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MULTIDIMENSIONAL INVESTIGATION OF THE LINK BETWEEN

MENTAL FATIGUE AND MOTIVATION

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Overview

Mental fatigue (MF), consisting primarily in the subjective feeling of a deteriorated ability to engage in mental activities, is a very important phenomenon which interferes with our well-being in everyday life. It can affect not only our social and economic life but also our psychological and medical condition. The prevalence and severity of fatigue complaints have steadily increased in the general population (Van'T Leven, Zielhuis, Van Der Meer, Verbeek, & Bleijenberg, 2010), including the burn-out syndrome, a wide range of disorders such as cancer, Parkinson's disease, Multiple sclerosis etc. and conditions of brain damage such as stroke and traumatic brain injury etc..

However, despite its importance, the conceptualization and operationalization of MF have not sufficiently advanced since the early 1900s, such that the cognitive and neural mechanisms involved in its build-up remain currently unknown. Thus, there is an urgent need for further investigations to better understand the MF phenomenon. The objective of the present thesis was to tackle this issue by addressing whether MF is the consequence of a temporary degradation of cognitive resources or altered motivational states which impede the recruitment of otherwise preserved cognitive resources.

A widely accepted view in the literature is that MF results from an alteration of motivational processes, particularly in the basal ganglia (Boksem & Tops, 2008; Chaudhuri & Behan, 2000; 2004; Dobryakova, DeLuca, Genova, & Wylie, 2013; Hockey, 1997; Kurzban, Duckworth, Kable, & Myers, 2013). However, the

empirical evidence supporting this theory is imperfect and sometimes contradictory. Therefore, we tested this hypothesis in the present work with two original experimental studies wherein MF was induced by performing a cognitively demanding task over a prolonged period of time in healthy participants. Then, the psychometric, behavioral and psychophysiological consequences of MF were measured during a cognitively challenging task with systematic variation in monetary rewards. We found that the different indicators of motivation or task engagement remained constant during the experiment and failed to show a correlation with various markers of MF (Article 1 in Chapter II). Importantly, we did not find any relationship between the neural underpinnings of MF and motivation (Article 2 in Chapter II). These results let us to assume that MF alters brain resources or impair their recruitment through other mechanisms than motivation in healthy participants. We believe that these findings mark an important step forward in the understanding of the fundamental mechanisms of MF which provides a strong basis for future researches and in the long-term will help the diagnosis and treatment of MF in medicine.

I. INTRODUCTION

I.1. Conceptualization and operationalization of mental fatigue

I.1.1. Definition and classification of fatigue

I.1.1.1. What is fatigue and why is it important?

Fatigue is a common complaint in patients as well as in the general population (Van'T Leven et al., 2010). Simply put, it may primarily consist of a subjective feeling of excessive tiredness, bodily discomfort, insufficient concentration, and inability or disinclination to engage in any activity (Boksem, Meijman, & Lorist, 2005; Boksem & Tops, 2008; Brown, 1994; A Chaudhuri & Behan, 2000; Cope, 1992; Hockey, 1997; Kurzban et al., 2013; Shen, Barbera, & Shapiro, 2006; Yoshitake, 1978), but it can also be accompanied by objectively measureable behavioral and/or psychophysiological changes (Blain, Hollard, & Pessiglione, 2016; Boksem, Meijman, & Lorist, 2006; Hopstaken, van der Linden, Bakker, Kompier, & Leung, 2016; Lorist et al., 2009; Wang, Trongnetrpunya, Babu, et al., 2016). It is a very important phenomenon since it may have a profound negative impact on quality of life. Individuals with fatigue generally have difficulties in activities of daily living which in the long run may affect different aspects of their life and may result in domino-like collapse: decreased work productivity, social life and well-being caused by fatigue can lead to negative changes in career, economic status, social role and health condition etc.. Moreover, work absenteeism due to fatigue imposes an economic burden on society (Jason, Evans, Brown, & Porter, 2010). Fatigue may also be a life threatening condition. It

has been found as a potential causal factor in fatal roadway crashes (Patel, Lal, Kavanagh, & Rossiter, 2011; Dyani Saxby, Matthews, Hitchcock, & Warm, 2007). The prevalence of fatigue is high in both the general population and patients. In the Netherlands, a survey-based study revealed that one-third of the general population experienced fatigue for either short (< 6 months) or long periods [chronic fatigue and chronic fatigue syndrome (CFS) > 6 months] (Van'T Leven et al., 2010). The situation is even more serious in Japan where approximately one-third of the general population suffers from chronic fatigue (Watanabe et al., 2008). Fatigue complaints are typical in many neurological disorders including, multiple sclerosis (MS), stroke, traumatic brain injury, Parkinson's disease (PD) and Alzheimer's disease etc.. In MS and PD, at least 30% of the patients consider fatigue as their most disabling symptom (Kluger et al., 2013). Furthermore, the presence of fatigue is also high in psychiatric- [e.g. depression, CFS] and in general medical and other conditions (e.g. cancer, sleep problems, heart- and cardiovascular disease, myasthenia gravis, fibromyalgia etc.). Many cancer patients, who are exposed to chemotherapy or radiation therapy, face severe fatigue (Saligan & Kim, 2012).

Despite the fact that fatigue is a serious phenomenon and it has been intensively investigated since its first appearance as a public health problem in the mid-19th century, it remained a challenging scientific and medical conundrum (Kuppuswamy, 2017; Torres-Harding & Jason, 2005). There is no consensus on its definition and no gold standard available for its quantification. This issue, which

may be attributed to the lack of systematic investigations, makes it difficult to answer the following fundamental questions:

- What are the neurobiological origins of fatigue?
- What is the functional role of fatigue?
- How can fatigue be assessed reliably?
- How can we prevent or treat fatigue?

1.1.1.2. Classification of fatigue concepts

In order to better understand fatigue, it may be classified into different categories (Hornsby, Naylor, & Bess, 2016; Lal & Craig, 2001). The classification may be based on the consideration of different aspects such as the manifestation (subjective vs. objective), the disease-relatedness (primary vs. secondary), the underlying nervous system (central vs. peripheral), the time-span (acute/physiological vs. chronic/pathological; state vs. trait) and/or the quality (mental vs. physical) of fatigue etc..

Subjective vs. objective fatigue

A widely used classification of fatigue is to make a distinction between its subjective (feeling of fatigue) and objective manifestations (changes in behavior and psychophysiological state). Subjective fatigue can be assessed by using self-reported questionnaires (see Section I.1.3.1.1.) while objective fatigue is measured

in terms of performance decrements (see Section I.1.3.1.2.) and psychophysiological parameters such as eye-blinks, heart rate (variability), neural activity (see Section I.1.3.1.3.), muscle strength etc.. According to Kluger et al. (2013), it is very important to distinguish between these different dimensions of fatigue, which they term fatigue (subjective feeling) and fatigability (performance, physiology), since they may often occur independently [e.g. increased subjective feeling of fatigue is not necessarily accompanied by objective changes in performance: (Hockey, 1997; Thorndike, 1900), see more detail below]. Thus, investigating only one dimension of fatigue (subjective feeling, objective behavioral- or physiological changes) could impede our understanding of the entire phenomenon (Phillips, 2015; Shen et al., 2006). Different types of fatigue introduced hereunder can be manifested both subjectively and objectively.

Primary vs. secondary fatigue

Primary fatigue is a sort of fatigue that is not associated with any other medical condition and is caused by its primary neural changes (DeLuca, 2005) which, however, remain unclear. In turn, secondary fatigue is a type of fatigue which is caused by other medical condition such as sleep disorders, depression etc. (DeLuca, 2005). For example, in MS, primary fatigue is considered to be the consequence of the disease itself and to be unrelated to secondary causal factors such as sleep problems and depression etc. (Bakshi, 2003; Kos, Kerckhofs, Nagels, D'hooghe, & Ilsbroukx, 2008; Wilting et al., 2015). In PD, primary- and secondary fatigue have been proposed to represent fatigue in the absence or in

the presence of mood disorders and excessive daytime sleepiness, respectively (Kostić, Tomić, & Ječmenica-Lukić, 2016).

Central vs. peripheral fatigue

Both central and peripheral fatigue falls under the umbrella term of primary fatigue. These types of fatigue are mediated by the central and peripheral nervous system, respectively. Peripheral (muscular) fatigue, which is only physical, may result from an impaired neuromuscular transmission or insufficient muscle metabolism (Aaronson et al., 1999). According to Chaudhuri and Behan (2000; 2004), central fatigue consists in an inability to initiate and maintain any kind of activity (mental, physical) requiring self-motivation, and is presumably caused by a failure in the non-motor function of the basal ganglia. Fatigue in MS was very similarly defined by the MS Council for Clinical Practice Guidelines (1998): “a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual or desired activities”.

Acute vs. chronic fatigue

Chronic (pathological) and acute (physiological) fatigue may be distinguished by their origin, temporal dynamic and recovery chance (Jason et al., 2010; Karshikoff, Sundelin, & Lasselin, 2017; van der Linden, 2011): chronic fatigue lasts for more than 6 months while acute fatigue for only a short period of time. In opposition to acute fatigue, chronic fatigue is not associated with previous effort investment. Furthermore, the possibility for a recovery in chronic fatigue is very small or even lacking compared to acute fatigue which can be treated (van der Linden, 2011).

State vs. trait fatigue

State and trait fatigue actually show similarities to acute and chronic fatigue, respectively: state fatigue is also a momentary condition related to effort investment while trait fatigue is a stable condition unrelated to previous effort. However, this distinction represents more whether one's fatigue is mediated by personality characteristic (Genova et al., 2013; Hanken, Eling, & Hildebrandt, 2014; Neumann et al., 2014; Wylie & Flashman, 2017).

Mental (cognitive) vs. physical fatigue

Another widely used classification of fatigue is to distinguish between its mental and physical qualities (Hornsby et al., 2016; Lal & Craig, 2001). Mental fatigue, which is often observed following prolonged periods of demanding mental activity, consists in an inability or disinclination to engage in additional mental activities and in reduced cognitive functions [e.g. impaired planning (van der Linden, Frese, & Meijman, 2003), attention (Boksem et al., 2005, 2006), inhibition (Kato, Endo, & Kizuka, 2009) and working memory (Benoit et al., 2018)]. Since cognitive functions are often declined with fatigue, some uses the term of cognitive- instead of mental fatigue (Ackerman & Kanfer, 2009; Borragán, Slama, Bartolomei, & Peigneux, 2017; Borragán, Slama, Destrebecqz, Peigneux, & Albert, 2016; Wang et al., 2016). Physical fatigue, which is generally the consequence of prolonged and intense physical exercise, refers to an inability or disinclination to continue further physical activities and is characterized by muscular exhaustion (Barth, Holding, & Stamford, 1976). Despite the striking differences between mental- and physical

fatigue, some has questioned the need for this distinction (Hancock et al., 2017) since mental and physical fatigue may be connected through common physiological resources (Marcora, Staiano, & Manning, 2009; Hancock et al., 2017). However, this hypothesis has not yet been proven, and altogether, the majority of the studies have investigated mental and physical fatigue separately (Inzlicht & Marcora, 2016; Marcora et al., 2009; Van Cutsem et al., 2017).

I.1.2. The scope and the objective of the present work

This thesis focuses on mental fatigue (MF), which is difficult to investigate in laboratory environment since no standard procedure [similar to the Trier Social Stress Test for the investigation of psychological stress (Kirschbaum, Pirke, & Hellhammer, 1993)] exists for its induction and measurement. Both subjective (feeling) and objective (performance decrements, changes in psychophysiological parameters) MF have been observed following sleep deprivation (Ahn, Nguyen, Jang, Kim, & Jun, 2016) or prolonged engagement in a driving (Borghini, Astolfi, Vecchiato, Mattia, & Babiloni, 2012; Thiffault & Bergeron, 2003) or cognitive task (Blain et al., 2016; Lorist et al., 2009; van der Linden et al., 2003; Wang, Trongnetrpunya, Samuel, Ding, & Kluger, 2016). According to Desmond and Hancock (2001), two types of task-related fatigue exist, namely active and passive. This distinction originates from research into driver fatigue (Saxby, Matthews, Warm, Hitchcock, & Neubauer, 2013; Saxby et al., 2007). Active fatigue is generally caused by a condition with high demands (overload: e.g. high traffic density, low visibility and curved road over a prolonged period of time) which requires high task engagement while passive fatigue is caused by a condition with

low demands (underload: e.g. low traffic density, high visibility and straight road over a prolonged period of time) which is associated with low task engagement. This latter type of task-related fatigue (passive) has been closely linked to vigilance decrement which is further elaborated below (see Section I.1.4.2.).

In the present work, MF, which was investigated using both subjective (psychometric) and objective (behavioral, psychophysiological) measures in healthy individuals (20-35 years), was considered to be active and acute since it was induced by performing highly demanding tasks (Sudoku puzzle, modified Stroop task) for a prolonged period of time (90-120 min), and therefore, it lasted only temporarily.

As mentioned before, such fundamental question as the cognitive and neurobiological origins of fatigue remained unanswered. The objective of the present work was to better explore these mechanisms by testing a prevailing view in the literature that MF results from an alteration of motivational processes, particularly in the basal ganglia (Boksem & Tops, 2008; Chaudhuri & Behan, 2000; 2004; Dobryakova et al., 2013; Hockey, 1997; Kurzban et al., 2013).

I.1.3. How to induce and measure mental fatigue?

I.1.3.1. Task-related mental fatigue: direct and indirect method

As already mentioned, the present thesis investigated task-related MF which can be induced and measured by using either the direct or indirect method. The direct or continuous method consists in performing a single cognitive activity

over a prolonged period of time (Bills, 1937; Noll, 1932). MF is then assessed by using subjective (i.e. the extent to which someone is feeling fatigued) and objective measures (e.g. performance decrements and/or psychophysiological changes, namely, autonomic and neural). In opposition to this method, the indirect approach involves separate mental activities for MF inducement (a loading task) and measurement (a probe task) (Posner & Boies, 1971; Sternberg, 1966). Thus, prior to and after MF inducement (loading task), a second task (probe) is performed in order to evaluate MF. This method has also been used to study ego-depletion [state of compromised self-control (Baumeister, Bratslavsky, Muraven, & Tice, 1998)] which has been viewed as an account for MF ((Inzlicht, Schmeichel, & Macrae, 2014); see more details below).

The advantage of using the indirect method is that the impact of potential confounding factors such as boredom [e.g. off-task thoughts, over-estimated time perception, negative affect (Raffaelli, Mills, & Christoff, 2017)] can be reduced or avoided (Ackerman, 2011, Hockey, 2013). However, this method raises the question of the transferability of MF between tasks: the transfer of the effect of MF from one task (loading) to the other (probe), and the possibility of recovery from MF by a change in task. A series of studies (Hockey & Earle, 2006; Persson, Welsh, Jonides, & Reuter-Lorenz, 2007; Schellekens, Sijtsma, Vegter, & Meijman, 2000; van der Linden et al., 2003; Vickery, 1931; Webster, Richter, & Kruglanski, 1996) indicated that the effect of fatigue is general and there is no room for recovery if the probe task is at least as demanding as the loading task. For example, Arai (1912) and Vickery (1931) found that the effect of MF transfers from

mental addition to subtraction but not the other way around. Furthermore, the after-effects of fatigue were also found in studies where both the loading- and the probe tasks required the use of executive functions (Persson et al., 2007; van der Linden et al., 2003). Studies consisting of real-life tasks such a simulated workday (Hockey & Earle, 2006) or academic examination (Webster et al., 1996) for MF inducement (loading task) and holiday planning or social judgement (Hockey & Earle, 2006; Webster et al., 1996) for MF evaluation (probe task) also showed transferability of MF.

In studies using the direct or indirect method for the induction of MF, the main task characteristics which have been manipulated are task duration (time-on-task: TOT) and/or cognitive demands (Blain et al., 2016; Boksem et al., 2006; Borragán et al., 2017; Hopstaken, van der Linden, Bakker, & Kompier, 2014; Lorist et al., 2009; Wang, Trongnetrpunya, Babu, et al., 2016). Increasing TOT and/or higher cognitive demands have been thought to increase MF (DeLuca et al., 2005). However, its manifestation in feeling, behavior and psychophysiological state is not universal. Early studies of MF have already revealed that there is often a discrepancy between its experiential (i.e. increased feeling of fatigue) and behavioral (i.e. preserved performance) dimensions (Schellekens et al., 2000; Thorndike, 1900). The possible reasons for this discrepancy are discussed below (see Section I.1.3.1.2.).

I.1.3.1.1. Subjective evaluation of mental fatigue: questionnaires

The subjective feeling of fatigue can be assessed by means of self-reported questionnaires (Christodoulou, 2005) that are either uni- or multidimensional (Whitehead, 2009). The unidimensional questionnaires [e.g. Brief Fatigue Inventory (BFI: (Mendoza et al., 1999)), Fatigue Severity Scale (FSS: (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989)), Fatigue Symptom Inventory (FSI: (Hann, Denniston, & Baker, 2000)), Fatigue Impact Scale (FIS: (Fisk et al., 1994)) etc.] consisting of one or more item(s) focus on only the severity of fatigue. In opposition to this questionnaire type, the multidimensional ones [e.g. Multidimensional Assessment of Fatigue (Belza, 1995), Multidimensional Fatigue (Symptom) Inventory (MFI: (Smets, Garssen, Bonke, & De Haes, 1995); MFSI: (Stein, Martin, Hann, & Jacobsen, 1998))] comprise several items classified into different subscales which represent, for example, the impact of subjective fatigue on daily life functioning, mental (e.g. distractibility, impaired concentration) and physical activities or the feelings that accompany fatigue (e.g. motivational: apathy). Both the uni- and multidimensional questionnaires can be used to assess the temporal dynamics of fatigue [e.g. fatigue right now (BFI), past week or further in the past (BFI, FIS, FSI, MFSI)]. Furthermore, there are questionnaires that can be used in either clinical- (e.g. FIS in MS patients, MFSI in cancer patients) or healthy population [e.g. Borg Rating of Perceived Exertion scale (Borg, 1970)]. Overall, it remains unclear which type of questionnaire is more advantageous (Kluger, Krupp, & Enoka, 2013). The proponents of the multidimensional questionnaires (Kluger et al., 2013; Stein et al., 1998) argue that such a complex

phenomenon as the subjective feeling of fatigue has to be assessed by using as many factors as possible (e.g. the impact of fatigue on daily life functioning, mental and physical activities, and the feelings related to fatigue etc.) while others claim that the subjective evaluation of fatigue has to be kept as simple as possible by focusing only on the severity of fatigue and not on feelings related to fatigue (e.g. apathy) which may be better assessed by other specific questionnaires.

There are different types of scales to rate items in fatigue questionnaires. The most widely used one is the Likert scale which consists in a range of response possibilities for instance from 1 – “not at all” to 5 – “completely” to describe how much someone agrees or disagrees with a given statement (e.g. in questionnaires described above). The visual analogue scale (VAS) works to the same extent as the Likert scale. However, here the line of the VAS has to be bisected [e.g. Visual Analogue Scale for Fatigue (Lee et al., 1991)]. The least used scale is the binary one [e.g. Fatigue Scale (Chalder et al., 1993)] which consists of only two response possibilities (yes or no) in order to demonstrate whether fatigue is presented.

Since the objective of this thesis was to reveal whether alteration in motivational states plays a role in the build-up of healthy individuals' fatigue, we used a modified version of the Multidimensional Fatigue Inventory (Gentile, Delarozière, Favre, Sambuc, & San Marco, 2003; Smets et al., 1995), to assess not only MF but also motivation. This questionnaire consists of 20 items grouped into different dimensions such as general- and mental fatigue, reduced activities and motivation (see Table I.1.). The items have to be rated by using a Likert scale (see above). The time course of fatigue experienced is not specified in this

questionnaire. However, in the experiments presented hereunder (see Chapter II) the participants were asked to rate the statements as a function of their momentary feeling.

Dimensions	Items
General fatigue	Je me sens en forme./I feel fit.
	Physiquement, je ne me sens pas capable de faire grand-chose./Physically I feel only able to do a little.
	Je me sens très actif./I feel very active.
	Je me sens fatigué(e)/I feel tired.
	Physiquement, je peux faire beaucoup./Physically I can take on a lot.
	Je me sens reposé(e)/I am rested.
	Physiquement, je me sens en mauvais état./Physically I feel I am in a bad condition.
	Je me fatigue facilement./I tire easily.
	Physiquement, je me sens en parfait état./Physically I feel I am in an excellent condition.
Mental fatigue	Quand je fais quelque chose je peux me concentrer dessus./When I am doing something, I can keep my thoughts on it.
	Je redoute d'avoir des choses à faire./I dread having to do things.
	J'arrive bien à me concentrer./I can concentrate well.
	Me concentrer sur quelque chose me demande beaucoup d'effort./It takes a lot of effort to concentrate on things.
	Je n'ai rien envie de faire./I don't feel like doing anything.
	Mes pensées s'égarent facilement./My thoughts easily wander.
Reduced activities	Je pense que je fais beaucoup de choses dans une journée./I think I do a lot in a day.
	Je pense que je ne fais pas grand chose dans une journée./I think I do very little in a day.
	Je mène peu de choses à bien./I get little done.
Motivation	J'ai envie de faire des tas de choses agréables./I feel like doing all sorts of nice things.
	J'ai un tas de projets./I have a lot of plans.

Table I.1. The Multidimensional Fatigue Inventory. Modified from (Gentile et al., 2003).

The self-reported questionnaires offer many advantages (e.g. they are cheap, simple to use at any time, and easy to analyze) but the enormous amount of factors (see Figure I.1.) affecting the way how individuals experience fatigue may lead to huge between-subjects variability which makes the generalization of the results more difficult (Ackerman, 2011).

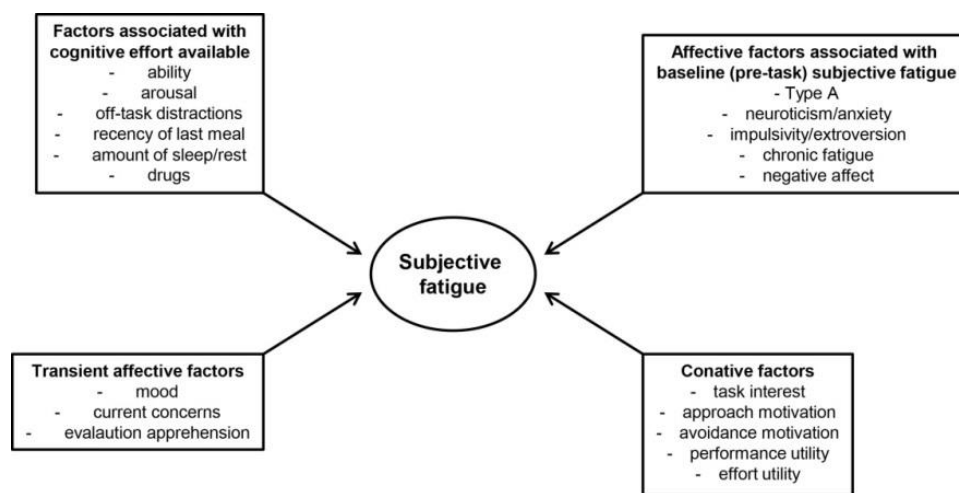


Figure I.1. Factors potentially causing between-subjects' variability in the experience of fatigue. Modified from (Ackerman, 2011).

I.1.3.1.2. Behavioral measures of mental fatigue: performance decrements

The behavioral manifestation of MF, consisting mostly of longer reaction time and reduced accuracy over TOT, has been investigated in a wide range of cognitive tasks, including impaired planning (van der Linden et al., 2003), attention (Boksem et al., 2006), inhibition (Kato et al., 2009), task switching (Borragán et al., 2016; Lorist et al., 2009), interference control (Persson, Larsson, & Reuter-Lorenz,

2013), working memory (Benoit et al., 2018) and inter-temporal choice (Blain et al., 2016). These findings indicate that activities requiring substantial cognitive control are sooner or later susceptible to the detrimental effects of MF. Thus a challenging feature of these studies is their variable task duration (from minutes to hours), which makes the generalization of findings on MF difficult. To date, it remains unclear what the standard time is to induce MF by a cognitively demanding task. In contrast to the increase in the subjective experience of MF, task performance does not necessarily deteriorate over time. For example, Davis (1946) revealed different patterns of behavior (withdrawal, normal, overactivity) in which TOT resulted in reduced, preserved or improved performance. Furthermore, Ackerman and Kanfer (2009) also showed that despite subjective experience of fatigue, participants performed better in a long (5.5 hour) than a short version (3.5 hour) of a cognitive ability test. The lack of behavioral correlates of MF could be due to compensatory mechanisms or training and learning effects (Ackerman & Kanfer, 2009; Davis, 1946; Hockey, 1997; 2013). Hockey's model of compensatory control (see for more details in Section I.2.2.1.) has often been used to explain this discrepancy between the increased subjective feeling of fatigue and maintained performance (see Table I.2.: fatigue mode-resistance). The model argues that the initial maintenance of performance through heightened mental effort (resource mobilization; see for more details about mental effort in Section I.1.4.1.1.) incurs a cost over TOT which corresponds to the increased subjective feeling of fatigue. The effects of training and learning on performance can also occur with TOT, obscuring the behavioral correlates of MF. In order to overcome these limitations, Blain et al. (2016) suggested to measure the participants' preference by means of

intertemporal choice [namely the propensity to favor immediate reward (10€) vs. delayed reward (50€)] instead of their performance over TOT (> 6 hours). This approach prevents the occurrence of compensatory mechanisms and training/learning effects, allowing the behavioral correlates of MF to be observed. However, despite these caveats, many studies have succeeded in reporting performance decrement (Hopstaken, van der Linden, Bakker, & Kompier, 2015; Hopstaken et al., 2016; Lorist et al., 2009; van der Linden et al., 2003). For instance, a recent study (Borragán et al., 2017) inspired by the time-based resource-sharing model (Barrouillet, Bernardin, & Camos, 2004; Barrouillet & Camos, 2007) demonstrated that a task requiring high cognitive load (limited time to process cognitive demands) can induce MF in terms of both feeling and performance decrement within a short period of time (16 minutes). Thus, in summary, these findings (Ackerman & Kanfer, 2009; Blain et al., 2016; Borragán et al., 2017; Davis, 1946) point out that there is an urgent need for a systematic investigation of task duration and demands in order to clarify a standard procedure for the inducement of MF.

Fatigue mode	Subjective state	Performance decrement	After-effects
Acceptance	minor fatigue	+	-
Resistance	↑ effort ↑ fatigue	-	+
Strain	sustained ↑ effort and fatigue	slight	+

Table I.2. Task-related fatigue: feeling and performance. Modified from (Hockey, 2013). ↑ = increase; ↓ = decrease; + = yes; - = no.

Besides the temporal (TOT) and cognitive demand characteristics of a task, there are additional task features that may elicit subjective (i.e. increased subjective feeling of fatigue) and objective behavioral MF (i.e. performance decrements). Ackerman (2011) categorized these factors based on the major components of the attention(al resources) and information processing theories which have been used to interpret MF (see Section I.2.1.2.). The amount of limited attentional resources may be depleted by a task which is not only cognitively demanding and long but is also exempted from rest breaks and learning effects (Arai, 1912), and requires the performer to reply within a short period of time as accurately as possible (Ackerman et al., 2011). The allocation of the attentional resources depends on arousal and/or motivational factors. For example, if performing a task is not highly rewarding and intrinsically interesting/enjoyable, and there is no performance feedback provided, MF may appear (Ackerman et al., 2011). However, it is important to note that an uninteresting and unenjoyable activity may lead to boredom which is not consistent with MF (see Section

I.1.4.2.2.). Furthermore, performing a task in the presence of such general stressors as heat, poor light and/or loud noise etc. may also contribute to MF (Ackerman et al., 2011) since they draw away attentional resources from the task. The majority of these task features and general stressors have not been systematically studied, thus it is difficult to determine which of these factors contribute the most to the build-up of objective, behavioral and subjective MF (Ackerman, 2011).

In addition to task characteristics, there are the so-called state variables such as sleepiness, time of day and post-lunch dip which may also facilitate the development of task-related fatigue through the modulation of one's arousal level (Ackerman, 2011; Ackerman et al. 2017). Sleepiness and arousal fluctuations, which are often improperly considered as MF, are further discussed below (see Section I.1.4.4. and I.1.4.1.2.).

I.1.3.1.3. Psychophysiological measures of mental fatigue

MF can manifest itself not only in terms of subjective experience and/or performance decrement but also in terms of psychophysiological changes. The psychophysiological consequences of MF remain a matter of speculation but changes in the electrical activity of the brain (measured by electroencephalography: EEG), in spontaneous eye-blink (measured by eye-tracker, video camera or electrooculography: EOG) and in the autonomic nervous system (indexed by means of electrocardiography :ECG) have been shown to covary with MF (e.g. Borghini et al., 2012; Craig, Tran, Wijesuriya, & Nguyen, 2012; Stern, Boyer, & Schroeder, 1994). The autonomic nervous system is

responsible for the regulation of involuntary bodily functions through its sympathetic and parasympathetic branches in order to maintain homeostasis. The sympathetic (“fight or flight”) system activates the body in response to a stimulus which is accompanied by an increase for example in heart rate while the parasympathetic one promotes “rest-and-digest” functions in the opposite way.

1.1.3.1.3.1. Electroencephalography

Frequency bands: theta and alpha

EEG has been extensively used to investigate the influence of MF on brain activity (Barwick, Arnett, & Slobounov, 2012; Boksem et al., 2005; Borghini et al., 2012; Craig et al., 2012; Käthner, Wriessnegger, Müller-Putz, Kübler, & Halder, 2014; Kato et al., 2009; Lal & Craig, 2002; Lorist et al., 2000; Lorist et al., 2009; Lorist, Boksem, & Ridderinkhof, 2005; Trejo et al., 2015; Wang, Trongnetrpunya, Wascher et al., 2014; Zhao, Zhao, Liu, & Zheng, 2012). Despite the fact that the sources of MF (e.g. sleep deprivation, simulated driving or cognitive task performance over a prolonged period of time) and other factors (e.g. sample size, number and distribution of electrodes, presence or absence of correlations performed between the subjective or objective behavioral dimension of MF and psychophysiological changes) were inconsistent between studies, a systematic review revealed (Craig et al., 2012; Craig & Tran, 2017) that significant increases in the low frequency bands as the theta and alpha were generally associated with MF in healthy subjects. The theta rhythm (4-7.5 Hz frequency band) has been considered to reflect psychological states (e.g. decreased alertness during

drowsiness) and reduced information processing while the alpha rhythm (8-13 Hz frequency band) has been linked to arousal level [high amplitude and low frequency alpha activity presumably correspond to low cortical arousal (Tran, Craig, & McIsaac, 2001)] and mental activity (Lal & Craig, 2001). In most studies, due to the small number of cortical sites (< 10) it remained unclear whether the increases in theta and alpha activity during MF were global or regional (Craig et al., 2012). More recent investigations using a bigger number of electrodes (19-60) revealed that the theta activity mostly increases in frontal and parietal regions while the alpha activity increases in frontal, parietal and occipital regions (Craig et al., 2012; Käthner et al., 2014; Trejo et al., 2015; Wascher et al., 2014).

Event-related potentials: ERN and P300

Besides the frequency components of the EEG, other components such as event-related potentials (ERPs) have also been found to be associated with MF in healthy individuals (Boksem et al., 2006; Käthner et al., 2014; Kato et al., 2009; Lorist et al., 2005; Zhao et al., 2012). The peak amplitude of the error-related negativity (ERN), which is a proxy of the performance/error-monitoring function of the ACC occurring right after an erroneous response, was observed to decrease over TOT associated with MF (Boksem et al., 2006; Kato et al., 2009; Lorist et al., 2005). Furthermore, several studies reported that the P300 amplitude decreased while the P300 latency increased with MF induced by TOT (Cheng, Lee, Shu, & Hsu, 2007; Hopstaken et al., 2014; Käthner et al., 2014; Kato et al., 2009; Murata, Uetake, & Takasawa, 2005; Uetake & Murata, 2000). This ERP is a positive deflection peaking around 300 ms after stimulus onset (Sutton, Tueting, Zubin, &

John, 1967) and has been thought to reflect the intensity and the timing of information processing (Polich & Kok, 1995) which is presumably impaired during MF.

1.1.3.1.3.2. Eye blinks

Changes in the parameters of spontaneous eye-blink [e.g. rate: closing and reopening of the eyelids at a given frequency; duration: consisting of the closing and reopening time (Caffier, Erdmann, & Ullsperger, 2003)], measured by EOG/eye-tracker/video camera, have also been linked to MF. Stern et al.'s review (1994) on studies investigating the link between eye-blink parameters and MF led to the conclusion that blink rate could be used as a potential measure of MF associated with TOT. Barbato et al. (1995) reported a significant increase in healthy participants' blink rate after 1 night of total sleep deprivation which is a common source of MF. Morris and Miller (1986) observed that pilots, who were partially sleep deprived, committed more errors in a flight simulator task over 4.5 hours. This performance decrement was significantly correlated with an increase in self-reported fatigue, and was best predicted by a decrease in blink amplitude and an increase in blink- and long closure rate. Caffier et al. (2003) studied eye-blink parameters [duration, rate, closing-, proportion of long closure- and reopening time] in an alert (before working day) and a drowsy/sleepy (after working day) condition in healthy participants. Besides the measures of eye-blink parameters using an infrared sensor, the subjective feeling of drowsiness/sleepiness was also evaluated by means of different scales prior to and following working. The results showed that most eye-blink parameters except the rate increased as a function of

drowsiness. Wijesuriya, Tran, & Craig (2007) investigated blink rate and eye-closure time as potential indicators of MF in a simulated driving task. A significant increase in these parameters was revealed by comparing pre- vs. post-measurements of MF. In Craig et al.'s study (2012), healthy individuals participated in a simulated driving task until they showed characteristics of MF which was verified by means of increased subjective feeling of fatigue, blink rate and long closure time (300 ms-400 ms). It is noteworthy, however, that these studies do not allow us to dissociate the influence of MF and sleepiness on eyeblink rate (see section I.1.4.4.).

