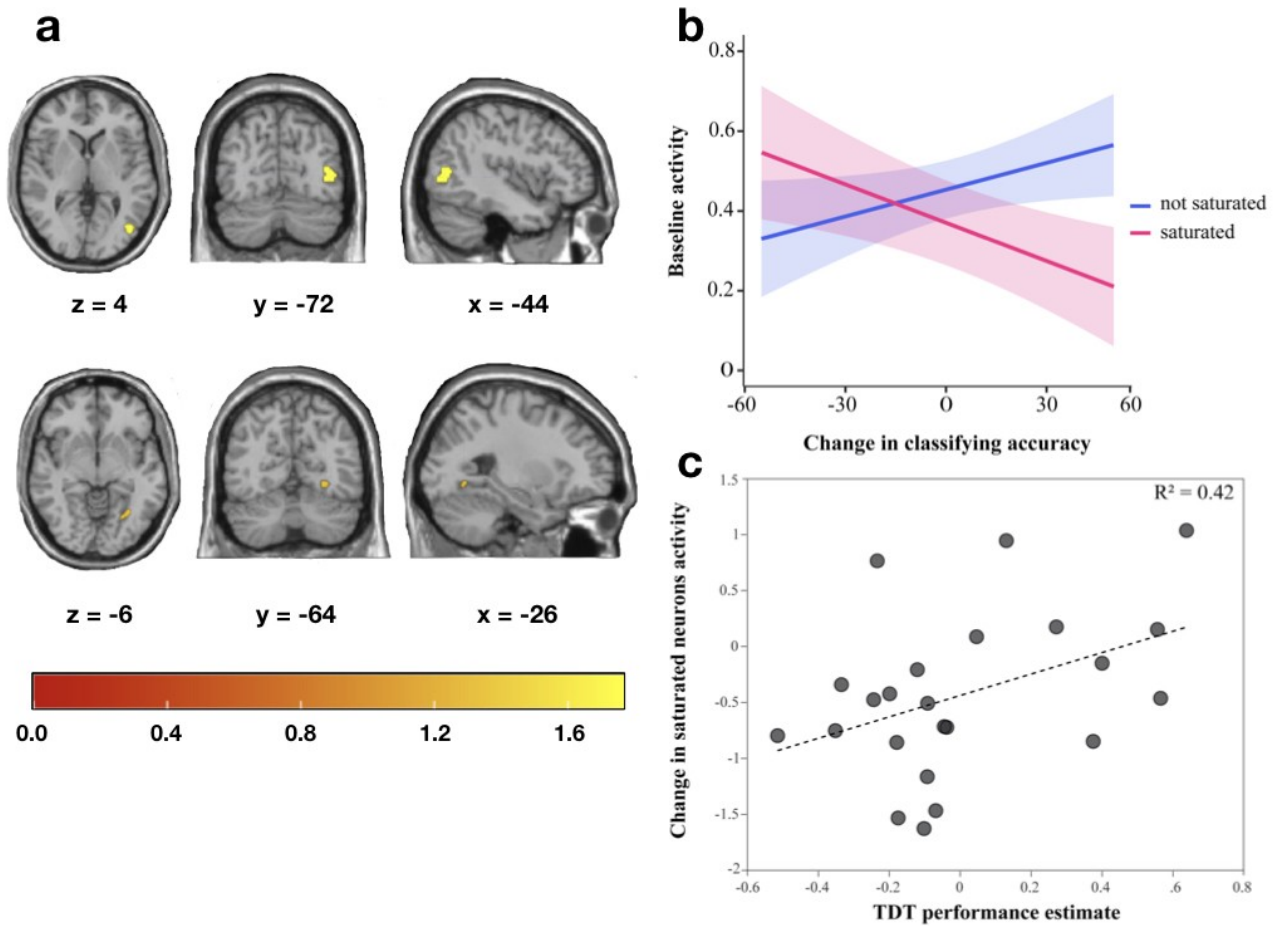


Figure 4: a) Graphical representation in the MNI space of the clusters, contralateral to saturation, that presented significant changes in BOLD signal before and after saturation across participants. b) Fit of the mixed model ran on the voxel-wise baseline activity in the subject-specific ROI (y axis) as a function of the change in the voxel-wise quadrant classifying accuracy (x axis) for both conditions (color), shaded areas represent the standard error. c) Scatterplot of the change in the estimated brain activity of neurons within the ROI responding to stimulation in the saturated portion of the visual field (y-axis) and the change in the performance of the behavioral task (x-axis) across the experiment.

