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"*UNVEILING THE INTERPLAY BETWEEN SENSORY ATTENUATION AND FATIGUE: INSIGHTS FROM HEALTHY POPULATION AND NEUROLOGICAL DISORDERS*"

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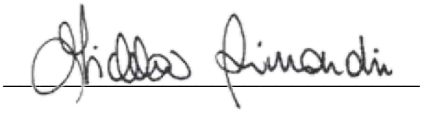
Signature 

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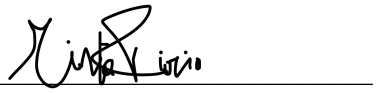
Signature 

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General Introduction

To navigate the world effectively, our brain integrates sensory inputs both within and outside the body. Proprioceptive cues tell us where our limbs are, interoceptive signals related to conditions like hunger or fatigue inform us about internal states, and sensory feedback — whether externally generated (e.g., visual cues, unexpected touch) or self-produced (e.g., self-generated touch) — helps us adjust to external demands and interact with our surroundings. Together, these inputs shape not only our actions but also how we perceive our bodies.

Fatigue offers a compelling example of this integration in action. It arises from the complex interplay between interoceptive and exteroceptive signals, and it alters how we perceive our body and control our movements. In conditions of intense physical exertion or prolonged mental focus, we often experience significant changes: our limbs may feel heavier, tasks seem more effortful, and movements lose their fluidity. But what is fatigue exactly? What mechanisms underpin this universal yet misunderstood experience?

Fatigue is more than mere exhaustion. It represents a complex interaction between the body's physical or cognitive limitations and the brain's ability to process and predict sensory information. This poorly explored brain-body connection holds significant implications for both neuroscience and clinical practice. The heart of my research is the investigation of the connection between fatigue and sensory attenuation —the brain's ability to predict and modulate the sensory consequences of self-generated actions.

Fatigue, whether physical or mental, is a universal experience and a central symptom in numerous neurological and non-neurological conditions (Dittner et al., 2004; Gallagher et al., 2010). Defined as an overwhelming sense of tiredness, exhaustion, and lack of energy (Di Vico et al., 2021), fatigue can manifest in multiple domains, from reduced motor performance (Enoka & Duchateau, 2008; Kluger et al., 2013) to impaired decision-making (Blain et al., 2016, 2019; Wiehler et al., 2022) and motivation (Gibson et al., 2003; Linnhoff et al., 2019; Marcora, 2008). Parallel to the study of fatigue is the investigation of sensory attenuation, i.e., the brain's predictive ability to reduce responses to the sensory consequences of self-generated actions (Blakemore et al., 2000). This perceptual mechanism is central for smooth sensorimotor control (Voss et al., 2007) and maintaining a clear sense of control over our movements (Haggard, 2017). Though traditionally studied in isolation, growing evidence suggests a critical interplay between fatigue and sensory attenuation (Kuppuswamy 2017, 2022).

The Sensory Attenuation Model of Fatigue (SAF; Kuppuswamy, 2017) provides a theoretical framework for this interaction. It posits that impaired sensory predictive mechanisms lead to a heightened sense of perceived effort, a core feature of fatigue. My work builds on the SAF model, addressing the interplay between fatigue and sensory attenuation

through a multidisciplinary approach. By integrating theoretical perspectives with experimental studies across clinical and healthy populations, my research aims to bridge gaps in current knowledge and advance understanding in this underexplored area.

Understanding the interaction between fatigue and sensory attenuation is particularly significant, as it offers a pathway to address the current shortage of objective methods for assessing fatigue. Fatigue is a debilitating symptom across a wide range of conditions, from neurodegenerative diseases like Parkinson's Disease (PD) to Functional Movement Disorders (FMD) (Finsterer & Mahjoub, 2014; Gallagher et al., 2010). It impairs quality of life, resists conventional treatments, and is often not alleviated by rest (Kostić et al., 2016; Pauletti et al., 2023). Despite its widespread impact, fatigue remains challenging to assess objectively, as its evaluation predominantly relies on self-reported, subjective measures.

The SAF model suggests that sensory attenuation may play a role in the mechanisms underlying fatigue, potentially serving as an objective and measurable marker of fatigue. By exploring the interplay between fatigue and sensory attenuation, we aim to pave the way for the development of novel, objective, and reliable methods for fatigue assessment across diverse populations and clinical conditions.

This thesis is organized into two parts, each addressing distinct but interconnected aspects of the interplay between fatigue and sensory attenuation.

The first part (Chapters 1 to 4) explores the theoretical and empirical basis of the relationship between fatigue and sensory attenuation, drawing on evidence from both clinical and healthy populations.

The first chapter provides a comprehensive review of the relationship between fatigue and sensory attenuation. It introduces key concepts, including definitions, theoretical models, and neurological evidence supporting their interaction. This chapter lays the groundwork for understanding how fatigue might interact with predictive mechanisms in the sensorimotor domain.

The second chapter focuses on the interplay between fatigue and sensory attenuation in PD, a condition characterized by motor impairments and a high prevalence of fatigue. By examining how fatigue interacts with sensory attenuation in PD, this study offers insights into the mechanisms linking fatigue and sensory processing in neurodegenerative disorders.

Expanding beyond PD, the third chapter explores the interaction between fatigue and sensory attenuation in FMD, a condition where motor symptoms occur without structural brain abnormalities. This preliminary investigation of sensory attenuation in FMD population provides valuable insights into functional mechanisms of fatigue and their sensory correlates.

The fourth chapter shifts the focus to healthy populations, with the aim of exploring whether the SAF model can also explain physiological fatigue. Moreover, this chapter embraces the complexity of fatigue by expanding the investigation on a potential link between sensory attenuation and performance fatigability— an objective decrease in performance due to induced fatigue. By exploring this interaction in non-clinical settings, this study sheds light on the broader relevance of fatigue-sensory attenuation interplay.

The second part of the thesis (Chapters 5 and 6) broadens the exploration of fatigue and sensory attenuation, investigating their potential interactions with other processes central to the brain-body connection, like body perception and sensory integration. This part aims to deepen our understanding of the interconnected roles of fatigue, sensory prediction, and multisensory processing. In this section, sensory attenuation is examined beyond the sensorimotor domain, delving into its auditory aspects, while fatigue is explored within the context of its mental domain.

The first chapter of Part 2 explores the impact of mental fatigue on hand weight perception, a novel paradigm for studying the relationship between fatigue and bodily self-perception. This study investigates whether mental fatigue alters the perceptual bias of underestimating one's hand weight, advancing our understanding of the embodied experience of fatigue.

The final chapter examines the influence of interoceptive vestibular signals on auditory sensory attenuation. Using stochastic galvanic vestibular stimulation (sGVS), this study investigates how interoceptive information shapes sensory predictive mechanisms, offering new perspectives on the multisensory integration underlying sensory attenuation.

The work conducted in the last three years made significant contributions to our understanding of fatigue and sensory attenuation's connection, bridging theoretical and empirical perspectives. Part 1 reveals the critical interplay between fatigue and sensory attenuation, offering insights into their co-modulation in healthy individuals, and in patients with neurological disorders. Part 2 extends this understanding into novel domains, highlighting how fatigue and sensory attenuation interact also with processes related to body perception and sensory integration.

Together, these studies establish a foundation for future research, bringing significant evidence to the SAF model and offering a fresh understanding of the connection between these two phenomena.