I.1.3.1.3.3. Electrocardiography

Heart rate (HR: beats per minute) and heart rate variability [HRV: variation in heart beats by calculating the beat-to-beat (RR) time intervals], measured by ECG, have also been shown as potential indicators of MF (Borghini et al., 2012; Zhao et al., 2012). HR has been shown to decrease and HRV to increase concurrently with MF (Mascord & Heath, 1992). The latter parameter (HRV) can be analyzed either in the time- or frequency-domain (Heinze et al., 2009; Kuratsune, 2012; Patel et al., 2011). In the time-domain, the RR time intervals can be analyzed with descriptive statistics (e.g. mean, standard deviation). In the frequency-domain, the frequency components of HRV can be characterized using, for example, power spectral analysis which reflects the function of the autonomic nervous system: very low frequency (0.001-0.04 Hz) and low frequency (0.04-0.15 Hz) are thought to depend on both sympathetic and parasympathetic influences whereas high frequencies

(0.15-0.4 Hz) depend only parasympathetic activity (Bilchik & Berger, 2006; Kleiger, Stein, & Bigger, 2005; Zhao et al., 2012).

I.1.4. Concepts related to mental fatigue

As mentioned above (see Section I.1.3.1.2.), there are certain task characteristics which can contribute to the build-up of MF by affecting the availability and allocation of mental effort. However, these factors may elicit not only MF but also arousal fluctuation, vigilance decrement, boredom, (acute) stress and (state) anxiety. Although these concepts are distinct from MF, they are often confused, not only in everyday life but even in scientific research and clinical practice. Furthermore, sleepiness, which is often intermixed with MF, has also been known to influence vigilance and arousal (Lim & Dinges, 2008; Tassi, Bonnefond, Hoeft, Eschenlauer, & Muzet, 2003). Hereafter, I briefly describe mental effort which is strongly related to MF, and I also summarize the concepts of arousal, vigilance, boredom, stress, anxiety, sleepiness and depression using an operational approach in order to better distinguish them from MF.

I.1.4.1. Mental effort, task engagement and arousal

I.1.4.1.1. Mental effort and task engagement

Similar to MF, mental effort (ME) is also a challenging phenomenon. It has been often identified as attention, motivation, difficulty and cognitive control (Westbrook & Braver, 2015). Engagement in a task with high cognitive control demands is typically perceived as effortful and thus aversive. The extent to which

someone is engaged in a demanding task can be primarily evaluated by means of self-reported questionnaires [e.g. by rating how difficult/aversive someone finds further exertion of ME in a given activity (Hart & Staveland, 1988; Hopstaken et al., 2014)] and more objectively by means of task/effort avoidance [e.g. by measuring the tendency how much someone devalues effortful rewards (Benoit et al., 2018; Kool, McGuire, Rosen, & Botvinick, 2010; Vassena et al., 2014; Westbrook, Kester, & Braver, 2013)]. Amongst the psychophysiological measures of ME such as EEG [e.g. suppressed alpha power and increased P300 amplitude in association with increased ME (Keil, Mussweiler, & Epstude, 2006; Sterman, Schummer, Dushenko, & Smith, 1988; Ullsperger, Metz, & Gille, 1988)], HR(V) [increasing HR and decreasing HRV with higher ME (Mulder, 1986; O'Hanlon, 1972; Schellekens et al., 2000; Veltman & Gaillard, 1996)], skin conductance [higher skin conductance level with ME exertion (Venables & Fairclough, 2009a)] and pupil size [increasing pupil size with increasing ME (van der Wel & van Steenbergen, 2018)], the latter one has been most consistently found to relate to ME.

The reason why ME is perceived as aversive and how it is allocated to task performance have been intensively studied (Kool & Botvinick, 2013; Kool et al., 2010; Kool, Shenhav, & Botvinick, 2017; Kurzban et al., 2013; Massar, Lim, Sasmita, & Chee, 2016). Shenhav et al. (2017) have operationalized ME in terms of information processing: they have considered it as a mediator between the characteristics of a given task and one's information processing capacity, and thus task performance, which regulates cognitive control. Since one's decision to

engage in a demanding activity (to allocate cognitive control under certain circumstances) seems to be driven by motivation and volition, ME has been viewed in terms of reward-based decision-making which comprise cost-benefit computations [e.g. (Kool et al., 2017; Shenhav, Botvinick, & Cohen, 2013): expected value of control theory], namely, the benefit of cognitive control is weighted against its inherent cost. This so-called intrinsic cost specifies a limit for the allocation of cognitive control at one time entailing opportunity cost (Kurzban et al., 2013; see for more details in Section I.2.2.4.) which means that cognitive control cannot be allocated to another valuable option.

The investment of ME might be also explained by Aston-Jones and Cohen's (2005) adaptive gain theory of locus-coeruleus (LC). This theory argues that the LC plays a role in the regulation of task engagement through utility-based evaluations, and in optimizing task performance. The LC is a brainstem nucleus that synthesizes the neurotransmitter norepinephrine (NE)/noradrenaline, which is known to be involved in mediating arousal (Reimer et al., 2016; see Section I.1.4.1.2.). Engagement in a demanding task depends on its expected utility which results from a tradeoff between its expected costs and benefits. As a function of increasing or decreasing utility, task engagement can be favored or undermined, respectively. If task engagement is favored one finds the effort worth and exploits the available benefits/task-related sources of reward (exploitation behavior, see Figure I.2.). While if it is undermined (task disengagement) one finds the effort unworthy and decides to explore other options (exploration behavior, see Figure I.2.). These types of behavior are thought to be mediated by the phasic

(characterized by medium tonic and robust phasic LC activity) and tonic LC activity (characterized by high tonic LC activity) which drives exploitation and exploration, respectively (see Figure I.2.). This indicates that performance changes as a function of the level of tonic LC activity (see Figure I.2.). It was observed that impaired performance is associated with low and high levels of tonic LC activity while optimal performance with moderate level of tonic and prominent phasic LC activity (Aston-Jones & Cohen, 2005; Murphy, Robertson, Balsters, & O'connell, 2011; see Figure I.2.). This inverted U-shape relationship between performance and tonic LC activity is consistent with the classical Yerkes-Dodson law (Yerkes & Dodson, 1908) which describes the relation between performance and arousal in the same manner (see Figure I.2.). Since the LC-NE activity cannot be directly assessed, its plausible proxy measures are the pupil diameter and the P300 amplitude (Eckstein, Guerra-Carrillo, Miller Singley, & Bunge, 2017; Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010; Jepma & Nieuwenhuis, 2011; Larsen & Waters, 2018; Murphy et al., 2011; Nieuwenhuis, Aston-Jones, & Cohen, 2005; Nieuwenhuis, De Geus, & Aston-Jones, 2011) which also showed an inverted U-shape relation to performance (Gilzenrat et al., 2010; Jepma & Nieuwenhuis, 2011; Murphy et al., 2011; see Figure I.2.).

The link between mental effort, task engagement and mental fatigue

Despite the fact that Hockey's compensatory control model (Hockey, 1993; 1997; 2011; 2013) implicates that the subjective feeling of MF may be strongly associated with the increased cost of ME due to the compensatory resource mobilization to maintain task performance, the link between MF and ME has been

only recently investigated both psychometrically and behaviorally. Benoit et al. (2018) hypothesized that the cost of ME would be increased by subjective MF. However, surprisingly, they did not find any relation between the subjective dimensions of ME and MF, but on the other hand they revealed a relation between their behavioral correlates: namely, MF-induced performance decrement was correlated with task avoidance. Benoit and his colleagues (2018) have argued that these findings falsify the hypothesis that the compensatory resource mobilization gives rise to subjective MF (Hockey, 1993; 1997; 2011; 2013) because it should have also increased task avoidance which was absent in the present study.

Others (e.g. Hopstaken et al., 2014; Meijman, 2000; van der Linden, 2011) have also assumed a potential relation between MF and ME wherein MF could be viewed as an interruption mechanism (a stop signal) to maintain motivational balance through the suspension of costly activities (task disengagement, see Figure I.2.). Additional theories which also promote the motivational account of MF are discussed below (see Section I.2.2.).

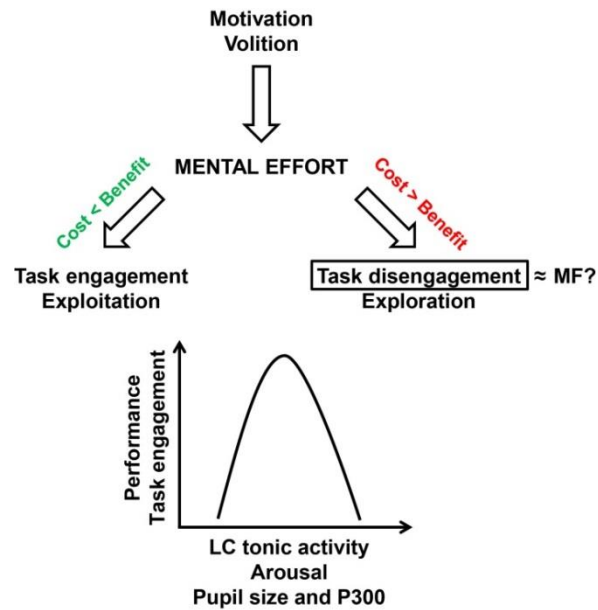


Figure I.2. The link between mental effort, task engagement and mental fatigue

This figure depicts the relation between performance/task engagement and arousal on the one hand, and between performance/task engagement and LC activity and its proxy measures (pupil size, P300) on the other hand.

Finally, evidence in favor of the relationship between MF and ME can be found in psychophysiology. Inspecting the psychophysiological correlates of ME and MF (Table I.3.), reveals opposite patterns of variation (e.g. when ME increases the HR increases and the HRV decreases while during MF these electrophysiological correlates change in the opposite direction) which indicates that MF could be indeed associated with lower effort mobilization in accordance with the motivational account of MF.

Psychophysiological measure	Increased ME	Increased MF
EEG alpha power	↓	↑
ERP P300 amplitude	↑	↓
HR	↑	↓
HRV	↓	↑

Table I.3. Opposite patterns of variation in the psychophysiological correlates of ME and MF

I.1.4.1.2. Arousal fluctuation

Arousal can be described as a global brain state across the sleep-wake spectrum (Oken, Salinsky, & Elsas, 2006) which is controlled and mediated by brainstem NE as mentioned above (Berridge, 2008; Reimer et al., 2016). This psychophysiological state drives one's responsiveness to sensory stimuli (Berridge, 2008; McGinley, David, & McCormick, 2015), performance (Aston-Jones & Cohen, 2005; Cools & D'Esposito, 2011; Murphy et al., 2011; Yerkes & Dodson, 1908) and cognition (Sara & Bouret, 2012). It has been shown that arousal co-varies with motivation since larger incentives enhanced it (Kahneman & Peavler, 1969). A prominent measure of arousal fluctuation is the pupil which has been shown to dilate with higher levels of arousal (Bradley, Miccoli, Escrig, & Lang, 2008; Gilzenrat et al., 2010; Kahneman, 1973; Reimer et al., 2014). Another technique used to track fluctuations in arousal is the EEG (Hegerl & Ulke, 2016; Huang et al., 2015; Klimesch, 1999). Klimesch (1999) revealed that drops in

arousal are associated with increases in the theta and alpha band powers. These findings indicate that decreased arousal could be potentially associated with increased MF which is also accompanied by an increase in these frequency bands (Craig et al., 2012). However, the relation between the changes in the level of arousal and cortical activation is questionable since in many EEG studies arousal has been investigated as a phenomenon consistent with vigilance (Oken et al., 2006; see Section I.1.4.2.1.) which has also been used interchangeably with MF (Lim et al., 2010). Thus, it is difficult to make a conclusion about the relation between arousal fluctuation and MF on the basis of current EEG literature. However, pupillometry seems to be a good method to clear the relation between arousal and MF. In their study, Benoit et al. (2018) found that arousal was not associated with MF, indexed by pupil size, since it was unresponsive to the fatigue manipulation.

I.1.4.2. Vigilance decrement and boredom

I.1.4.2.1. Vigilance decrement

Our ability to process information depends on two activation states which correspond to phasic (selective attention) and tonic (sustained attention) alertness (Oken et al., 2006; Weinbach & Henik, 2012). From a psychological point of view, tonic alertness, better known as vigilance, refers to the ability to sustain attention to a mental activity over time (Davies & Parasuraman, 1982; Mackworth, 1948; Parasuraman, 1988; Tassi et al., 2003). In the domain of transportation, this phenomenon has been extensively studied, since even a small drop in one's vigilance can result in fatal outcomes. There exists different tasks, namely the

Clock test (Mackworth, 1948), the Continuous Performance task (Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956), the Psychomotor Vigilance task (Dinges et al., 1997) and the Sustained Attention to Response task (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997) for the evaluation of sustained attention. These tasks generally consist of rare targets that may be interleaved with distractors (Clock test, Continuous Performance task and Sustained Attention to Response task) or not (Psychomotor Vigilance task). In all tasks, participants have to detect the targets as soon and accurately as possible. The decrements in one's vigilance, characterized by slower RT, increasing amount of missed targets or increasing theta activity (Paus et al., 1997), have been discussed either in the framework of underload/mindlessness/boredom or overload/resources/fatigue theories (Pattyn, Neyt, Henderickx, & Soetens, 2008; Thomson, Besner, & Smilek, 2015; see Table I.4.). The mindlessness theory posits that the vigilance decrement is due to the monotonous and unstimulating nature of the given task which elicits boredom/disinterest associated with task-unrelated thoughts/mind-wandering, and can be attenuated by reward and motivation, while the resource theory posits that it results from the overuse of the information-processing resources and cannot be overcome by heightened reward and motivation. Pattyn et al. (2008) tested these theories and found that vigilance decrement is the consequence of boredom and not MF. However, other studies have questioned this view (Dillard et al., 2014; Grier et al., 2003; Gunzelmann et al., 2011; Head & Helton, 2014; Thomson et al., 2015).

	Theoretical account of vigilance decrement	
Vigilance decrement	Underload/Mindlessness	Overload/Resource-depletion
Are vigilance tasks effortful?	-	+
How should increasing task demands affect the decrement?	decrement should get larger or remain unchanged	decrement should get larger
How should increasing task engagement affect the decrement?	decrement should get smaller	decrement should get larger or remain unchanged
How should TOT affect mind-wandering frequency?	frequency should increase	frequency should decrease

Table I.4. Theoretical account of vigilance decrement
Predictions of the underload/mindlessness and overload/resource depletion theories about vigilance decrement. Modified from (Thomson et al., 2015).

I.1.4.2.2. Boredom

Boredom is also an ill-defined phenomenon, and thus hardly measureable. It has often been viewed as a state resulting from an under-arousing environment (e.g. task monotony) or as an emotion which functions as an interruption mechanism to maintain one's motivation (Goldberg, Eastwood, LaGuardia, & Danckert, 2011; Raffaelli et al., 2017).

Since boredom is a poorly known phenomenon, it is difficult to objectively distinguish from MF. However, there exist some theories about their distinction.

Myers (1937) hypothesized that boredom occurs when task engagement is undermined due to the lack of interesting information while MF is more likely to evolve as a failure of concentration. Welford (1968) differentiated between boredom and MF in the arousal-information processing framework. He suggested that boredom is the consequence of a low level of arousal (underload) caused by the insufficient information experienced in a task (e.g. low levels of cognitive demands) while a high level of arousal due to information overload leads (e.g. high levels of cognitive demands) to fatigue. According to O'Hanlon (1981), the difference between boredom and MF is based on task features such as the frequency of a given stimulus. Highly repetitive stimuli often trigger boredom, while fatiguing activities are more often characterized by richer and more complex stimulation. Furthermore, these phenomena can be distinguished by the way they can be remedied. While boredom can be overcome by switching to another activity, it is not a solution to MF (Myers, 1937).

1.1.4.3. Stress and anxiety

Stress can be classified as either acute (momentary and short-term) or chronic (long-term). Here the focus is on acute stress which may evolve during task performance. This unpleasant state can be characterized by the subjective feeling of strain, performance decrement (Matthews et al., 2000) and by a change in the level of stress hormones. When a threat to performance is detected the fast-acting sympathetic adrenomedullary (SAM) and the slower-acting hypothalamic pituitary adrenal (HPA) pathway is activated by the hypothalamus (Henry & Stephens, 1977). The former system (SAM) stimulates the release of adrenaline

(epinephrine)/noradrenaline (norepinephrine) while the latter system (HPA) controls cortisol secretion.

A model which has accounted for both the subjective feeling of stress and fatigue is Hockey's compensatory control model (1997) which highlights the importance of effort-management in goal-maintenance (see Section I.2.2.1.). In a demanding situation wherein one's performance is under threat an upper control loop is engaged in the regulation of effort-management which consists in two coping strategies, namely, active and passive. Active coping accompanied by high effort (strain mode/compensation) is associated with adequate performance and thus with goal-maintenance while passive coping accompanied by low effort (disengaged mode) is associated with impaired performance and thus downgraded goal. Independently of the degree of effort-mobilization, state anxiety increases during demanding task execution [a momentary psychophysiological response to an adverse situation (Spielberger, 1966) which is the most commonly assessed by the State-Trait Anxiety Inventory (Spielberger, 1983)]. During active coping it is driven by the cost of effort while during passive coping it is driven by the drop in performance. Furthermore, Hockey (1993; 1997; 2011; 2013) has argued that the cost of effort during active coping may be responsible for the subjective feeling of fatigue. These types of coping modes (Mulder, Leonova & Hockey, 2003) are consistent with the ones defined by Frankenhaeuser (1986) who distinguished different psychophysiological adjustments as active coping with and without distress (strain and engaged mode, respectively) and passive coping with distress (disengaged mode) to a highly demanding work environment (see Table I.5.).

According to Frankenhaeuser (1986), the engaged mode of work management is similar to Csikszentmihályi's flow state (1990) when one is deeply engaged in a self-initiated activity wherein her/his skills are not challenged by the demanding work environment. From physiological point of view, this mode can be characterized by increased levels of adrenaline/noradrenaline and decreased levels of cortisol. In the strain mode, these stress hormones tend to be increased while in the disengaged mode only cortisol increases (Frankenhaeuser, 1986; Hockey, 1997). These responses indicate that the increase in the level of adrenaline and noradrenaline may correspond with higher effort investment while the change in the level of cortisol with the feeling of anxiety.

As the strain mode indicates, stress and fatigue may simultaneously occur. However, the causality between these phenomena remains unclear, and in addition, it is also unknown whether the stress marker, cortisol, changes as a function of fatigue. Doerr et al (2015) investigated the causality between acute stress and fatigue in healthy students who either had their regular week at the beginning of the semester (control condition) or prepared for their final examination during 5 days (stress condition). The link between these phenomena was assessed by means of self-reported questionnaires, and more objectively by salivary cortisol. In both conditions, a reciprocal relationship was found between subjective stress and fatigue, measured both momentarily and over time, and which was not mediated by cortisol. In contrast, cortisol did not correlate with the subjective feeling of fatigue. These findings may indicate that only phenomenal stress and fatigue are related to each other.

Mode	Control	Effort	Performance (goal status)	Subjective state	Stress markers*
Strain	low	High	adequate (protected)	anxiety fatigue	A & NA ↑ cortisol ↑
Disengaged	low	Low	reduced	anxiety	cortisol ↑
Engaged	high	Moderate	optimal	flow	A & NA ↑ cortisol ↓

Table I.5. Psychophysiological adjustments to high demands work environments. Modified from (Hockey, 1997; 2013). ↑ = increase; ↓ = decrease; A = adrenaline; NA = noradrenaline.

1.1.4.4. State variables contributing to the build-up of task-related mental fatigue

1.1.4.4.1. Sleepiness

Sleeping is everyone's basic need which is indispensable to our optimal functioning. It is regulated by a balance between our sleep and wake periods which are further controlled by our internal circadian clock throughout a day. When there is an irrepressible need for sleep, we talk about sleepiness/drowsiness (Pigeon, Sateia, & Ferguson, 2003) which can be distinguished as normal and pathological. Normal/physiological sleepiness (mean sleep latency > 10 min, (Carskadon & Dement, 1981)) occurs when our circadian rhythm varies as a function of the time of day and reminds us that sleep is needed, while pathological sleepiness (mean sleep latency < 5 min, (Carskadon & Dement, 1981)) occurs, generally at unusual time (Duntley, 2005), when the normal functioning of the homeostatic (sleep-wake

cycle) and circadian system is disrupted. Excessive sleep deprivation, medical disorders (e.g. sleep disorders) and drugs, can cause this latter type of sleepiness which may be accompanied by the symptom of incapacitating MF (Dinges, 1995; Dinges et al., 1997; Friedmann et al., 1977; Shen et al., 2006).

The term of MF is often used interchangeably with sleepiness, even though they correspond to clearly distinct concepts. First, MF is not in association with the function of the circadian system and does not incline to sleep. In the case of acute MF, it is rather the consequence of performing a cognitively demanding activity over a prolonged period of time (see Section I.1.3.1.2.), and may function as an interruption mechanism to maintain motivational balance (see Section I.2.2.). Second, while standardized tests exist for the objective evaluation of sleepiness (e.g. Multiple Sleep Latency Test, Maintenance of Wakefulness Test), these are absent in the case of MF (Duntley, 2005). Third, sleepiness can be alleviated or overcome by sleep, while this restorative function is ineffective against chronic MF (Balkin & Wesensten, 2011).

I.1.4.4.2. Depression

Fatigue is not only a risk factor for depression (Johnson, 2005) but it also a common symptom within it (Demyttenaere, De Fruyt, & Stahl, 2005). Constant et al. (2011) compared cognitive deficits in patients with CFS [a medical condition characterized primarily by a chronic or relapsing fatigue, short-term memory problems and by muscle weakness (Fukuda et al., 1994)] to patients with Major Depressive Disorder (MDD) and healthy individuals and found that patients with MDD suffered from fatigue (< CFS patients' subjective fatigue) while patients with

CFS from moderate depression (< MDD patients' subjective depression). Moreover, cognitive impairments in MDD patients correlated to both subjective feeling of fatigue and level of depression, while this relation was absent in patients with CFS.

Similarly to fatigue, depression is also associated with a decrease in self-initiated voluntary action (Kuppuswamy, 2017) which depends on the motivational (action initiation) and executive system (action execution). The motivational system further consists of the directional and activational subsystems which determine the direction (stimulus preference) and the vigor (response intensity) of the behavior (John D. Salamone, Yohn, López-Cruz, San Miguel, & Correa, 2016). According to Kuppuswamy (2017), fatigue and depression can be distinguished as a function of the dysfunctionality of these subsystems. In contrast to depressed individuals, fatigued ones are generally interested in an action but they are unable to initiate/perform it. Thus, in fatigued individuals, the dysfunctionality of the activational system is more likely than the dysfunctionality of the directional system.

I.2. Theories of mental fatigue

The theories attempting to understand the nature of MF can be separated in two broad categories: the early theories suggested that MF is related to an alteration in cognitive resources while later ones claimed that it is rather due to an inadequate recruitment of unaltered cognitive resources which may consist in a problem of compromised control due to motivational issues.

I.2.1. Resource-based views of mental fatigue

I.2.1.1. Ego-depletion

In our everyday life, self-control (cognitive control) plays an important role in the suppression of those impulses and dominant responses which may lead to an inappropriate behavior such as overeating or spending money beyond our means. According to Baumeister et al.'s strength model (1998), self-control strength relies on a limited/finite resource which can be quickly (approximately 10 min) exhausted by an excessive use of self-control. Thus, subsequent self-control becomes impossible, resulting in a performance decrement known as the ego-depletion effect or temporary self-regulatory fatigue (Baumeister et al., 1998; Inzlicht & Berkman, 2015). In dozens of studies, this phenomenon has experimentally been tested by using the transfer or sequential paradigm (Hagger, Wood, Stiff, & Chatzisarantis, 2010), which consists of two consecutive tasks, the depleting and the dependent one, both requiring self-control. Based on the strength model of self-control, performance of the experimental group should be impaired on the dependent task compared to a control group, for whom the depleting task does not demand self-control.

Importantly, one must be very cautious about the resource account of ego-depletion and thus MF. First, a major issue of the strength model which really undermines its credibility is that the depletion of the presumable physiological resource, namely glucose (Gailliot & Baumeister, 2007), is doubtful (Kurzban, 2010; Molden et al., 2012). Second, the model does not adequately take into

account psychological factors such as motivation (Muraven & Slessareva, 2003; Vohs, Baumeister, & Schmeichel, 2012). And finally, the actual existence of the ego-depletion effect is strongly controversial due to its extremely low estimated effect size and the publication bias within this research field (Blázquez, Botella, & Suero, 2017; Hagger et al., 2016).

Initial research on blood glucose showed that higher cognitive demands decrease its amount (Fairclough & Houston, 2004; Scholey, Harper, & Kennedy, 2001), which in turn can be restored by sugar consumption (Scholey, Harper and Kennedy, 2001). Gailliot et al. (2007) found that excessive self-control resulting in the ego-depletion phenomenon is also accompanied by a concomitant decrease in the level of blood glucose which can also be overcome by glucose intake. However, these findings were challenged by Kurzban (2010) who argued that self-control should affect the amount of blood glucose not only relative to a control task but also to the baseline glucose level which was ignored in the ego-depletion literature; and by Molden et al. (2012) who found that only swishing and not ingesting glucose improved self-control while the level of blood glucose remained unchanged.

Furthermore, the observation that motivational factors also affect fatigue is another piece of evidence against the central tenet of the strength model that self-control relies on blood glucose. If it was true, the exhaustion of this resource by self-control should not be restored by simple changes in motivation. According to Muraven and Slessareva (2003), the ego-depletion effect can be eliminated by incentives. They found that depleted participants who believed that their efforts in a

subsequent task including self-control would help others or bring them benefits performed better than the ones who were also depleted but lacking incentives for additional activity. Vosh, Baumeister and Schmeichel (2012) revealed similar findings, by manipulating the participants' belief about their unlimited willpower and the importance of the upcoming self-control task to be performed, but the participants impaired self-control was only vanished when it was mild.

The major tenet of the strength model, according to which self-regulation relies on limited energy, originated from the physical fatigue view that a muscle can become exhausted following a period of exertion (Baumeister et al., 1994; Muraven, Baumeister, & Tice, 1999). This motivated Evans, Boggero, & Segerstrom (2016) to use the central governor theory of physical fatigue (Noakes, 1997) as a framework to understand better the ego-depletion phenomenon or self-regulatory fatigue. According to the central governor theory, there has to be a governor (a central nervous system mechanism) which evaluates both the available physiological resources and psychological factors and thus can limit further exertion of effort in order to maintain homeostasis and avoid physical breakdown. Despite the fact that this theory accounts for both the physiological substrates and psychological factors, and the ultimate role of physical fatigue is known (a signal to avoid physical breakdown), this theory has been questioned because of its incapacity to account for the influence of motivation on fatigue (Inzlicht & Marcora, 2016).

1.2.1.2. Mental fatigue viewed within the theoretical framework of attention(al effort) and information processing

The theories of resource allocation (e.g. Ackerman & Kanfer, 2009; Kahneman, 1973; Kanfer & Ackerman, 1989; Ackerman, 2011) have aimed at understanding how the attentional effort-task performance relation changes as a function of task demands which can be used to interpret fatigue-related performance decrements on the one hand and subjective MF on the other hand.

1.2.1.2.1. Kahneman's resource allocation theory

Some tried to understand MF within the theoretical framework of attention and information processing. According to Kahneman's (1973) resource allocation theory, attention(al effort) is based on a pool of limited available resources which is associated with task performance. The availability of these resources depends on the individual's arousal level (see Figure I.3.; e.g. the higher the individual's arousal level is, the larger the amount of the available attentional resources is). As a function of task demands and various sources of arousal (e.g. stimulus intensity, anxiety etc.), this capacity (attentional/mental effort) can be distributed amongst different mental activities (e.g. when someone is writing a doctoral thesis, the attentional resources can be devoted to writing and to other off-task activities such as mind-wandering/worrying about the forthcoming deadline for submitting the thesis) by an allocation policy (see Figure I.3.) which is governed by enduring dispositions (e.g. automatic orientation to a novel stimulus), momentary intentions (task goal) and by feedback from ongoing activities (Audiffren, Tomporowski, & Zagrodnik, 2009). A feedback loop assesses whether someone's task goals are

being met and whether there is a need to manipulate the intensity of arousal (e.g. increase or decrease) or to change the allocation policy of the activities to which attention is devoted. In this model, MF could be viewed as a depletion of the available resources and manifested as a performance decrement (Kahneman, 1973; Ackerman, 2011).

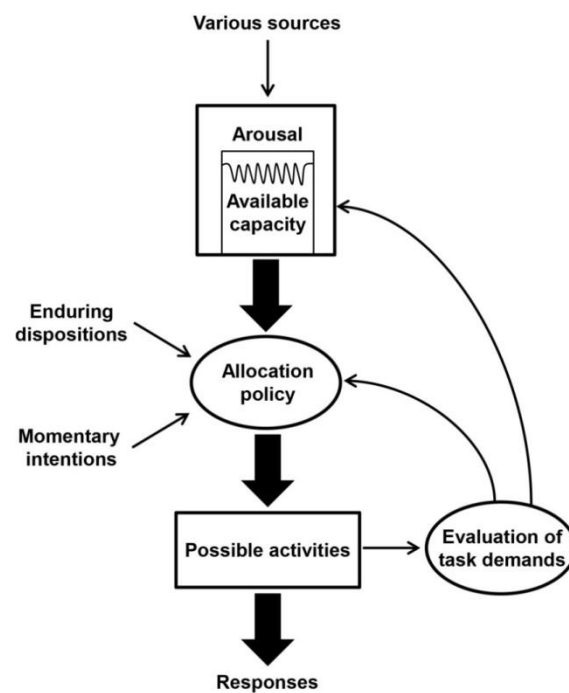


Figure 1.3. Kahneman's model of resource allocation
The main components of the given model such as the pool of limited available resources, allocation policy and the evaluation of task demands, and their relations are depicted in this figure. Modified from (Ackerman, 2011).

I.2.1.2.2. Kanfer and Ackerman's integrated resource allocation theory

This theory is built upon Kahneman's resource allocation theory (see above), but importantly, it also accounts for the individual differences in cognitive ability and motivation which contribute to the amount and allocation of attentional resources, respectively, affecting task performance over time.

According to Kanfer and Ackerman (1989), the individual differences in general cognitive (intellectual) ability index the amount of attentional resources which have to be devoted to a given task (see Figure I.4.) while the individual differences in motivation play a role in allocating these attentional resources to different activities during task engagement in two ways, namely, distally and proximally (see Figure I.4.). By the interaction of different subjective functions [i.e. perceived effort-performance, performance-utility and effort-utility, (Kanfer, 1987)], the distal motivational processes influence how the proportion of an individual's total attentional resources devoted to goal attainment is determined [see Figure I.4.; Kanfer and Ackerman, 1996]]. The proximal motivational processes influence the sub-allocations of the initially (distally) allocated attentional resources (Kanfer, 1996) between such activities as off-task thoughts, task effort and self-regulation (see Figure I.4.; Kanfer and Ackerman, 1989). Amongst these activities, self-regulation is the most crucial since it affects both the distal and proximal motivational processes by determining the allocations to on-task activity [see Figure I.4.; (Kanfer and Ackerman, 1996)]. In order to attain the task goal when it is more difficult than expected, the goal commitment can be increased or the mind-wandering can be decreased by self-regulation which either increases resource

allocation to task effort or decreases it to off-task activity (Kanfer and Ackerman, 1996). The features of this model are also relevant in the interpretation of the effects of MF on one's behavior. For example, as mentioned earlier, self-regulation to achieve a task goal is resource consumptive (Kanfer and Ackerman, 1996) which depletes the available resources and thus likely giving rise to fatigue-related performance decrements.