Correlation between classifier performance and behavior

No significant correlation was observed between the estimates of behavioral performance in the TDT and the difference between baseline and conclusion accuracy of the classifier exploiting the saturated ROI in the localizer data ($R_{(21)} = -.08$, $CI = -0.47, 0.34$, $p = .72$).

Correlation between brain contrasts and behavior

The correlation between the estimates of behavioral performance in the TDT and the change in the univariate localizer brain signal within the subject-specific saturated ROIs revealed a significant positive correlation ($R_{(21)} = .42$, $CI = 0.01, 0.71$, $p = .048$; see figure 4c), meaning that people who had a decrease in the average value of brain activity within the saturated ROI displayed a larger loss of performance in TDT when the target was within the saturated quadrant.

Subjective fatigue

Concerning the pen and paper questionnaires, the statistical tests confirmed that there was a strong increase in the perception of both fatigue ($T_{(21)} = -7.61$, $p < .001$, $d = 1.52$) and sleepiness ($Z = -4.18$, $p < .001$, $r = -0.87$) during the experiment.

Correlations between subjective and objective fatigue

No significant correlation was found between the performance change in the TDT and the evolution of subjective fatigue between sessions ($R_{(22)} = -0.22$, $CI = -0.57, 0.22$, $p = 0.3$). On the other hand, a significant negative correlation was found between self-reported sleepiness change and behavioral estimates of TDT performance ($R_{(21)} = -0.54$, $CI = -0.79, -0.16$, $p < 0.001$; see figure 5), indicating that participants who performed worse in the saturated quadrant in the second TDT session tended to report greater levels of perceived sleepiness at the end of the experiment.