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PART 1

The Interplay Between Fatigue and Sensory Attenuation: Clinical Insights and Behavioral Evidence

(Studies conducted at the University of Verona)

Chapter 1: The interplay between fatigue and sensory attenuation

This chapter is based on the manuscript entitled *'Bridging Gaps Between Sense of Agency and Fatigue: A Scoping Review and a New Neurobehavioral Perspective'*, currently under review at *Cognitive, Affective, and Behavioral Neuroscience*.

Introduction

At the end of a long day filled with meetings, deadlines, and countless tasks, or following an intense workout that pushes our physical limits, we often experience a familiar sensation: fatigue. This pervasive feeling of exhaustion, both physical and mental, is a universal human experience (Di Vico et al., 2021). It serves as a reminder of our body's limits and the necessity for rest and recovery (Raizen et al., 2023). Fatigue affects not only our energy levels but also our motivation, concentration, and overall ability to engage with the world around us (Herlambang et al., 2019; Müller & Apps, 2019).

Despite its commonality, the underlying mechanisms of fatigue remain complex and poorly understood. What exactly causes this sensation? How does our body signal that we have reached the threshold of our physical or mental capabilities? Traditionally, fatigue has been considered a straightforward consequence of prolonged activity or exertion, leading to depletion of energy resources (Ament et al., 2009; Sahlin et al., 1998). However, emerging research suggests that the picture is far more complex (Marcora, 2008), involving not just physiological factors but also cognitive and perceptual processes.

A recent theoretical model, the Sensory Attenuation Model of Fatigue (SAF; Kuppuswamy, 2017), has begun to explore the idea that fatigue may be closely linked to our brain's predictive mechanisms, particularly in relation to sensory processing. The model posits that fatigue could be understood as a consequence of poor sensory attenuation, leading to an increased perception of effort during actions. This perspective shifts the focus from peripheral factors, like muscle fatigue, to central mechanisms within the brain that influence how we perceive and control our movements (Kuppuswamy, 2017; 2022).

Sensory attenuation refers to the phenomenon where sensations resulting from self-generated movements are perceived as less intense compared to externally generated stimuli (Shergill et al., 2003, 2005). This process is thought to arise from the brain's ability to predict the sensory consequences of our own actions, effectively attenuating the expected sensations (Bays et al., 2008; Kiepe et al., 2021). Sensory attenuation allows us to distinguish between sensations caused by our own movements and those caused by external forces (Blakemore et al., 2000), contributing to our sense of agency—the feeling that we are in control of our actions and their outcomes (Haggard, 2017).

The notion that impaired sensory attenuation could lead to fatigue introduces a novel way of understanding this sensation (Kuppuswamy, 2017). According to the SAF model, when the brain's predictive mechanisms are compromised, self-generated actions feel more effortful because the expected reduction in sensory feedback does not occur. This increased perception

of effort can contribute to feelings of fatigue, even in the absence of peripheral muscle exhaustion.

However, this model primarily stems from insights on pathological fatigue, such as that experienced in conditions like multiple sclerosis, Parkinson's disease (PD) or Functional Movement Disorders (FMD). Empirical evidence supporting the role of sensory attenuation in everyday, non-pathological fatigue is still limited. Consequently, significant gaps remain in our understanding of how sensory attenuation relates to fatigue in both healthy individuals and those with clinical conditions. Addressing these gaps is crucial for developing a comprehensive model of fatigue that accounts for both physiological and perceptual factors.

This chapter aims to explore the phenomena of fatigue and sensory attenuation in depth, examining their definitions, underlying mechanisms, and the evidence suggesting a possible interaction between them. We will begin by delving into the current understanding of fatigue, discussing traditional theories alongside newer models that emphasize cognitive and motivational contributions. Subsequently, we will introduce the concept of sensory attenuation, exploring how it contributes to our sense of agency and how its dysfunction might influence the experience of fatigue. Finally, we will integrate neuroimaging evidence, offering new insights into how these phenomena interact at neural levels.

Fatigue

The term "fatigue" is commonly used to describe the feeling of exhaustion, weariness, and lack of energy that can arise when the limit of available physical or mental resources has been reached (Di Vico et al., 2021). Fatigue is a physiological phenomenon whose manifestation in the general population tends to be transient and easily overcome with rest (Solomon & Manea, 2022). If fatigue persists and manifests with high intensity over a long period, then it is referred to as "pathological" fatigue. Pathological fatigue is experienced even at rest and limits the subject's daily functionality and quality of life (Finsterer & Mahjoub, 2014; Gallagher et al., 2010).

The term fatigue carries a profound duality, leaving it suspended between subjective feelings of fatigue (i.e., perceived fatigue) and the observable effects of this condition (i.e., objective fatigability) (Kluger et al., 2013). Also, fatigue is a multifaceted phenomenon encompassing mental and physical domains (Solomon & Manea, 2022). The following paragraphs will tackle the complexity of this phenomenon by providing an overview of subjective and objective dimensions of fatigue in the mental and physical domains.

Subjective perceived fatigue vs. objective performance fatigability

The crucial first step in understanding fatigue lies in differentiating subjective perceived fatigue from objective performance fatigability (Enoka & Duchateau, 2008; Kluger et al., 2013; Tanaka, 2015).

Perceived fatigue is the subjective feeling of tiredness, weariness, and exhaustion reported by the subject (Dittner et al., 2004). It can refer to a momentary and transient sensation experienced in the current moment (defined as "state" perceived fatigue) or to the usual feeling of fatigue, stable over time and assessed retrospectively (defined as "trait" perceived fatigue) (Enoka et al., 2021; Kowalsky et al., 2021).

A concept often misunderstood with that of perceived fatigue is the sense of effort. The sense of effort pertains to the feeling of strain and work concomitant with the execution of voluntary actions, with its intensity escalating as the level of exertion increases (Pageaux, 2016). The close connection between perceived fatigue and effort has been investigated in both physiological (de Morree et al, 2012; Pageaux et al., 2015) and clinical contexts, such as stroke (De Doncker et al., 2021; Kuppuswamy et al., 2015a; 2015b), multiple sclerosis (Kuppuswamy, 2022), and chronic kidney disease (Macdonald et al., 2012). The sense of effort is crucially involved in subjective perceived fatigue (Kuppuswamy, 2017) but it only partially coincides with it.

A key to dissociating the two phenomena rests in subjective motivation. Milyavskaya and collaborators (2021) found that participants perceived less fatigue and chose more effortful tasks if they were interested in and motivated toward them. This aligns with a previous study by the same authors, in which effort (induced by asking participants to manipulate a four-digit number mentally) was contrasted with boredom (induced by letting participants passively observe visual stimuli). Participants experienced more fatigue in the boredom condition despite reporting less effort (Milyavskaya et al., 2019). Conversely, when subjects were motivated and performed an interesting activity, they perceived less fatigue even for objectively demanding activities (Milyavskaya et al., 2021). These observations hint at a dissociation between the sensation of effort and perceived fatigue.

While perceived fatigue is subjective, performance fatigability represents a measurable, objective decline in cognitive or motor function during a task. This decline, characterized by reduced strength, speed, or accuracy (for example), gradually develops with prolonged activity and is assessed through objective task performance measures (Enoka & Duchateau, 2008; Enoka et al., 2021).