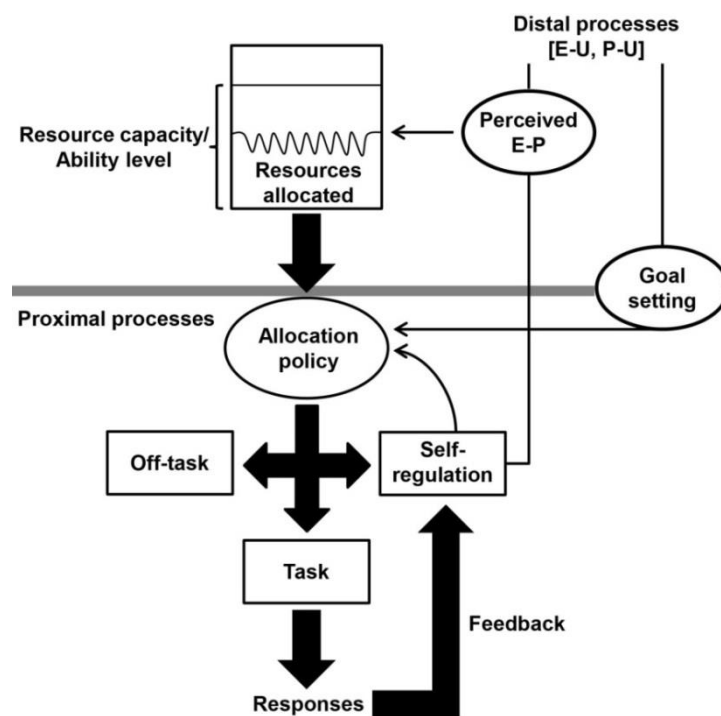


Figure I.4.. Kanfer and Ackerman's model of integrated resource allocation
The contribution of cognitive ability and motivational processes (distal and proximal) to the amount and allocation of attentional resources, respectively.
Modified from (Ackerman, 2011). E= effort; P = performance; U = utility.

I.2.1.2.3. Ackerman and Kanfer's model of fatigue-related performance decrements and subjective fatigue

In contrast to the previous models (Kahneman, 1973; Kanfer and Ackerman, 1989), Ackerman and Kanfer (2009; 2011) give an explanation not only for fatigue-related performance decrements but also for subjective fatigue in their model. Furthermore, this model accounts not only for the changes in resource availability and allocation as a function of one's arousal level (Kahneman, 1973), cognitive ability, motivation (Kanfer and Ackerman, 1989) and perceived functions [i.e. perceived effort-utility and performance-utility, Kanfer (1987)] but also for the following findings and notions:

- Davis (1946) demonstrated that one's performance can be impaired, maintained or improved over TOT.
- The subjective feeling of fatigue accumulated over TOT can be restored with rest and sleep (Grandjean, 1968).
- Similar to Schmidtke (1976), Ackerman and Kanfer (2009; 2011) also differentiated willing to spend capacity (the amount of attentional effort that an individual would be willing to exert on a task in order to attain a task goal) from reserve/emergency capacity (a reserve granted for situations when task demands exceed an individual's intended level of effort to exert on the given task) (Earle, Hockey, Earle, & Clough, 2015).

- Ackerman and Kanfer's model (2009; 2011) also features Hockey's (2011) effort monitor, which plays a role in effort management (see Section I.2.2.1) as a function of the task goal.

In Ackerman and Kanfer's model (2009; 2011), fatigue-related performance changes are described in the context of an "electrical circuit" where the main and reserve effort available to the individual are represented by batteries, respectively (see Figure I.5.). The main effort available can decrease over TOT (see Figure I.5.). Furthermore, off-task thoughts also lure attentional resources away from task performance (see Figure I.5.). The battery of main effort available can become discharged with increasing TOT. In this case, an individual can allocate additional resources from the battery including reserve effort. Thus, when the attentional resources are allocated to the task by reserve effort (see Figure I.5.) task performance can be improved, maintained or impaired as a function of the level of main and reserve effort available and the amount of effort allocated only to the task (see Figure I.5.). If both batteries are exhausted fatigue-related performance decrements certainly occur. This can be overcome by rest and sleep which re-charge the batteries (see Figure I.5.). One's subjective feeling of fatigue may also change as a function of available effort stored in the main and reserve batteries (see Figure I.5.). The level of subjective fatigue may increase if the initial amount of available effort is low (e.g. due to sleep deprivation or off-task thoughts). An increase in the subjective feeling of fatigue may affect both motivation (which plays a major role in effort-allocation) and off-task thoughts (see Figure I.5.), but

importantly, these mechanisms are not one-directional since the feeling of fatigue can be overcome by motivation (see Figure I.5.).

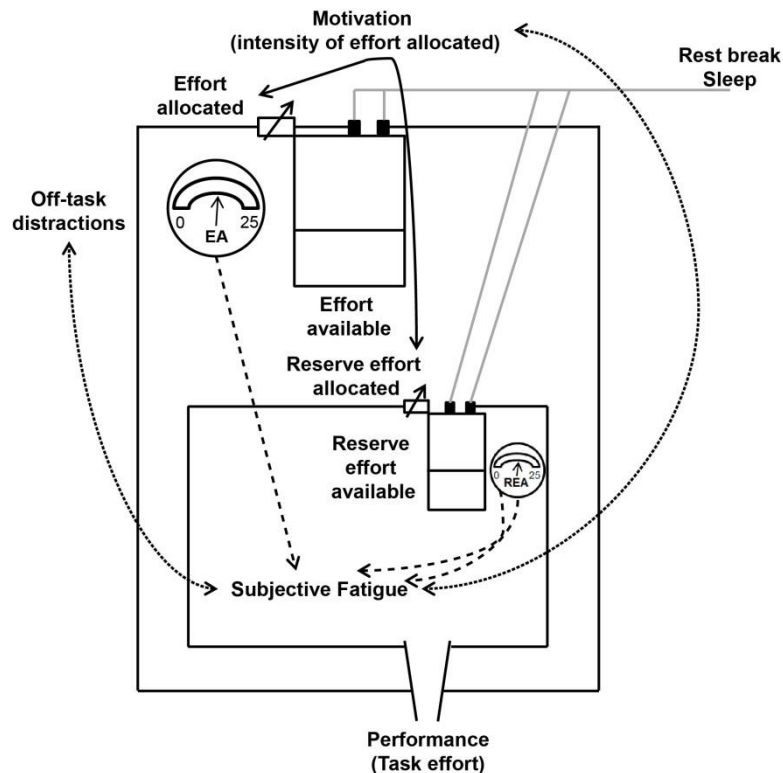


Figure I.5. Ackerman and Kanfer's model of subjective fatigue and fatigue-related performance decrements

This figure depicts the main and reserve effort available as “batteries” which are rechargeable by rest and sleep. As a function of one’s motivation, the available effort is allocated to task performance but it can also be drawn away by off-task distractors. The evolution of fatigue (subjective and objective, behavioral) depends on how much the batteries are discharged. Modified from (Ackerman, 2011). EA = effort available; REA = reserve effort

available.

I.2.2. Theories assuming impaired control in the presence of unaltered cognitive resources caused by a motivational issue

As shown in the previous section, there is no strong evidence that an alteration in cognitive resources is responsible for the build-up of MF (feeling and/or performance impairment). Another line of theories suggests that MF results from adaptive mechanisms which affect the recruitment of otherwise unaltered resources through motivational processes.

I.2.2.1. Hockey's motivational control theory

Hockey was amongst the first to posit that MF may result from a control problem rather than from loss of resources (Hockey, 1993; 1997; 2011; 2013). His model shares similarities with Kahneman's resource allocation theory (1973). However, here the allocation of effort depends on performance evaluation and can result not only in an increase of the effort budget (when performance is lower than expected), as in Kahneman's model (1973), but also in its decrease (when performance is larger than expected). Furthermore, an additional important feature of Hockey's model is that it accounts for the subjective feeling of fatigue. This subjective feeling of fatigue, which consists in a conflict between current and competing task goals, actually appears as an interruption mechanism in order to maintain motivational balance. When the current task goals are found less valuable and/or too demanding over time, they become re-assessed as a function of the competing goals.

The “general” compensatory control model, which was originally developed to better understand the maintenance of performance under stress (Hockey, 1993; 1997), suggests the existence of a performance protection strategy. This model assumes that a central goal stimulates individuals’ task performance which is stabilized by overcoming the discrepancy between the goal state and performance feedback either through a lower- or upper control (feedback) loop. The lower loop is engaged in the regulation of routine activities for automatic performance while the higher one is responsible for effort-management in situations when performance-protection is seriously threatened. This effort-management, which is thought to be an executive function, allows the individual either to increase effort expenditure (active coping) thus maintaining performance or to downgrade goal pursuit and to keep (or reduce) current effort expenditure (passive coping) thus letting performance to drop. These strategies are capable of reducing the discrepancy between goal state and performance feedback but at different costs. The first strategy referring to increased effort investment for performance maintenance incurs higher costs such as the feeling of fatigue. However, if the discrepancy between the goal state and performance feedback is too large withdrawal from the task is promoted.

The “general” compensatory control model was followed by the preliminary version of the compensatory control model of fatigue which accounts for fatigue more explicitly (Hockey, 2011). It is also a two-level control system but functions of goal maintenance and effort management are differentiated. And furthermore, an effort monitor is also proposed which mediates the need for effort management as

a function of the goal state. When goal maintenance becomes difficult the management of effort strongly increases thus fatigue may concomitantly increase.

In a further version of the compensatory control model of fatigue (see Figure 1.6., Hockey, 2013), a 3rd executive function, namely performance evaluation (see Figure 1.6.), has been proposed besides goal- and effort regulation. As previously shown, the maintenance of performance is costly. However, if a task goal is found to be important individually or it is expected to bring more benefits than costs, this goal is selected amongst competing ones and maintained through a goal regulation mechanism (see Figure 1.6.). When action monitoring (see Figure 1.6.) in the negative feedback loop identifies that the maintenance of the goal is not seriously threatened by competing goals, the task is performed through the lower control loop. However, in addition to the competing goals (see Figure 1.6.), cognitive (e.g. personal goals), somatic (e.g. emotional goals referring to needs such as eating, drinking), and environmental events (e.g. noise, temperature which may interact with somatic goals) may also threaten the selected task (see Figure 1.6.). If the performance evaluation system detects these events as a major threat to goal maintenance it activates the effort regulation system for an increase in the effort budgeted for goal pursuit through the upper control loop (see Figure 1.6.). As already mentioned above, performance protection may be too costly thus the individual may reduce the goal pursuit or even replace it by a competing goal. In sum, this model argues that the subjective feeling of fatigue may be associated with the operation of the effort regulation system in terms of its intensity.

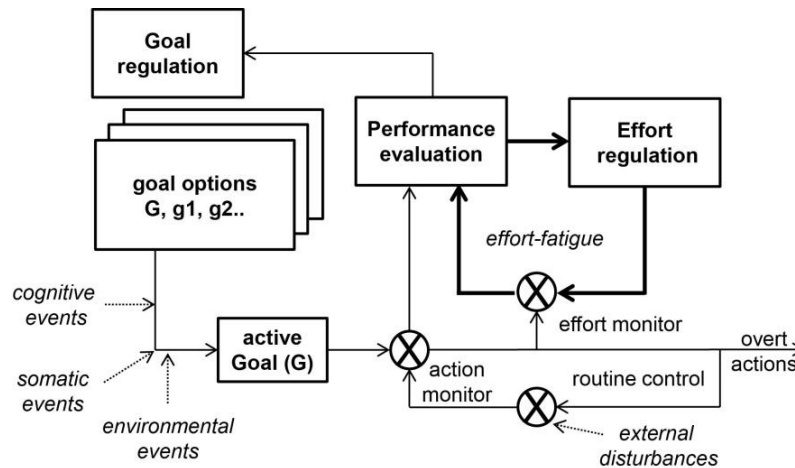


Figure I.6. Motivational control theory

This figure depicts the main components of Hocke's motivational control model which are the goal regulation, performance evaluation and effort regulation system. The effort regulation system is activated when goal maintenance is under threat and an increase in the effort budget is needed in order to achieve the selected goal. Presumably, the subjective feeling of fatigue is associated with effort regulation. Modified from (Hockey, 2013).

A plausible neural implementation of the compensatory control model involves the prefrontal cortex (PFC), the anterior cingulate cortex (ACC) and the basal ganglia, which are known to be involved in executive functions such as the regulation of a goal (selection, maintenance, change) and effort, and/or may be responsible for fatigue (Miller & Cohen, 2001; Chaudhuri & Behan; 2000; 2004; Hockey, 2013). This approach seems to be valid since Wang et al. (2016) have recently found that the drop in brain activity and performance was preceded by a strong association between the activity in the anterior frontal region and maintained

task performance, which indicates the existence of compensatory processes in response to MF.

1.2.2.2. Chaudhuri and Behan's model of central fatigue

Chaudhuri and Behan (2000) also looked at the relation between MF, more specifically central fatigue (see Section 1.1.1.2.), and motivation, and consistently with Hockey (1993; 1997), they also regarded MF as a result of an effort control problem due to a motivational issue. According to them, self-initiated work output (see Figure 1.7.) is determined as a function of exerted effort which is controlled by motivational input (internal, external) and by a feedback of perceived effort from sensory, motor and cognitive systems. Furthermore, it can also be regulated by factors of the internal (e.g. homeostatic) and external (e.g. temperature) environment. Any change in the variables regulating work output can lead to central fatigue which might be related to a basal ganglia dysfunction.

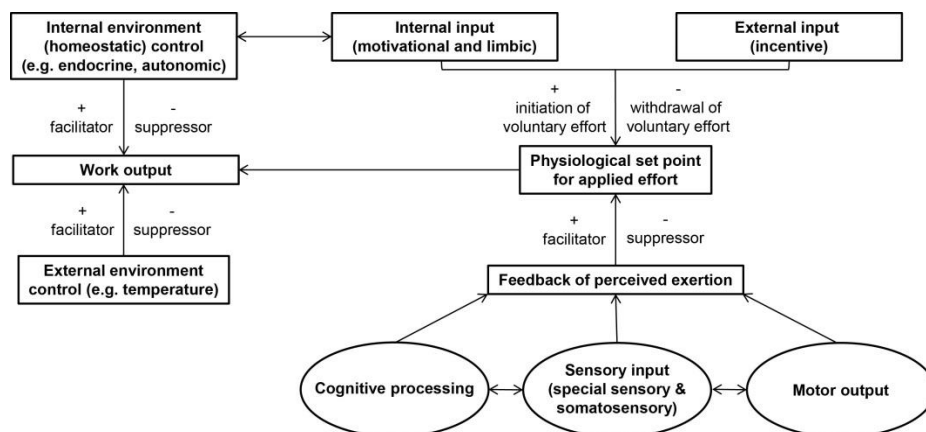


Figure 1.7. Variables influencing self-initiated work output. Modified from

(Chaudhuri and Behan, 2004).

The reward system

The basal ganglia, consisting a group of subcortical nuclei as the striatum (dorsal striatum: caudate and putamen; ventral striatum: nucleus accumbens), the globus pallidus (internal and external), the substantia nigra (pars compacta and pars reticulata) and the subthalamic nucleus, has originally been known to be involved in motor control. However, it has also been found to play an important role in non-motor functions such as motivated behavior and reward processing (Pessiglione et al., 2007; Schmidt et al., 2008a; Schmidt, Lebreton, Cléry-Melin, Daunizeau, & Pessiglione, 2012; Schultz & Dickinson, 2000; Vassena et al., 2014). The multiple functions of the basal ganglia can be interpreted by its major connections with the prefrontal cortex (PFC) and the thalamus. The dorsal and ventral striatum receive projections from the dorsolateral PFC and the ventromedial PFC, respectively. The former area has been thought to be implicated in action planning and information integration (Bonelli & Cummings, 2007) while the latter structure is involved in processing of affective information and subjective value (O'Doherty, 2011). Furthermore, the striatum also receives projections from the ACC (Dobryakova et al., 2013) which has a putative role in error monitoring, effort computation and reward-based decision making (Boehler et al., 2011; Boksem et al., 2006; Holroyd & Coles, 2002; Moeller, Tomasi, Honorio, Volkow, & Goldstein, 2012; M.E. Walton, Kennerley, Bannerman, Phillips, & Rushworth, 2006). Another important input to the striatum (dorsal) is the dopaminergic one from the substantia nigra pars compacta (nigrostriatal pathway).

The ventral striatum also receives dopamine from the ventral tegmental area (mesolimbic pathway) which also has major projections to the PFC (mesocortical pathway). Through the pallidum (globus pallidus), the striatum has inputs to the thalamus which has been regarded as a final pathway of the basal ganglia projections to the cortex (Chaudhuri and Behan, 2000). According to Chaudhuri and Behan (2000, 2004), any malfunction in the basal ganglia such as dopamine imbalance in the striato-thalamo-cortical loop can lead to MF.

The brain reward system, including the basal ganglia, but also other regions such as insular cortex and amygdala, is involved in the processing of reward in terms of emotional response (liking: find something pleasant = hedonic impact), motivational incentivisation (wanting: motivated to obtain the formerly pleasant reward again = incentive salience) and reinforcement learning (Berridge, Robinson, & Aldridge, 2009; Kringelbach & Berridge, 2016). The incentivisation of behavior through reward is referred to as extrinsic motivation (even though it may also include motivation through the avoidance of punishment), while intrinsic motivation refers to doing an inherently interesting and enjoyable activity which satisfies one's innate psychological needs for self-determination (amount of perceived autonomy) and for the feeling of competence (e.g. achieving success by doing a task, Deci and Ryan, 1985; Ryan & Deci, 2000).

1.2.2.3. Boksem and Tops's cost-benefit view of mental fatigue

Along the same line as Hockey (1993; 1997) and Chaudhuri and Behan (2000; 2004), Boksem and Tops (2008) have also promoted the notion that MF

consists in a control mechanism which drives the individuals away from costly activities towards more rewarding ones. More specifically, they have viewed MF as an effort-reward imbalance. When the effort invested in task performance is proportionally larger than its associated reward, the motivation to further engage in the task decreases and MF appears, which may result from the cost-benefit analysis of continued task performance and may lead to disengagement from the task (Tops et al., 2004; Boksem and Tops, 2008). Furthermore, in accordance with Chaudhuri and Behan (2000; 2004), Boksem and Tops (2008) have also attributed an important role to the basal ganglia and the dopamine neurotransmitters (Salamone, Aberman, Sokolowski, & Cousins, 1999; Walton, Bannerman, Alterescu, & Rushworth, 2003; Walton, Bannerman, & Rushworth, 2002) in the plausible neural implementation of MF. However, in their neural framework for MF viewed as an effort-reward imbalance (see Figure I.8.), they have also focused on other structures from the brain reward system (e.g. ACC, OFC), known to be involved in the cost-benefit evaluation of actions (Boksem and Tops, 2008). Regions which are primarily implicated in reward and punishment processing are the OFC, BLA and the insula (see Figure I.8). The integration of multiple reward sources, which motivates behavior, takes place in the ACC (see Figure I.8). Then, the transformation of this reward input into behavioral output is mediated by the corticostriatal projection from the ACC to the Nucleus Accumbens (see Figure I.8). Since the outcome driven by behavior is continuously evaluated, the information whether they are better or worse than expected is conveyed to the ACC and PFC (see Figure I.8) in order to strengthen neural connections underlying successful behavior (better than expected) or wipe out unsuccessful behavior

(worse than expected). Boksem and Tops have suggested that the ACC integrates not only reward information but also the cost of energy expenditure signaled by the insula (see Figure I.8) which enables optimal decision-making based on cost-benefit computations. If the cost-benefit balance of the expected future state is better than the current one then the behavior is energized which is mediated by the projections from the ACC to the amygdala and Nucleus Accumbens (see Figure I.8). Furthermore, they also propose that the cholinergic projection from the basal forebrain to the PFC (see Figure I.8), which plays a role in attention and top-down control (Sarter, Givens, & Bruno, 2001), may be attenuated by changes in dopaminergic levels in Nucleus Accumbens and manifested in reduced attention and impaired cognitive control which often characterize MF.

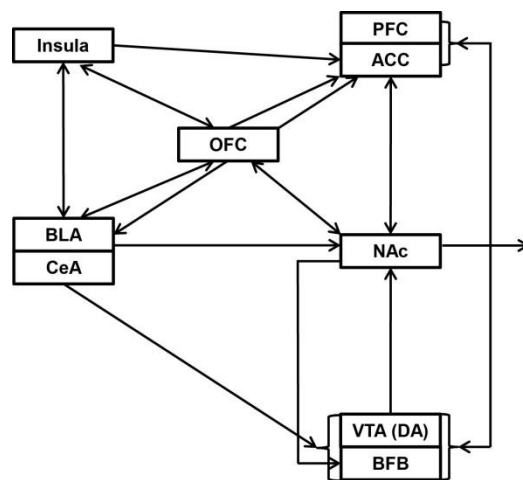


Figure I.8. Neural implementation of Boksem and Tops's cost-benefit view of MF

This figure depicts the interactions of neural structures that are involved in effort-reward computations which presumably play a role in the build-up of

MF. Modified from (Boksem & Tops, 2008). ACC = Anterior Cingulate Cortex; BLA = Basolateral Amygdala; CeA = Central Nucleus of the Amygdala; OFC = Orbitofrontal cortex; PFC = Prefrontal Cortex; NAc = Nucleus Accumbens; VTA = Ventral Tegmental Area; BFB = Basal Forebrain; DA = Dopamine; ACh = Acetylcholine

1.2.2.4. Kurzban et al.'s opportunity cost model

Kurzban et al. (2013) have also stated that MF rather arises from a problem of the management of control than from a progressive loss of resources (Baumeister et al., 1998), and have interpreted the experience of an unpleasant feeling (e.g. mental effort, mental fatigue) as a state which indicates a conflict between the current activity and the competing ones. This conflict represents the adaptive problem of simultaneity on which Kurzban et al.'s (2013) opportunity cost model is based. From an evolutionary perspective, the problem of simultaneity means that not everything can be done at once. A concomitant, general solution to overcome this issue is prioritization which consists in choosing only one option at the cost of the alternative ones. From a computational perspective, during prioritization, the costs and benefits of the current and alternative options are computed and compared in order to make a decision about either maintaining current activity or continuing with the next best one. When the mental processes are further allocated to the current activity, opportunity cost appears which corresponds to the value of the next best alternative compared to the present choice (see Fig I.9.), and can be determined by the factors shown in Figure I.10.

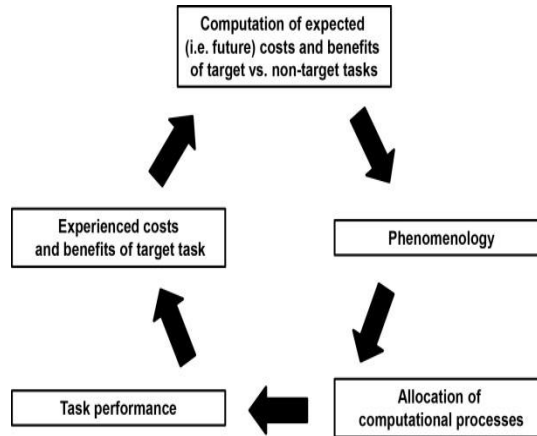


Figure I.9. Opportunity cost model

Once the expected costs and benefits of the target and non-target tasks are computed, one gets the feeling where the computational processes should be allocated in order to optimize the costs and benefits. This allocation determines performance on both the target and non-target task. Then, the same sequence is restarted by the experience of the costs and benefits of the target task. Modified from (Kurzban et al., 2013).

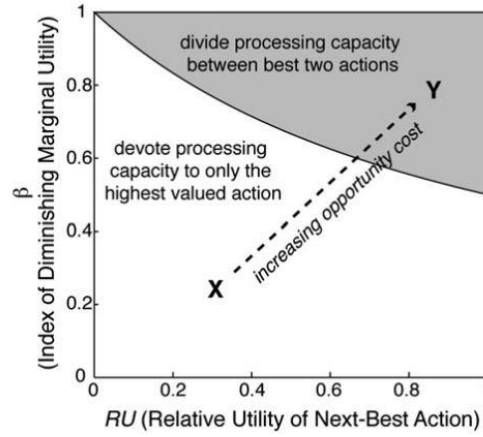


Figure I.10. Factors determining opportunity cost

As previously described, the activity with the highest expected utility is always prioritized. However, when the relative utility (RU) of the next best activity $[(a_2); (RU(a_2) = \frac{U(a_2, a_2)}{U(a_1, a_1)})]$ and the index of diminishing marginal utility (β) to devoting computational resources only to the current best activity (a_1) relative to two activities are high (a_1 and a_2), the utility (U) of performing two activities (a_1 and a_2) is bigger than performing only one activity (a_1) as expressed and illustrated:

$$U(a_1, a_2) > U(a_1, a_1) \text{ when } \beta + \beta * RU(a_2) > 1$$

In this model, learning of the utilities and opportunity costs plays an important role in the dynamics of mental effort and performance, because the utility of the next-best activity may change over time or one cannot know its value with any certainty. Thus, importantly, the mental resources in Kurzban et al.'s (2013) opportunity cost model are considered as finite, divisible and constant over time.

In summary, according to Kurzban et al. (2013), the subjective experience of MF can be interpreted as a state proportionally related to the amount of opportunity cost which may drive the individual towards newer, potentially more rewarding activities.

I.3. Empirical studies addressing the link between mental fatigue and motivation

To date, despite the importance of the question whether MF is caused by a progressive loss of cognitive resources or by an inadequate recruitment of preserved cognitive resources due to a progressive loss of motivation, only few studies have investigated the relation between MF and motivation (Boksem et al., 2006; Lorist et al., 2009; Hopstaken et al., 2014; 2015; 2016) by using a combination of psychometric, behavioral and psychophysiological (e.g. EEG/ERP, pupillometry, structural and functional MRI) measures in healthy individuals.

Amongst the first ones, Boksem et al. (2006) and Lorist et al. (2009) empirically addressed the link between MF and motivation based on the cost-benefit imbalance view of MF (Tops, 2004; Boksem & Tops, 2008; see above). They found following MF-inducement that the manipulation of extrinsic motivation, including social comparison and monetary reward, failed to recover the participants' pre-fatigue level of performance, implying that MF might not depend only on an effort-reward imbalance.

Hopstaken and his colleagues (2014, 2015, 2016) have also favored the cost-benefit account of MF (Tops, 2004; Boksem and Tops, 2008), more

specifically the one based on opportunity cost (Kurzban et al., 2013; see above), which is characterized by task disengagement. They found that after MF-inducement the manipulation of extrinsic motivation recovered the participants' pre-fatigue level of performance indicating their reengagement in the task. However, due to a major limitation in all of these studies, namely the lack of evaluation of manipulation of extrinsic motivation before MF-inducement (motivation manipulation at baseline), it is impossible to interpret these findings. This methodological issue was also presented in previous studies based on the same principle (Boksem et al., 2006; Lorist et al., 2009). Furthermore, Hopstaken et al. (2014, 2015, 2016) also misinterpreted the change in the participants' baseline pupil diameter in response to task engagement/disengagement. They showed that the participants' baseline pupil diameter decreased with TOT which, in contrast to the behavioral results (impaired performance), actually represents increasing task engagement over time (Gilzenrat et al., 2010) arguing against a task disengagement account of MF.

Taken all together, the starting point of our first study, described in the following chapter (see Chapter II.1.), was to overcome the methodological problems presented in previous studies by evaluating the effect of extrinsic motivation manipulation at different time points and not only after MF-inducement in order to clarify whether the build-up of MF can be indeed explained in relation to motivational alterations. Furthermore, in our study, we also attempted to prevent boredom by using different tasks for MF-inducement and -evaluation (indirect

method) in contrast to the previous studies shown above which consisted of only one task (direct method).

II. ARTICLES

II.1. Dissociation between mental fatigue and motivational state during prolonged mental activity¹

¹ Gergelyfi M, Jacob B, Olivier E and Zénon A (2015) Dissociation between mental fatigue and motivational state during prolonged mental activity. *Front. Behav. Neurosci.* 9:176. doi: 10.3389/fnbeh.2015.00176

II.1.1. Abstract

Mental fatigue (MF) is commonly observed following prolonged cognitive activity and can have major repercussions on the daily life of patients as well as healthy individuals. Despite its important impact, the cognitive processes involved in MF remain largely unknown. An influential hypothesis states that MF does not arise from a disruption of overused neural processes but, rather, is caused by a progressive decrease in motivation-related task engagement.

Here, to test this hypothesis, we measured various neural, autonomic, psychometric and behavioral signatures of MF and motivation (EEG, ECG, pupil size, eye blinks, skin conductance responses, questionnaires and performance in a working memory task) in healthy volunteers, while MF was induced by Sudoku tasks performed for 120 minutes. Moreover extrinsic motivation was manipulated by using different levels of monetary reward.

We found that, during the course of the experiment, the participants' subjective feeling of fatigue increased and their performance worsened while their blink rate and heart rate variability increased. Conversely, reward-induced EEG, pupillometric and skin conductance signal changes, regarded as indicators of task engagement, remained constant during the experiment, and failed to correlate with the indices of MF. In addition, MF did not affect a simple reaction time task, despite the strong influence of extrinsic motivation on this task. Finally, alterations of the motivational state through monetary incentives failed to compensate the effects of MF. These findings indicate that MF in healthy subjects is not caused by an

alteration of task engagement but is likely to be the consequence of a decrease in the efficiency, or availability, of cognitive resources.

II.1.2. Introduction

Mental fatigue (MF) is a recurring problem in the daily life of many people and remains a challenging symptom for clinicians (Walker et al., 1993; Pawlikowska et al., 1994). In healthy subjects it can be the consequence of prolonged and intense cognitive activity (van der Linden et al., 2003), while in patients, it can become a permanent condition (Millikin et al., 2003). MF consists primarily in the subjective feeling of a deteriorated ability to engage in mental activities, but it can also be objectively measurable in terms of performance decrements (Schwid et al., 2003; Lorist et al., 2009). MF is distinct, albeit closely related to the concept of vigilance (Thiffault & Bergeron, 2003), which refers more specifically to the capacity to sustain attention over time. Vigilance is typically assessed by measuring the speed and variability of responses during simple detection tasks, such as the psychomotor vigilance task (PVT), and/or by evaluating electrophysiological changes in the EEG theta band (Paus et al., 1997). Vigilance typically decreases following sleep deprivation (Dorrian et al., 2005) while, in the absence of sleep deprivation, drops in vigilance have been attributed to “boredom”, i.e. the incapacity to maintain sustained attention during simple unstimulating tasks (Frankmann & Adams, 1962; Mackworth, 1968), even though some studies have questioned this view (Smit et al., 2004; Smit, et al., 2004a; Gunzelmann et al., 2011).

The cognitive mechanisms at the origin of MF remain poorly understood. In particular, it is still unclear whether the decreased performance associated with MF is caused by a progressive deterioration of the cognitive resources (e.g.

attention, memory) or by an inadequate recruitment of unaltered cognitive processes, caused by a loss of motivation. To date, despite the importance of this question (Hockey, 2011; Chaudhuri and Behan, 2000; Kurzban et al., 2013; Botvinick & Braver, 2014) only few studies have looked at the relation between MF and motivation. Chaudhuri and Behan (2000) have proposed that MF could, at least partly, result from a loss of motivation to engage in self-initiated tasks and that pathological fatigue would be the consequence of an alteration of the motivational brain circuits, including the basal ganglia. Tops et al. (2004) suggested that MF could be viewed as an effort/reward imbalance: when the effort is proportionally larger than the associated reward, the motivation to engage in the task decreases and MF appears. Along the same lines, Hockey (2011) and others (Kurzban et al., 2013; Botvinick & Braver, 2014) have argued that fatigue consists in a control mechanism that drives individuals away from prolonged tasks and towards newer, potentially more rewarding activities.

However, previous studies have found that monetary incentives provided after fatigue inducement failed to recover the pre-fatigue level of performance, suggesting that MF might not depend only on a cost/benefit imbalance (Boksem et al., 2006; Lorist et al., 2009). In a recent study representative of this approach, Hopstaken and colleagues measured various psychophysiological variables during a fatiguing task (Hopstaken et al., 2014). They found that following fatigue, increasing extrinsic motivation recovers pre-fatigue level of performance, and argued that this provides evidence in favor of a fatigue-induced task disengagement from the task. However, without assessing the effect of extrinsic

motivation on performance before fatigue inducement, it is impossible to interpret this finding, because performance is evaluated in two different motivational states: a low motivational state and a high motivational state before and after fatigue inducement, respectively. This confound also applies to previous studies based on the same principle (Boksem et al., 2006; Lorist et al., 2009). In addition, the pupillometric findings from Hopstaken and colleagues (2014), showing that pupil baseline diameter decreased with time-on-task, suggest, in contrast to the behavioral results, that task engagement increased over time (Gilzenrat et al., 2010), arguing against a task disengagement account for MF.

In addition to its subjective and behavioral effects, fatigue is also known to impact psychophysiological and neurophysiological variables. In a range of studies using cognitive tasks (e.g. the Stroop task or a simulated driving/flight task) over a prolonged period of time, EEG correlates of fatigue have been investigated. The most consistent changes observed with time-on-task have been an increase in the low frequency bands (delta: 0-4 Hz; theta: 4-8 Hz and alpha: 8-12 Hz) together with an decrease in the beta frequency bands (12-20 Hz) (Lal & Craig, 2002; Boksem et al., 2005; Borghini et al., 2012; Craig et al., 2012; Zhao et al., 2012; Barwick et al., 2012; Borghini et al., 2012; Wascher et al., 2014), and an increase in the P300 latency (Kaseda et al., 1998; Kato et al., 2009). Another technique used to track MF is the ECG: the heart rate decreases while the heart rate variability (HRV) increases with MF (Egelund, 1982; Mascord & Heath, 1992). Fairclough et al. (2005), for instance, found that the power of middle-frequency component of the HRV (0.1 Hz sinus arrhythmia) increased while the participants performed the

Multi-attribute Task Battery over a period of 64 minutes. In addition to its relation to MF, the heart rate and HRV also index task difficulty, such that higher heart rate and lower HRV are associated with larger effort mobilization (O'Hanlon, 1972; Mulder, 1986; Veltman & Gaillard, 1996; Schellekens et al., 2000). This opposite pattern of ECG correlates between MF and mental effort suggests that MF could indeed be associated to lower effort investment, in accordance with the motivational account of MF. Finally, in addition to these electrophysiological correlates, eye blink parameters are also known to vary with time-on-task (Stern et al., 1994; Van Orden et al., 2001). The average blink duration, and the proportion of long blinks, have been associated to subjective drowsiness (i.e. the propensity to fall asleep, Caffier et al., 2003), vigilance drops (McIntire et al., 2014) or performance drops during prolonged tasks following sleep deprivation (Morris & Miller, 1996). In contrast, blink frequency may be more related to MF *per se* (Martins and Carvalho, 2015).