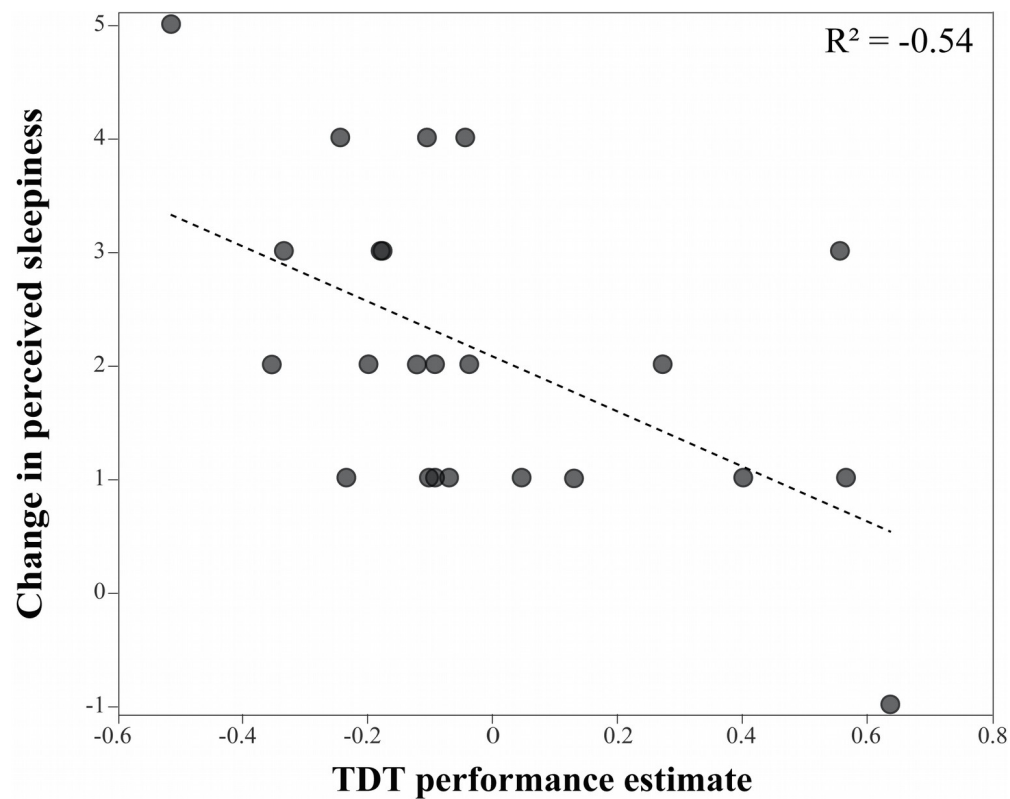


Figure 5: Scatterplot of the change in the self-reported perceived sleepiness scores (y-axis) and the change in the performance of the behavioral task (x-axis) across the experiment

Discussion

In the present work, we found proof of specific, passively induced, neural fatigue. We replicated our finding that objective fatigue manifests itself after ~40 minutes of passive visual stimulation, in a behavioral task that involved identical stimuli in a delimited portion of visual field. This result has been found consistently across repeated experiments (Ioannucci et al., 2021), when other variables such as motivation and level of skill in the fatiguing task are controlled for. Thereby, this objective fatigue effect cannot be explained by motivational accounts of mental fatigue (Boksem & Tops, 2008; Kurzban et al., 2013), nor disproven by motivational accounts that posit the objective component of fatigue as secondary with respect to the subjective one (Hockey, 2011).

Here we show that the accuracy of a classifier trained to decode participants' functional brain activity mirrored the results found in the behavior of those same participants, displaying a saturation-specific loss of performance (figures 2 and 3b).

Moreover, we found that voxels responding more strongly to the stimuli employed in the saturation procedure exhibited the largest loss of classifying accuracy, suggesting a direct link between the level of activity during saturation and the consecutive disruption (figure 4b).

This finding of specific neural fatigue was additionally corroborated by the correlation revealed between the difference (conclusion – baseline; figure 4c) in estimates of brain activity in response to the stimuli in the saturated quadrant within the saturated ROIs and the estimates of performance in the TDT. To our best knowledge, this is one of the first cases of clear-cut relation between specifically induced neural fatigue and objective fatigue in human participants.

The above-mentioned behavioral consequences of fatigue occurred along with an increasing sense of fatigue and sleepiness in all the participants, as predicted. Admittedly, most experimental settings are likely to induce some measure of fatigue, sleepiness or boredom – all closely related constructs. However, the correlation we witnessed between the quantified performance alteration and the sensation of sleepiness (figure 5) provides a link between objective performance and subjective states that resonates with the notion that this construct is hardly distinguishable from fatigue (Phipps-Nelson et al., 2011; Shen et al., 2006; Tran et al., 2020), especially in experimental settings. The present results indicate that by maintaining specific neural assemblies active over a prolonged period of time, passive visual stimulation brings them to the point of disruption due to overwork (Ioannucci et al., 2021). Our work was inspired by methodology employed in closely related scientific domains, such as perceptual learning (Censor et al., 2006, 2009, 2016; Censor & Sagi, 2008; Karni & Sagi, 1991, 1993) and perceptual deterioration (Mednick et al., 2002, 2005, 2008; Mednick & Boynton, 2004).

The majority of previous research stemming from these literatures has tended so far to theorize, or find, an involvement of the primary visual cortices in their phenomenon of interest. In the earliest reports on perceptual learning, the enhancement effect was interpreted in terms of “local plasticity induced by retinal input in early visual processing in human adults, presumably at the level of orientation-gradient sensitive cells in the primary visual cortex” (Karni & Sagi, 1991).

Across the years, other investigators have built upon these theories by means of functional neuroimaging. For example, Schwartz et al. found evidence that the retinotopically-specific region of the early human cortex displayed diverging activity during TDT, in a trained eye vs untrained eye contrast. Functional connectivity analysis performed with this region as seed failed to find any involvement of other areas (Schwartz et al., 2002). However, caution is advisable when interpreting an absence of results in such deterministic terms (Makin & Orban de Xivry, 2019). In partial disaccord, studies on primates recording directly in the visual cortices have found extrastriate V4 neurons to be more prominently involved in perceptual learning than V1 cells (Raiguel et al., 2006; Yang & Maunsell, 2004).