Mental and physical dimensions of perceived fatigue and performance fatigability

Perceived fatigue and performance fatigability can be found in mental and physical domains. Mental perceived fatigue can be further classified into cognitive and affective fatigue. Cognitive fatigue indicates a self-reported feeling of cognitive weariness, lack of mental energy, distraction, and confusion that results from increased cognitive load and reduced mental resources (Linnhoff et al., 2019; Solomon & Manea, 2022). Affective fatigue, on the other hand, is influenced by psychological factors such as mood, emotional exhaustion, motivation, willpower, and attitude and can occur in psychiatric disorders such as major depression and addiction (Solomon & Manea, 2022). In the physical domain, perceived fatigue is defined as the subjective feeling of exhaustion, weakness, and depletion of physical energy that could result from high-intensity muscular activity involving prolonged physical exertion (Billones et al., 2021; Pattyn et al., 2018).

On the other hand, performance fatigability at the mental level is defined as the progressive decline in optimal performance under acute or sustained cognitive load (Holtzer et al., 2011). It involves a reduction in concentration and increased reaction time during cognitive tasks. At the physical level, performance fatigability indicates the progressive decline of performance during demanding and intense physical tasks. Previous taxonomies have associated physical fatigability with neuromuscular fatigue, a progressive reduction in the ability of a muscle to produce or maintain the required power or force (Edwards et al., 1981; Kennedy et al., 2013). Physical fatigability can also be divided into central and peripheral components. Peripheral physical fatigability involves alterations at or below the neuromuscular junction; central physical fatigability is determined by a progressive reduction in the level of voluntary muscle activation mediated by intrinsic motoneuronal, spinal, and supraspinal factors (Allman & Rice, 2002; Boerio et al., 2005). In a pathological context, central fatigability can be frequently found in multiple sclerosis and Parkinson's disease, while peripheral fatigability is more likely in neuromuscular disorders and muscle ischemia (Solomon & Manea, 2022).

In conclusion, subjective perceived fatigue and objective performance fatigability transcend a simplistic and one-dimensional characterization. Given the purpose of my research, my focus will be on the subjective dimensions of mental and physical fatigue, which will be referred to from here on as "fatigue". When referring to the measurable and objective decrease in cognitive and physical performance, the term "performance fatigability" will be used. Correspondingly, "pathological fatigue" will allude to the symptom of fatigue encountered within pathological contexts and assessed by clinical approaches.

Theoretical models of fatigue

Despite decades of research and numerous theories on fatigue (Abbiss & Laursen, 2005; Finsterer & Mahjoub, 2014; Marcora, 2008), a comprehensive understanding remains elusive. This highlights the need to reject simplistic, unidimensional models and embrace the complex, multidimensional nature of fatigue mechanisms (Pattyn et al., 2018).

One of the most popular theories proposed to explain fatigue is the Central Governor Model (St Clair Gibson & Noakes, 2004). The model postulated that various afferent sensory inputs, such as sensory information coming from the cardiovascular system, the thermoregulatory system, and the muscular system, are used to regulate exertion to prevent threats to body homeostasis. Subconscious pathways continuously monitor these inputs, regulating physical performance through a central control system (i.e., the central governor) based on feedback and feedforward signals (Abbiss & Laursen, 2005; Tornero-Aguilera et al., 2022). Therefore, fatigue is experienced as the result of altered homeostasis (Gibson et al., 2003; Pattyn et al., 2018) and can be more generally described as a mental representation of the physiological changes occurring in the body (Damasio, 1999; Gibson et al., 2003).

However, the Central Governor Model has been questioned over the last few years as "[…] *inconsistent, unnecessarily complex, and biologically implausible […]"* (Marcora, 2008). The main criticism is related to the sense of effort, which, following the Central Governor Model, appears to be an unnecessary and unjustified element in the experience of fatigue (Marcora, 2008). The Central Governor Model argues that subconscious regulation of the afferent sensory systems by the central governor could cause exhaustion no matter how much effort is perceived.

To overcome this limitation, Marcora proposed the Psychological-Motivational Model based on the Motivational Intensity Theory (Marcora, 2008; Wright, 1996). This model suggests a view of fatigue as related to psychological and motivational factors, pointing to a central role of effort sensation in fatigue mechanisms.

In the Psychological-Motivational Model, fatigue is experienced when a task requires the maximum amount of effort the subject wants to exert (motivation) or when the subject believes to have exerted the maximum amount of effort possible and the continuation of exercise is perceived as impossible.

Methods for investigating fatigue

Measures of fatigue mainly rely on self-administered and self-report scales that assess state or trait fatigue. State fatigue (i.e., the momentary and transient feeling of fatigue) is commonly measured through the Visual Analog Scale (VAS), a one-dimensional fatigue rating

scale in which the level of perceived fatigue is indicated on a continuous line whose values range from 0 ("no fatigue") to, for example, 10 ("maximum fatigue")(Desramé et al., 2023).

Self-administered questionnaires are usually preferred for assessing trait fatigue (i.e., the persistent feeling of fatigue and the susceptibility to experiencing it). The most widely used questionnaires include the Fatigue Severity Scale (FSS; Di Vico et al., 2021; Lerdal, 2022), Multidimensional Fatigue Inventory (MFI; Smets et al., 1995), Fatigue Assessment Inventory (FAI; Shahid et al., 2011), and the Modified Fatigue Impact Scale (MFIS; Larson, 2013). In addition to these scales, there are also disease-specific scales such as the Parkinson Fatigue Scale (PFS-16; Brown et al., 2005) and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F; Smith et al., 2010), which are mainly used to carry out screening in patients with suspected pathological fatigue.

Despite the widespread use of self-reports for assessing perceived fatigue, recent research highlights the limitations of this approach and emphasizes the need for objective measures to complement subjective evaluations (Blain et al., 2016; Wiehler et al., 2022). According to these studies, the use of subjective rating scales and questionnaires is particularly limiting in that they rely on the subject's introspective abilities, which can sometimes be impaired, especially in clinical populations (González-Fernández et al. 2014; Wiehler et al., 2022). Furthermore, subjective scales lack specificity to fatigue, potentially conflating it with related yet distinct constructs like sleepiness and boredom, and may be susceptible to social desirability bias (Wiehler et al., 2022). In addition to these scales, therefore, these studies propose a more objective measure of fatigue. For example, a measure of cognitive fatigue is based on economic decisions, i.e., choices in which participants must decide their monetary benefits, which may be immediate but reduced or delayed but higher (Blain et al., 2016; Wiehler et al., 2022). Protocols involving economic decisions have indeed shown that in the presence of cognitive fatigue, participants tend to make more impulsive choices, opting for immediately rewarding alternatives that involve less effort (Blain et al., 2016; 2019; Wiehler et al., 2022). Given these results, economic choice protocols appear to be highly effective for objectively measuring cognitive fatigue.

Sensory attenuation

Have you ever tried to tickle yourself, only to find it impossible? This curious inability highlights a fundamental aspect of sensory processing: Sensory Attenuation (SA), the perceptual phenomenon where sensory stimuli resulting from self-initiated actions are perceived as less intense compared to the same stimuli externally generated (Dewey & Knoblich, 2014; Hughes et al., 2013). This process is fundamental to our interaction with the

world, enabling us to distinguish between self-generated sensory events and externally produced ones (Blakemore et al., 2000). SA is influenced by two key temporal mechanisms: temporal predictability and temporal control (Kiepe et al., 2021). Temporal predictability refers to the ability to anticipate when a sensory event will occur, while temporal control denotes the ability to directly control the timing of a stimulus through one's own behavior (Hughes et al., 2013).