In the present study, we aimed to investigate whether MF is caused by a progressive disengagement from the task. We evaluated MF throughout the execution of a Sudoku task by using subjective ratings, objective behavioral performance, neural and autonomic variables known to covary with MF: EEG, ECG and blink rate. We then evaluated intrinsic motivation and measured the effect of the manipulation of extrinsic motivation on behavior and on a series of physiological factors known to be sensitive to mental effort, and thus providing an indirect measure of task engagement: pupil diameter (Beatty, 1982), EEG (Venables & Fairclough, 2009) and skin conductance response (Kahneman, 1973;

Pessiglione et al., 2007). Importantly, we assessed the effect of extrinsic motivation at different time points during the experiment, allowing motivational effects on behavior to be compared before and after fatigue inducement. Finally, in order to evaluate task-unspecific fatigue effects and to get rid of the boredom confound caused by the repeated execution of the same task for prolonged periods of time (Hockey et al., 2013), we used different tasks to induce (Sudoku task) and measure (working memory task) fatigue.

The hypothesis that MF would be caused by a disengagement from the task led us to make the four following predictions: 1) task engagement should decrease over time, 2) this decrease should correlate with subjective and/or objective assessments of MF, 3) reward manipulation should at least partly alleviate the detrimental effect of MF and 4) MF should influence all tasks that are sensitive to motivational factors.

II.1.3. Materials and Methods

II.1.3.1. Participants

Eighteen healthy subjects (8 females) participated in this study (age=25.72±3.54, mean±sd). The participants were recruited in accordance with the following criteria: they had to be performing at least one Sudoku grid per month, to be aged between 20-35 years old, had to be right-handed, have normal or corrected-to-normal visual acuity, not to be under medical treatment and not to be a smoker. Subjects provided written informed consent prior to the experiment and receive financial compensation for their participation (~60-80 euros). All the

participants were naive regarding the aim of the study. The study was approved by the local ethics committee (Comité d' Ethique, hospital-facultaire de l'UCL).

II.1.3.2. Tasks

In order to keep the subjects intrinsically motivated during the experiment we used the indirect method to assess the behavioral effects of MF (Ackerman, 2011). The indirect method consists in using different tasks to induce and to evaluate fatigue. MF was induced by performing a computerized version of the popular Sudoku game. The behavioral effect of MF was measured by using a working memory (WM) task in which extrinsic motivation was manipulated by means of different levels of reward. The effect of this reward manipulation was controlled with a simple RT (SiRT) task.

Mental fatigue inducement: Sudoku puzzle

The objective of the Sudoku puzzle is to fill the cells of a 9 x 9 grid, further divided into 3 x 3 subgrids, with digits from 1 to 9, every digit occurring only once in a row, a column and a subgrid of the puzzle (see Figure II.1.1A). Subjects entered their response by clicking the left mouse button on a Sudoku cell; this made a numerical keypad to pop up, allowing them to pick a number to fill the cell. Feedback was given on each cell, thus the subjects could use a strategy consisting in picking randomly the numbers until the right one comes up. In order to prevent this strategy, we applied a scoring system with +8 points per correct response and -20 points per wrong response. At the beginning of each Sudoku task, the average

number of empty cells was 47 ± 11 , and thus, the maximum amount of points that the subjects could win for a single grid was around 375.

Sudoku grids were collected from a website², categorizing the grids into four difficulty levels: easy, medium, hard and absurd. In addition, within each of these categories, grids are assigned a given number of stars (from 1 to 6) specifying more precisely their difficulty level. This particular scoring method has been validated in a previous computational study, using Sudoku grids from the same website (Ercsey-Ravasz & Toroczkai, 2012).

We pretested the Sudoku grids having different difficulty levels in a pilot study performed on a group of healthy subjects ($n = 8$, age 20-35 years). This allowed us to confirm that higher difficulty levels led to higher median RT. It also showed that, given the variability in performance between the subjects, the difficulty level had to be adjusted on a subject-by-subject basis. Based on these findings, we established the following rule to choose the appropriate difficulty level for each subject participating in the main experiment. During a training session, the median of the RTs was computed for each grid performed. For median RT under 5 s or above 10 s, a more difficult or an easier Sudoku task was given to the subject, respectively. If the median RT was under 5 s but the number of errors was above 5 per grid, the difficulty level was maintained constant. It could occur that the easiest Sudoku task was too difficult for a subject; in this case some of the cells of the Sudoku grid were prefilled in order to make it easier. The procedure was stopped, and the level of each subject determined, whenever a grid was completed with a

² <http://www.sudokuoftheday.co.uk/>

median RT between 5 and 10 s, and less than 5 errors per grid. This procedure resulted in 13 subjects undergoing easy Sudoku grids (mean $\pm$ sd “stars” number: 2.7 $\pm$ 0.4) and 5 subjects performing Sudoku grids of medium difficulty (“stars” number: 2.8 $\pm$ 0.6).

During the experimental session, the Sudoku task was performed for 2 hours (4 blocks of 30 minutes), intermingled with 5 blocks of MF evaluation (see below for further details).

Mental fatigue measurement: Working Memory (WM) task

The cognitive effect of MF was measured by means of a WM task in which extrinsic motivation was manipulated by using three different levels of reward: 1, 10 and 50 points. In order to increase the difficulty of the task, two different conditions were randomly interleaved during each block of 14 trials. In a first condition called “8”, seven numerals ranging between 1 and 8 were presented in a random order (e.g. 2, 4, 7, 5, 1, 8, 6) and the task consisted of reporting the missing number (“target” number) in the series (3 in the above example, see Figure II.1.1B). In the “9” condition, eight numerals between 1 and 9 were presented, and the task was the same as above. The subjects did not receive any feedback about their performance.

At the beginning of each 14-trial block of the WM task, the participants were informed about the actual amount of reward (1, 10 or 50 points) that they could gain for each correct response in the upcoming block. In addition, for the 1 and 50 points conditions, a sentence displayed on the screen provided a

recommendation about the strategy the subjects should adopt to maximize their earnings (see Figure II.1.1D). Following the display of the reward condition, the participants were allowed to trigger the task whenever they wished by pressing a key on the keyboard. The “decision time” that was spent between the display and task onset was measured. At the end of 14 trials, the final score was shown on the screen for 2000 ms. Subjects were aware that these points were converted into actual money at the end of the experiment.

Control of extrinsic motivation: Simple Reaction Time (SiRT) task

To control the effect of the reward manipulation on extrinsic motivation, 6 blocks of SiRT task were also performed between each Sudoku block, randomly interleaved with the WM task. In this control task, participants had to press the left mouse button as fast as possible every time a red triangle appeared on the screen (see Figure II.1.1C). Given that the sum of response times was fixed during a block, the faster the participants responded, the more trials they could perform and the more points they could gain.

The Sudoku, WM and SiRT tasks were implemented in Matlab 7.5 (The MathWorks, Natick, Massachusetts, USA) and were displayed by means of the psychophysics toolbox (Brainard, 1997) and an in-house graphics toolbox (CosyGraphics).

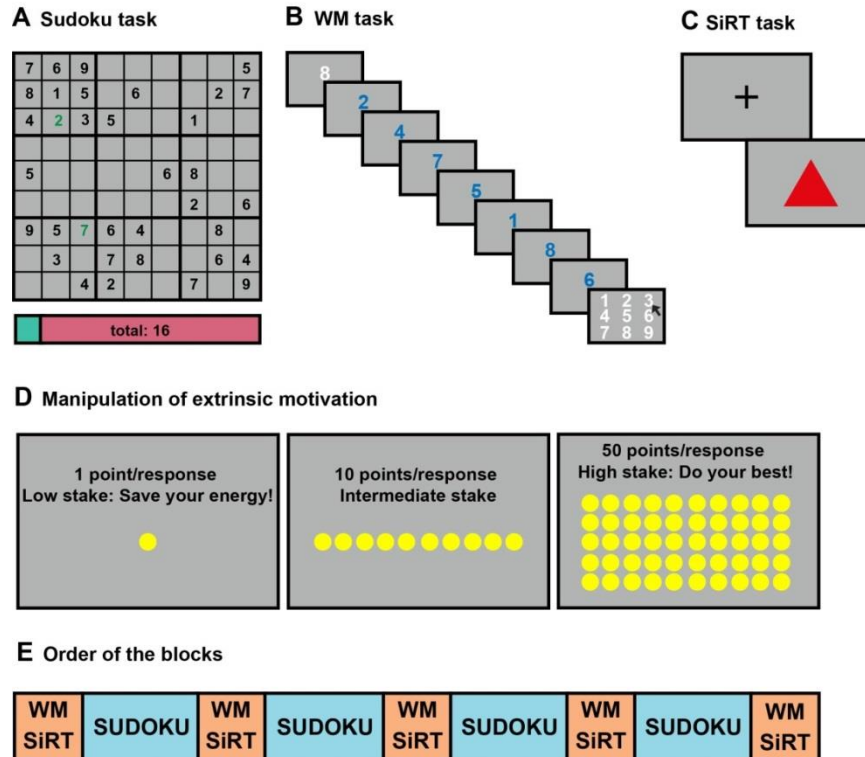


Figure II.1.1. Experimental tasks and design. **(A)**, An example of a Sudoku puzzle used to induce MF. Incorrect responses were highlighted by a red colored number and signaled by an auditory signal, which faded away after 1.5 s, while correct responses were displayed in green and triggered a sound sample corresponding to the Japanese word for that number. The points already earned were displayed on the score bar at the bottom of the screen, and were illustrated graphically by the proportion of the cyan color on that bar. Whenever a grid was fully completed, a brief music sample was played and a short fireworks animation was shown on the screen. **(B)**, In the MF evaluating WM task, the length of the number series (called

condition 8) was first presented in white for 1500 ms, followed by the numerals composing the series (2, 4, 7, 5, 1, 8, 6), in blue. Each numeral was displayed for 400 ms. The missing element (3) of the number series had to be selected with the computer mouse from a numeric keypad shown on the screen. **(C)**, In the control SiRT task, the subject had to press the left mouse button as fast as possible when a red triangle appeared on the screen. A fixation cross (+) was displayed between these stimulus presentations for a duration varying, according to a geometric distribution, from 500 to 3000 ms. The RTs of the subjects were summed up after each trial and the task ended when this sum reached a total of 6000 ms. **(D)**, The reward condition (1, 10 or 50 points) and recommended strategy was instructed at the beginning of each block. When the reward was 1 point per correct response, we proposed them to “save their energy”, and they were advised “to do their best” when the reward was 50 points. **(E)**, Order of the MF evaluation and inducement blocks. Each 30 minute-long MF inducement blocks (4 blocks in blue) consisted of Sudoku puzzles, while each 14 minute-long MF evaluation blocks (5 blocks in orange) included 6 sub-blocks of SiRT and 6 sub-blocks of WM tasks. These sub-blocks were randomly interleaved, and each block was repeated twice as a function of reward condition (1, 10, 50 points).

II.1.3.3. Physiological measurements

EEG signals were acquired by means of the ASA-lab recording system (ANT Inc., The Netherlands) using 32 Ag-AgCl electrodes placed on the scalp based on the international 10/20 system (Waveguard32 cap, Cephalon A/S, Denmark). Recordings were made in an electrically shielded room. Horizontal and

vertical eye movements (saccades) and blinks were also recorded using two additional surface electrodes placed close to the outer canthus of the right eye and on the upper-left side of the right eye. Two additional electrodes were attached to the left and right forearms in order to monitor the electrocardiographic (ECG) signal. Electrode impedances were kept below 25 k Ω . The signals were amplified and digitized using a sampling rate of 500 Hz.

An EyeLink 1000 eye-tracker (SR Research Ltd., Kanata, Ontario, Canada) monitored eye movements, blinks and pupil diameter at a sampling frequency of 500 Hz.

Skin conductance responses (SCRs) were recorded by means of a CED 2502 skin conductance unit (Cambridge Electronic Design, UK) and sampled at 100 Hz.

II.1.3.4. Subjective measures

Finally, a modified version of the Multidimensional Fatigue Inventory (MFI) (Gentile et al., 2003) and the Post-experimental Intrinsic Motivation Inventory (IMI)³, were used to evaluate the participants' fatigue and intrinsic motivational state at the beginning and at the end of the experiment. The MFI contains 20 items classified into 4 dimensions: general fatigue, MF, reduced activities and motivation. The statements have to be rated on a 5-point Likert scale (from "Yes, that is true" to "No, that is not true") representing the subject's current feeling. Low MFI scores reflect a higher degree of fatigue. From the 45 items included in the Post-

³ <http://www.selfdeterminationtheory.org/intrinsic-motivation-inventory/>

experimental IMI, we used only those included in the 3 subscales we deemed relevant to assess intrinsic motivation in our task, namely interest/enjoyment, perceived competence and effort/importance. In this questionnaire, participants have to rate each item on a 7-point Likert scale (from “Not at all true to “Very true”). The higher the score on a subscale, the more the given trait is represented.

Additionally, the State-Trait Anxiety Inventory (STAI) (C. Spielberger, 1983) and the Beck Depression Inventory (BDI) (Beck et al., 1961) were used to assess trait anxiety and depression. The STAI is a 40-item inventory divided into 2 subscales. We used only the second 20-item subscale in this study in order to evaluate the subject’s anxiety traits. A score between 1 and 4 (from “Almost never” to Almost Always”) has to be provided for each statement. Higher scores suggest more severe degree of anxiety. The 21-item BDI has different groups of statements. A score from 14 to 19 indicates a mildly depressed state while a score over 20 is indicative of clinical depression.

II.1.3.5. Design and experimental procedure

The participants (n=18) had to attend two sessions (training and experiment). The aim of the training session was to tune the difficulty level of the Sudoku task to the subject’s ability (see above) and to practice the WM task in order to decrease the influence of training during the main experiment. This training session was always conducted in the morning (between 10:00 and 12:00 AM) and took about 90 minutes. At the beginning of this session the subjects received instructions related to the tasks (Sudoku task, SiRT task and WM task) and were informed about the experimental procedure. Then, the subjects

underwent the Sudoku difficulty tuning procedure described above. Thereafter, they practiced six blocks of the WM task. Subjects received auditory feedback about their performance only in the 3 first blocks of this task. Participants also performed the SiRT task once.

At the end of this training session, every subject received five Sudoku grids adapted to his/her ability and two inventories (BDI and STAI) to be filled at home. The Sudoku tasks and the inventories had to be completed and sent back before the second, experimental session. At least 1-day break was imposed between the two sessions.

The experimental session was always run in the afternoon or early in the evening (between 2:00 and 8:00 PM) and lasted between 4 and 5 hours. Participants first filled out the MFI and IMI questionnaires. Then they seated in front of the computer for the remaining of the experimental session, at a distance of 0.80 m from the PC monitor in a dimly illuminated, electrically shielded and sound-attenuated room. The EEG cap was then placed, the impedance of the electrodes adjusted and then EyeLink camera and skin conductance unit was set up. Immediately before the experiment, written instructions were given to the subjects. The 190 minute-long experiment was then started, in which four 30-minute blocks of Sudoku were performed, intermingled with 5 blocks of MF evaluation (see Figure II.1.1E). In each Sudoku block, different grids were provided to the subject until the 30-minute time limit was reached (mean number of grids performed: 3 ± 1). No break was allowed between the 9 blocks (5 MF evaluation + 4 Sudoku blocks). At the end of the experiment, the subjects had to complete the

same inventories as before the experiment. The order of the statements in these inventories was pseudo-randomized. Finally, the points collected during the Sudoku, the WM and the SiRT tasks were converted into euros and added together to determine compensation that the participants received at the end of the experiment.

II.1.3.6. Data and statistical analyses

Behavioral data

Most statistical analyses were performed with Matlab 7.5 (The MathWorks, Natick, Massachusetts, USA) and consisted in t-tests, two-way repeated-measures ANOVAs with BLOCK (1-5) and REWARD (1, 10 or 50) as independent variables and Pearson correlations whenever the normality of the data allowed us to use this test. Normality was ensured by examining the residuals by means of a Q-Q plot. In particular, the residuals from the accuracy data, which typically exhibit a skewed distribution, were in our case satisfactorily normal, allowing us to use simple parametric tests. When necessary, log-transformation (Keene, 1995) was used on non-normally distributed data. In some instances reported in the results Section, when transformations failed to normalize the data, Spearman correlations were used. Pairwise post-hoc comparisons were Bonferroni corrected. If Bonferroni adjusted post-hoc tests failed to reach significance despite significant main effects, ANCOVAs were used to evaluate the continuous effect of BLOCK and REWARD.

Physiological data

In order to evaluate whether a given physiological variable could be regarded as a marker of motivation, we followed the same rationale as in previous studies (Locke & Braver, 2008; Schmidt et al., 2012), namely we considered that 1) it should correlate with the reward value in the WM task and 2) the reward-induced signal changes should correlate with the reward-induced changes in behavior. These correlations were performed by means of ANCOVAs including the physiological variable as dependent variable, the behavioral performance as continuous independent variable and the subject as random factor. In order to ensure that the correlations reflected only the reward-induced changes that were common in the physiological marker and the behavioral performance, the effect of the block was removed from both variables by subtracting the blockwise average from the data prior to running the ANCOVA. Conversely, to assess the correlation between the effect of blocks (i.e. the fatigue effect) on the behavior and on the physiological markers, the reward-induced changes were removed by subtracting the reward-wise averages from the data.

EEG data

We focused our analysis of the EEG data gathered solely during the WM task. Two subjects were discarded from this analysis because of a technical issue. The EEG processing steps were performed by means of Letswave ⁴ and Matlab 8.0 (The MathWorks, Natick, Massachusetts, USA). Continuous EEG recordings

⁴ <http://nocions.webnode.com/letswave/>

were average-referenced offline. Ninety-second long EEG epochs were aligned on the onset of each WM task and transformed into the frequency domain using a fast Fourier transform. The frequency spectrum was then cropped between 0 and 150 Hz with a 0.5 Hz resolution, log-transformed and z-scored in order to ensure the normality of the distribution. Average EEG spectral power was computed for each subject and condition in six frequency bands: delta (0-4 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta (15-30 Hz), low gamma (30-60 Hz) and high gamma (60-140 Hz). The effects of reward and block order on EEG activity were investigated separately by means of regressions on dependent samples with cluster-based permutation tests, correcting for multiple comparisons (Oostenveld et al., 2011).

ECG data

The same subjects as for the EEG analyses were excluded. ECG signals were preprocessed similarly to the EEG signals. The segmentation of the ECG signals also resulted in thirty 90-second long epochs for every subject. Thereafter, a finite impulse response band-pass filter with cut-off frequencies 10-20 Hz was used. The R peaks of the ECG signals were detected offline and the inter-beat interval (IBI) between the consecutive R deflections was computed. To assess the HRV, we used the non-linear Poincaré plot analysis (Piskorski & Guzik, 2007), which consists in representing each IBI against the IBI that precedes it (IBI_t versus IBI_{t-1}) (see Figure II.1.2A).

Pupil diameter and eye blink parameters

In the WM task, data were also missing for two subjects (different from the ones excluded from the EEG analysis) because their unconstrained head movements resulted in the loss of the pupil signal and thus they had to be excluded from additional analyses. Pupil response was computed as the difference between the peak amplitude of the pupil during each trial and its baseline at trial onset (Zénon et al., 2014) (see Figure II.1.2B). Then, the median of these trial-by-trial changes in pupil size was calculated blockwise. Blink rate as a measure of MF was also computed for every subject and log-transformed. Furthermore, the median of the blink durations (log-transformed) and the proportion of long blink durations (proportion of blinks lasting longer than 300 ms, Caffier et al., 2003) were also computed blockwise.

Skin conductance response

Eight consecutive subjects had to be excluded from the analysis due to a technical problem, which resulted in the data not being properly recorded. The low-pass and high-pass filtered SCR responses were analyzed separately (cutoff frequency 0.1Hz, see Figure II.1.2C). In each frequency range, the standard deviation of the amplitude of the SCRs was computed for every condition across subjects.

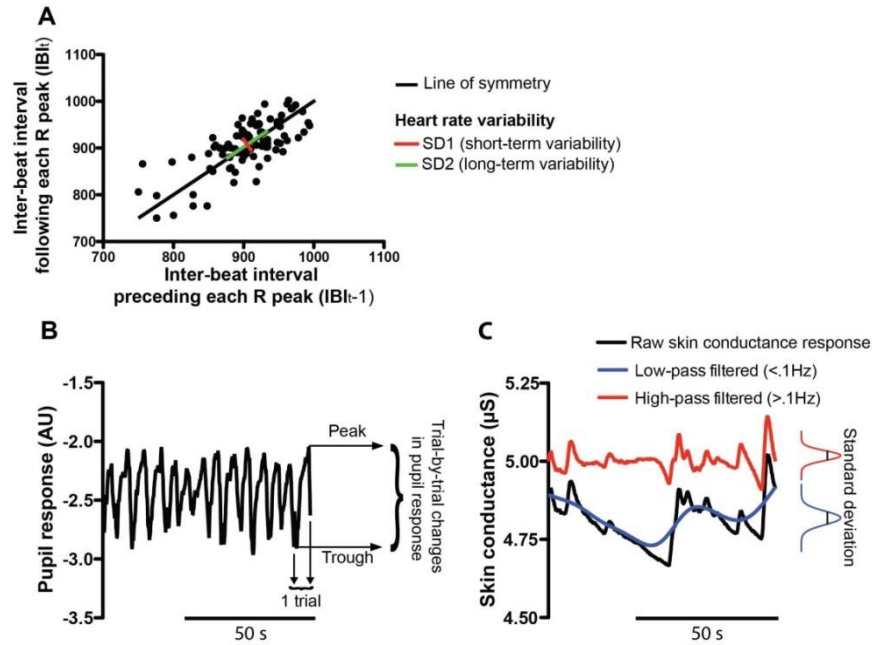


Figure II.1.2. Physiological measures. **(A)**, The heart rate variability was assessed by Poincaré plot analysis which represents each IBI against the IBI that precedes it (IBI_t versus IBI_{t-1}). This analysis results in two statistics: the short-term heart rate variability (SD1 in red) is the standard deviation perpendicular to the line of symmetry while the long-term heart rate variability (SD2 in green) is computed along the line of symmetry of the plot. **(B)**, Example pupil size recording during the WM task. The pupil response was computed as the trialwise peak-to-peak difference. Lower and upper peaks of the pupil response in an example trial (trial n°14) are represented by black arrows. **(C)**, Example skin conductance signal obtained during the WM task. The standard deviation of the amplitude of the skin conductance responses (SCRs) was computed for different frequency bands. The

raw SCRs are shown in black while SCRs filtered in the low (<0.1 Hz) or high frequency band (>0.1 Hz) are represented in blue and red, respectively.

II.1.4. Results

II.1.4.1. Evidence for MF emergence during the experiment

The Sudoku task was performed with high accuracy (95.84 % of correct responses) with a median RT ranging between 3.16 and 8.53 s per Sudoku cell; this task was successful in inducing MF, as shown in the following psychometric, behavioral and physiological analyses. Scores on the general fatigue subscale of the MFI showed that the subjects were significantly more fatigued after the experiment than before (paired samples t-tests: $t(17) = 5.56$, $p < 0.0001$, see Figure II.1.3A). In the WM task, two-way RM ANOVA on accuracy revealed a significant main effect of BLOCK ($F(4,68) = 2.52$, $p < 0.05$, see Figure II.1.3B). An ANCOVA including the BLOCK condition as a continuous variable was performed to investigate the nature of this effect. The best result was obtained when using the square of the block number (quadratic BLOCK effect: $F(1,485) = 4.15$, $p = 0.0436$, linear BLOCK effect: $F(1,485) = 4.01$, $p = 0.047$), showing that the subjects' performance, following an initial improvement, got gradually worse over time (see Figure II.1.3B).

We investigated whether this drop in performance correlated with the increased level of subjective fatigue. Based on earlier studies (Krupp & Elkins, 2000; Bryant et al., 2004), we did not expect to see any correlation between the subjective and objective indices of fatigue. The objective fatigue index was

computed by taking the slope of the regression line between the accuracy in the WM task and block order, starting from block 2 to avoid the initial effect of training. We found a non-significant trend toward a positive correlation (Pearson correlation: $r = 0.45$, $p = 0.059$), i.e. subjects with a large increase in subjective fatigue paradoxically tended to maintain a higher level of performance in the WM task across block repetitions.

In addition to subjective and behavioral measures, physiological measures also provided evidence for the emergence of MF. A physiological variable was regarded as an index of MF when it was found to vary across block repetition in such way that correlated with the time-induced changes in behavior.

Cluster-based permutation tests were performed on the EEG electrodes and frequency bands to assess the effect of block on the EEG signal during the WM task (see Methods II.1.3.9.). In the high gamma band, a marginally significant BLOCK effect (p following cluster-based correction = 0.0842) was revealed in the left frontal region (F7, FC5) showing that the amplitude tended to increase across block repetitions, possibly corresponding to an electrophysiological signature of MF. The BLOCK effect on the other frequency bands was not significant ($p > 0.1$).

The heart rate analysis unveiled a main effect of BLOCK (two-way RM ANOVA: $F(4,60) = 27.33$, $p < 0.0001$, see Figure II.1.3C) on the IBI. This revealed that heart rate decreased across block repetition, presumably reflecting an increased level of fatigue (post-hoc tests: all comparisons with block 1, $p < 0.0001$; block 3 and 5 versus block 2, $p < 0.001$). The non-linear Poincaré plot analysis

used to assess the HRV (see Figure II.1.2A & II.1.2B) allowed us to reveal a main effect of BLOCK (two-way RM ANOVA: $F(4,60) = 11.84$, $p < 0.0001$, see Figure II.1.3D) on SD1. This shows that the short-term HRV (SD1) also increased over time (post-hoc tests: HRV was higher in the 3rd, 4th and 5th blocks compared to the 1st block, and in the 4th and 5th block compared to the 2nd and 3rd block, all $p < 0.05$). The long-term HRV (SD2) also increased across block repetition (two-way RM ANOVA: $F(4,60) = 13.32$, $p < 0.0001$, see Figure II.1.3D). Post-hoc tests showed that SD2 increased significantly in the 3rd, 4th and 5th block compared to the 1st and 2nd blocks. Significant increase of SD2 was also observed in the 4th and 5th blocks compared to the 3rd block (all p -values < 0.05).

Furthermore, for the blink rate, a significant main effect of BLOCK order was found (two-way RM ANOVA: $F(4,60) = 3.77$, $p < 0.01$, see Figure II.1.3E) which is also known to be sensitive to fatigue (Martins and Carvalho, 2015). The blink rate increased as a function of block order, reflecting an increasing level of fatigue (post-hoc tests: 4th and 5th block higher than the 1st block, all p values < 0.05). The main effect of BLOCK order was also significant for the blink duration (two-way RM ANOVA: $F(4,60) = 2.56$; $p = 0.0476$), however the post-hoc tests with Bonferroni correction failed to reveal any significant pairwise comparison (all p -values > 0.1). In addition, an ANCOVA including the block condition as a continuous variable failed to show any significant BLOCK effect (quadratic BLOCK effect: $F(1,191) = 0.44$; $p = 0.5095$; linear BLOCK effect: $F(1,191) = 1.05$; $p = 0.3079$). Two-way RM ANOVA on the long blink durations showed only a marginally significant BLOCK effect ($F(4,60) = 2.12$; $p = 0.0889$). The lack of significant block effect on these eye blink

parameters was not unexpected, since eye blinks appear related more consistently to drowsiness and drops of vigilance rather than mental fatigue (Morris & Miller, 1996; Caffier et al., 2003; McIntire et al., 2014).

The block-related changes in the long-term HRV (SD2) and blink rate were negatively correlated with the block effect on WM task performance (ANCOVAs, SD2: $F(1,223) = 6.94$, $p = 0.009$; blink rate: $F(1,223) = 6.04$, $p = 0.0148$), confirming that these changes on SD2 and blink rate could be regarded as indices of MF. In contrast, blink duration correlated positively with WM task performance ($F(1,223) = 9.7$, $p = 0.0021$). This appeared to be caused by the initial improvement in the WM task accuracy between the 1st and 2nd block, accompanied by a concurrent increase in blink duration. To account for this potential confound, Pearson correlation analyses were performed. We first computed the slope of the regression of blink duration and accuracy as a function of the block order, starting from the 2nd block. Then we computed the correlation between these values. This analysis revealed a non-significant negative correlation between the subject-by-subject slopes of the block effect on blink duration and the subject-by-subject slopes of the block effect on WM task accuracy (Pearson correlation: $r = -0.0291$; $p = 0.9148$), confirming that the changes in blink duration failed to track the changes in MF. The time-related changes in IBI and short-term HRV (SD1) also failed to show any significant correlation with the time-related changes in the WM task results (ANCOVAs, IBI: $F(1,223) = 2.2$, $p = 0.1399$; SD1: $F(1,223) = 1.19$, $p = 0.2764$), and thus these latter measures were not considered as markers of MF in the current study.

Pearson and Spearman correlations were performed between the change in the subjective feeling of fatigue (general fatigue subscale of the MFI) and subject-by-subject slopes of the block effect on each of the physiological measures of MF (IBI, SD1, SD2, blink rate, blink duration). None of these correlations were significant (all p -values > 0.1).

Low scores in the second subscale of the STAI (37.28 ± 8.27 , mean $\pm$ SD) and in the BDI (5.39 ± 4.35 , mean $\pm$ SD) showed that the subjects did not suffer from any anxious or depressive disorders when they participated in the experiment. Furthermore, these scores did not significantly correlate with the subjective feeling of fatigue (Spearman correlations, STAI: $r = -0.2673$, $p = 0.2837$; BDI: $r = -0.2917$; $p = 0.2402$), indicating that anxiety and depression did not play any role in the development of subjective fatigue.

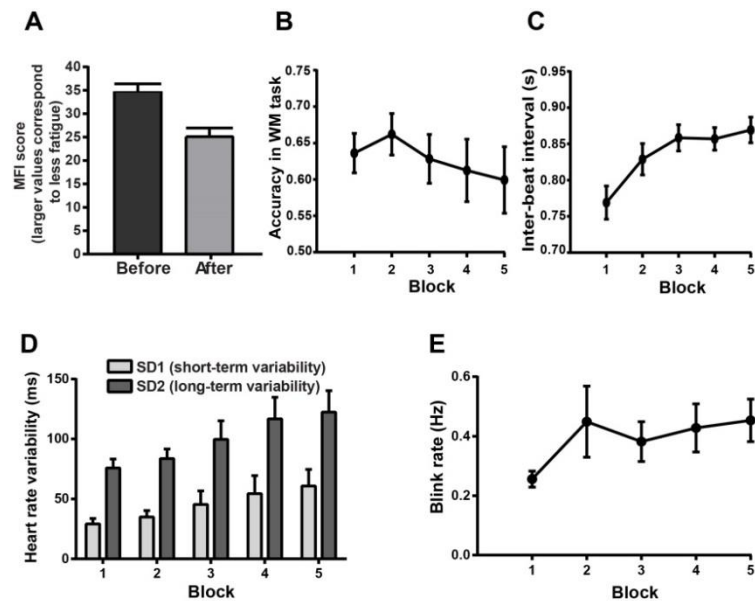


Figure II.1.3. Psychometric, behavioral and physiological evidence for MF. Error bars represent standard errors of the mean. **(A)**, Mean score on the general fatigue subscale of the Multidimensional Fatigue Inventory (MFI) before and after the experiment. Following the experiment, smaller average MFI indicates a higher level of subjective fatigue. **(B-E)**, Block-related behavioral and physiological changes indicative of MF in the WM task. **(B)**, Mean accuracy in the WM task across block repetition. **(C)**, Mean values for inter-beat interval (IBI) in the WM task across block repetition. **(D)**, Short- and long-term heart rate variability in the WM task as a function of the block order. **(E)**, Average blink rate in the WM task as a function of block order.

II.1.4.2. Evidence for motivation manipulation efficacy

The efficacy of reward manipulation (1, 10 or 50 points) on behavioral performance was studied both in the SiRT and fatigue-evaluating WM task. In addition, we looked at the effect of the reward on the physiological variables, which were considered as valid markers of motivation whenever they varied in proportion to the reward value and correlated with the reward-induced behavioral changes.

A significant main effect of REWARD on the log-transformed RT gathered during the SiRT task showed that the participants responded faster for higher incentives (two-way RM ANOVA: $F(2,34) = 14.34$, $p < 0.0001$, see Figure II.1.4A). For this reward effect, post-hoc tests with Bonferroni correction revealed that the subjects were significantly faster in the highest-reward condition (50 points) when compared to the medium (10 points) and to the lowest-reward conditions (1 point). Subjects were also significantly faster in the medium-reward condition than in the lowest-reward condition (all p -values < 0.005).

A significant main effect of REWARD was also found for the accuracy in the WM task (two-way RM ANOVA: $F(2,34) = 7.43$, $p < 0.001$, see Figure II.1.4B) showing that the subjects were more accurate when the incentive was the highest (Bonferroni corrected post-hoc tests: 50 versus 10 or 1, $p < 0.05$).