Another notable study on the topic didn't exclusively focus on the retinotopically mapped portions of the early visual areas, investigating also the activity within the middle frontal gyrus, the superior parietal gyrus and the interparietal sulcus, however being also limited in this case to univariate contrasts of activity estimates within these ROIs (Yotsumoto et al., 2008).

Concerning perceptual deterioration, Mednick et al. found proof of alterations in the signal within early visual area V1 following extended repetitions of the TDT (4h in one day). Yet, also in this case, the followed procedure was to single out areas of the participant's visual cortices and contrast the activity in each area with itself in the various experimental conditions (Mednick et al., 2008).

Here, by combining the subject-specific approach with a univariate test between the brain scans at baseline and conclusion of the experiment, we were able to identify the cluster of voxels that were predominantly affected by the saturation procedure across the majority of participants, without enforcing an *a priori* anatomically determined comparison.

As could have been expected, these clusters lied within the visual cortex, precisely in functionally defined areas V4 and V5. Therefore, our results point to an involvement of the extra-striate cortex, in line with previous accounts in the domain of perceptual learning (Raiguel et al., 2006; Yang & Maunsell, 2004).

Indeed, V4 is thought to contain neuronal populations tuned to the orientation of basic visual stimuli (Roe et al., 2012), such as the lines employed in the present study. While V5 is believed to be implicated, to some degree, in the perception of movement (Born & Bradley, 2005), therefore reasonably being expected to respond to the stimuli of the localizer trials, due to their continuous 7.5 Hz fluttering. Accounts of mental fatigue that posit its origin as the product of functional alterations that take place in over-worked cellular populations provide potential explanations as to which may be the processes taking place within these areas. One of the main candidates is the mechanism of consumption and storage of glucose, the brain's main source of energy. It has been argued that performance decrements arising during extended task repetition are related to abrupt use of this molecule, paired with reduced replenishing from the astrocyte support network (Christie & Schrater, 2015; Killeen et al., 2016). It must be noted that the association between decreased global availability of glucose and cognitive activity has been contested by some authors as being confounded by extra-experimental factors (Kurzban, 2010).

Nevertheless, at the local level, research assessing the release of lactate, a molecule derived from glucose and thought to be the most immediately available fuel of neurons (Magistretti & Allaman, 2018), in response to repeated visual stimulation found proof of alterations in the concentrations of

this metabolite, along with glutamate, related to concurrently measured BOLD signal (Bednařík et al., 2015).

An alternative theory postulates the accumulation of toxic metabolites as a consequence of prolonged cognitive effort (Holroyd, 2016; McFarland, 1971). Scarce direct evidence has been so far found for a direct link between objective fatigue in mental activities and accumulation of specific metabolites, with the sole study testing this assumption speculating the found effect, a correlation between neuronal pH and decreased performance in a serial calculation task, to be a consequence of the lactate cycle (Kato et al., 1999).

On the other hand, a few studies have associated glutamate (Rönnbäck & Hansson, 2004), tryptophan (Yamashita, 2020), tyrosine (Felger et al., 2013) and amyloid beta (Holroyd, 2016) with subjective fatigue, however given the opacity of this construct further research is needed to validate such claims. Furthermore, it is often not clear if the increase in metabolites witnessed in experimental settings, additionally mostly carried out on pathological populations, is a consequence of progressive accumulation over time, or results from changes in the steady-state levels of the studied metabolites.

Finally, an ulterior possibility for cerebral functional alterations underlying fatigue may be found in an investigation employing deep electroencephalographic recordings on sleep deprived rats (Vyazovskiy et al., 2011). Indeed, this study found a remarkable correlation between specific neuronal assemblies displaying sleep-like activity and behavioral deficits. However, as mentioned in the introduction, the present study aimed at shedding light on where and if fatigue-induced functional alterations were occurring in the task-relevant neural networks, as found in other works employing different tasks, longer paradigms and univariate fMRI analyses (Blain et al., 2016; Gergelyfi et al., 2021; Tanaka et al., 2006). Thereby, it was not designed to reveal the how, which will need careful, purposely designed, investigations.