SA is thought to have a strong adaptive nature, considering SA reduces the salience of predictable, self-produced stimuli, allowing us to focus cognitive resources on external, unpredictable, and potentially dangerous inputs (Myers et al., 2020; Shergill et al., 2003; 2005). Beyond its everyday implications, SA plays a central role in how we perceive, predict, and control our actions, contributing to our sense of agency—the feeling of being in control of our movements and their outcomes (Haggard, 2017).

Theoretical Frameworks Explaining Sensory Attenuation

Multiple models have been proposed to explain the mechanisms underlying SA. These models differ in scope, with some focusing on motor-based processes while others extend to broader frameworks like predictive coding and active inference.

The Comparator Model

The Comparator Model (Blakemore et al., 2001; David et al., 2008) is one of the most influential models for explaining SA. This model revolves around the concept of feedforward information, which predicts the sensory consequences of a particular motor plan (Blakemore et al., 1998, 2002; Synofzik et al., 2008).

When initiating a movement, the brain generates a motor command and an associated efference copy—a duplicate of the motor command used internally to predict the sensory outcomes of the movement. This efferent copy is then compared to the ongoing movement, allowing the central nervous system to assess any potential mismatch. When predicted and actual sensory inputs match, the sensory outcome of the action is attenuated, helping the generation of a sense of agency. A mismatch between predicted and actual sensory feedback generates a prediction error, which can disrupt SA and reduce the sense of agency over the action (Synofzik et al., 2008). The proposed main function of SA in these models is to anticipate and cancel the sensory effects of self-movement, thereby enabling the differentiation of self-initiated from externally caused changes in sensory inputs (Wolpert & Miall, 1996).

The phenomenon of tickling, as discussed earlier, provides a compelling demonstration of the functioning of this model. The inability to tickle oneself arises because the motor

command for the tickling action generates an efference copy predicting the sensory outcome. This prediction aligns perfectly with the sensory feedback, leading to attenuation of the ticklish sensation (Blakemore et al., 2000).

The Comparator Model postulates that SA only occurs with active, self-generated movements (Kiepe et al., 2021). However, evidence from different sensory domains presents contrasting findings. For example, Kilteni et al. (2020) demonstrated that tactile SA occurs only when the sensation is a direct consequence of active movement. In contrast, Kaiser and Schütz-Bosbach (2018) observed auditory SA even during passive perception of predictable stimuli, such as externally-generated auditory cues preceded by a predictive signal. This discrepancy underscores a critical limitation of the Comparator Model: its inability to account for variations in SA across distinct sensory modalities. This shortcoming is partly addressed by the predictive coding framework, which prioritizes the role of stimulus predictability in driving SA. Unlike the Comparator Model, predictive coding posits that SA can arise independently of sensory modality or whether the stimulus is linked to active or passive movements, provided the stimulus is predictable.

Predictive Coding Framework

The Predictive Coding Framework provides a more comprehensive view of SA by situating it within the brain's hierarchical predictive mechanisms (Idei et al., 2022). This framework posits that the brain constantly creates predictions about upcoming sensory changes based on prior information, which are then compared against actual sensory evidence (Kiepe et al., 2021). Discrepancies between predictions and actual inputs, known as prediction errors, serve as signals to update the brain's models, refining future predictions in a continuous Bayesian updating process (Friston et al., 2016). The ultimate goal of this system is to minimize prediction errors, thereby maximizing the utility of the predictive model (Kiepe et al., 2021). A key feature of this framework is active inference, where motor behavior is integral to minimizing prediction error. Self-initiated actions are performed to align sensory inputs with predictions, thereby reducing prediction errors and maintaining a coherent model of the environment (Parr et al., 2021). During the brief period when predicted outcomes and actual sensory feedback have yet to align, signals from self-initiated actions are attenuated. This attenuation marks these stimuli as originating from the self, effectively lowering their precision and drawing less attentional resources to them (Brown et al., 2013). This process is thought to allow the brain to allocate its computational resources toward unexpected external stimuli, which are more critical for updating the model and maintaining adaptive behavior. The predictive coding framework extends beyond the motor-based forward models by suggesting that sensory attenuation applies not only to self-generated actions but also to all anticipated

sensory inputs, regardless of their source. This broader applicability implies that attenuation depends on the predictability of stimuli, not solely on the self-initiation of motor responses. For example, predictable external stimuli might also be attenuated if their outcomes are accurately anticipated (Friston, 2013). However, self-generated actions are particularly reliable sources of prediction, making their sensory consequences more precise and thereby facilitating SA.

The predictive coding framework considers temporal predictability central to SA. According to this view, attenuation occurs because predictable stimuli—whether self-initiated or externally generated—require fewer attentional resources for processing. In contrast, forward models emphasize the necessity of self-initiated motor behavior for SA, suggesting that temporal predictability alone is insufficient to elicit attenuation.

Measuring Sensory Attenuation

To empirically investigate sensory attenuation, researchers have developed behavioral and neurophysiological paradigms. These methods evaluate the differential processing of self-generated versus externally generated stimuli across sensory modalities.

Force-Matching Tasks

The force-matching task is one of the most widely used paradigms for assessing sensory attenuation in the sensorimotor domain (Sato, 2008; Shergill et al., 2003; 2005; Weiss et al., 2011). In this task, participants are first let to experience a target force applied on their finger and then asked to reproduce the same target force either by pressing directly on the stimulated finger with the contralateral hand or using an external device (e.g., a button or a joystick). Participants tend to exert more pressure when reproducing the target force by directly touching their finger, compared to using an external device. This is due to SA: when participants press directly, the sensory feedback is more predictable. Conversely, when finger pressure is mediated by an external device, the force feels less directly controlled and therefore less predictable. This reduced predictability minimizes SA, allowing participants to reproduce the target force with greater accuracy. The force-matching task is particularly reliable because it provides a concrete demonstration of SA that aligns with everyday experiences. It underscores how the brain processes sensory feedback differently depending on whether an action is self-initiated or externally mediated (Shergill et al., 2003).

A recent study by Kilteni and Ehrsson (2017) raises important questions about whether the external mediation of an object is sufficient to disrupt SA. In their study, the authors used a drumstick to test the hypothesis that self-produced touches applied with a tool would be attenuated in the same way as direct touches made with one's fingers. Their results

demonstrated that self-produced touch applied via a hand-held tool was indeed subject to SA, similar to direct touch. This finding suggests that the somatosensory consequences of actions involving hand-held tools are predicted and attenuated just as they are during actions performed without tools. This highlights the effector-independent nature of forward sensory models, which allow hand-held tools to function as extensions of the hands in terms of sensorimotor predictions. However, their study also showed that the use of a completely external device, such as a slider, led to a more accurate reproduction of force.

Electrophysiological and Neuroimaging Techniques

SA has also been studied using neurophysiological and neuroimaging techniques. In the sensorimotor domain, the study by Palmer and collaborators (2016) provides a compelling example. The authors investigated whether the physiological reduction of cortical somatosensory evoked potentials (SEPs) during movement could explain SA. While the primary (N20–P30) and secondary (P45–N55) components of the SEP showed significant attenuation during movements, this attenuation was not significantly different between self-directed stimuli and externally generated indirect stimuli. This finding suggests that the physiological reduction of early SEP components is not the primary mechanism underlying SA. However, analysis of a later SEP component (N55–P100) revealed an overall decrease in mean amplitude during the self-condition compared to the external condition, indicating that attenuation of this component may causally influence self-generated stimuli perception, ultimately contributing to SA.