REWARD also affected the “decision time” between the display of the reward condition and the task onset, triggered by the subject through a key press (two-way RM ANOVA: $F(2,34) = 13.94$, $p < 0.0001$, see Figure II.1.4C). Indeed,

subjects waited longer before starting the task when the reward was the highest (post-hoc tests: 50-points versus 10-points or 1-point reward conditions, $p < 0.01$).

In the WM task, some physiological variables were found to change in proportion to the reward incentive. High gamma band activity correlated significantly (p values following cluster-based correction < 0.05 , see Figure II.1.4D) with the reward incentive in the occipital region. Higher activity was observed with higher incentives on POz, O1 and Oz electrodes. The reward also had a significant effect on the pupil response (two-way RM ANOVA: significant main effect, $F(2,30) = 5.72$, $p < 0.01$, see Figure II.1.4E). Indeed, higher incentives led to larger pupil responses (post-hoc tests: reward conditions 50 or 10 versus reward condition 1, and 50 versus 10, all $p < 0.05$). In addition a main effect of REWARD on the low-frequency responses of the SCR was found (two-way RM ANOVA: $F(2,18) = 5.8$, $p = 0.05$, see Figure II.1.4F), indicating that SCR increased as a function of higher incentives (post-hoc tests: 50-points versus 1-point reward condition, $p < 0.05$) while the other SCR frequency band ($>.1\text{Hz}$) did not show any significant effect (all $p > .05$).

Reward-induced changes in EEG and pupil response were found to correlate significantly with the reward-induced behavioral changes (ANCOVAs, EEG: $F(1,463) = 4.58$, $p = 0.0328$; pupil response: $F(1,223) = 31.53$, $p < 0.0001$), confirming that these measures can be regarded as markers of motivation. The effect of reward on SCR failed to correlate with the reward effect on behavior (ANCOVA: $F(1,132) = 1.07$, $p = 0.3037$). This lack of correlation might be due to the smaller sample size obtained for the SCR analysis ($n=10$); therefore, in this

particular case, we analyzed the correlation with participant's behavior slightly differently. We correlated the slope of the regression line obtained, for each subject, between reward and accuracy, on the one hand, and between reward and SCR, on the other hand. We found a significant positive relation between the reward effect on accuracy and behavior (Spearman correlation: $r = 0.73$, $p = 0.0212$) indicating that SCR can also be regarded as a marker of motivation.

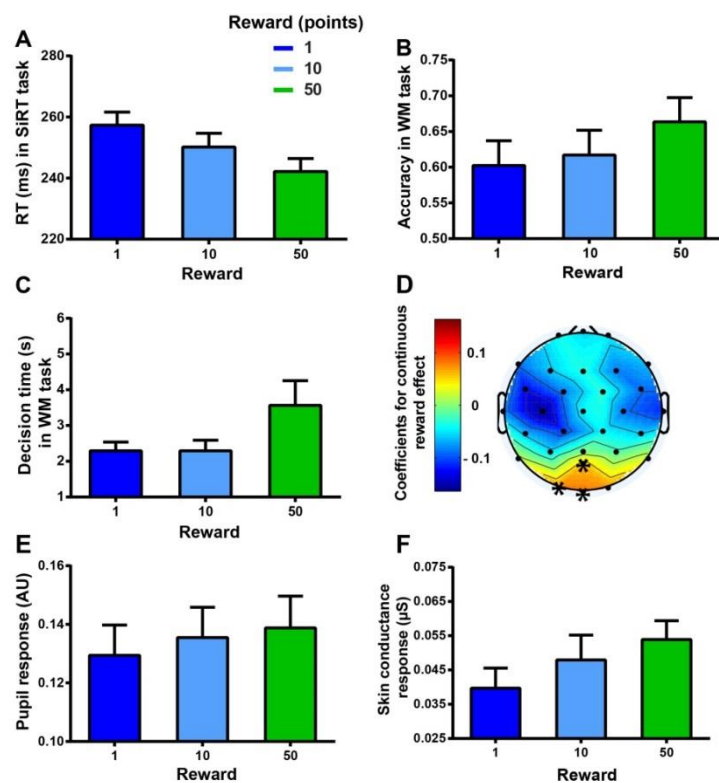


Figure II.1.4. Markers of motivation. Error bars represent standard errors of the mean. **(A)**, Mean RT (ms) as a function of the reward condition in the SiRT task. **(B)**, Mean accuracy as a function of the reward condition in the WM task. **(C)**, Mean decision time (s) as a function of reward condition in the WM task. **(D)**,

Coefficients of the reward effect on the high gamma band (60-140 Hz) activity in the WM task. Higher incentives led to higher activation on POz, Oz, and O1 electrodes (marked by asterisks, $p < 0.05$). **(E)**, Mean pupil response as a function of reward condition in the WM task. **(F)**, Mean skin conductance response as a function of reward condition in the WM task.

II.1.4.3. Evidence for motivational fluctuations during the experiment

Regarding the subjective assessments of motivation, we found that the subjects' task interest/enjoyment and perceived competence were significantly decreased at the end of the experiment (paired sample t-tests, interest/enjoyment: $t(17) = 6.30$, $p < 0.0001$; perceived competence: $t(17) = 2.57$, $p < 0.05$), while their effort and its perceived importance in task performance were not (paired sample t-test, effort/importance: $t(17) = -0.49$, $p = 0.625$).

Conversely, two-way repeated measures ANOVAs on the physiological markers of motivation gathered in the WM task did not reveal any significant decrease across block repetition (EEG: $F(4,60) = 1.83$, $p = 0.1343$, see Figure II.1.5A; pupil response: $F(4,60) = 1.08$, $p = 0.37$, see Figure 5B; SCR: $F(4,36) = 1.1$, $p = 0.37$, see Figure II.1.5C). The probability of this negative result being genuine was assessed by means of the Bayes factor (BF) estimation method (Masson, 2011). The BF indicates how much more likely the null hypothesis is with respect to the alternative hypothesis, given the data. For the abovementioned non-significant block effect on EEG, pupil response and SCR, the BF was equal to 102.3691, 443.0648 and 158.2374, respectively. These BFs provide strong evidence in favor of the null hypothesis.

We found a significant main effect of BLOCK on RT in the SiRT task (two-way RM: $F(4,68) = 12.31$, $p < 0.0001$, see Figure II.1.5D). Multiple comparisons with Bonferroni correction showed that the participants were significantly faster (all p -values < 0.05) in the 3rd, 4th and 5th blocks than in the 1st block. Furthermore, a significantly faster RT was found in the last block than in the 2nd and 3rd block (all p -values < 0.05). This finding that responses get faster across block repetition in the SRT task argues also against a decrease in motivation over time.

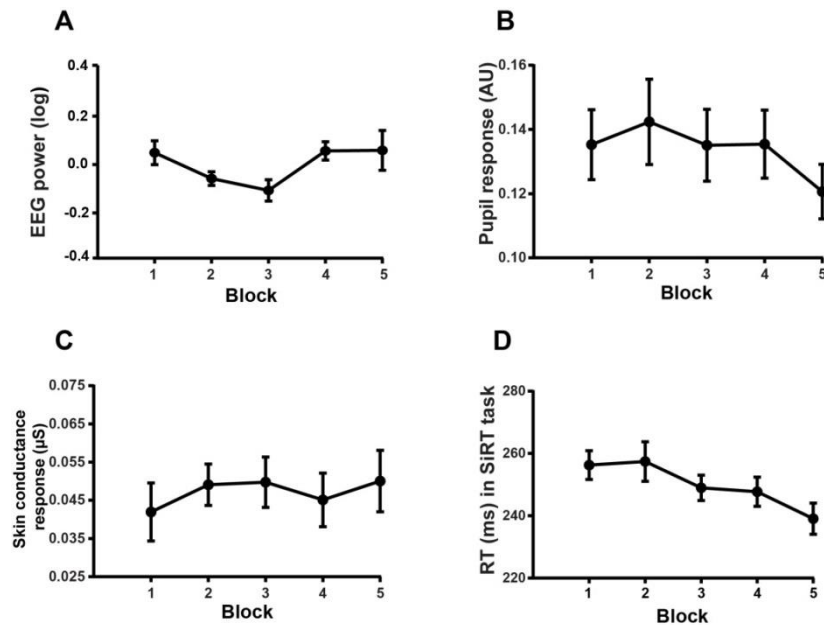


Figure II.1.5. Block effect on the markers of motivation. **(A)**, Mean EEG power averaged over the frequencies and electrodes isolated by the cluster-based permutation test in the WM task. **(B)**, Mean pupil response as a function of block condition in the WM task. **(C)**, Mean skin conductance response as a function of

block condition in the WM task. **(D)**, Mean RT (ms) as a function of block condition in the SiRT task.

II.1.4.4. Interaction between MF and motivation

Finally, in order to evaluate whether the extrinsic motivational manipulations interacted with the fatigue effect, we looked at the interactions between REWARD and BLOCK. The two-way repeated measures ANOVAs on physiological markers of motivation failed to show any significant interaction between REWARD and BLOCK (EEG: $F(8,120) = 0.52$, $p > 0.5$, $BF = 5.49 \times 10^7$, see Figure II.1.6A; pupil response: $F(8,120) = 0.68$, $p > 0.5$, $BF = 1.7 \times 10^7$, see Figure II.1.6B; SCR: $F(8,72) = 0.78$, $p > 0.5$, $BF = 1119900$, see II.1.Figure 6C) indicating that the motivational value of the reward did not change throughout the experiment. This lack of interaction was also found on performance in the SiRT ($F(8,136) = 0.74$, $p = 0.65$, $BF = 1.81 \times 10^8$, see Figure II.1.6D).

Regarding the subjective assessment of motivation, the decrease in the interest/enjoyment subscale of the IMI did not significantly correlate with either the subjective (general fatigue subscale of the MFI) or the objective measure of MF (objective fatigue index, see Results II.1.3.1.). The non-significant correlation between motivation and either the subjective (Pearson correlation: $r = 0.31$, $p = 0.21$, $BF=1.6973$) or objective measure of fatigue (Pearson correlation: $r = -0.15$, $p = 0.55$, $BF=3.4664$) indicated that the increase in the subjective feeling of fatigue and the drop in performance cannot be attributed to a decrease in intrinsic motivation. Correlation between the perceived competence subscale of the IMI and

the subjective or objective measures of fatigue did not also reveal any significant relation (Spearman correlation: all p -values > 0.1).

According to our third prediction, the performance in the WM task should have dropped more in the low stake condition than in the high stake condition. However, the interaction between REWARD and BLOCK on the performance in the WM task accuracy was not significant ($F(8,136) = 1.28$, $p = 0.2508$, $BF=3.02 \times 10^{-8}$, see Figure II.1.6E), indicating that the detrimental effect of MF (performance decrement) could not be overcome even when the incentives were high (50 points).

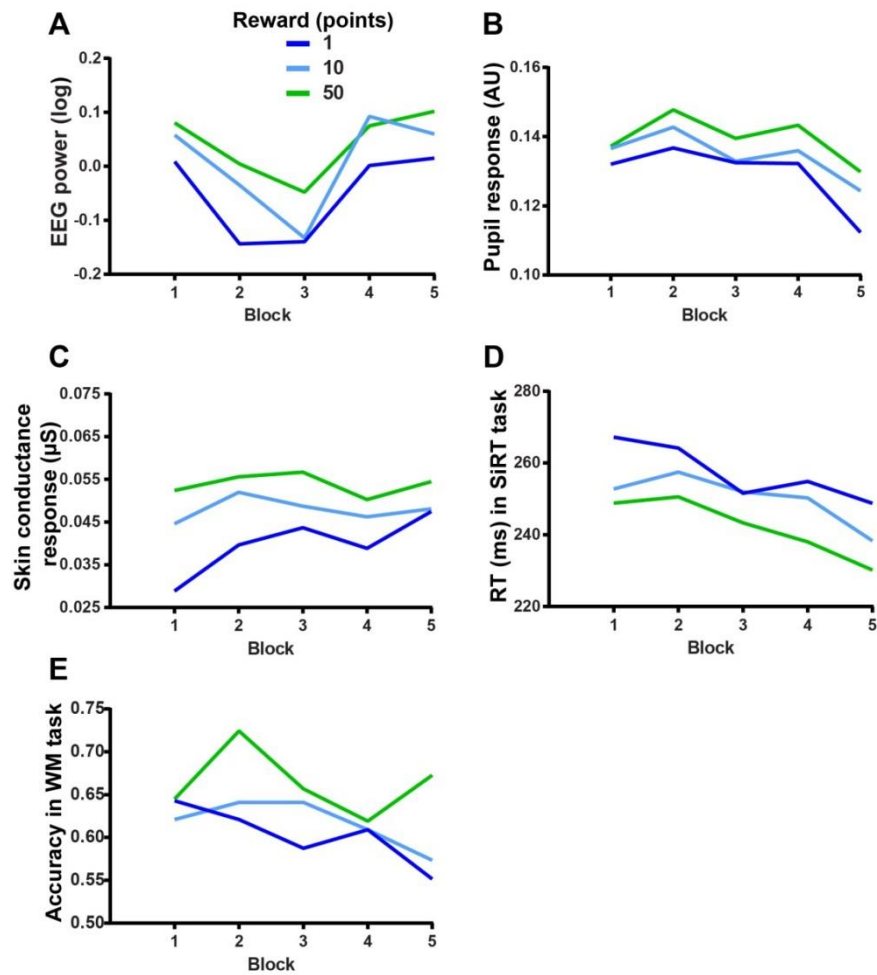


Figure II.1.6. Reward-block interactions on **(A)**, EEG power during the WM task (averaged over the cluster) **(B)**, pupil response during the WM task **(C)**, skin conductance response during the WM task, **(D)**, RT in the SiRT task and **(E)**, accuracy in the WM task.

II.1.5. Discussion

In the present study, we attempted to find evidence for the causal role of a progressive decrease of task-related motivation in the emergence of MF. We evaluated MF by means of subjective ratings, behavioral performance and physiological markers. Despite a very significant increase in subjective fatigue at the end of the experiment, the deterioration of behavioral performance in the WM task was small. This is however a common finding in the literature (DeLuca, 2005), possibly because subjects maintain their performance despite MF by means of a compensatory increase in mental effort (Hockey, 1997; Nakagawa et al., 2013; Esposito et al., 2014). In addition, we found that two well-known psychophysiological signatures of MF, namely long-term HRV (SD2) (Mukherjee et al., 2011) and blink rate (Stern et al., 1994), increased over time and correlated with the concurrent drop in performance. In contrast, the drop in heart rate, known for long to occur concurrently to the development of fatigue (Arai, 1912), failed to correlate with the fatigue indices; to the best of our knowledge, it is the first time that correlations between these measures are investigated. It could thus be proposed that the drop in heart rate corresponds in fact to a phenomenon that, although occurring concomitantly with fatigue, bears no relation to the mechanisms involved in the development of MF, such as the adoption of a prolonged sedentary position.

Along the same lines, it could also be argued that the decrease in performance and the changes in the physiological markers of MF could have been caused by other phenomena, such as a drop of vigilance (Oken et al., 2006).

Changes in the level of vigilance are defined operationally as a slowing of the RTs in easy detection tasks after a prolonged period of time (Pattyn et al., 2008). Here, on the contrary, we observed a clear decrease of RT over time in the SiRT task, indicating that there was no drop of vigilance over the course of our experiment. We also failed to find the classical EEG signature of vigilance drops, consisting in an increase in the theta frequency band over time (Paus et al., 1997). Along the same line, the eye blink parameters that are regarded as markers of drowsiness and drops in vigilance i.e. the average blink duration and the proportion of long blinks (Caffier et al., 2003; McIntire et al., 2014), failed to change with time-on-task, also arguing against changes in drowsiness/vigilance over time in our experiment. Thus it seems sensible to conclude that behavioral and physiological block-related changes that we observed in the current study were indeed specific markers of progressive MF.

The hypothesis that MF would be caused by a loss of motivation led to a series of testable predictions. First, we expected the indicators of motivation to decrease across block repetition. To tackle this prediction, we measured motivation by means of subjective ratings, behavioral performance and physiological markers. We were able to isolate three physiological indicators of motivation that increased with reward and correlated with its behavioral effects, namely high gamma band activity in the occipital EEG, pupil size, and SCR. The pupil and SCR responses to motivation confirmed the conclusion of earlier studies reporting a relationship between these physiological variables and motivational status (Kahneman & Peavler, 1969; Schmidt et al., 2008). However, the EEG

correlate of motivation was less expected. To our knowledge, it is the first time that high gamma power increases in the occipital region are described in relation to motivation, which is classically associated with power suppression in the alpha frequency range (Keil et al., 2006; Ewing & Fairclough, 2010). However, a recent study (Ossandón et al., 2011) has described similar electrophysiological phenomena in relation to manipulations of the task difficulty. A study using fMRI also revealed an enhanced activation in the visual association cortex as a function of higher incentive during the performance of a WM task (Krawczyk et al., 2007) and other studies have also described increased gamma band activity in other parts of the brain in relation to motivation or task engagement (Fründ et al., 2007; Mulert et al., 2007; Tan et al., 2013; Bosman et al., 2014). It could be hypothesized that an increase in mental effort, which can be caused both by higher task difficulty and higher motivation (Kurzban et al., 2013), would be responsible for the changes in the occipital region that we observed. Finally, it is worth mentioning that these reward-related EEG changes could not be elicited by the visual features of the display used to inform the subjects about the reward condition, since the EEG signals included in the analyses followed the offset of this display.

Amongst the motivational markers we evaluated, only the subjective ratings indicated a decrease over time, while the other indicators failed to show any significant change. The difference between the subjective evaluation and objective measures of motivation might result from the fact that the interest/enjoyment subscale of the IMI evaluates the pleasure experienced during the task execution and the perceived competence subscale estimates how the

participants perceive their performance in the task while the objective motivational measures could relate more to the motivation-dependent mental effort invested during the task (Heitz et al., 2008; Venables & Fairclough, 2009). In accordance with this view, we found that the effort/importance subscale of the intrinsic motivation questionnaire failed to show any change at the end of the experiment. Therefore, it appears that while the subjects maintained their mental effort throughout the experiment, their subjective experience of the task changed, becoming more and more unpleasant over time.

Our second prediction was that the behavioral decrease in performance over time should be proportional to the progressive build-up of fatigue. All the correlation analyses showed that the blockwise changes in motivation, evaluated by the different measures described above, did not vary commensurately with the progressive increase in MF. This provides strong evidence that any motivational changes that might occur during the experiment cannot be causally linked to the concurrent development of MF.

Third, we predicted that reward manipulations, by compensating a possible decrease of motivation, would, at least partly, alleviate the effects of fatigue. In contrast, the absence of reward-block interaction in the different markers of motivation indicates that reward manipulations failed to compensate the effect of MF. Indeed, if fatigue were caused by a loss of motivation, we would have expected the performance to drop more in the low-reward condition than in the high-reward condition, thereby resulting in a significant interaction between reward and block order. However, our results show that the subjects could not overcome

the detrimental effects of MF, despite a high extrinsic motivation. This lack of effect cannot be explained by a progressive loss of interest in the monetary incentive, since the effect of reward on the SiRT task performance and on all the motivational indicators described above remained unchanged during the course of the experiment.

Finally, given that the SiRT task was influenced by motivational manipulations, we expected MF to affect performance during this task as well. However, we found that the performance in the SiRT task increased over time, clearly indicating that it was not affected by MF.

Since the present findings consist mostly in absence of effects, we attempted to evaluate how strongly we can trust these negative results on the basis of Bayes factor analyses (Masson, 2011). Most of these analyses provided strong to very strong evidence in favor of the null hypothesis. However, the correlations between the subjective motivational variables and the subjective fatigue index provided only weak evidence. Thus, we cannot affirm with certainty that larger samples would not allow to uncover a significant relation between some of these variables. However, given the caveats discussed above regarding the interpretation of the subjective intrinsic motivation variables, and given that all the other analyses provided very clear evidence against the main hypothesis of a causal link between fatigue and motivational loss, we do not believe that this slightly less conclusive finding should significantly alter our conclusion.

A noteworthy limitation of the present study, which is in fact common to many fatigue-related studies, is the lack of a control condition in which no fatigue would be induced. The decision not to include such a control condition was made because of the difficulty of choosing an appropriate control task - which had to be neutral in terms of fatigue and motivational effects – and because it was possible to circumvent this shortcoming by relying on correlation analyses between the fatigue indices and the changes observed in the dependent variables. This method allowed us to maintain a reasonable level of specificity of the fatigue effects, despite the absence of control. Future studies, using such a control condition, could provide a more robust confirmation of the present findings.

To sum up, the present results indicate that MF is not caused by a progressive disengagement from the task, or motivational decline. Importantly, we do not claim that drops in motivation never happen concurrently to MF, nor that these motivational drops never contribute to MF but rather that loss of motivation cannot be considered as a necessary causal factor in the development of MF. These findings strongly question the mechanisms actually responsible for MF. These likely engage either the disruption of cognitive resources - for instance through progressive metabolic alterations - or changes in cognitive control impeding the availability of these resources (van der Linden et al., 2003, Hockey, 2011, Kurzban et al., 2013, Ishii et al., 2014). Future work should aim at addressing the nature of these metabolic and/or functional alterations.

II.1.6. Acknowledgements

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II.2. Mental fatigue depresses task-related cortical responses⁵

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II.2.1. Abstract

Long-lasting and demanding cognitive activity typically leads to mental fatigue (MF). Indirect evidence suggests that MF may be caused by altered motivational processes. Here, we tested this hypothesis with functional neuroimaging. We hypothesized that if MF consists in an alteration of motivational states, associated neural changes should specifically affect the brain motivation circuit.

Twenty-six healthy participants (14 females) underwent a FATIGUE and a CONTROL session on different days. In the FATIGUE session, MF was induced by performing a demanding cognitive task during 90 minutes, whereas in the CONTROL session, participants were asked to read magazines for the same period of time. We measured the neural consequences of MF during a working memory task with block-wise variations in monetary reward. Prior to and following the MF inducement and measurement, we also assessed the participants' momentary fatigue, anxiety state and intrinsic motivation.

Subjective MF, but not its behavioral manifestations, was associated with a global, brain-wide depression of the task-evoked neural responses, whereas regions modulated by reward were not specifically affected. In addition, subjective MF led to increased resting-state functional connectivity within the regions of the default mode network.

These results indicate that subjective MF is associated with depressed task-specific brain responses and cannot be reduced to an alteration of

motivational processes. The lack of relation between the decreased brain responses and the behavioral performance suggests the existence of compensatory mechanisms, which were not observable with standard neuroimaging techniques.

Keywords: mental fatigue, motivation, fMRI, reward circuit

II.2.2. Introduction

Prolonged execution of demanding cognitive tasks leads to mental fatigue (MF) which refers primarily to the subjective feeling of a deteriorated ability to initiate and/or maintain mental activities (A Chaudhuri & Behan, 2000). MF can also be accompanied, albeit inconsistently, by objective behavioral alterations (van der Linden et al., 2003; DeLuca et al., 2008; Hopstaken et al., 2014; Borragán et al., 2017) and psychophysiological changes (Boksem et al., 2006; Lorist et al., 2009; Hopstaken et al., 2014, 2015, 2016; Gergelyfi et al., 2015). The neural origin of these subjective and objective manifestations of MF is poorly understood. A central question which remains unanswered is whether MF is caused by the progressive depletion of cognitive resources (Gergelyfi et al., 2015; Hopstaken et al., 2015) or by adaptive mechanisms that would alter motivational processes and block the recruitment of otherwise preserved resources (Hockey, 1997; Chaudhuri and Behan, 2000; Boksem and Tops, 2008; Kurzban et al., 2013; Westbrook and Braver, 2016).

The majority of the studies that have investigated the neural mechanisms of fatigue were performed on clinical populations including chronic fatigue syndrome (Cook, O'Connor, Lange, & Steffener, 2007; F. P. de Lange et al., 2004; G. Lange et al., 2005; Miller et al., 2014; Mizuno et al., 2016; Okada, Tanaka, Kuratsune, Watanabe, & Sadato, 2004), multiple sclerosis (DeLuca et al., 2008; Filippi et al., 2002; Genova et al., 2013) and Parkinson's disease patients (Lou, Kearns, Oken, Sexton, & Nutt, 2001; Sáez-Francàs et al., 2014). Among these studies, those that have addressed the neural correlates of subjective MF have

reported inconsistent findings, with either increased ((G. Lange et al., 2005): superior parietal lobule, supplementary and premotor regions; (Cook et al., 2007): cerebellar, temporal, cingular and frontal regions; (Genova et al., 2013): caudate nucleus; (DeLuca et al., 2008): frontal, parietal, extrastriate cortex) or decreased activations in various brain regions ((Filippi et al., 2002): intraparietal sulcus, rolandic operculum, thalamus; (Cook et al., 2007): posterior parietal cortex, BA40; (Miller et al., 2014): caudate, globus pallidus; (Mizuno et al., 2016): putamen).

In healthy participants, frontal regions were found to be responsible for the compensatory processes allowing participants to maintain performance despite fatigue (Wang et al., 2016) or to be particularly sensitive to prolonged task performance (specifically medial frontal gyrus (Blain et al., 2016)). MF has also been described to decrease anterior cingulate responses to errors with time-on-task, while concurrent increased activations were found in dopaminergic midbrain (Moeller et al., 2012). According to Moeller et al. (Moeller et al., 2012), these results suggest that the dopaminergic midbrain could play a compensatory role by maintaining task engagement in the presence of MF. However, Nakagawa and colleagues have reported a deactivation in the dopaminergic midbrain following fatigue (Nakagawa et al., 2013) and a larger mean diffusivity (a global measure of white matter integrity) in the right putamen of healthy subjects with high subjective trait fatigue (Nakagawa, Takeuchi, Taki, Nouchi, & Kotozaki, 2016). These findings resonate with models of fatigue that attribute a central role to the basal ganglia in the symptomatology of fatigue (Boksem & Tops, 2008; A Chaudhuri & Behan, 2000; Abhijit Chaudhuri & Behan, 2004). This brain region is thought to be

important to determine and implement motivational states (Pessiglione et al., 2007; Schmidt et al., 2008b, 2012; Vassena et al., 2014) and therefore, its disruption in association with fatigue would go along with the view that fatigue consists in a disruption of motivational processes (Hockey, 1997.; Kurzban et al., 2013; Hopstaken et al., 2016). However, the lack of consistency in the earlier findings fails to provide convincing experimental support for these models.

The aim of the present study was to provide a systematic investigation of the relationship between the neural circuits involved in MF and motivation. We relied on performance-contingent monetary rewards to manipulate the motivational state during the evaluation of MF while fMRI scans were carried out. We hypothesized that if MF consists in a loss of motivation, the regions involved in the brain reward system should be specifically affected by MF.

II.2.3. Materials and methods

II.2.3.1. Participants

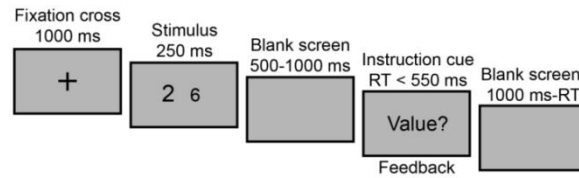
Twenty-six healthy subjects (14 females; age = 23.81 ± 3.17 , mean $\pm$ sd) participated in this study. The participants had to meet the following criteria for participation: absence of contraindication for MRI, age between 20 and 35, right-handedness, normal or corrected-to-normal visual acuity, no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

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

II.2.3.2. Experimental tasks

In order to limit the confounding effect of boredom, we used different tasks to induce and measure MF. In the FATIGUE session, MF was induced by performing a modified Stroop task for at least 90 minutes (see Figure II.2.1A). Then the neural effects of MF were assessed by measuring the participant's blood-oxygen-level dependent responses while they were engaged in the Missing Number task (see Figure II.2.1B) wherein they were asked to report the missing element of number series at different levels of difficulty, with monetary rewards varying block-wise. In the CONTROL session, the subjects also performed this Missing Number task but following reading magazines for 90 minutes. In both sessions, prior to and after the different tasks, questionnaires [Multidimensional Fatigue Inventory (MFI), State-Trait Anxiety Inventory (STAI) and Intrinsic Motivation Inventory (IMI)] were used to evaluate the participants' fatigue, anxiety state and task interest/enjoyment (see Figure II.2.1C).

(A) Stroop task



(B) Missing Number task

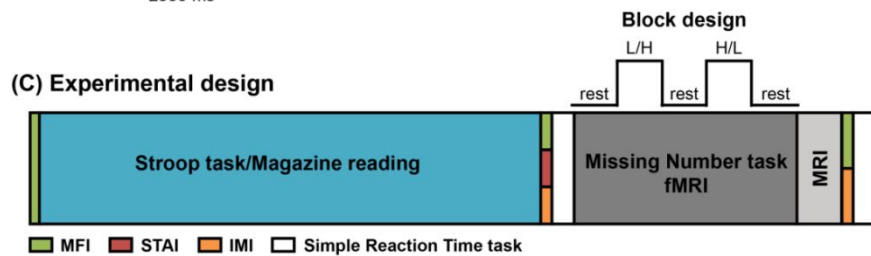
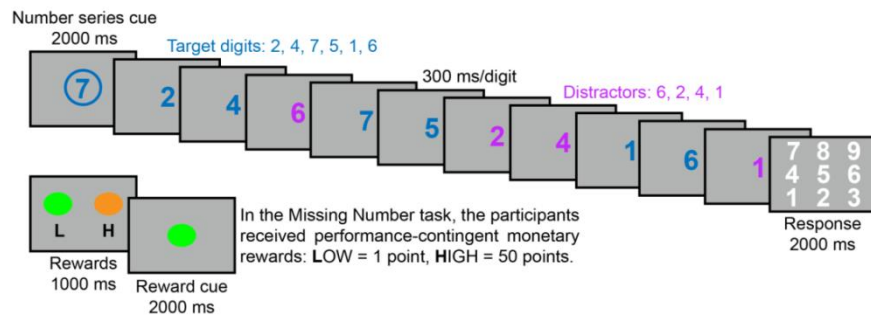


Figure II.2.1. Experimental design

(A) In the Stroop task, the stimulus appeared for 250 ms following a fixation cross (1000 ms). After a 500-1000 ms delay (blank screen), the instruction cue (“value” or “size” in this example) was presented for 550 ms. Participants had to respond before the end of the cue presentation, and were given an auditory feedback afterwards. The delay between the cue onset and the beginning of the next trial was fixed at 1000 ms, independently of the participants’ RT. After the participants’ response, the screen remained blank until the beginning of the next trial. **(B)** At the beginning of every trial of the Missing Number task, a 2000 ms cue informed the

participant on the number series condition for the next trial (7 in the present example) and on the color defining the target digits (blue or magenta, indicated by the color of the cue). Each digit in the series (target digits or distractors) was presented for 300 ms. The missing element of the number series had to be selected by pressing the corresponding number on a numeric keypad (whose layout was consistent with computer numeric keypads), which was also shown on the screen for 2000 ms. The display (2000 ms) of the reward condition (1 or 50 point(s) per correct response) was preceded by a reward information display of 1000 ms, which reminded the color-reward association rule to participants. **(C)** Prior to and following the FATIGUE manipulation (Stroop task) or CONTROL condition (magazine reading), and after the fatigue evaluation (using block-designed fMRI paradigm and the Missing Number task), questionnaires were used to assess the participants' subjective fatigue (MFI) and anxiety (STAI) states and their task interest/enjoyment (IMI). The effect of reward on extrinsic motivation was controlled by means of the Simple Reaction Time task, performed before and after the Missing Number task.

Mental fatigue (MF) inducement: Stroop task

In accordance with earlier studies, we used a modified version of the Stroop task, including interleaved "number" and "arrow" Stroop trials, to induce MF (Barwick et al., 2012; Moeller et al., 2012; Wang et al., 2016; Wang, Ding, & Kluger, 2014). The exertion of cognitive control in the Stroop task recruits frontal regions which have been recently implicated in MF processes. In the "number" Stroop, pairs of digits (ranging from 1 to 9) were presented in the middle of the

computer screen. After a delay, a cue then indicated whether the participants had to report the larger digit in terms of “value” or in terms of “size” (see Figure II.2.1A; left or right key on the numeric keypad). In the “arrow” Stroop, arrows were displayed at the top or bottom of the screen and following the instruction cues, participants had to report either the “location” or “direction” of the arrow (up or down key). The blocks included 92 trials per condition (value, size, location and direction). Additionally, the trials were equally divided into congruent (e.g. large/small digit with large/small value, upward/downward pointing arrow with corresponding up/down location) and incongruent trials (e.g. large/small digit with small/large value, upward/downward pointing arrow with down/up location). Finally, the number of consecutive trials with the same condition followed a geometric distribution. Subjects were instructed to be as fast and accurate as possible in every trial.

Control of mental fatigue (MF): magazine reading

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

Mental fatigue (MF) evaluation: Missing Number task

The Missing Number task contained three conditions: number series 7 (including numbers from 1 to 7), 8 (numbers from 1 to 8) and 9 (numbers from 1 to 9). The number of digits shown was always inferior to the range of possible values (i.e. 6 numbers were shown in number series 7 (see Figure II.2.1B); 7 numbers in number series 8, and 8 numbers in number series 9) and the participants were asked to report the digit that was missing from the series. In addition, four distractor digits, whose color differed from the target color, were interleaved with the target digits (see Figure II.2.1B). Participants were instructed to perform the task as fast and accurately as possible by using an MRI-compatible numeric keypad, developed in-house. They did not receive any performance feedback.