The method employed here has proven reliable in inducing objective fatigue while controlling for common confounds and may thus provide a reliable platform for further experiments.

Limitations

The main limitation of the present work is, presumably, the lack of reliable estimates of brain activity during the TDT, which transferred the burden of hypothesis testing onto the brain estimates of activity during the localizer, as contemplated in the pre-registration (<https://osf.io/vkrst>). In hindsight, this is likely explained by the diverging design of the tasks. In the TDT trials, the stimuli are presented for very brief periods (0.34 sec) and are mostly identical across conditions, as only the 3 peripheral target lines relocate from trial to trial, while the background embedding of horizontal lines remains constant. Accordingly, other experimental works seeking to investigate its neural signature have either devised methodological changes in order to compare between conditions and/or focused on predetermined anatomically defined areas (Mednick et al., 2008; Schwartz et al., 2002; Yotsumoto et al., 2008). On the other hand, localizer sessions had much longer, stable trials (12 sec) with clearly distinct stimuli, thus allowing for more precise contrasts of brain activity in response to them.

Our approach centered on task-related networks may have overlooked the contribution from task un-related systems, and more specifically of “facilitation” and “inhibition” system, akin to those present in the domain of physical fatigue (Ishii et al., 2014). These systems were identified as the “limbic-basal ganglia-thalamus-frontal” network in the case of the facilitation system, and as the “insular-posterior cingulate” in the case of the inhibition system, with the latter found to be involved in fatigue on top of task-related regions only for pathological samples. At any rate, the evidence supporting the existence of these systems is limited and comes from studies that do not involve perceptual tasks such as the present one.

No significant correlation was found between the accuracy of the MVPA classifier and the accuracy of participants. MVPA investigations that assess changes in activity inside brain regions in relation to the evolution of performance in a task are seemingly a minority in the literature, as most experiments are concerned with exploiting this method to localize brain networks underlying their phenomenon of interest. Within this minority, accounts of direct correlation between classifier accuracy and behavioral measures are scarce, with few notable exceptions (Haynes & Rees, 2005; Kok et al., 2012). As MVPA output is determined by the unique patterns of activation recorded rather than the magnitude of the activity, the overwhelming majority of brain – behavior correlations are carried out by taking the mean beta value in the relevant voxels, an approach with which we did find a meaningful correlation.

Likewise, we did not observe a significant correlation between subjective fatigue score change and objective fatigue performance decrement.

Accordingly, such correlation is rarely observed in the field (DeLuca, 2007). However, we had previously reported such a correlation employing similar methods in two separate samples (Ioannucci et al., 2021). In the present work, a correlation was found instead between the sleepiness reports and the behavioral performance, which may be partially explained by the supine position participants had to assume during the MRI session (Kräuchi et al., 1997), potentially causing the sleepy state to overshadow the fatigue state. In any case, sleepiness may be considered to be a request for rest in order to recover from fatigue (Kumar, 2008), and the two often follow very similar evolutions (Chervin, 2000; Hossain et al., 2003; Lichstein et al., 1997). Coherently, some contend that it is highly challenging to distinguish reliably between the two states (Phipps-Nelson et al., 2011; Shen et al., 2006; Tran et al., 2020).

Conclusion

Taken together, our results bring substantial, novel proof that specific functional neural networks can be fatigued by overwork, even if passive. Further research is needed to characterize exactly what type of process, among candidates in the literature (glucose/lactate cycle, accumulation of metabolites or local sleep) takes place in the task-relevant functional brain networks.

We argue that the results found are a strong indicator that some forms of mental fatigue in healthy individuals, at least the ones not muddled by boredom or diverging motivation, are likely to arise from measurable changes in the biological circuitry that underlie them.

CHAPTER 4 – GENERAL DISCUSSION

The goal of the present thesis was to contribute to the understanding of cognitive fatigue and, specifically, its neural underpinnings. As outlined in the introduction, despite decades of study and conspicuous amounts of experimental work carried out in this field, there are still major points of contention that remain to be tackled, especially with regards to the functional and motivational perspectives on the nature of fatigue.