In addition, neuroimaging studies reveal decreased blood-oxygen-level-dependent (BOLD) responses in the somatosensory cortices during self-generated tactile stimuli (Bays et al., 2005; Blakemore et al., 2000; Gu et al., 2024; Shergill et al., 2003, 2013).

The neurophysiological underpinnings of SA have been also investigated in the auditory domain by comparing the evoked response to self-initiated and externally-initiated sounds (Han et al., 2021; Horváth, 2015). There is substantial evidence that certain components of the auditory-evoked potential are reduced in amplitude when participants listen to sounds initiated by their own motor actions (e.g., speaking), compared to when they passively listen to externally-produced sound (Ford et al., 2007). This effect has been most consistently observed with the N1 component (Elijah et al., 2018; Mifsud et al., 2016; Oestreich et al., 2016), but has also been identified with the Tb (Han et al., 2021; SanMiguel et al., 2013) and P2 components (Han et al., 2021; Knolle et al., 2012; Horváth & Burgyán, 2013). Neuroimaging studies complement these findings, showing that self-generated stimuli, such as speaking, attenuate activity in the Superior Temporal Gyrus (STG) (Agnew et al., 2013; Fu et al., 2006; Gu et al., 2024).

The insights gained from these neurophysiological and neuroimaging studies will be revisited in a later section of this chapter, where we will delve deeper into their implications for understanding the neural mechanisms underpinning SA.

The Sensory Attenuation Model of Fatigue

The Sensory Attenuation model of Fatigue (SAF; Kuppuswamy, 2017) represents an innovative framework for understanding how SA interacts with the experience of fatigue. As previously described, SA is strongly associated with the brain's ability to formulate sensory predictions about action outcomes. In typical conditions of intact SA, the brain effectively predicts the sensory consequences of self-generated movements, including the effort required for these actions. This predictive mechanism leads to a natural attenuation of self-produced stimuli, enabling self-produced actions to be perceived as relatively effortless.

Conversely, when SA is low or absent, the brain's ability to attenuate sensory feedback from self-generated actions is compromised, leading to imprecise predictions of action outcomes and an exaggerated perception of effort associated with self-initiated movements (Kuppuswamy, 2017).

In other words, when the sensory inputs from self-produced actions are not adequately attenuated, the mismatch between predicted and actual sensory feedback amplifies the perception of effort, which represents the basis of fatigue (Kuppuswamy, 2017).

According to the SAF model, the pathological high sense of effort is attributed to altered integration of sensory exteroceptive signals or heightened prediction errors arising from disruptions in sensory predictions (Kuppuswamy, 2022). This perspective differs from another theoretical model, that is, the metacognitive theory of dyshomeostasis, according to which fatigue, particularly chronic fatigue, can be described as a metacognitive phenomenon due to a reduction in the perceived sense of self-efficacy and control over one's body states (Stephan et al., 2016). In the presence of persistent dyshomeostasis, due, for example, to inflammation or neurotransmitter imbalances, continuous unsuccessful attempts to re-establish homeostasis lead to a reduced sense of control and self-efficacy (Stephan et al., 2016). The dyshomeostasis theory emphasizes the importance of internal bodily information, whereby the perception of a mismatch between expected and perceived body state is interpreted as interoceptive inconsistency.

In contrast, the SAF model emphasizes the importance of processing sensory information external to the body, such as visuo-tactile information related to the action, in explaining the persistence of fatigue, even when homeostasis is restored. Although interoceptive cues may also contribute to the experience of fatigue, according to the SAF model,

the determining factor in the perception of effort lies in the processing of afferent sensory information.

Despite offering an innovative perspective, the SAF model has some limitations. While the model establishes an interaction between SA, effort, and fatigue, it falls short of elucidating the specific mechanisms through which SA influences distinct dimensions of fatigue, such as performance fatigability. Furthermore, the SAF model is predominantly focused on pathological fatigue, offering limited insight into the mechanisms underlying physiological fatigue. This narrow focus underscores the need for further research to address both the physiological and pathological aspects of fatigue across healthy and clinical populations.

Neuroimaging evidence of shared neural mechanisms between SA and fatigue

Neuroimaging studies offer preliminary evidence to support the interplay between SA and fatigue. As previously discussed, one of the most widely accepted theories attributes fatigue to detecting homeostatic changes at both physiological and psychological levels, encompassing heightened ventilation, heart rate, temperature, and diminished attention and motivation (Gibson et al., 2003). Similarly, the experience of action attribution is based on the individual's ability to process interoceptive and exteroceptive information to compare one's expectations with the actual sensorimotor consequences of voluntary action (Blakemore et al., 2000; Seghezzi et al., 2019a, 2019b). To better understand the potential interactions between SA and fatigue, examining specific brain regions whose functioning may be shared between these two phenomena is crucial.

The role of the insula

The insula plays a crucial role in interoceptive processes, encoding information from homeostatic shifts and internal body signals (Craig, 2009; Hanken et al., 2014; Liu et al., 2018). For this reason, the insula may represent a critical region for both SA and fatigue.

Evidence supporting the role of the insula in interoceptive processes stems mainly from neuroimaging studies that have found a strong correlation between interoceptive accuracy and increased activation and gray matter volume of the insula (Critchley et al., 2004). Considering its involvement in processing unconscious internal body states and interoceptive sensations, the insula's contribution to self-generated action processing became evident (Haggard, 2017; Tisserand et al., 2023). Farrer and Frith (2002) identified a positive correlation between bilateral insula activity and the degree of self-attribution of actions. Similarly, other studies observed

amplified insular activations when contrasting externally generated stimuli with self-generated ones, underscoring insula involvement in discriminating between these sensory inputs (Gu et al., 2024; Stripeikyte et al., 2021) These findings suggest that the insula serves as a critical hub for multisensory integration, merging congruent multimodal sensory inputs linked to voluntary actions and attributing them to the self (Gu et al., 2024).

Bilateral lesions of the insula have also been linked to the emergence of a neuropsychological condition called anosognosia for hemiplegia (Karnath & Baier, 2010). Individuals with this condition believe that they still retain control over the paralyzed side of the body. The most accepted interpretation of this condition is that the lesion of the insula impairs the movement monitoring process that compared prediction and actual action feedback (Sperduti et al., 2011). Furthermore, the insula seems to be implicated in the pathophysiology of schizophrenia, a psychiatric disorder characterized by alterations of self-awareness and profound disturbances in the SA that often lead to the misattribution of one's actions to external sources (Kozáková et al., 2020; Maeda et al., 2013; Sheffield et al., 2020), thus further supporting the link between the insula and the SA.

The insula is also crucially involved in the perception of effort and perceived fatigue, given its contribution to processing sensory signals related to shifts in internal homeostasis (Kuppuswamy, 2022). In patients with Parkinson's disease, increased fatigue correlates with reduced metabolic activity in the insula and altered connectivity between the insula and several areas, such as somatosensory and prefrontal cortex (Cho et al., 2017; Kuppuswamy, 2022). Neuroimaging studies have also demonstrated reduced cortical thickness of the right insula and increased gray and white matter atrophy in the Anterior Cingulate Cortex (ACC) in multiple sclerosis patients with severe fatigue symptom (Andreasen et al., 2010; Hanken et al., 2014). Moreover, these patients usually show greater activation of the ACC during motor tasks compared to patients without the symptom of fatigue (Filippi et al., 2002).