In the Missing Number task, the performance-contingent monetary rewards were color-coded (see Figure II.2.1B) and the subject-specific arbitrary rule linking the color cue to the reward value was reminded to the participant at the beginning of each block. Then, the reward color for the block was shown in order to inform the participant about the reward they would receive for each correct response in the upcoming trials.

Control of reward effect: Simple Reaction Time task

The impact of monetary reward on extrinsic motivation was evaluated by means of a Simple Reaction Time task in which subjects had to press the left mouse button as fast as possible whenever a red triangle appeared on the screen following a fixation cross. This fixation cross was presented for a variable duration

(from 500 ms to 3000 ms) following a geometric distribution. During a block, the sum of the response times was fixed to a total of 6000 ms. Thus, the faster the participants responded, the more trials they could perform and the more points they could gain. The reward condition was instructed in the same form as in the Missing Number task, with the same color code (see Figure II.2.1B).

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

II.2.3.3. Subjective measures

Multidimensional Fatigue Inventory (MFI): General fatigue subscale

In both sessions, a modified version of the MFI (Gentile et al., 2003) was used to assess the participants' subjective feeling of fatigue in the beginning, in the middle (after Stroop task/magazine reading) and in the end of the experiment. Due to the time constraints, and because of the need to assess fatigue repeatedly, we included only the "global fatigue" subscale from the inventory. This subscale was shown to track mental fatigue reliably in our previous study (Gergelyfi et al., 2015). Every statement has to be rated on a Likert scale ranging from 1 to 5 (with anchors of "Yes, that is true" and "No, that is not true"). The lower the MFI score, the higher the level of subjective fatigue.

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

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

State-Trait Anxiety Inventory: state anxiety

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

II.2.3.4. Design and experimental procedure

The experiment included three sessions (TRAINING, FATIGUE and CONTROL), performed on different days. The purpose of the TRAINING session (70-80 minutes) was to familiarize the participants with the numeric keypad and the

reward system used during the experiment and to help participants approach asymptotic performance in the tasks, so as to minimize order effects. After being informed about the general experimental procedure and completing the informed consent and MR contraindication forms, participants practiced a total of 184 trials of the Stroop task (see above), 180 trials of the Missing Number task (see above) and 4 blocks (88 trials on average) of the Simple Reaction Time task (see above). In all tasks, participants received feedback about their performance.

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

Both the CONTROL and FATIGUE sessions started with participants receiving instructions and filling the Multidimensional Fatigue Inventory (MFI) questionnaire (see above), assessing their subjective feeling of fatigue (see Figure 1C). Then, they performed either the Stroop task (FATIGUE) or magazine reading (CONTROL) for 90 minutes (see Figure II.2.1C). The Stroop task normally included 4 blocks, but its actual duration depended on the fMRI scanner availability, in order to prevent the participants from recovering between the end of the Stroop task execution and the beginning of the neuroimaging acquisition. Consequently, 8 participants performed 5 blocks and 1 participant performed 6 blocks whereas 3 participants did not fully complete the 4th block. Each block consisted of 368 trials

and lasted around 22,5 minutes. Participants received trial-wise auditory feedback on their performance and block-wise feedback on the number of trials performed correctly. In the CONTROL session, participants read magazines of their choice, displayed on the computer screen, for 90 minutes without being granted access to the Internet or their phone. Following either the Stroop task (FATIGUE) or magazine reading session (CONTROL), the subjects' fatigue, motivational and anxiety state were assessed by means of the MFI, IMI and STAI questionnaires, respectively (see above and Figure II.2.1C). Following these questionnaires, participants performed 4 blocks of Simple Reaction Time task (see above; 4 minutes) and then entered the MR scanner to perform the Missing Number task (see above and Figure II.2.1C). The average time delay between the end of the Stroop task or magazine reading and the beginning of the fMRI recording was 26.3 (SD = ± 9.51) and 31.2 (SD = 6.79) minutes, respectively. In both sessions, the Missing Number task included 4 runs. Every run included ten blocks of 6 trials (46,8 seconds per block). The reward condition varied block-wise, with 5 blocks (thus 30 trials) in each reward condition (1 point or 50 points). Every run started and finished with a 4.5-second blank screen. An additional 11.7-second blank screen was also shown at the end of each block. The total run duration was around 10 minutes. After the 2nd run, a 6-minute resting-state block was performed, during which the participants were instructed to close their eyes and let their mind wander without falling asleep. Following the last run of the Missing Number task, an 8-minute anatomical scan was performed. In the end of the experiment, the Simple Reaction Time task and the questionnaires (MFI and IMI) were performed again (see Figure II.2.1C). The total duration of a session was approximately 3 hours.

After the last session, the participants were informed about the total amount of monetary reward gained throughout the experiment.

II.2.3.5. Data and statistical analysis

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

Behavioral data

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

Generalized Linear Mixed Models (GLMMs) were performed in the SAS software. In all models, all fixed effects were allowed to vary between subjects in the random part of the model. In the modified version of the Stroop task, the number of blocks varied between participants due to the availability of the MR scanner as mentioned above (see Design and experimental procedure). In order to analyze the effect of time-on-task on accuracy and log-transformed RT, we grouped the data in 5 successive bins, from beginning to the end of the task. The GLMM analysis was performed on both accuracy and RT where the main factors

(time bins, congruency) and their interactions were modeled as fixed effects. In the Missing Number task, the model included the session condition (FATIGUE, CONTROL), reward cue (1, 50), number series (7, 8, 9) and their interactions as fixed effects. In the Simple Reaction Time task, the GLMM was performed on log-transformed RT with session condition (FATIGUE, CONTROL), time of performance (before, after MR scan), reward (1, 50) and their interactions as fixed effects.

fMRI data

Imaging acquisition parameters

Functional, resting-state and anatomical scans were performed with a 3T scanner (Achieva, Philips Healthcare, Eindhoven, The Netherlands) with a 32-channel phased array head coil using the following parameters:

- the functional and resting-state scans were acquired using echo time: TE = 27 ms, repetition time: TR = 2250 ms, flip angle: FA = 85°, 41 slices acquired in an ascending order, slice thickness = 3 mm, field of view: FOV = 123 x 123 mm², acquisition matrix = 80 x 80 (reconstruction 80²). Each run of the functional scan included 280 volumes while the resting-state scan consisted of 164 volumes.

- a 3D heavily T1-weighted image was also recorded at the end of the MRI session. This anatomical 3D sequence consisted of a gradient echo sequence with an inversion prepulse (turbo field echo) acquired in the sagittal plane using the following parameters: TR = 9.1 ms, TE = 4.6 ms, FA = 8°, 150 slices, slice

thickness = 1 mm, in-plane resolution = $0.81 \times 0.96 \text{ mm}^2$ (acquisition)
reconstructed in $0.75 \times 0.75 \text{ mm}^2$, FOV = $240 \times 240 \text{ mm}^2$, acquisition matrix = 296×251 (reconstruction 320^2), SENSE factor = 1.5 (parallel imaging).

fMRI preprocessing and analysis

BrainVoyager QX 2.8. (Brain Innovation BV, Maastricht, Netherlands) was used to preprocess and analyze the functional neuroimaging data acquired during the Missing Number task (see Figure II.2.1B). The preprocessing consisted of the following steps: slice time correction, motion correction and temporal filtering (high-pass, cutoff: 2 cycles/run). Motion correction was performed by aligning volumes from all runs to the first volume of the last run in a given session (FATIGUE and CONTROL), since the anatomical image was acquired in the end of the experiment. Hence, co-registration parameters were calculated only between the last functional run and anatomical image. The motion parameters (detrended motion variables, their temporal derivative and spikes in the motion pattern) and the global signal (average of brain-wise BOLD signal) were regressed out from the signal in each voxel using a GLM with these variables as predictors (Power et al., 2014). The spikes corresponded to volumes in which root mean square displacement from the previous volume exceeded 0.25 mm (Satterthwaite et al., 2013). In order to ensure that the motion correction did not itself cause artefactual results, we first confirmed that the participants' in-scanner motion did not differ between experimental conditions. To this end, we used a Generalized Linear Mixed Model (GLMM), considering either translation or rotation as dependent variable (derived as the root mean square of the temporal derivative of all 3 axes)

and reward and session conditions as binary predictors. None of the main effects or interactions were significant (all $p > 0.08$; see Figure II.2.2A). Then, all images were spatially normalized into Talairach space (Talairach and Tournoux, 1988). Spatial smoothing was performed with a Gaussian kernel with a full-width at half-maximum (FWHM) of 5 mm, in order to account for anatomical variability between subjects.

Statistical analysis was performed on group ($n = 25$) data using a General Linear Model (GLM) with random effects. Four contrasts were explored: reward ($[(HIGH\ FATIGUE + HIGH\ CONTROL) - (LOW\ FATIGUE + LOW\ CONTROL)]$, $\Delta BOLD_{REWARD}$); session ($[(HIGH\ FATIGUE + LOW\ FATIGUE) - (HIGH\ CONTROL + LOW\ CONTROL)]$, $\Delta BOLD_{SESSION}$); reward-session interaction ($[(HIGH\ FATIGUE - LOW\ FATIGUE) - (HIGH\ CONTROL - LOW\ CONTROL)]$, $\Delta BOLD_{INTERACTION}$), and task ($[(HIGH\ FATIGUE + LOW\ FATIGUE) + (HIGH\ CONTROL + LOW\ CONTROL)]$ -rest, $\Delta BOLD_{TASK}$).

Statistical maps (t-statistics) computed according to the contrasts of interest were displayed on the average of the participants' T1-weighted scans and corrected for multiple comparisons using the cluster-size thresholding plugin (1000 permutations; (Forman et al., 1995; Goebel, Esposito, & Formisano, 2006)). Unless otherwise specified, the voxel-level threshold was set to 0.001, uncorrected; while the cluster-level threshold was set to 0.05. Clusters surviving multiple comparisons correction were labeled. Brain-behavior correlations (Spearman's r-statistics) were performed between the participants' change in task-related BOLD responses across sessions ($\Delta BOLD_{SESSION}$, beta weights) on the one

hand and changes in questionnaire scores ($\Delta\text{MFI}_{\text{CTR-FAT}}$, $\text{STAI}_{\text{FAT-CTR}}$ & $\text{IMI-MissingNumber}_{\text{FAT-CTR}}$, see below) or behavioral performance ($\text{MissingNumber}_{\text{CTR-FAT}}$, $\text{Stroop}_{\text{FAT}}$, see below) on the other hand. Significant correlation maps (group map consisting of Pearson's r-statistics) were then compared with the reward statistical map ($\Delta\text{BOLD}_{\text{REWARD}}$, $[(\text{HIGH FATIGUE} + \text{HIGH CONTROL}) - (\text{LOW FATIGUE} + \text{LOW CONTROL})]$) and task activation maps ($[(\text{HIGH FATIGUE} + \text{LOW FATIGUE}) + (\text{HIGH CONTROL} + \text{LOW CONTROL})] - \text{rest}$, $\Delta\text{BOLD}_{\text{TASK}}$):

- the degree of overlap o , between the maps was computed at different thresholds as $o_{t_x, t_y} = 100 \cdot \left(\frac{\sum x_{t_x} \cap y_{t_y}}{N} - \left(\sum \frac{x_{t_x}}{N} \cdot \sum \frac{y_{t_y}}{N} \right) \right)$

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

- the correlation between average reward ($\Delta\text{BOLD}_{\text{REWARD}}$) or task ($\Delta\text{BOLD}_{\text{TASK}}$) t-values and each brain-behavior correlation coefficients (fatigue map) was computed across voxels (see for example Figure II.2.11). Because

neighboring voxels tend to correlate with each other, one cannot use standard correlation p-values. Therefore, we also used a bootstrap approach to determine statistical significance by computing the distribution of correlation coefficients on a thousand shuffled versions of the questionnaire scores. P-value was computed as: $\frac{(1+\sum C_{sh} \geq C)}{N+1}$, with C_{sh} corresponding to the vector of shuffled correlation coefficients and C to the actual correlation coefficient obtained on non-shuffled data.

Since the reward contrast ($\Delta\text{BOLD}_{\text{REWARD}}$) highlighted not only motivation-related regions but also the task-related ($\Delta\text{BOLD}_{\text{Task}}$) areas that were modulated by reward, we isolated regions-of-interest (ROI) that have been classically associated to motivation and reward processing (see Figure II.2.2B): dorsal ACC (dACC) = [± 5 6 40], ventromedial prefrontal cortex (vmPFC) = [± 7 48 2], anterior insula (aIns) = [± 36 14 13], nAc = [± 8 8 -2], ventral pallidum (VP) = [± 11 -2 -1], VTA = [± 3 -19 -10], SN = [± 10 -16 -9] and amygdala (Amg) = [± 22 , -16, -13]. The coordinates of these ROIs were taken on the basis of the Talairach atlas (Mai, Paxinos and Voss, 2008) wherein coordinates of voxels representing a given ROI were collected, and then a 5 mm spherical radius was generated around the center of this cluster by using the Talairach coordinate to spherical VOI plugin in BrainVoyager QX 2.8. (Brain Innovation BV, Maastricht, Netherlands).

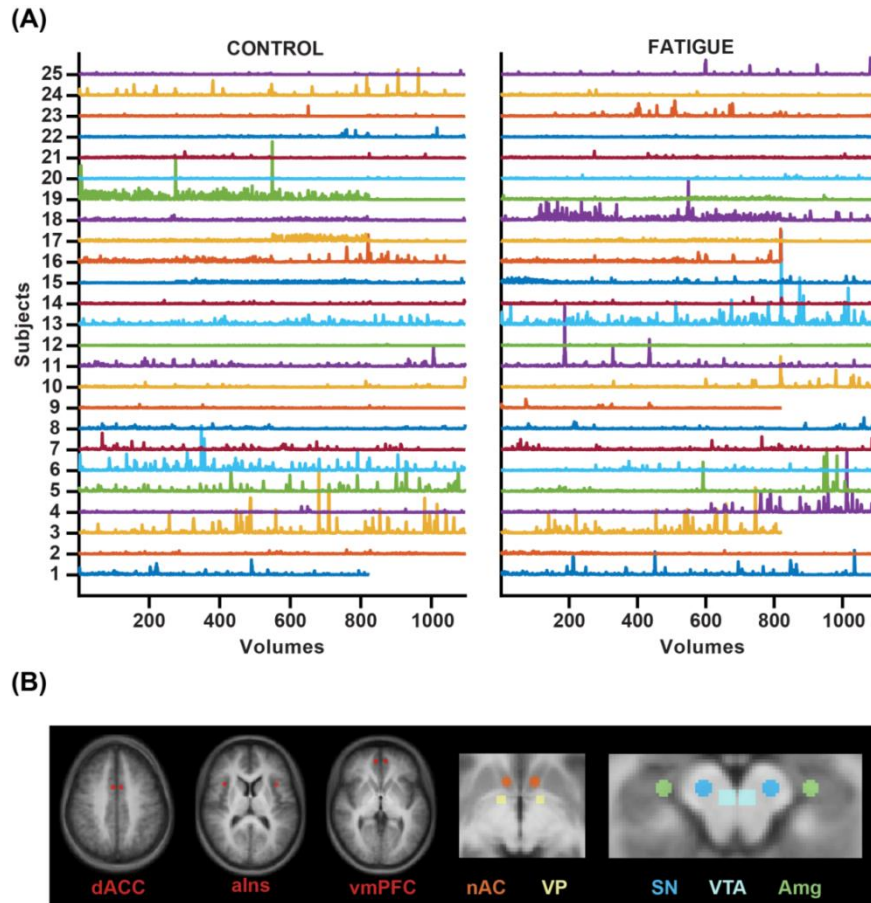


Figure II.2.2. Participants' in-scanner motion and ROI definition

(A) Individual in-scanner temporal derivative of the average translation motion is shown during the CONTROL (left panel) and FATIGUE (right panel) condition. For each subject ($n = 25$) and condition (2), the data from all acquisition runs (4) were concatenated together. Participants' motion did not differ between the conditions.

(B) ROIs classically implicated in reward processing and motivation, whose reward/task contrast and fatigue effects are illustrated in Panels A-D in Figure II.2.11.

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

II.2.4. Results

II.2.4.1. Psychometric and behavioral results

The FATIGUE manipulation led to increased subjective feeling of fatigue [$\Delta\text{MFI}_{\text{CTR-FAT}}$: $t_{(48)} = 3.91$, $p = 0.00029$; ΔMFI refers to the CONTROL-FATIGUE difference of the difference between the post- and pre-task measurements, $\Delta\text{MFI}_{\text{FAT}} = -6.84 \pm 6.96$; $\Delta\text{MFI}_{\text{CTR}} = -0.4 \pm 4.4$, mean $\pm$ SD], but also to increased anxiety ($\text{STAI}_{\text{FAT-CTR}}$: $t_{(48)} = 2.20$, $p = 0.0324$; $\text{STAI}_{\text{FAT}} = 37.92 \pm 6.99$; $\text{STAI}_{\text{CTR}} = 33.76 \pm 6.34$, mean $\pm$ SD). Participants' task interest/enjoyment was significantly lower for the FATIGUE than the CONTROL task (Stroop versus magazine reading: $\text{IMI}_{\text{FAT-CTR}}$: $t_{(24)} = -3.28$, $p = 0.0019$; $\text{IMI}_{\text{FAT}} = 3.27 \pm 1.41$; $\text{IMI}_{\text{CTR}} = 4.49 \pm 1.20$; mean $\pm$ SD). But importantly, the participants' interest/enjoyment in the Missing Number task did not differ across sessions ($\text{IMI-MissingNumber}_{\text{FAT-CTR}}$: $t_{(24)} = -0.58$, $p = 0.5662$; $\text{IMI-MissingNumber}_{\text{FAT}} = 3.83 \pm 1.23$; $\text{IMI-MissingNumber}_{\text{CTR}} = 4.03 \pm 1.29$; mean $\pm$ SD). None of these psychometric measures correlated between each other (all $p > 0.15$).

During the FATIGUE session, we found that general performance improved over time in the Stroop task due to training (GLMM: main effect of time-on-task; accuracy: $F(1,39249) = 20.56$, $p < 0.0001$; RT: $F(1,36477) = 32.73$, $p < 0.0001$; see Panels A & C in Figure II.2.3), but the effect of difficulty (i.e. congruency) increased with time-on-task (GLMM; accuracy: $F(1,39249) = 9.90$, $p = 0.0017$; RT: $F(1,36474) = 3.07$, $p = 0.0797$; see Panels B & D in Figure II.2.3), probably reflecting the buildup of fatigue effects on performance (congruency was

also significant on its own: accuracy: $F(1,39249) = 353.22, p < 0.0001$; RT: $F(1,36477) = 53.65, p < 0.0001$; see Panels A & C in Figure II.2.3). The effect of fatigue on Stroop task performance was indexed by taking the slope of the congruency x time-on-task effect on accuracy (StroopFAT). The steepness of this slope indicated how much the effect of congruency changed over time. We found that StroopFAT correlated negatively with $\Delta MFI_{CTR-FAT}$ (i.e. smaller increases of congruency effects were associated with larger subjective fatigue; Spearman $r = -0.47, p = 0.02$; see Figure II.2.3E). Even though this may seem counter-intuitive, it is in accordance with the compensatory hypothesis wherein maintenance of performance over time incurs the cost of increased subjective feeling of fatigue (Gergelyfi et al., 2015; Hockey, 1997; McAllister et al., 1999, 2001). As a side note, we found a positive correlation between StroopFAT and $IMI_{FAT-CTR}$ whose interpretation is unclear but may suggest that maintenance of performance over time leads to decreased intrinsic motivation in the task (Spearman $r = 0.52, p = 0.01$; no correlation with $STAI_{FAT-CTR}$: $p = 0.2597$).

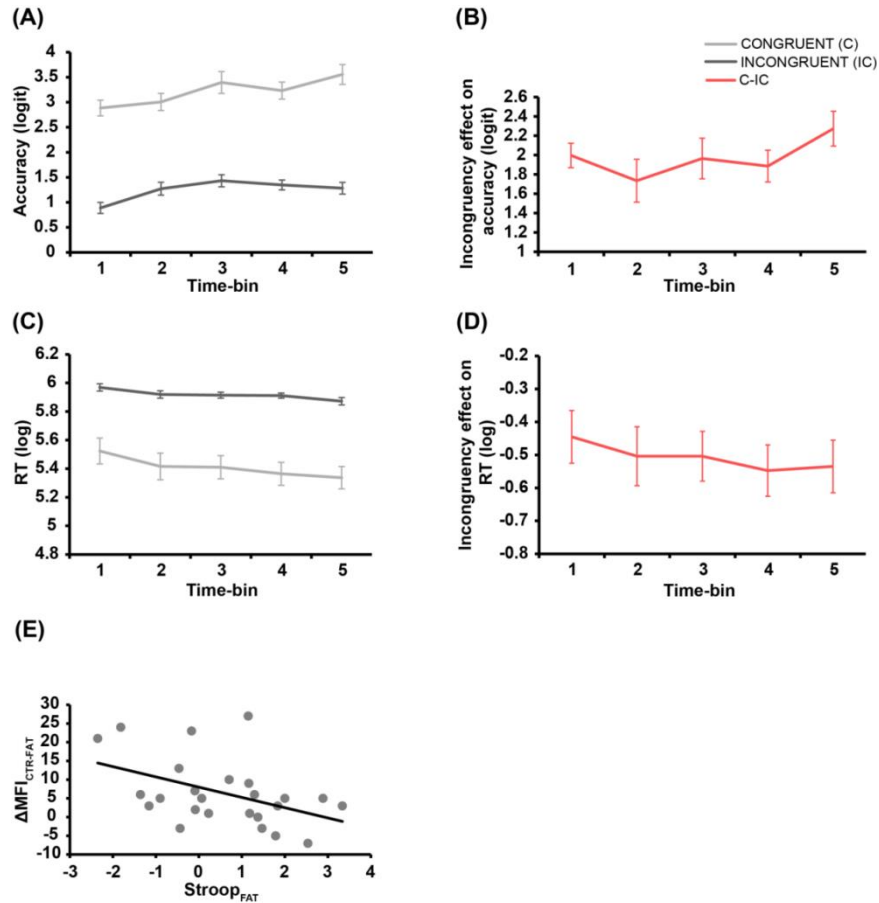


Figure II.2.3. Behavioral evidence for MF in the Stroop task

Error bars represent the standard error of the mean. **(A)** Mean accuracy (logit) in the congruent and incongruent conditions with time-on-task. **(B)** The change in the incongruency effect on accuracy (logit) over time was used to index objective fatigue. **(C)** Mean RT in the congruent and incongruent conditions with time-on-task. **(D)** The effect of incongruency on RT (log) with time-on-task. **(E)** Correlation between the change in incongruency effect (Stroop_{FAT}) on the x-axis and the change in $\Delta MF|_{CTR-FAT}$ on the y-axis. The maintenance of participants' performance

(low values on the x-axis) was associated with higher subjective fatigue (large values on the y-axis) presumably representing the involvement of compensatory mechanisms.

In the Missing Number task, we found a significant effect of SESSION on accuracy (GLMM with REWARD, SESSION and SERIESLENGTH as within-subject factors and MFI as between-subject factors; SESSION: $F(1,11744) = 4.00$, $p = 0.046$; see Figure II.2.4A), with participants performing worse in the FATIGUE than in the CONTROL session. There was no correlation between the effect of fatigue on the Missing Number task performance (accuracy: $\text{MissingNumber}_{\text{CTR-FAT}}$) and $\text{Stroop}_{\text{FAT}}$ on the one hand (Spearman $r = 0.11$, $p = 0.612$) and between $\text{MissingNumber}_{\text{CTR-FAT}}$ and questionnaire scores on the other hand ($\Delta\text{MFI}_{\text{CTR-FAT}}$, $\text{STAI}_{\text{FAT-CTR}}$ and $\text{IMI-MissingNumber}_{\text{FAT-CTR}}$; all $p > 0.2$). We also found a significant main effect of REWARD and SERIESLENGTH on Missing Number accuracy (REWARD: $F(1,11744) = 4.26$, $p = 0.039$; SERIESLENGTH: $F(1,11744) = 67.13$, $p < 0.0001$; see Figure II.2.4A), with participants performing better in the easy than in the difficult SERIESLENGTH conditions and when the REWARD was large. Importantly, none of the interactions were significant (all $p > 0.4$, see Figure II.2.4A), in particular the REWARD-SESSION interaction ($F(1,11744) = 0.36$, $p = 0.546$), indicating that the effect of reward on accuracy did not change across sessions.

The absence of changes between sessions in the behavioral signature of motivation was also confirmed with the Simple Reaction Time task. There was a significant main effect of REWARD on participants' RT ($F(1,24) = 8.10$, $p = 0.0089$; see Figure II.2.4B) but there was no main effect of SESSION ($F(1,24) = 1.31$, $p =$

0.2631; see Figure II.2.4B) or REWARD-SESSION interaction ($F(1,24) = 0.04$, $p = 0.8383$; Figure II.2.4B). The participants' RT was faster after than before the Missing Number task (effect of TIME POINT: $F(1,24) = 31.28$, $p < 0.0001$; Figure II.2.4B). Furthermore, the effect of TIME POINT on participants' RT changed across sessions ($F(1,24) = 4.36$, $p = 0.0475$; Figure II.2.4B), with the change in RT following the Missing Number task being larger in the FATIGUE ($t(1,24) = 5.42$, $p < 0.0001$) than the CONTROL session ($t(1,24) = 2.48$, $p = 0.0888$, PLANNED COMPARISON). There was no difference in performance in the Simple Reaction Time task between the CONTROL and FATIGUE sessions when performed either before ($t(1,24) = -2.23$, $p = 0.1449$) or after the Missing Number task ($t(1,24) = 0.51$, $p = 0.9559$; see Figure II.2.4B). Finally, there was neither significant TIME POINT-REWARD ($F(1,24) = 1.03$, $p = 0.3197$; see Figure II.2.4B) nor triple, TIME POINT-REWARD-SESSION interaction ($F(1,24) = 1.84$, $p = 0.1872$; see Figure II.2.4B).

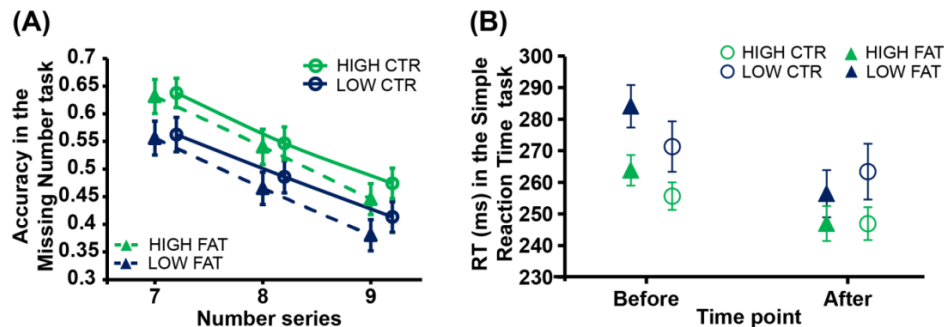


Figure II.2.4. Behavioral evidence for MF in the Missing Number task and for the absence of relation between MF and motivation

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

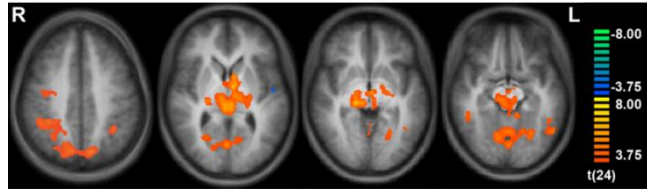
II.2.4.2. Whole-brain fMRI analysis

The effect of reward manipulation on BOLD responses was analyzed in two ways. First, we compared brain activations in high and low reward blocks $[(HIGH\ FATIGUE + HIGH\ CONTROL) - (LOW\ FATIGUE + LOW\ CONTROL)]$, $\Delta BOLD_{REWARD}$, random-effects group GLM analysis, voxel- $p < 0.001$, uncorrected; cluster-level corrected < 0.05). This analysis revealed modulations of brain activations in motor cortex, visual areas (Brodmann areas: 17, 18, 19), precuneus, fusiform gyrus (FFG), basal ganglia and thalamus but no effect in other components of the classical reward circuit [e.g. anterior cingulate (ACC) and nucleus accumbens (nAc); see Figure II.2.5A and Supplementary Table S1]. We also performed an event-related analysis of the BOLD response to the presentation of the reward cue $[(HIGH\ FATIGUE + HIGH\ CONTROL) - (LOW\ FATIGUE + LOW\ CONTROL)]$, random-effects group GLM analysis, voxel- $p < 0.001$, uncorrected; cluster-level corrected < 0.05). In contrast to the block design,

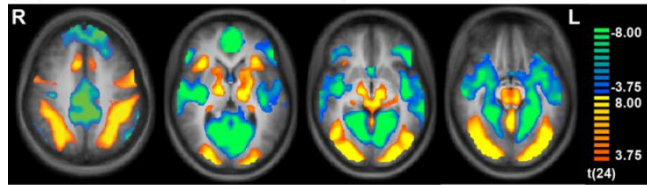
this event-related approach was more successful in highlighting significant responses in the classical reward circuit regions (see Supplementary Table S2).

In the block design, task execution evoked positive BOLD responses $((\text{HIGH FATIGUE} + \text{LOW FATIGUE}) + (\text{HIGH CONTROL} + \text{LOW CONTROL})) - \text{rest}$, $\Delta\text{BOLD}_{\text{TASK}}$, random-effects group GLM analysis, voxel- $p < 0.001$, uncorrected; cluster-level corrected < 0.05) in motor and visual areas (Brodmann areas: 17, 18, 19), ACC, FFG, thalamus and dorsal striatum (see Figure II.2.5B and Supplementary Table S3) while task-evoked signal decrease was observed mostly in the default mode network (DMN; see Figure II.2.5B and Supplementary Table S3). In the event-related approach, the task-evoked responses $((\text{HIGH FATIGUE} + \text{LOW FATIGUE}) + (\text{HIGH CONTROL} + \text{LOW CONTROL})) - \text{rest}$, see Supplementary Table S4) were similar to the ones observed in the block-based analysis (see Figure II.2.5B and Supplementary Table S3).

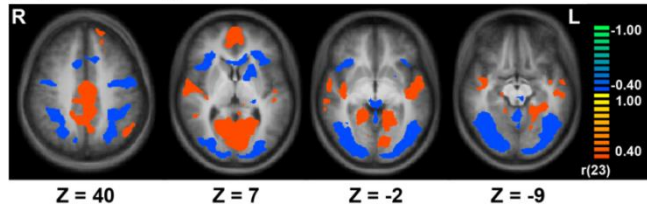
(A) Reward-related brain responses



(B) Task-evoked brain responses



(C) Main fatigue map



(D) Main fatigue map restricted to Missing Number task clusters

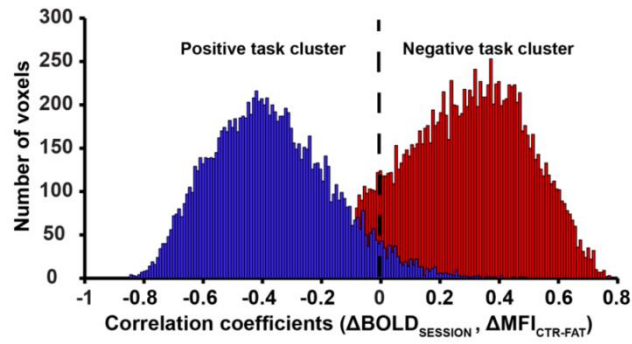


Figure II.2.5. The effect of the reward and fatigue manipulations on brain responses

(A) Block-based reward contrast $((\text{HIGH FATIGUE} + \text{HIGH CONTROL}) - (\text{LOW FATIGUE} + \text{LOW CONTROL}))$, $\Delta\text{BOLD}_{\text{REWARD}}$. Z coordinates are in Talairach space. (B) Task execution evoked positive BOLD responses $((\text{HIGH FATIGUE} + \text{LOW FATIGUE}) + (\text{HIGH CONTROL} + \text{LOW CONTROL})) - \text{rest}$, $\Delta\text{BOLD}_{\text{TASK}}$ in motor and visual areas (Brodmann areas: 17, 18, 19), ACC, FFG, thalamus and dorsal striatum while task-evoked signal decrease was observed mostly in the default mode network (DMN). (C) Correlation maps between the participants' subjective feeling of fatigue ($\Delta\text{MFI}_{\text{CTR-FAT}}$) and the session-related changes in BOLD responses $((\text{HIGH FATIGUE} + \text{LOW FATIGUE}) - (\text{HIGH CONTROL} + \text{LOW CONTROL}))$, $\Delta\text{BOLD}_{\text{SESSION}}$ were thresholded at voxel- $p < 0.05$, uncorrected and $p < 0.05$, cluster-level corrected). (D) Negative and positive correlations were found between the participants' subjective feeling of fatigue and their brain responses in the positive and negative Missing Number task clusters, respectively.