One of these points consists in the need for a task that may reliably be used to assess the impact of fatigue on its performance, while affording the possibility to be adapted to the level of skill of agents engaged in it, and to control for the most common confounding factors related to fatigue, notably those linked with motivation. As attested by several reviewers, an elegant solution to such necessity was found, by building upon methods previously employed in similar research areas. Indeed, the use of the Texture Discrimination Task answered the above-mentioned issues and provided a clean framework to employ as foundation in the search for the neural bases of passively induced fatigue in specialized neuronal assemblies. In any case, it must be kept in mind that what follows are personal, although rigorous, interpretations of results yet to be sanctioned by peer-review, and thus susceptible to change.

In the first study described in chapter 2, the devised experimental design was validated, revealing that specific visual fatigue could be induced by passive stimulation. We also confirmed the conjecture that this effect would be influenced by arousal, manipulated through varying difficulty of tasks in another sensory modality. Thus, we brought forth proof for a remarkable cross-sensory interaction where identical visual stimuli may elicit different patterns of behavioral (and, presumably, cortical) response, depending on auditory cognitive load.

This finding was further corroborated by the relation observed, across the three samples, between the pupil size of participants – which serves as a marker of arousal – and their performance drop in the TDT.

Concurrently to the local, specific, passively-induced manifestations of objective fatigue, participants reported a sizable increase in their perceived levels of subjective fatigue and sleepiness. Showing, once again, how these two constructs are associated in experience.

Additionally, a meaningful correlation was observed between the objective and subjective components of fatigue, all the more noteworthy as it is rarely observed in the literature (DeLuca, 2007). Yet, as mentioned in the introductory paragraphs, our current tools do not clearly distinguish what exactly is measured by the employed questionnaires, for example in quantifying how much boredom influences the fatigue scores.

In light of the above, it is interesting to notice how participants who underwent the easier versions of the auditory tasks and did not display specific objective fatigue, rather improving temporarily their performance in the saturated portion of the visual field, still reported increased levels of fatigue and sleepiness across the experiment. This is presumably due to being engaged in a repetitive task for a prolonged period of time, consisting in the so-called ‘time-on-task’ effect.

Nevertheless, cortical activity recorded by EEG in response to the saturated stimuli did not differ to the one in response to stimulation in the non saturated portion of the visual field. This disappointing result is in stark contrast with previous works in the domain of habituation (Grandstaff & Pribram, 1972) and adaptation (Vergeer et al., 2017), which predicate decreases in the recorded electrophysiological activity of neurons responding to the repeatedly-presented stimuli.

As the potential explanations for this discrepancy were discussed in the relevant section of the manuscript, they shall not be repeated here. In any case, this lack of results highlighted the need to

reconsider the choice of neuroimaging tool to assess the neural bases of passively induced visual fatigue. Therefore, an updated version of the experimental design had to be devised.

It was possible to do so while testing other properties of the observed effect. Notably, its specificity to properties of the saturating stimulation, such as the eye and orientation, as done in the perceptual learning (Karni & Sagi, 1991; Schwartz et al., 2002) and deterioration (Mednick et al., 2005; Mednick & Boynton, 2004) literatures. Thus, the two additional experiments from chapter 2 were prepared and carried out.

Since the specific fatigue effect was prominent in the first half of the experiment in the group undergoing the harder version of the auditory tasks, while tending to be blurred out by a more generalized loss of performance in the second half, the follow-up experiments were restricted to this portion of the design. The results from these additional, smaller, experiments not only confirmed the original finding of specifically induced visual fatigue in a total sample of 78 participants⁵, but also further characterized it as being restricted to the stimulated eye and orientation of the stimuli. Partially similar results in the above-mentioned literatures have been interpreted in terms of an involvement of early visual cortices (Karni & Sagi, 1991; Mednick et al., 2005).

Moreover, the tendency for correlation between the objective and subjective components of fatigue in the adopted paradigm was confirmed. Still, although these experiments proved to be, at least partially, successful, a fundamental question remained unanswered: are there observable fatigue-induced alterations taking place in the task-relevant neural networks? Indeed, given the lack of EEG results in experiment 1 and the eye-specificity found in experiment 2, it could be speculated that the witnessed effects could be taking place in the retina⁶ of participants, regardless of the divergence of outcome mediated by cross-sensory arousal and cognitive load.