The connection between SA and fatigue seems to be explained by the role the insula plays in the emergence of prediction errors. The SAF model postulates that fatigue arises from an amplified perception of effort due to unfulfilled predictions, that is, increased prediction errors (Kuppuswamy, 2017). According to this model, when the anticipated effort associated with an action is not met, individuals experience an altered sense of effort during the execution of the action. Considering the insula's involvement in detecting perturbations in bodily homeostasis and prediction errors, it is reasonable to hypothesize a direct involvement of the insula in the interplay between SA and fatigue.

In summary, the insula's involvement in motor prediction and bodily change recognition underscores its role as a nexus for the SA and the perception of effort, ultimately casting light on the onset of fatigue.

The role of the cerebellum

Widely recognized for its contributions to motor control (Bastian, 2006; Manto et al., 2012), the cerebellum also assumes a pivotal role in non-motor functions, such as self-motion perception (Baumann et al., 2015), action-feedback comparative process (Blakemore et al., 1998) and homeostasis regulation (Casamento-Moran et al., 2023).

To better understand the link between cerebellum functioning and SA, it is necessary to refer to the Comparator Model (Blakemore et al., 2001). According to this model, brain areas involved in action-feedback comparisons become more active whenever a mismatch occurs between the predicted and actual outcomes of an action (Welniarz et al., 2021). In a study by Blakemore and colleagues (1998), increased activation was observed in the right cerebellar cortex when the executed movement lacked the expected subsequent tactile sensation, in contrast to conditions where the self-initiated movement culminated with the expected sensory consequences. Similarly, a later study by the same group (Blakemore et al., 2001) showed that the activation in the right cerebellar cortex was higher as the temporal gap between the self-produced movement and the subsequent tactile feedback increased, further corroborating the involvement of this brain region in the comparison between expectations and feedback. Similarly, findings by van Kemenade et al. (2019), found a positive correlation between cerebellar activity and the temporal delay between movement initiation and visual feedback, especially when the subject initiated the action.

These findings underscore the cerebellum's central role in bridging predictive and comparative processes essential for SA (Blakemore et al., 2001; Tanaka et al., 2020; Welniarz et al., 2021; Kilteni & Ehrsson, 2020). A recent meta-analysis by Gu et al. (2024) further corroborates the cerebellum's involvement in SA. The analysis highlighted increased activation in the right cerebellar anterior lobe during self-generated conditions compared to externally generated stimuli. The authors propose that the cerebellum, in conjunction with sensory cortices, fronto-parietal networks, and the motor system, forms part of the feedforward network responsible for predicting action outcomes and comparing them with actual sensory feedback. Conversely, regions such as the insula, superior temporal gyrus, and middle temporal gyrus, which are more active during externally triggered stimuli, are implicated in a feedback network. Together, these feedforward and feedback networks collaboratively contribute to SA effect (Gu et al., 2024),

The role played by the cerebellum in motor control and homeostasis regulation appears to be crucial also in the context of fatigue. A study by Casamento-Moran and colleagues (2023) found that reduced cerebellar activity after a fatigue-inducing task correlated with lower

physical fatigue, increased variability in movement, and reduced motor control, suggesting a role for the cerebellum in fatigue regulation and self-movement perception.

Moreover, studies in pathological conditions have brought further evidence of cerebellum contribution to the genesis of fatigue (Capone et al., 2020; Novo et al., 2018). A significant example is represented by patients with Spinocerebellar Ataxia, where cerebellar lesions or dysfunction might hinder the adaptation to changing internal conditions, contributing to bodily dyshomeostasis and reported fatigue (Casamento-Moran et al., 2023). The cerebellum may modulate individual interoceptive capabilities, consequently influencing fatigue perception. In other words, these results suggest that the cerebellum might adjust how accurately, sensitively, and consciously we perceive internal body signals related to fatigue, thus influencing how fatigued we feel.

Given the relevance that the cerebellum has on action-feedback comparison processes, motor control, and interoception, we can consider the cerebellum a bridge region linking the SA with the experience of fatigue.

The role of the Prefrontal Cortex and its connections

Recent studies have highlighted the importance of prefrontal areas in the processes of self-attribution and self-other differentiation. A study by de Bézenac and collaborators (2018) showed that medial prefrontal cortex (mPFC) activity and its connections are involved in self-action attribution processes. Connectivity between mPFC and other areas (e.g., the anterior and paracingulate cortex and the lateral-occipital gyrus) was higher as misattributions of an outcome due to ambiguity increased.

The importance of PFC in the SA is crucial when looking at its extensive connectivity with regions implicated in SA-related, particularly the feedback (e.g., superior temporal gyrus and insula) and feedforward (e.g., cerebellum) networks (Gu et al., 2024).

Within the feedforward network, areas such as the cerebellum, pre-motor cortex, motor cortex, and fronto-parietal network are central to action prediction and align with the mechanisms of forward modeling. Specifically, parietal regions contribute to the comparison between predicted action and sensory consequences. Activation in the inferior parietal lobe, particularly the angular gyrus, was higher in case of a mismatch between expected visual consequences related to self-movement and real sensory feedback (Farrer & Frith, 2002). This discrepancy detection mechanism could contribute to SA by enabling individuals to distinguish between self-generated actions and externally induced events.

The PFC also plays a relevant role in the context of fatigue. The basal ganglia-thalamus-PFC circuit is considered one of the crucial networks involved in the pathophysiology of fatigue

in clinical conditions (Capone et al., 2020; Chaudhuri & Behan, 2004; Wylie et al., 2020). Specifically, pathological fatigue may be linked to disturbances in the non-motor functions of the basal ganglia (BG) and the connections among these subcortical structures, the thalamus, and the PFC (Chaudhuri & Behan, 2004; Dobryakova et al., 2013). This dysfunction appears to induce altered integration of sensory-motor-affective signals, potentially underpinning the heightened perception of effort, a critical element in fatigue (Di Vico et al., 2021; Kuppuswamy et al., 2022). Evidence supports the role of reduced activity of the BG-thalamus-PFC network in the onset of fatigue. Roelcke and collaborators (1997) observed a decreased glucose metabolism in the BG-Thalamus-PFC network in multiple sclerosis patients with pathological fatigue. In addition, a more recent study by Inglese and coworkers (2007) found a significant association between fatigue severity and blood flow and volume reduction in the thalamus and BG. Lastly, studies in patients with focal lesions in the ventromedial prefrontal cortex have reported higher levels of fatigue in these patients compared to healthy subjects or patients with other focal prefrontal lesions (Pardini et al., 2010).

Many additional studies support the contribution of the BG-Thalamus-PFC network in the onset of pathological fatigue. Correlations between alterations in dopaminergic and serotonergic neurotransmitter functions in the BG and related areas, and pathological fatigue have been found in several clinical conditions such as Parkinson's Disease (Pavese et al., 2010) and Chronic Fatigue Syndrome (Yamamoto et al., 2004).