The session $((\text{HIGH FATIGUE} + \text{LOW FATIGUE}) - (\text{HIGH CONTROL} + \text{LOW CONTROL}))$, $\Delta\text{BOLD}_{\text{SESSION}}$ and reward-session interaction $((\text{HIGH FATIGUE} - \text{LOW FATIGUE}) - (\text{HIGH CONTROL} - \text{LOW CONTROL}))$, $\Delta\text{BOLD}_{\text{INTERACTION}}$ contrasts resulted in no significant effect in the block-based analysis at voxel- $p < 0.001$, uncorrected; cluster-level corrected $p < 0.05$. However, in the event-related analysis, the session contrast $((\text{HIGH FATIGUE} + \text{LOW FATIGUE}) - (\text{HIGH CONTROL} + \text{LOW CONTROL}))$ highlighted some significant changes across sessions (see left image in Figure II.2.6 and Supplementary Table

S5). We found that the FFG and the visual areas (Brodmann areas: 18, 19), which were highly active during the task (see Figure II.2.5B and Supplementary Table S3 and S4), were more deactivated with fatigue. These fatigue-induced deactivations were also observed in the block-based analysis when analyzed with a more liberal threshold (see right image in Figure II.2.6). These findings confirm that regions that are the most active during the task are also the most affected by fatigue. The reward-session interaction contrast also resulted in no significant effect in the event design $((\text{HIGH FATIGUE} - \text{LOW FATIGUE}) - (\text{HIGH CONTROL} - \text{LOW CONTROL}))$.

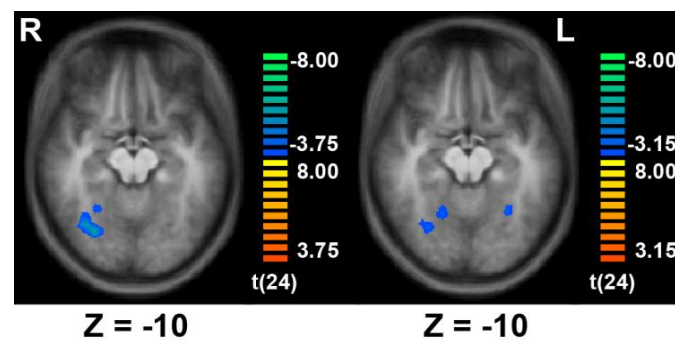


Figure II.2.6. Contrast between control and fatigue sessions

Event-related (left) and block-based (right) session contrast $((\text{HIGH FATIGUE} + \text{LOW FATIGUE}) - (\text{HIGH CONTROL} + \text{LOW CONTROL}))$. Event-related map is thresholded at voxel- $p < 0.001$, uncorrected and $p < 0.05$, cluster-level corrected. Block-based map was computed with more liberal threshold ($p < 0.005$), given lack of effect with conservative analysis. In both maps, FFG activations are decreased in the fatigue condition.

In order to verify that the motion correction procedure was not causing some of the observed effects, we reanalyzed the raw data without motion correction (see Panels A & B in Figure II.2.7) which led to results consistent with those obtained with motion corrected data (see Figure II.2.5A and II.2.5B).

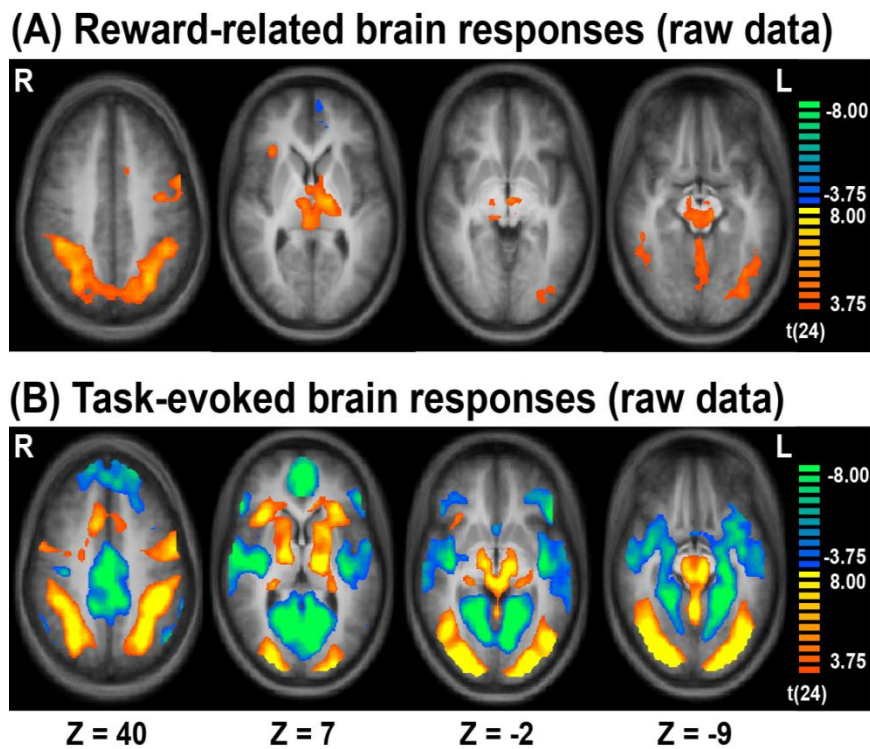


Figure II.2.7. fMRI analysis without motion correction

(A) Block-based reward contrast [(HIGH FATIGUE + HIGH CONTROL) – (LOW FATIGUE + LOW CONTROL)]. **(B)** Block-based task contrast [(HIGH FATIGUE +

LOW FATIGUE) + (HIGH CONTROL + LOW CONTROL)] – rest (voxel- $p < 0.001$, uncorrected; cluster-level corrected $p < 0.05$).

II.2.4.3. The neural correlates of MF

The effect of fatigue on the brain was evaluated by correlating the behavioral fatigue indices ($\text{MissingNumber}_{\text{CTR-FAT}}$, $\text{Stroop}_{\text{FAT}}$, $\Delta\text{MFI}_{\text{CTR-FAT}}$) with the between-session difference in brain activity $([(\text{HIGH FATIGUE} + \text{LOW FATIGUE}) - (\text{HIGH CONTROL} + \text{LOW CONTROL})], \Delta\text{BOLD}_{\text{SESSION}})$. In addition, we also performed similar correlations with the stress and motivation indices ($\text{STAI}_{\text{FAT-CTR}}$ and $\text{IMI-MissingNumber}_{\text{FAT-CTR}}$). We found that across the brain, changes in the task-positive and task-negative regions (see Figure II.2.5B and Supplementary Table S3) correlated negatively and positively with the change in MFI score, respectively (see Panels C & D in Figure II.2.5 and Supplementary Table S6). This correlation map will be hereafter referred to as the main fatigue map. When averaging the BOLD responses within the whole task-positive cluster, we found that the between-session change in activation in this cluster correlated strongly with the change in the subjective fatigue score (Spearman correlation between $\Delta\text{BOLD}_{\text{SESSION}}$ and $\Delta\text{MFI}_{\text{CTR-FAT}}$: $r = -0.70$, $p = 0.00011$; see Figure II.2.8A), while it failed to correlate with any of the other measures (Spearman correlations: $\text{Stroop}_{\text{FAT}}$: $r = 0.31$, $p = 0.1266$; $\text{MissingNumber}_{\text{CTR-FAT}}$: $r = -0.18$, $p = 0.4024$; $\text{STAI}_{\text{FAT-CTR}}$: $r = -0.1112$, $p = 0.5968$ and $\text{IMI-MissingNumber}_{\text{FAT-CTR}}$: $r = -0.052$, $p = 0.8066$; see Figure II.2.8A). Likewise, the average between-session decrease of BOLD responses in the task-negative network also correlated specifically, albeit positively with $\Delta\text{MFI}_{\text{CTR-FAT}}$ (Spearman correlation: $r = 0.54$, $p = 0.0055$; see Figure

II.2.8B), while it also failed to show any correlation with the other indices (Spearman correlation: $STAI_{FAT-CTR}$: $r = 0.28$, $p = 0.1786$ and $IMI-MissingNumber_{FAT-CTR}$: $r = -0.22$, $p = 0.2896$; see Figure II.2.8B) even though some correlations approached significance ($Stroop_{FAT}$: $r = -0.39$, $p = 0.0529$; $MissingNumber_{CTR-FAT}$: $r = 0.39$, $p = 0.0530$). In other words, subjective fatigue induced a global decrease in task-related activations/deactivations throughout the brain. Similar, albeit less strong results were obtained with the event-related response to the reward cue presentation, which also varied in proportion to the MFI score (Spearman correlation: $\Delta MFI_{CTR-FAT}$: $r = -0.4758$, $p = 0.0162$; all other correlations: $p > 0.1$, see Panel C in Figure II.2.8 and Supplementary Table S7; Spearman correlation: $\Delta MFI_{CTR-FAT}$: $r = 0.4411$, $p = 0.0273$; $STAI_{FAT-CTR}$: $r = 0.4956$, $p = 0.0118$, all other Spearman correlations: $p > 0.1$, see Panel D in Figure II.2.8).

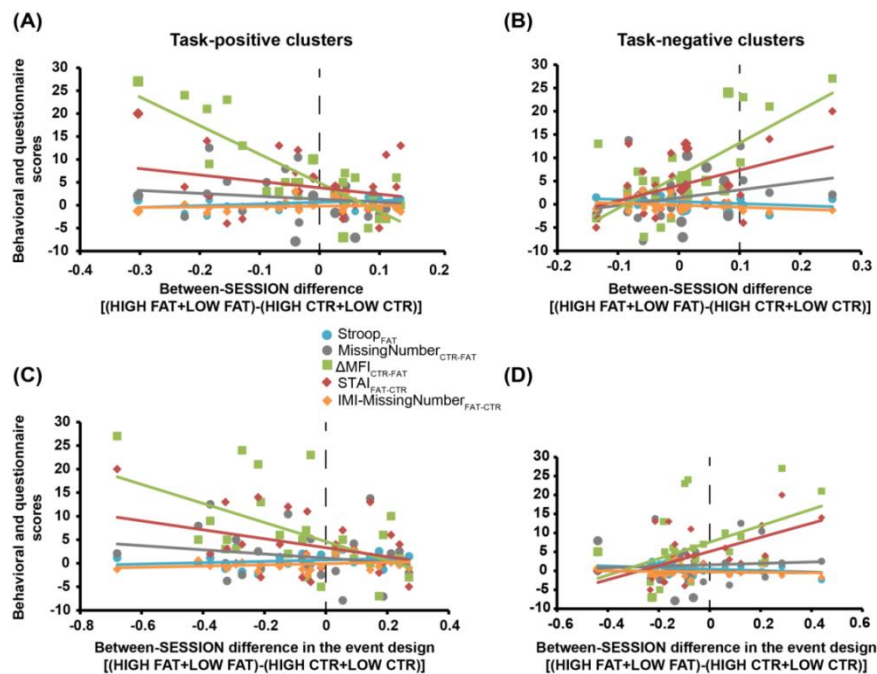


Figure II.2.8. Modulation of brain responses by subjective MF

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

Finally, in the resting-state data, we found that while the functional connectivity pattern did not differ significantly across sessions, the between-session change in connectivity also correlated with $\Delta\text{MFI}_{\text{CTR-FAT}}$, especially in the DMN (see Figure II.2.9 and Supplementary Table S8), such that connectivity increased between the seed regions of the DMN in proportion to the level of subjective fatigue.

II.2.4.4. No evidence for a causal link between MF and motivation

We then investigated the topographical relation between the reward-related brain activations ($\Delta\text{BOLD}_{\text{REWARD}}$, t-values, see Figure II.2.5A) and the fatigue map (correlation between $\Delta\text{BOLD}_{\text{SESSION}}$ and $\Delta\text{MFI}_{\text{CTR-FAT}}$, see Figure II.2.5C). The proportion of overlap between the maps was compared, at different thresholds, with the one expected by chance (see Methods). We found that the reward contrast maps failed to show significant overlap with the fatigue map, whereas we observed a strong overlap between the fatigue and the task-related maps. This was true both for task-positive and task-negative regions and with both block- (see Panels A-D in Figure II.2.10) and event-related designs (see Panels E-H in Figure II.2.10). We then looked at the voxel-by-voxel correlations between these maps (reward-related responses vs fatigue map, task-related responses vs fatigue map, in both designs, and for task-positive and task-negative regions). The fatigue map failed to show any significant correlation with the reward contrast map obtained from the block-based analysis (positive task regions: bootstrap significance test: $p = 0.4096$, negative task regions: $p = 0.2707$) but a strong correlation with the task-related map (globally: $p < 0.0001$; positive task regions only: $p < 0.0001$, negative task regions only: $p < 0.0001$; see Panels A & B in Figure II.2.11). We also found similar results when looking at the event-related reward contrast (all $p > 0.1$; see Panels C & D in Figure II.2.11).

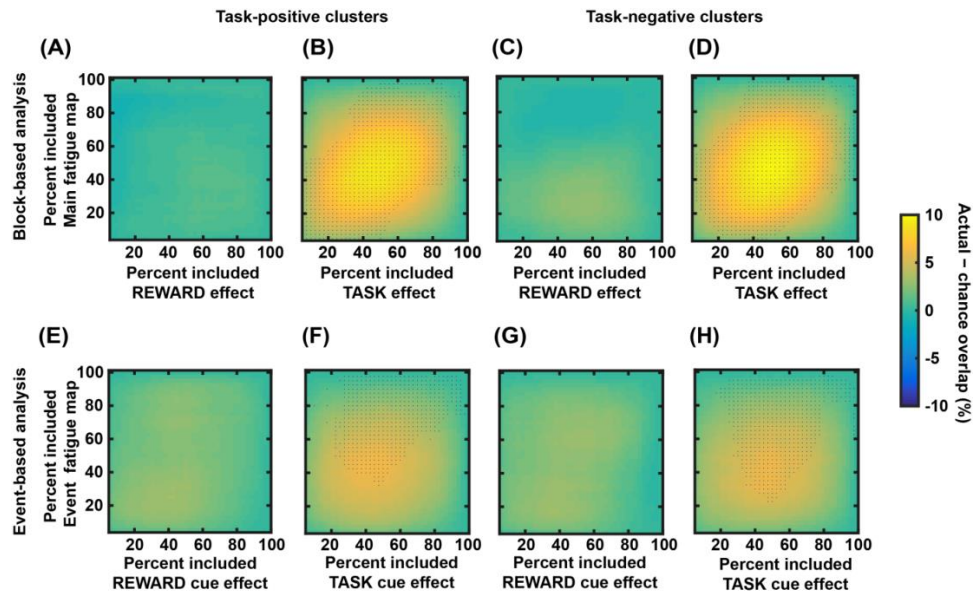


Figure II.2.10. Lack of overlap between reward and fatigue map in the block- and event-based analysis

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

based analysis: (E-F) Overlap between the event fatigue map and the reward cue effect **(E)** or task cue responses **(F)** in the positive Missing Number task clusters. Same convention as in Panel A. **(G-H)** Overlap between the event fatigue map and the reward cue effect **(G)** or the task cue effect **(H)** in the negative Missing Number task clusters.

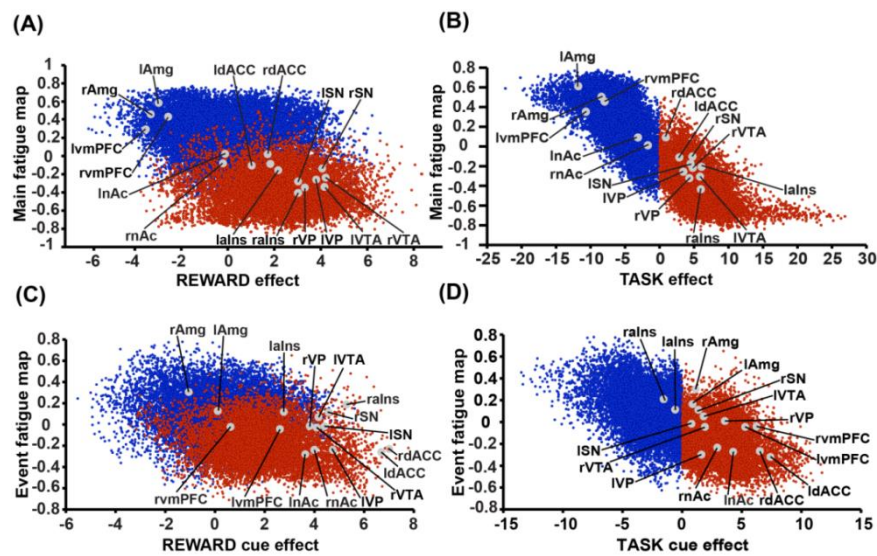


Figure II.2.11. Lack of correlation between reward and fatigue effects across voxels

(A-B): Block-based analysis: (A) Voxel-by-voxel correlations between the main fatigue map (correlation coefficients are plotted on the y-axis) and the reward-related responses (t-values are plotted on the x-axis) in the positive (in red) and the negative (in blue) Missing Number task clusters. The classical reward-motivational ROIs are shown as gray circles. **(B)** Voxel-by-voxel correlation between the main fatigue map and the task-related responses (t-values on the x-

axis). **(C-D) Event-based analysis: (C-D)** Voxel-by-voxel correlations between the event fatigue map (correlation coefficients are plotted on the y-axis) and the reward-related responses (t-values are plotted on the x-axis) on the one hand and between the event fatigue map and the task-related responses on the other hand in the positive and the negative Missing Number task clusters.

II.2.5. Discussion

In the present study, we investigated the relationship between the neural underpinnings of MF and extrinsic motivation to find out whether the buildup of MF is due to a disruption of the motivational circuits. To this end, we assessed the neural effects of MF on BOLD activations during the execution of a challenging working memory task wherein participants' extrinsic motivation was manipulated by different levels of monetary reward.

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

behavioral and neural markers, further confirming that motivation and fatigue were independent.

The motivation hypothesis led to another important prediction: the neural changes induced by fatigue should affect the motivation circuit specifically. We investigated the topographical relation between the reward-related brain responses and the fatigue maps. None of the fatigue maps inspected in this study showed overlap or correlation with the corresponding reward contrast maps. But strikingly, the fatigue maps were found to show a strong overlap and correlation with the task-related activations. These findings indicate that MF depressed activity brain-wide and not specifically in the regions that are implicated in the classical motivation circuit. The lack of specific alteration of the motivation circuit challenges earlier theoretical models that have proposed that fatigue issues from the disruption of motivation and cost-benefit evaluation processes (Boksem & Tops, 2008), specifically within the basal ganglia (A Chaudhuri & Behan, 2000; Abhijit Chaudhuri & Behan, 2004).

Decreases in brain activations in relation to the subjective or behavioral manifestations of MF were reported previously in patients with neurological disorders (Cook et al., 2007; Dobryakova et al., 2013; Miller et al., 2014; Mizuno et al., 2016). In healthy participants, two neuroimaging studies reported decreased activation in specific frontal brain regions in relation to behavioral markers of fatigue. Persson et al. (Persson et al., 2013) found that the fatigue-induced decrement in verb generation performance correlated with decreased activation in the left inferior frontal gyrus. Furthermore, Blain et al. (Blain et al., 2016) revealed

that fatigue increased inter-temporal choice impulsivity and that this behavioral change was related to decreased activation in the middle frontal gyrus. In a near-infrared spectroscopy study, Suda et al. (Suda et al., 2009) found that participants' subjective feeling of fatigue was associated with a decreased reactivity in the ventrolateral prefrontal cortex. Finally, alpha-band power in visual cortex has been shown to decrease with time-on-task commensurately with the increase in subjective fatigue (Ishii et al., 2013) and with the decline in performance (Tanaka, 2015). The results of the present study suggest that the seemingly specific alteration observed in these studies might in fact highlight the disruption of the brain regions that are the most active during the task.

Both subjective and objective consequences were observed following the fatigue manipulation: the participants experienced a higher feeling of fatigue, and performed worse in the Missing Number task. In agreement with the literature (Bryant et al., 2004; L. B. Krupp & Elkins, 2000), these subjective and objective dimensions of MF did not correlate with each other. A classical explanation to this lack of correlation is the compensatory hypothesis whose central tenet is that the initial maintenance of performance with time-on-task incurs a cost, manifesting itself phenomenologically as the subjective feeling of fatigue (Hockey, 1997). Therefore, when performance starts to drop, subjective MF is already high. Our findings in the Stroop task are in agreement with this view, since we found that the increase in the incongruency effect with time-on-task correlated negatively with the participants' subjective feeling of fatigue.

Strikingly, the neural alteration observed in relation to subjective fatigue failed to show any relation to task performance. This lack of consequence of decreased brain activations on performance may suggest the presence of compensatory networks, whose activity could allow performance to be maintained despite the alteration of the task network. However, we did not find evidence for such brain regions. One potential reason for this lack of evidence for compensation is that we measured only the BOLD signal in this neuroimaging study. Consequently, we were not able to measure all the possible neural changes that may have compensated the decreased BOLD activations (e.g. oscillatory activity). Likewise, BOLD measures did not allow us to detect changes in baseline brain activity. MF could have, for instance, increased baseline brain metabolism such that absolute activations during the task would be unchanged, but task-evoked responses would appear to be decreased, similarly to what we found in the present study. This hypothesis, however, fails to explain the accompanying diminution of the deactivations that we found following MF, since it would predict increased rather than decreased deactivations. Finally, the link between brain activations and task performance is certainly highly nonlinear, and may involve ceiling effects wherein, after passing some threshold, increasing brain activations further would fail to impact on performance. If our highly motivated participants were in this putative plateau region of the activation-performance function, decreasing activations closer to threshold would indeed have failed to have any observable consequence on behavior.

Another marker of fatigue in this study was the increased functional connectivity revealed within the DMN. Similar findings were reported in a recent resting-state fMRI study investigating the neural mechanisms of subjective fatigue (Esposito et al., 2014). Esposito et al. (Esposito et al., 2014) found that subjective MF increased resting-state signal fluctuations in the medial frontal gyrus, a region of the anterior DMN believed to be more active during self-referential thoughts. The causal relationship between the decrease in task-related activity and the increase in resting-state functional connectivity remains unknown but should be investigated in detail in future studies.

The efficacy of the reward manipulation was confirmed in both the Missing Number task and the Simple Reaction Time task, in which participants performed better for high than low rewards. The block-based analysis of the reward effect showed modulations of caudate, putamen, globus pallidus, thalamic nuclei, subthalamic nucleus, VTA and SN activity. Interestingly, major components of the classical motivation circuit, such as the ACC and the nAc failed to show differential responses in high versus low reward blocks. In contrast, these structures responded to the value of the reward indicated by the cue (even though nAc activations passed only at more liberal thresholds). These findings suggest that brain responses in these regions are sensitive to phasic presentation of reward magnitudes but are not involved in the maintenance of the motivational state over time.

In conclusion, the present study shows that MF does not disrupt the motivational circuit specifically but rather impairs a large network of brain

structures. These findings suggest that MF alters brain resources, or impairs their recruitment through other mechanisms than motivation in healthy participants, in agreement with our previous study (Gergelyfi et al., 2015). However, the nature of these resources and the mechanisms that drive their recruitment remain unknown. Future studies should address these questions, by using other neuroimaging techniques, such as magnetic resonance spectroscopy or arterial spin labelling.

II.2.6. Supplementary Tables

Brain area/structure	Peak x	Peak y	Peak z	t-value	p-value	Number of voxels
Reward-related activations (((HIGH FAT+ HIGH CTR)-(LOW FAT+LOW CTR)))						
BA4	46	-7	46	4.27	0.00027	128
BA5	22	-42	43	3.99	0.00053	3
BA6	45	-7	46	4.39	0.00020	416
BA7	-6	-76	43	5.49	0.00001	5972
BA17	19	-73	7	3.86	0.00074	4
BA18	3	-70	5	5.12	0.00003	813
BA19	-50	-58	-8	5.08	0.00003	1260
BA20	49	-35	-14	5.06	0.00004	166
BA23	0	-73	9	3.94	0.00062	11
BA24	-15	2	29	4.87	0.00006	137
BA27	19	-28	-3	3.91	0.00065	2
BA28	12	-19	-19	5.90	0.00000	115
BA30	3	-70	7	5.52	0.00001	777
BA31	-15	-70	28	5.38	0.00002	210
BA34	11	-16	-17	4.69	0.00009	11
BA35	14	-22	-18	4.89	0.00006	12
BA37	45	-40	-11	5.79	0.00001	1611
BA39	30	-58	39	4.12	0.00039	10
BA40	-36	-52	43	4.91	0.00005	2228
Corpus Callosum	0	-30	7	5.38	0.00002	118
Caudate Body	-9	-4	15	6.97	0.00000	3040
Caudate Head	-6	5	5	5.12	0.00003	55
Caudate Tail	-15	-20	19	4.80	0.00007	134
Putamen	-17	-1	15	5.19	0.00002	347
Medial Globus Pallidus	-15	-7	-2	4.88	0.00006	151
Lateral Globus Pallidus	-24	-13	1	4.82	0.00007	245
Anterior Nucleus	6	-7	13	7.37	0.00000	645
Medial Dorsal Nucleus	6	-10	13	7.30	0.00000	2135
Lateral Dorsal Nucleus	-10	-19	14	5.83	0.00000	205
Lateral Posterior Nucleus	-18	-22	13	6.26	0.00000	628
Midline Nucleus	-6	-16	14	6.09	0.00000	122
Ventral Anterior Nucleus	-10	-5	14	6.45	0.00000	394
Ventral Lateral Nucleus	10	-10	13	6.07	0.00000	1140
Ventral Posterior Lateral Nucleus	-15	-16	4	5.88	0.00000	525
Ventral Posterior Medial Nucleus	15	-19	1	5.79	0.00001	201
Pulvinar	3	-28	7	6.34	0.00000	2733
Medial Geniculum Body	15	-25	-2	7.47	0.00000	127
Lateral Geniculum Body	20	-25	-2	4.53	0.00014	18
Hypothalamus	-9	-8	-5	4.20	0.00032	34
Subthalamic Nucleus	14	-13	-1	5.18	0.00003	343
Mammillary Body	13	-22	-2	5.45	0.00001	450
Ventral Tegmental Area	5	-20	-12	5.44	0.00001	123
Substantia Nigra	9	-19	-14	7.40	0.00000	1280
Red Nucleus	6	-22	-14	6.71	0.00000	1671
Cerebellum	3	-52	-35	8.35	0.00000	138325
Reward-related deactivations (((HIGH FAT+ HIGH CTR)-(LOW FAT+LOW CTR)))						
BA6	-48	-10	7	-4.43	0.00018	31
BA13	-39	-19	19	-5.73	0.00001	1171
BA22	-51	-13	10	-4.68	0.00009	156
BA40	-48	-22	17	-4.13	0.00038	39
BA41	-51	-14	10	-4.63	0.00010	153
BA42	-55	-15	13	-4.04	0.00048	15
BA43	-51	-10	10	-4.26	0.00027	42

Table S1. Brain areas modulated by reward

Peak Talairach coordinates of the significant clusters in the reward contrast map (voxel-p < 0.001, uncorrected; cluster-level corrected p < 0.05). BA refers to Brodmann areas. CTR: CONTROL condition; FAT: FATIGUE condition.

Brain area/structure	Peak x	Peak y	Peak z	t-value	p-value	Number of voxels
Reward cue-related activations (([HIGH FAT+HIGH CTR])-(LOW FAT+LOW CTR))						
BA3	-41	-16	52	5.01	0.00004	82
BA4	49	-7	46	6.26	0.00000	837
BA6	-3	-1	49	6.37	0.00000	3757
BA7	13	-61	52	4.54	0.00013	245
BA13	39	14	13	5.97	0.00000	326
BA19	18	-83	40	3.91	0.00066	10
BA24	6	8	37	7.78	0.00000	1563
BA31	20	-28	38	5.51	0.00001	205
BA32	6	8	38	7.25	0.00000	1109
BA35	19	-22	-11	3.78	0.00091	1
BA44	-42	5	7	5.81	0.00001	75
Corpus Callosum	-11	25	0	4.52	0.00014	9
Caudate Body	-12	5	13	6.11	0.00000	1307
Caudate Head	-12	17	1	6.51	0.00000	1656
Putamen	-18	8	-2	6.91	0.00000	3908
Ventral Pallidum	-12	0	1	4.59	0.00012	123
Medial Globus Pallidus	-10	2	1	5.41	0.00001	324
Lateral Globus Pallidus	-15	5	-5	6.67	0.00000	525
Anterior Nucleus	9	-7	13	5.74	0.00001	272
Medial Dorsal Nucleus	-6	-19	4	6.48	0.00000	1036
Lateral Dorsal Nucleus	-12	-17	14	5.68	0.00001	84
Lateral Posterior Nucleus	-14	-18	13	5.36	0.00002	117
Midline Nucleus	-8	-19	14	5.06	0.00004	57
Ventral Anterior Nucleus	-12	-7	13	6.03	0.00000	101
Ventral Lateral Nucleus	12	-13	3	6.11	0.00000	921
Ventral Posterior Lateral Nucleus	-13	-16	7	5.07	0.00004	72
Ventral Posterior Medial Nucleus	-13	-18	6	4.69	0.00009	39
Pulvinar	-6	-25	4	5.17	0.00003	81
Hypothalamus	-8	-6	-3	3.78	0.00092	1
Ventral Tegmental Area	-5	-17	-11	4.41	0.00019	123
Subthalamic Nucleus	12	-16	-5	5.83	0.00000	161
Mammillary Body	-9	-19	4	5.50	0.00001	257
Substantia Nigra	12	-16	-7	5.60	0.00001	197
Red Nucleus	-6	-19	-1	4.78	0.00007	58
Optic Tract	2	-25	3	5.79	0.00001	60
Cerebellum	-27	-49	-23	7.28	0.00000	138325
Reward cue-related deactivations (([HIGH FAT+HIGH CTR])-(LOW FAT+LOW CTR))						
BA 6	23	23	57	-4.59	0.00012	359
BA 7	39	-64	43	-4.26	0.00027	42
BA 8	33	21	52	-3.84	0.00079	2
BA 39	42	-61	34	-4.59	0.00012	171
BA 40	42	-62	43	-3.91	0.00066	8

Table S2. Brain areas sensitive to the phasic presentation of reward

Peak Talairach coordinates of the significant clusters in the reward cue contrast map (voxel-p < 0.001, uncorrected; cluster-level corrected p < 0.05). BA refers to Brodmann areas. CTR: CONTROL condition; FAT: FATIGUE condition.