⁵ *To be precise, the 24 participants in the easy condition of experiment 1 did not display objective fatigue*

⁶ *Which is part of the central nervous system*

In order to provide insight into this query, in chapter 3 the previously employed design was adapted to match the requirements of a functional magnetic resonance imaging experiment. A modern multi-variate approach was favored due to its properties that allow to adapt to the individual's unique pattern of brain activity and to mimic their behavioral output, by the proxy of classifying accuracy. Through this final experiment, the behavioral results of objective specific fatigue were once again replicated, bringing the total sample onto which this effect was experimentally induced, regardless methodological variations, to 102 participants⁵.

However, in this case, no correlation was found between the objective and subjective estimates of fatigue, in line with most of the literature on the topic (DeLuca, 2007). Yet, a correlation was found with the evolution of self-reported sleepiness, which, as has been outlined in the present work, may be considered to be the construct most closely related to fatigue.

Importantly, evidence was found for changes in the brain activity in response to the saturated stimuli arising from the experimental procedure. More-so, these changes taking place in the subject-specific neural networks responsible for the processing of the stimuli correlated directly with the objective manifestation of specific visual fatigue.

Lastly, a striking similarity was highlighted between the accuracy output of both human participants and a classifying algorithm exploiting their neural activity. Building onto these results stemming from multi-variate methods, a more classical univariate approach revealed the areas most disrupted by saturation to lay within the extra-striate visual cortices of participants, in line with parts of literature that exploited the TDT to investigate perceptual learning (Raiguel et al., 2006; Yang & Maunsell, 2004). Overall, the results of the experiment in chapter 3 provide a neural foundation for the effects witnessed across the empirical works presented in this thesis, along with strong support for the notion that fatigue alters the activity of local, task-related, neuronal assemblies due to prolonged over-work. This is compatible with findings of metabolic alterations in the concentrations

of lactate, glucose and glutamate in the visual cortex following stimulation (Bednařík et al., 2015), and with reports of fatigue-induced alterations in task-relevant brain areas (Blain et al., 2016; Gergelyfi et al., 2021; Mednick et al., 2008; Vyazovskiy et al., 2011). Thus, justifying renewed interest in the functional accounts of fatigue presented in section 1.6.

Further research with other neuroimaging tools, such as Magnetic Resonance Spectroscopy, may shed further light onto the metabolic processes taking place in the wearied neural networks. Indeed, such was the project for which a mobility grant was secured during my doctorate, however the COVID-19 pandemic eventually deranged those plans.

In sum, across the trajectory of this academic work, an experimental design was prepared in order to induce and measure the effects of specific fatigue, resistant to the influences of its closely related constructs. As a general remark, it is safe to conclude from the comprehensive results that, all things being equal, prolonged over-work of cellular assemblies leads to their altered function and that specific fatigue effects can be observed when motivation and other confounds are controlled for. These specific fatigue effects were found to be reliably present in a time span considerably shorter than most research in the related literature. Such results are compatible with most functional perspectives on fatigue and resonate with the original interpretation of perceptual deterioration as dependent on overused local neural networks (Mednick et al., 2002).

Moreover, the effect size of this phenomenon could be expected to be reasonably large, given the non trivial replication rate across samples. Much of this is due, clearly, due to the fact that the notion of altered behavioral response following extensive stimulation or exercise is arguably as old as the field of cognitive science itself. Yet, the method implemented and conclusions reached in the present work still achieve to be novel and, hopefully, to add to the overall debate on cognitive fatigue. In any case, the impact of the reported findings would benefit from the replication of these in a domain different from the visual one.

To conclude, the most salient aspects of the presented research likely consist in its contribution to the distinction between motivation and fatigue, which may eventually become a possibility in everyday activities. A more thorough understanding of the phenomenon of fatigue could alleviate the risk of over-work syndromes, such as burn-out, and help in the prevention of fatigue-related accidents.

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