Conclusion

In summary, the interplay between SA and fatigue provides a novel framework for understanding fatigue beyond traditional models. Sensory attenuation plays a central role in our ability to predict and process sensory feedback from self-initiated actions, reducing their perceived intensity and facilitating interaction with the external world. Fatigue, on the other hand, reflects the subjective and objective manifestations of a diminished capacity to perform or sustain activities, influenced by both physiological and cognitive processes.

The Sensory Attenuation Model of Fatigue bridges these concepts by proposing that disruptions in sensory attenuation can heighten the perceived effort of self-generated actions, forming a basis for the experience of fatigue. This model underscores the importance of predictive mechanisms in reducing the mental and physical load of self-initiated movements, a process that may be impaired in pathological conditions.

Neuroimaging findings support the shared neural basis of SA and fatigue, implicating regions such as the insula, prefrontal cortex, and cerebellum. These areas are central to integrating sensory predictions, motor control, and interoceptive signals, offering a biological

foundation for the connection between SA and fatigue. These findings emphasize that fatigue is not merely a peripheral phenomenon but deeply intertwined with central processes that shape our perception of effort and action.

Looking ahead, further research is needed to refine the SAF model, particularly its application to non-pathological fatigue and its relevance across diverse contexts. Exploring how SA disruption contributes to fatigue could improve our understanding of this universal experience and help the formulation of strategies for managing fatigue in both healthy and clinical populations.

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Chapter 2: Exploring Fatigue and Sensory Attenuation in Parkinson's Disease: Insights from the Force Matching Task

This chapter is based on the manuscript entitled '*Abnormal Sensory Attenuation as a Potential Biomarker of Fatigue in Parkinson's Disease: An Experimental Study*', currently in preparation for submission.

Introduction

Parkinson's Disease (PD) is one of the most prevalent neurodegenerative disorders, with its prevalence increasing significantly with age in the general population (Pringsheim et al., 2014). PD is clinically characterized by a combination of motor and non-motor symptoms. The hallmark motor symptoms include bradykinesia, rigidity, resting tremor, and postural instability, primarily resulting from the degeneration of dopaminergic neurons in the substantia nigra (Kalia & Lang, 2015). In addition to these defining features, non-motor symptoms—such as cognitive decline, mood disorders, and sleep disturbances—are highly prevalent and profoundly affect patients' quality of life (Barone et al., 2009). Among these, fatigue stands out as one of the most common non-motor symptoms, impacting approximately 33%–58% of individuals with PD (Di Vico et al., 2021; Kostić et al., 2016; Pauletti et al., 2023; Pavese et al., 2010).

Beyond its high prevalence, fatigue is frequently reported by PD patients as one of the most disabling symptoms, often ranking above other motor symptoms due to its profound impact on quality of life (Elbers et al., 2014; Barone et al., 2009). However, despite its high prevalence and debilitating nature, the underlying mechanisms of fatigue in PD remain poorly understood, and limited research has explored its pathophysiology (Chaudhuri & Behan, 2004; Pavese et al., 2010). Most studies investigating fatigue have found that its severity does not correlate with PD duration, motor disability, or specific characteristics of anti-parkinsonian medications (Abe et al., 2000; Pavese et al., 2010). Moreover, while comorbid factors such as depression, anxiety, and sleep disturbances are thought to exacerbate the subjective experience of fatigue, they do not entirely overlap with it (Hagell & Brundin, 2009; Lou et al., 2001; Pavese et al., 2010). In fact, fatigue often persists as an independent symptom in PD, present even in non-depressed and well-rested patients (Pauletti et al., 2023; Friedman et al., 2007).

As outlined in Chapter 1, the Sensory Attenuation model of Fatigue (SAF), proposed by Kuppuswamy (2017), offers a potential framework that may help explain pathological fatigue. This model suggests that fatigue could result from impaired sensory attenuation (SA), This impairment leads to a distorted perception of effort, as the brain struggles to estimate the exertion needed for self-generated actions. Such a heightened perception of effort is the basis of the experience of fatigue, where even minimally demanding tasks feel disproportionately effortful (Kuppuswamy, 2017; 2022). A comprehensive description of the SAF model can be found in Chapter 1.

While the SAF model offers a compelling theoretical approach, there is currently limited empirical evidence supporting its application to fatigue in PD. The objective of this study is to examine fatigue symptom in PD, particularly whether patients experiencing fatigue exhibit a

measurable reduction in SA. By directly testing this hypothesis, our study seeks to provide new empirical support for the SAF model, contributing to a more comprehensive understanding of fatigue in PD and, ultimately, improving clinical strategies for managing this debilitating symptom.

Material and Methods

Participants

A power analysis was conducted to determine the required sample size for detecting differences in SA across three groups: healthy controls (HC), Parkinson's patients with fatigue (PD_Fatigue), and Parkinson's patients without fatigue (PD_NoFatigue). The analysis specifically targeted the interaction between Group (HC, PD_Fatigue, PD_NoFatigue) and Condition (Direct vs. Indirect) within the Force Matching Task. Using a repeated measures ANOVA framework, the effect size was estimated based on pilot data. The power analysis, performed with G*Power software (Faul et al., 2007), assumed a medium effect size ($f = 0.25$), a significance level (α) of 0.05, and a desired statistical power of 0.90. The results indicated that a minimum total sample size of 54 participants (18 per group) would be required to achieve sufficient power to detect significant effects and interactions.

To ensure the robustness of the study and account for potential dropouts, a total of 61 participants were recruited: 40 individuals diagnosed with PD and 21 HC. Fatigue severity was assessed in all participants using the Fatigue Severity Scale (FSS), a validated 9-item self-report questionnaire designed to evaluate persistent fatigue over the past two weeks (Krupp et al., 1989). An FSS score of 36 or higher was used to identify severe or pathological fatigue. Based on FSS scores, PD patients were divided into two subgroups: 20 individuals with fatigue (PD_Fatigue, FSS score ≥ 36) and 20 without fatigue (PD_NoFatigue, FSS score < 36). Healthy controls were included only if their FSS scores were below the threshold, ensuring the absence of significant fatigue. Additional inclusion criteria included: (1) a normal cognitive assessment as measured by the Montreal Cognitive Assessment (MoCA) with scores ≥ 26 for all participants, (2) Hoehn and Yahr (H&Y) stage between 1 and 2 for PD patients, and (3) lateralization of motor symptoms predominantly on one side of the body. These criteria ensured a homogenous and clinically well-characterized sample for the study.

The three groups (PD_Fatigue, PD_NoFatigue, and HC) were matched for demographic variables such as age, sex, or education level. Additionally, the two PD subgroups (PD_Fatigue and PD_NoFatigue) showed no significant differences in clinical variables, including disease duration, PD subtype, Levodopa Equivalent Daily Dose (LEDD), and motor impairment as measured by the Unified Parkinson's Disease Rating Scale III (UPDRS-III; Fahn and Elton,

1987), suggesting that the PD subgroups were well-matched in all key variables other than fatigue severity.

The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee (Comitato di Approvazione della Ricerca sulla Persona - CARP). Written informed consent was obtained from all participants prior to their inclusion in the study.