Brain area/structure	Peak x	Peak y	Peak z	t-value	p-value	Number of Voxels	Brain area/structure	Peak x	Peak y	Peak z	t-value	p-value	Number of Voxels
Task-related activations (([HIGH FAT + LOW FAT]) - ([HIGH CTR + LOW CTR]) - rest)							Task-related deactivations (([HIGH FAT + LOW FAT]) - ([HIGH CTR + LOW CTR]) - rest)						
BA1	-47	-23	32	12.08	0.00000	52	BA2	27	-37	65	-8.51	0.00000	99
BA2	-44	-26	54	13.50	0.00000	2696	BA3	36	-20	46	-8.56	0.00000	1543
BA3	-42	-25	56	14.72	0.00000	2442	BA4	33	-28	49	-8.29	0.00000	1050
BA4	-36	-23	55	12.09	0.00000	3627	BA5	-3	-41	48	-8.60	0.00000	1797
BA5	-36	-46	56	7.41	0.00000	129	BA6	-12	20	58	-10.02	0.00000	4380
BA6	-3	-1	55	11.72	0.00000	29752	BA7	-1	-54	52	-12.17	0.00000	5090
BA7	-24	-64	40	12.69	0.00000	19538	BA8	-24	29	50	-11.90	0.00000	5718
BA8	6	18	43	7.95	0.00000	650	BA9	-3	53	14	-14.77	0.00000	5756
BA9	-49	3	32	8.24	0.00000	2208	BA10	-3	53	13	-15.11	0.00000	3846
BA13	33	20	7	11.29	0.00000	3591	BA13	45	-16	4	-11.87	0.00000	6829
BA17	24	-86	-2	24.63	0.00000	4800	BA17	-6	-79	13	-17.05	0.00000	988
BA18	27	-85	-2	26.90	0.00000	10220	BA18	-9	-65	22	-19.78	0.00000	6526
BA19	32	-80	-10	20.40	0.00000	11867	BA19	-24	-49	-5	-22.34	0.00000	4039
BA20	50	-50	-14	7.72	0.00000	274	BA20	48	-6	-19	-7.86	0.00000	242
BA24	-4	5	47	8.02	0.00000	1269	BA21	48	-4	-19	-9.81	0.00000	2468
BA27	-18	-29	-2	4.60	0.00012	5	BA22	54	-10	7	-10.21	0.00000	3771
BA30	27	-76	5	7.43	0.00000	415	BA23	-9	-75	10	-16.45	0.00000	1217
BA31	18	-58	37	6.77	0.00000	1581	BA24	3	38	9	-10.67	0.00000	2865
BA32	6	14	42	9.36	0.00000	2750	BA25	3	14	-3	-8.72	0.00000	209
BA37	42	-64	-11	14.88	0.00000	8675	BA27	-15	38	0	-8.06	0.00000	124
BA39	-29	-56	39	10.36	0.00000	1783	BA28	-22	-20	-15	-11.73	0.00000	628
BA40	-36	-40	40	12.12	0.00000	15579	BA29	6	50	7	-10.65	0.00000	749
BA44	42	17	7	5.26	0.00002	74	BA30	-6	-66	7	-18.96	0.00000	3683
BA45	-30	25	7	8.14	0.00000	483	BA31	-9	-67	14	-15.02	0.00000	8547
BA47	32	24	2	6.76	0.00000	78	BA32	-3	47	7	-12.85	0.00000	2642
Caudate Body	-18	-4	19	11.21	0.00000	4976	BA33	-1	21	21	-4.72	0.00008	10
Caudate Head	15	14	4	5.59	0.00001	218	BA34	-27	2	-17	-11.88	0.00000	1303
Caudate Tail	-17	-20	19	8.89	0.00000	741	BA35	-20	-36	-10	-12.09	0.00000	860
Putamen	-18	5	15	10.44	0.00000	4356	BA36	-24	-43	-8	-17.76	0.00000	972
Ventral Pallidum	12	-4	1	6.97	0.00000	123	BA37	-24	-44	-8	-17.10	0.00000	693
Medial Globus Pallidus	15	-7	4	10.10	0.00000	719	BA38	33	4	-11	-9.13	0.00000	1368
Lateral Globus Pallidus	15	-5	4	9.27	0.00000	1111	BA39	-51	-64	22	-11.02	0.00000	2440
Anterior Nucleus	-10	-15	14	9.38	0.00000	216	BA40	-57	-52	28	-10.40	0.00000	2773
Medial Dorsal Nucleus	-11	-16	10	12.74	0.00000	701	BA41	57	-17	10	-8.83	0.00000	1780
Lateral Dorsal Nucleus	-12	-17	14	10.78	0.00000	256	BA42	59	-16	10	-9.23	0.00000	512
Lateral Posterior Nucleus	-14	-18	10	11.17	0.00000	552	BA43	54	-10	10	-9.59	0.00000	542
Midline Nucleus	-8	-17	14	8.39	0.00000	100	BA44	55	17	16	-5.12	0.00003	55
Ventral Anterior Nucleus	15	-9	10	12.38	0.00000	593	BA45	52	27	7	-9.46	0.00000	439
Ventral Lateral Nucleus	15	-10	10	12.99	0.00000	1922	BA46	48	32	13	-11.01	0.00000	747
Ventral Posterior Medial Nucleus	-13	-18	9	10.73	0.00000	160	BA47	-46	22	-2	-9.43	0.00000	1678
Ventral Posterior Lateral Nucleus	-13	-16	9	12.16	0.00000	276	Corpus Callosum	0	-43	13	-9.36	0.00000	1763
Pulvinar	-15	-23	16	9.40	0.00000	2007	Caudate Head	4	14	-2	-7.59	0.00000	300
Medial Geniculate Body	-11	-27	-5	4.74	0.00008	10	Putamen	31	-13	7	-9.35	0.00000	1526
Lateral Geniculate Body	25	-25	0	5.82	0.00000	109	Nucleus Accumbens	-6	7	-4	-4.55	0.00013	123
Hypothalamus	9	-8	-3	5.18	0.00003	17	Lateral Globus Pallidus	24	-4	-6	-6.54	0.00000	368
Subthalamic Nucleus	-9	-16	-2	10.66	0.00000	791	Medial Globus Pallidus	-21	-12	-6	-5.00	0.00004	37
Mammillary Body	-10	-16	-1	9.75	0.00000	385	Pulvinar	-9	-28	7	-4.54	0.00013	28
Ventral Tegmental Area	-5	-21	-9	7.88	0.00000	123	Amygdala	-21	-7	-18	-10.44	0.00000	2039
Substantia Nigra	-8	-25	-5	9.65	0.00000	1373	Hippocampus	-30	-22	-14	-14.34	0.00000	1207
Red Nucleus	-6	-25	-5	10.86	0.00000	2480	Optic Tract	-14	-7	-10	-4.75	0.00008	29
Hippocampus	30	-28	1	4.65	0.00010	22							
Cerebellum	29	-76	-16	15.39	0.00000	138325							

Table S3. Brain areas evoked by performing the task

Peak Talairach coordinates of the significant task-evoked clusters (voxel-p < 0.001, uncorrected; cluster-level corrected p < 0.05). BA refers to Brodmann areas. CTR: CONTROL condition; FAT: FATIGUE condition

Brain area/structure	Peak x	Peak y	Peak z	t-value	p-value	Number of voxels	Brain area/structure	Peak x	Peak y	Peak z	t-value	p-value	Number of voxels
Task cue-related activations (([HIGH FAT+LOW FAT]+[HIGH CTR+LOW CTR])-rest)							Task cue-related deactivations (([HIGH FAT+LOW FAT]+[HIGH CTR+LOW CTR])-rest)						
BA3	-49	-13	43	4.92	0.00005	306	BA1	61	-25	40	-5.03	0.00004	77
BA4	-3	-34	67	7.63	0.00000	1168	BA2	61	-19	26	-5.89	0.00000	448
BA5	-3	-37	55	8.81	0.00000	826	BA3	60	-22	38	-4.68	0.00009	77
BA6	-4	-1	52	7.84	0.00000	4187	BA4	60	-19	38	-4.01	0.00051	2
BA7	-2	-46	55	5.21	0.00002	141	BA5	40	-43	58	-5.47	0.00001	206
BA8	-29	42	38	5.18	0.00003	45	BA6	34	5	58	-8.29	0.00000	1780
BA9	-27	41	34	7.05	0.00000	279	BA7	-24	-52	58	-5.51	0.00001	1211
BA10	9	51	1	6.47	0.00000	1184	BA8	45	26	38	-8.39	0.00000	2344
BA17	-15	-94	-8	10.35	0.00000	832	BA9	42	23	37	-8.49	0.00000	1611
BA18	21	-85	-10	10.83	0.00000	2110	BA10	33	53	14	-9.51	0.00000	765
BA19	21	-84	-11	10.63	0.00000	1339	BA13	-33	22	4	-7.98	0.00000	1872
BA20	36	-41	-17	9.53	0.00000	424	BA17	-6	-78	10	-9.55	0.00000	1050
BA21	49	8	-23	5.17	0.00003	73	BA18	-9	-73	1	-13.49	0.00000	8669
BA23	-1	-31	28	5.51	0.00001	587	BA19	-8	-66	0	-8.89	0.00000	2284
BA24	-6	4	40	7.33	0.00000	2399	BA22	-45	-4	-3	-4.15	0.00036	4
BA27	-18	-31	-2	6.10	0.00000	174	BA23	-15	-70	13	-10.69	0.00000	423
BA28	22	-25	-8	5.01	0.00004	76	BA30	-3	-73	7	-10.58	0.00000	1839
BA29	3	-40	21	4.58	0.00012	87	BA31	-15	-66	14	-8.68	0.00000	1434
BA30	-18	-32	-3	4.86	0.00006	88	BA32	-5	24	42	-5.62	0.00001	27
BA31	3	-18	43	5.42	0.00001	571	BA36	-27	-40	-8	-4.50	0.00015	32
BA32	-6	6	40	7.41	0.00000	2242	BA37	-27	-45	-7	-4.47	0.00016	40
BA35	30	-28	-20	5.37	0.00002	86	BA39	43	-73	26	-4.74	0.00008	84
BA36	45	-39	-20	6.32	0.00000	92	BA40	42	-49	49	-7.72	0.00000	2507
BA37	42	-52	-17	10.72	0.00000	1653	BA41	-45	-20	13	-4.63	0.00011	56
BA38	46	11	-23	5.50	0.00001	120	BA43	-48	-17	16	-3.79	0.00090	1
BA39	43	-53	10	3.97	0.00057	4	BA44	54	17	17	-6.10	0.00000	680
Corpus Callosum	-15	29	7	7.80	0.00000	3498	BA45	-33	24	4	-8.09	0.00000	890
Caudate Body	-12	22	6	5.21	0.00002	226	BA46	42	41	7	-8.16	0.00000	1322
Caudate Head	-16	15	1	7.27	0.00000	1155	BA47	-33	24	2	-7.02	0.00000	468
Caudate Tail	-36	-26	-6	4.12	0.00039	4	Corpus Callosum	11	-1	22	-5.82	0.00000	168
Putamen	-16	11	1	7.84	0.00000	1695	Caudate Body	-18	-19	22	-6.14	0.00000	433
Lateral Globus Pallidus	-13	7	1	4.89	0.00006	24	Putamen	-27	-19	7	-5.89	0.00000	437
Anterior Nucleus	10	-15	14	4.61	0.00011	14	Lateral Globus Pallidus	-26	-18	5	-5.10	0.00003	35
Medial Dorsal Nucleus	-11	-16	10	6.50	0.00000	319	Ventral Posterior Lateral Nucleus	-22	-20	7	-4.05	0.00047	6
Lateral Dorsal Nucleus	12	-17	14	4.84	0.00006	29	Pulvinar	-23	-22	7	-4.56	0.00013	16
Midline Nucleus	9	-17	14	4.56	0.00013	32	Dentate	12	-45	-26	-6.79	0.00000	961
Ventral Lateral Nucleus	-12	-14	10	6.40	0.00000	172							
Ventral Posterior Nucleus	-14	-18	10	4.37	0.00021	8							
Ventral Posterior Medial Nucleus	-13	-18	9	4.51	0.00014	2							
Ventral Posterior Lateral Nucleus	-13	-16	9	5.57	0.00001	13							
Pulvinar	18	-34	4	7.59	0.00000	737							
Medial Geniculum Body	17	-26	-2	5.79	0.00001	50							
Lateral Geniculum Body	24	-26	-2	6.59	0.00000	34							
Subthalamic Nucleus	12	-17	-3	4.31	0.00024	8							
Mammillary Body	-10	-16	2	4.05	0.00046	6							
Substantia Nigra	15	-22	-6	5.45	0.00001	58							
Red Nucleus	6	-23	-3	4.51	0.00014	25							
Hippocampus	-33	-13	-17	4.06	0.00045	7							
Cytic Tract	2	-25	3	4.08	0.00043	15							

Table S4. Brain areas evoked by performing the task in the event-based analysis

Peak Talairach coordinates of the significant task cue-related clusters (voxel- $p < 0.001$, uncorrected; cluster-level corrected $p < 0.05$). BA refers to Brodmann areas. CTR: CONTROL condition; FAT: FATIGUE condition.

Brain area/structure	Peak x	Peak y	Peak z	t-value	p-value	Number of voxels
BA18	27	-69	-10	-6.06	0.00000	224
BA19	27	-67	-10	-6.06	0.00000	173
BA37	24	-51	-10	-4.18	0.00033	39

Table S5. Brain areas modulated by fatigue during the cue display

Peak Talairach coordinates of the significant session-related deactivations (voxel-p < 0.001, uncorrected; cluster-level corrected p < 0.05). BA refers to Brodmann areas. CTR: CONTROL condition; FAT: FATIGUE condition.

Brain area/structure	Peak x	Peak y	Peak z	r-value	p-value	Number of voxels	Brain area/structure	Peak x	Peak y	Peak z	r-value	p-value	Number of voxels
Main fatigue map (positive correlations)							Main fatigue map (negative correlations)						
BA 2	25	-37	67	0.44	0.02738	27	BA 2	-39	-29	31	-0.61	0.00113	349
BA 3	21	-28	58	0.57	0.00281	231	BA 3	-52	-10	43	-0.62	0.00100	142
BA 4	20	-28	57	0.51	0.01000	74	BA 4	-48	-7	47	-0.70	0.00012	531
BA 5	27	-40	58	0.66	0.00030	638	BA 6	36	-7	55	-0.81	0.00000	8709
BA 6	-18	23	56	0.72	0.00005	950	BA 7	-24	-67	49	-0.80	0.00000	4636
BA 7	-1	-40	46	0.72	0.00004	3732	BA 8	6	18	43	-0.51	0.00972	192
BA 8	-24	29	50	0.75	0.00001	1116	BA 9	-48	6	28	-0.70	0.00009	1220
BA 9	-3	50	14	0.71	0.00006	2660	BA 10	-33	41	19	-0.52	0.00818	90
BA 10	-3	50	13	0.73	0.00003	2117	BA 13	36	20	1	-0.67	0.00024	974
BA 13	33	-22	16	0.77	0.00001	2666	BA 17	-15	-94	-2	-0.73	0.00004	1062
BA 17	-6	-82	7	0.66	0.00030	596	BA 18	31	-88	1	-0.79	0.00000	2401
BA 18	-21	-54	4	0.73	0.00004	4219	BA 19	-42	-68	-14	-0.82	0.00000	1997
BA 19	-15	-49	1	0.68	0.00016	1639	BA 20	-36	-40	-18	-0.67	0.00021	236
BA 20	-30	-34	-15	0.52	0.00822	18	BA 24	15	8	46	-0.58	0.00221	211
BA 21	-57	-6	-5	0.67	0.00024	576	BA 30	25	-71	13	-0.55	0.00448	41
BA 22	-38	-55	19	0.67	0.00026	1624	BA 31	27	-75	18	-0.59	0.00186	42
BA 23	-3	-43	25	0.66	0.00035	1174	BA 32	9	11	43	-0.65	0.00048	574
BA 24	-2	-10	37	0.69	0.00014	1135	BA 37	39	-58	-11	-0.86	0.00000	1889
BA 27	-12	-34	2	0.54	0.00558	62	BA 39	43	-76	10	-0.56	0.00345	49
BA 28	21	-16	-17	0.69	0.00012	180	BA 40	-37	-43	46	-0.66	0.00034	2209
BA 29	3	-55	10	0.65	0.00049	259	BA 44	45	14	7	-0.68	0.00020	71
BA 30	-7	-55	7	0.77	0.00001	2513	BA 45	33	25	4	-0.67	0.00021	138
BA 31	-3	-43	40	0.78	0.00000	4962	BA 46	-45	20	25	-0.44	0.02912	9
BA 32	-2	47	9	0.64	0.00064	516	BA 47	-32	25	1	-0.66	0.00030	227
BA 34	24	2	-14	0.51	0.00884	95	Corpus Callosum	-3	24	10	-0.66	0.00034	1023
BA 35	-18	-36	-10	0.59	0.00175	163	Caudate Body	-15	-10	22	-0.60	0.00163	584
BA 36	-33	-34	-11	0.72	0.00006	505	Caudate Head	-10	20	4	-0.64	0.00050	258
BA 37	-30	-37	-8	0.71	0.00008	242	Caudate Tail	-19	-31	14	-0.57	0.00293	26
BA 38	36	3	-14	0.52	0.00778	120	Putamen	-21	8	7	-0.63	0.00077	796
BA 39	-40	-58	19	0.72	0.00004	2176	Medial Globus Pallidus	-15	-4	2	-0.42	0.03659	5
BA 40	51	-28	25	0.71	0.00007	846	Lateral Globus Pallidus	-15	0	9	-0.56	0.00371	79
BA 41	45	-31	17	0.65	0.00045	444	Anterior Nucleus	-9	-15	14	-0.50	0.01140	35
BA 42	59	-16	10	0.51	0.00846	196	Lateral Dorsal Nucleus	-10	-19	14	-0.62	0.00085	77
BA 43	-48	-13	14	0.49	0.01317	44	Lateral Posterior Nucleus	-20	-22	13	-0.63	0.00071	260
Corpus Callosum	-22	-49	6	0.58	0.00217	47	Medial Dorsal Nucleus	-9	-19	13	-0.64	0.00053	168
Putamen	33	-21	2	0.53	0.00630	9	Midline Nucleus	-8	-19	16	-0.64	0.00055	40
Pulvinar	-12	-31	4	0.58	0.00256	50	Pulvinar	-21	-28	10	-0.62	0.00103	424
Hippocampus	30	-10	-20	0.62	0.00099	179	Ventral Anterior Nucleus	-12	-3	13	-0.49	0.01205	12
Amygdala	21	-4	-11	0.49	0.01290	334	Ventral Lateral Nucleus	-14	-17	17	-0.54	0.00576	97
							Ventral Posterior Lateral Nucleus	-21	-22	9	-0.47	0.01854	13
							Ventral Posterior Medial Nucleus	-18	-22	9	-0.46	0.01940	15
							Red Nucleus	-6	-22	-5	-0.46	0.02153	14
							Cerebellum	33	-55	-26	-0.83	0.00000	138325

Table S6. Brain areas associated with the participants' subjective feeling of fatigue in the block-based analysis

Peak Talairach coordinates of the significant clusters in the main fatigue map (voxel-p < 0.05, uncorrected; cluster-level corrected p < 0.05). CTR: CONTROL condition; FAT: FATIGUE condition.

Brain area/structure	Peak x	Peak y	Peak z	r-value	p-value	Number of voxels
Event fatigue map (positive correlations)						
BA8	45	26	38	0.62	0.00087	53
BA9	45	31	30	0.73	0.00004	577
BA10	39	38	13	0.54	0.00495	457
BA13	36	20	1	0.76	0.00001	708
BA17	-12	-82	7	0.53	0.00644	257
BA18	6	-70	4	0.59	0.00187	731
BA19	6	-66	-1	0.48	0.01429	16
BA21	44	-3	-8	0.48	0.01479	18
BA22	48	-10	1	0.61	0.00115	238
BA23	9	-75	13	0.42	0.03778	4
BA30	-2	-73	6	0.50	0.01012	48
BA38	47	2	-8	0.59	0.00198	119
BA44	42	17	10	0.63	0.00078	118
BA45	49	26	21	0.63	0.00079	267
BA46	52	24	25	0.66	0.00032	561
BA47	36	20	-1	0.75	0.00002	408
Event fatigue map (negative correlations)						
BA6	-3	-1	49	-0.67	0.00027	2731
BA17	21	-91	-2	-0.51	0.00848	25
BA18	33	-71	-8	-0.69	0.00013	293
BA19	33	-68	-8	-0.59	0.00177	78
BA24	-3	-1	47	-0.59	0.00205	156
BA32	-3	14	40	-0.57	0.00317	396

Table S7. Brain areas associated with the participants' subjective feeling of fatigue in the event-based analysis

Peak Talairach coordinates of the significant clusters in the event fatigue map (voxel-p < 0.05, uncorrected; cluster-level corrected p < 0.05). BA refers to Brodmann areas. CTR: CONTROL condition; FAT: FATIGUE condition.

Seed ROI_1	Seed ROI_2	t-value	qFDR
right Middle Frontal Gyrus (rMFG)	lINS	4.5	0.0264
right Temporal Pole (rTpP)	ltoITG	4.35	0.0306
	rIns	4.15	0.0306
	laSMG	3.86	0.0328
	rpSMG	3.74	0.0328
	raSMG	3.74	0.0328
	left anterior Temporal Fusiform Cortex (laTFC)	3.6	0.0377
	rtoMTG	3.53	0.0386
left Superior Frontal Gyrus (ISFG)	rSPL	4.47	0.0287
left Superior Parietal Lobule (ISPL)	lsLOC	4.86	0.0113
right posterior Supramarginal Gyrus (rpSMG)	lAnG	4.33	0.0401
left Insular cortex (lIns)	rMFG	4.5	0.0264
left posterior Supramarginal Gyrus (lpSMG)	lAnG	4.17	0.0396
	right Lateral Parietal Cortex (RLP)	4	0.0396
	rAnG	3.87	0.0396
	right Inferior Frontal Gyrus, pars triangularis (rIFGtri)	3.64	0.0446
	Posterior Cingulate Gyrus (PCG)	3.56	0.0446
	LLP	3.53	0.0446
Lateral Parietal cortex (LLP)	rtoMTG	5.4	0.0031
	ltoMTG	4.92	0.0049
	ISPL	3.8	0.0386
	rpSMG	3.74	0.0386
	posterior Cingulate Cortex (PCC)	3.63	0.0386
	lpSMG	3.53	0.0386
	rSPL	3.53	0.0386
	rOFuG	3.37	0.0487
left Inferior Temporal Gyrus, temporooccipital part (ltoITG)	rTpP	4.35	0.0381
right Middle Temporal Gyrus, temporooccipital part (rtoMTG)	LLP	5.4	0.0031
left Middle Temporal Gyrus, temporooccipital part (ltoMTG)	LLP	4.92	0.0098
	laTFC	4.24	0.0249
	Medial Frontal Cortex (MFC)	3.88	0.0388
right Superior Parietal Lobule (rSPL)	ISFG	4.47	0.0287
left Angular Gyrus (lAnG)	rpSMG	4.33	0.024
	lpSMG	4.17	0.024
	laSMG	4.08	0.024
	lIns	3.75	0.0394
right Occipital Fusiform Gyrus (rOFuG)	ltoMTG	4.24	0.0498
left superior Lateral Occipital Cortex (lsLOC)	ISPL	4.86	0.0113

Table S8. MF globally increased resting-state connectivity

Correction for multiple comparisons was performed seed-wise at qFDR < 0.05.

ROI: region-of-interest.

III. DISCUSSION

In the above studies, multiple lines of evidence were accumulated in disfavor of the influential hypothesis that MF ensues from control mechanisms which modulate motivational processes and thus impede the recruitment of otherwise preserved cognitive resources. In contrast, this suggests that at least parts of the fatigue phenomenon ensue from progressive reduction of the pool of cognitive resources. In the first study (see Section II.1.), wherein the relation between MF and motivational state was studied using psychometric, objective behavioral and psychophysiological measures, we found that the markers of motivation or task engagement did not decrease over time as MF evolved and, furthermore, the detrimental effects of MF were not alleviated by manipulating motivation (see Section II.1.4.3-4.). The findings in the second, follow-up, study (see Section II.2.4.1-2. and II.2.4.4.) are in line with the previous ones (the effect of reward manipulation did not differ among the fatigue- and control condition) and, importantly, the fMRI investigation of the link between the neural underpinnings of MF and motivation also indicates that MF rather disrupts a larger network of brain structures than the ones known to be implicated in reward processing and motivation (see Section I.2.2.2-3.). Overall, these suggest that the mechanisms responsible for the buildup of MF alter or impair the recruitment of cognitive resources.

In what follows, I discuss recent proposals for the nature of the neurobiological resources whose alteration might contribute to the development of MF (Christie & Schrater, 2015; Holroyd, 2016). Then, I also argue why I consider

MF to be a multidimensional phenomenon and finally, I propose avenues for future research on MF.

The nature of cognitive resources

The lack of relation found between motivational states and MF at both the behavioral (Working memory/Missing Number task and Simple Reaction Time task) and psychophysiological level (EEG power, pupil- and skin conductance response, and fMRI BOLD signal changes) let us assume that the development of MF would rather be related to a change in brain resources. Several authors have proposed different accounts of the nature of these putative resources, which are detailed below (Christie & Schrater, 2015; Holroyd, 2016).

Holroyd (2016) proposes that MF does not stem from a depletion of a finite resource which drives cognitive control but from the accumulation of a toxic waste product in neural tissues produced by the exertion of cognitive control. The toxic waste product in question is amyloid- β ($A\beta$) peptides which, in healthy individuals, are continuously secreted into the interstitial fluid (ISF) during neural activity (Nitsch, Farber, Growdon, & Wurtman, 1993; Selkoe, 1993). If the $A\beta$ levels increase in the ISF a negative feedback loop is triggered which normalizes synaptic activity (Kamenetz et al., 2003). Then, the glymphatic clearance pathway removes the $A\beta$ waste from the brain through the exchange between the cerebral spinal- and interstitial fluid (Iliff et al., 2012, 2013). The secretion of $A\beta$ into the ISF varies over time (Cirrito et al., 2003). In healthy individuals, the rhythm of $A\beta$ level fluctuations across the day correlates with the sleep-wake cycle (Bateman, Wen,

Morris, & Holtzman, 2007; Kang et al., 2009) in a manner that the increased levels of A β are presumably related to wakefulness. The clearance of A β from the ISF increases with sleep while sleep deprivation destructs the regular morning reduction in its levels. Thus, the role of sleep might be the removal of the toxic waste (A β in ISF) accumulated across wakefulness (Xie et al., 2013) due to the deployment of cognitive control. According to Holroyd (2016), the subjective feeling of ME and MF would depend on the rate of ISF A β accumulation and with its overall levels, respectively. Furthermore, Holroyd (2016) also claims that these feelings would be attenuated by motivational incentives when the deployment of cognitive control was associated with more expected benefits than costs. The neural system which is presumably implicated in the production of waste product is the ACC-LC system (Holroyd, 2016). As discussed above (see Section I.1.3.1.3.1. or Section I.2.2.1-3.), the ACC is known to be involved in cognitive control, error-monitoring, effort-regulation/computation and reward-based decision-making (Miller & Cohen, 2001; Holroyd et al., 2002; Walton et al., 2006; Boehler et al., 2011), and it likely plays a role in the development of MF (Chaudhuri and Behan, 2000, 2004; Lorist et al., 2005; Boksem et al., 2006; Boksem and Tops, 2008; Moeller et al., 2012; Hockey, 2013). Under demanding control conditions, this brain region is assumed to recruit the LC which regulates arousal by NE release (Aston-Jones and Cohen, 2005; see Section I.1.4.1.). Holroyd (2016) suggests that the LC activity may contribute to the accelerated accumulation of A β by enhancing glial cells in response to high cognitive demands which also implies the production of neural waste, including A β , by facilitating learning processes involved in the shift from controlled to (control-independent) automatic processing, and by reducing the

volume of interstitial space which on the other hand increases the rate at which A β accumulates in the ISF.

As mentioned above, sleep is indispensable to our optimal functioning due to its restorative role. Earlier it was viewed as an “all-or-none”, ergo a global phenomenon which affect the whole brain and cannot co-occur with wakefulness (Krueger et al., 2008; Siclari & Tononi, 2017). However, in the last decades, there has been a tendency to view sleep as a local process which can co-occur with wakefulness in different areas of the brain (Siclari & Tononi, 2017). Based on animal studies (Krueger et al., 2008; Vyazovskiy et al., 2011), this sleep mode can be characterized by slow wave activity, which is a marker of Non-Rapid Eye Movement sleep, and by impaired behavior (Vyazovskiy et al., 2011). Vyazovskiy et al. (2011) found that in rats, who were awake over a prolonged period of time, the occurrence of local sleep in certain cortical neurons, accompanied by slow waves and by an impairment in a sugar pellet reaching task, was higher. According to these findings, it is probable that the extensive use of a brain area over a long period of time leads to the accumulation of a metabolic waste which results in local sleep and thus in MF.

According to Christie and Schrater’s (2015) hybrid model of limited resources and cost-benefit tradeoff, namely the optimal control model, the subjective feeling of MF can be viewed as a signal of partial glycogen depletion. This model of brain energy use over time proposes that cognitive resources, which can be dynamically utilized and replenished, rely on a metabolic substrate and that one’s performance can be altered by motivational factors. The metabolic resource

is glycogen which is a storage form of glucose in brain and can be found in astrocytic glial cells (Gailliot, 2008). Its levels have been observed to decrease during the day or sleep deprivation and to increase during sleep (Kong et al., 2002). Furthermore, Dienel & Cruz, (2015) also showed how important fuel glycogen is during neural activity by inhibiting its mobilization which resulted in excessive compensatory increase in glucose consumption. In light of these findings, it seems plausible that the depletion of glycogen stores due to sustained neural activity is implicated in the subjective feeling of MF. However, this hypothesis needs further experimental validation since Öz et al. (2007) did not find any detectable glycogen utilization in the visual cortex after visual stimulation.

Multi-dimensional nature of MF

As stated in the Introduction, MF primarily manifests itself as a subjective feeling (see Section I.1.1.1.) that can be assessed by self-reported questionnaires. In research and clinical practice, using questionnaires is advantageous (see Section I.1.3.1.1.), however, besides the difficulty to generalize questionnaire results (Ackerman, 2011; see Section I.1.3.1.1.), another problem is that they only indicate a limited part of such a complex phenomenon as MF. That is, they provide no substantial information about the causes and mechanisms involved in its buildup (Phillips, 2014; 2015; Veldhuizen, Gaillard, & de Vries, 2003), and thus impede our understanding of the entire MF phenomenon. In order to overcome this limitation and to know more about the dynamics of MF, the investigation of its objective behavioral and psychophysiological dimensions, and the interrelationship between the different dimensions is strongly advised (DeLuca, 2005; Phillips,

2014; 2015). For example, one would expect that the increased subjective feeling of MF is negatively correlated with the decrement in performance. However, as described in Section I.1.3.1.2., a discrepancy between these subjective and objective behavioral measures (high subjective MF associated with intact performance) may occur (Thorndike, 1900; Schellekens et al., 2000; Ackerman and Kanfer, 2009) which is presumably due to compensatory mechanisms to maintain performance (Hockey, 1997; 2013). This also indicates that focusing on only one dimension of MF is insufficient. Amongst the studies (Lorist et al., 2000; 2009; Boksem et al., 2005; Kato et al., 2008; Wascher et al., 2013; Käthner et al., 2014; Hopstaken et al., 2014; 2015; 2016) investigating the psychometric, behavioral and physiological correlates of MF in healthy individuals (average age around 22 years) while performing a cognitively demanding task over a prolonged period of time [1.5-6 hours; e.g. task-switching paradigm (Lorist et al., 2000; 2009), Go/NoGo task (Kato et al., 2008), visual attention task (Boksem et al., 2005; Wascher et al. 2013), n-back task (Hopstaken et al., 2014; 2015; 2016)], only a few of them looked at the relation between the different dimensions measured (Boksem et al., 2005; Wascher et al., 2013; Hopstaken et al., 2014; 2015; 2016). These latter studies provide more information about the dynamics of MF than the former ones which only report whether there was either an increase or decrease in the participants' subjective feeling of MF, performance and physiological activity independently of each other over time. For example, Boksem et al. (2005) revealed not only an increase in the participants' subjective ratings of aversion to continue performing a visual attention task and lower alpha power over TOT, which have been related to MF and task disengagement (Hopstaken et al., 2014; 2015; 2016

and see Section I.1.4.1.1.), but also a positive correlation between these variables making more probable that the phenomenon measured is indeed MF. Hopstaken et al. (2014; 2015) also found associations between the different measures of MF. The healthy individuals, who performed the n-back task over 2 hours, felt gradually more fatigued and less engaged in the task. These measures of subjective fatigue and loss of task engagement correlated with each other and with task performance: the more fatigued and the more aversion to task performance the participants felt, the worse they performed (Hopstaken et al., 2014; 2015). Furthermore, these variables were also associated with the decrease in the P300 amplitude (Hopstaken et al., 2014) which is a putative marker of MF/task disengagement.

In our papers (see Chapter II.), a multidimensional investigation of MF was also performed. In the 1st study, wherein the effects of MF on experience, behavior and autonomic processes (blink rate, HR(V), electrophysiology) were investigated over time while motivation was manipulated, we found that the participants' subjective feeling of fatigue increased and their performance in the WM task decreased while their blink rate and long-term HRV increased. The correlation analysis performed between these dimensions revealed a relation between the subjective feeling of MF and behavior on the one hand and between behavior and autonomic processes on the other hand (see Section II.1.4.1. and Figure III.1.). The higher the participants' subjective feeling of MF was, the smaller the decrement in their performance was, and the more their performance decreased the more their blink rate and long-term HRV increased. These correlations indicate

that compensatory mechanisms may indeed exist, and that blink rate and long-term HRV could be regarded as markers of MF. A decrease in the participants' heart rate was also revealed over time, however, it failed to correlate with either the participants' worsened performance or increased subjective feeling of MF. Thus, the change in heart rate could be due to another phenomenon which co-occurs, but does not share a common mechanism with MF. For example, an increase in blink rate itself over time could be related to the eyes' moisture level instead of MF since the eyes tend to turn dryer over time which can be attenuated by frequent blinks (Eckstein et al., 2017). That is why it is really important to use correlations to be able to relate a change in a psychophysiological variable not only to the time spent on a given activity.

In the 2nd study, wherein brain activity was compared between conditions of MF and control while motivation was manipulated, we found that the participants' increased subjective feeling of MF was accompanied with a global, brain-wide depression of the Missing Number task-evoked neural responses which was not associated with the performance decrements observed during MF (see Section II.2.4.3. and Figure III.1.). The lack of relation revealed between the changes in performance and brain activity under MF could be due to a task-unrelated network which is responsible for the maintenance of performance while task-related alterations in brain activity occur (Wang et al., 2016).

Overall, these findings indicate how complex MF is, and that multidimensional investigation is required in order to minimize the knowledge gaps about MF.

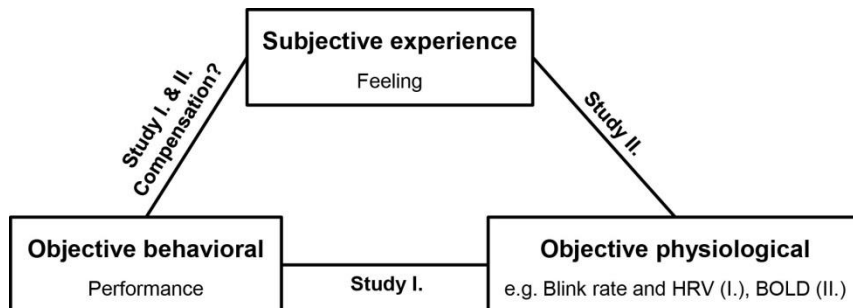


Figure III.1. Multidimensional investigation of MF

The subjective, objective behavioral and psychophysiological dimensions of MF and their interrelationships investigated in our studies.

Perspectives

As different sections of this thesis indicate (see Section I.1.1.1., I.1.3.1.1-2. and III.) a troublesome issue in fatigue research is the lack of a standard procedure to induce and measure MF. Thus, future research should focus on the development of reliable methods for inducing and measuring MF (Hornsby et al., 2016). It has been shown that cognitive control processes are sooner or later vulnerable to MF (see Section I.1.3.1.2.). However, it remains unclear how quickly MF evolves (Ackerman, 2011), and whether a particular process is more compromised by it than others (see Section I.1.3.1.2.).

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