Sensory attenuation evaluation

SA was evaluated using the Force Matching Task (FMT), adapted from previous studies (Shergill et al., 2003; Pareés et al., 2014; Palmer et al., 2016). Participants were seated comfortably with their arms placed on a table. The FMT was implemented using a device developed by our group and inspired by Palmer et al. (2016), fully controlled by a computerized program and designed to measure the participant's ability to match applied forces. In the task, an electric motor was attached to a lever, suspended above a padded support, with the left hand positioned palm-up underneath. The index finger of the left hand was taped securely to maintain stability and comfort during the trials. In each trial, one of three target forces (1N, 2N, or 3N) was randomly applied to the participant's left index finger via downward movement of the lever. The inclusion of these varying forces helped to minimize habituation effects. Participants were instructed to match the force perceived on their left index finger in two conditions. In the Direct condition, they directly applied the force with the right index finger on the left index finger through the lever. In the Indirect condition, participants pressed a button that activated the motor, which in turn controlled the lever and applied the force to their left index finger (Figure 1). Crucially, this Indirect condition aimed to create the perception that the force was generated by an external device (the motor), in contrast to the self generated force in the Direct condition.

A sensor attached to the lever recorded the target and reproduced forces in newtons during both the target force application and reproduction phases. The target force was applied for a fixed duration of 3 seconds. The reproduction phase had a maximum duration of 6 seconds; however, if no changes in the applied force were detected for 0.5 seconds, the system automatically advanced to the next trial. To ensure consistency across trials, the reproduced force was defined as the mean force recorded during the last 500 milliseconds of the reproduction phase, when the response was considered stabilized (McNaughton et al., 2021).

Each condition consisted of three blocks of 12 trials each (four trials for each target force), presented in a randomized order. Participants rested for one minute between blocks, and a five-minute rest period separated the two conditions. During the task, participants wore noise-canceling headphones to eliminate any potential auditory cues from the motor that might influence their performance. Auditory signals ("stimolazione," "go," and "stop") indicated the

onset of the target force as well as the beginning and end of the periods during which participants were required to match the force. Additionally, participants were instructed to maintain focus by looking straight ahead at a fixation point displayed on the computer screen. (Kilteni & Ehrsson, 2017a)

Prior to the main task, participants completed a 12-trial familiarization session for both the Direct and Indirect conditions to ensure they understood the task. The FMT was implemented with Psychtoolbox extension in MATLAB 2014.

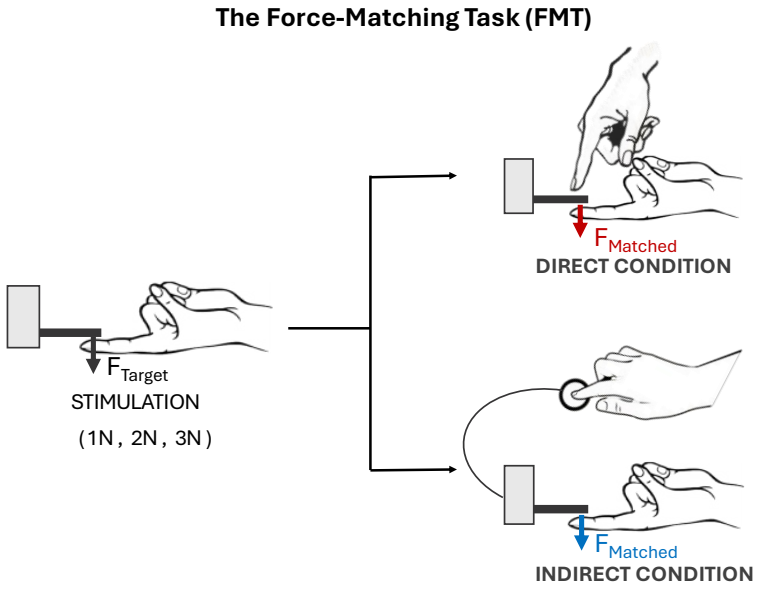

Figure 1. ***Force Matching Task (FMT).*** *In each trial, one of three target forces (1N, 2N, or 3N) was applied to the left index finger through the downward movement of a lever. Participants were instructed to reproduce the perceived force in two conditions: the Direct condition, in which participants pressed down on the lever with their finger to match the target force; and the Indirect condition, in which participants pressed a button on an external device to indirectly control the lever's movement, creating the perception that the reproduced force was externally generated. This distinction allowed for comparison between self-generated and externally perceived forces.*

The primary outcome measure was the SA index, calculated for each target force as the ratio between the force reproduced by the participant and the target force applied:

$$SA\ index = \frac{F_{matched}}{F_{target}}$$

Where $F_{matched}$ represents the force reproduced by the participant and F_{target} represents the force delivered by the motor. An SA index of 1 indicates accurate reproduction (i.e., the reproduced force equals the target force). An SA index greater than 1 indicates force overestimation, while an SA index lower than 1 indicates force underestimation.

Previous research has demonstrated that individuals tend to overestimate force in the Direct condition due to SA (Shergill et al., 2003; Pareés et al., 2014). Self-generated stimuli are perceived as less salient, leading to an increase in the force applied to match the target and, consequently, an SA index higher than 1. In contrast, matching forces via an external device (Indirect condition) reduces the occurrence of SA, resulting in more accurate force reproduction and an SA index closer to 1. To capture an individual's overall tendency, we also averaged the SA indices across all target forces, obtaining the Mean SA index.

To quantify the difference in SA between conditions, we calculated Delta SA as follows:

$$Delta\ SA\ =\ Mean\ SA\ index_Direct\ -\ Mean\ SA\ index_Indirect$$

Positive Delta SA values indicate an overestimation of the target force in the Direct compared to Indirect condition. In contrast, Delta SA values of zero indicate no difference between conditions.

Subjective measures

After each condition (Direct and Indirect), participants completed a set of four 10-cm Visual Analogue Scales (VAS) to evaluate their subjective experience and perceptions. The first VAS measured state fatigue perception, asking participants to rate their current level of fatigue, with scores ranging from 0 ('not at all') to 10 ('maximal fatigue'). The second VAS assessed perceived physical effort, ranging from 0 ('no effort') to 10 ('maximal effort'). The third VAS evaluated perceived precision, where participants rated the accuracy of their performance, with 0 indicating 'poor' and 10 indicating 'excellent'. Lastly, the fourth VAS assessed the perception of control over the task, with scores from 0 ('not at all') to 10 ('total control'). These scales provided a subjective measure of state fatigue, physical effort, perceived precision, and control immediately after each experimental condition.

Clinical Assessment

At the end of the experimental session, PD patients underwent an evaluation of motor symptom severity using the UPDRS-III, conducted in their *off* medication state. Following this, HC and PD patients, while in their *on* medication state, were assessed across four domains: fatigue severity, sleep quality, cognitive function, and mood disorders. Standardized and validated questionnaires were employed for these assessments, ensuring reliable measurements of non-motor symptoms. Collecting non-motor symptoms beyond fatigue was crucial for the study, as it allowed us to rule out the potential influence of fatigue-related factors, which might

otherwise confound the interpretation of fatigue-specific results factors (Siciliano et al., 2022). Our approach allowed for a comprehensive analysis of both motor and non-motor dimensions relevant to the study.

Fatigue severity was assessed using three measures. The FSS, as described above in *Participants* section, was the primary tool used to allocate PD patients to the PD_Fatigue or PD_NoFatigue groups, based on their fatigue severity (Herlofson & Larsen, 2002; Krupp et al., 1989). The Parkinson Fatigue Scale (PFS) further assessed the unique experience of fatigue in PD patients, specifically its interference with daily life (Brown et al., 2005). Additionally, the Multidimensional Fatigue Inventory (MFI) provided a broader evaluation of fatigue across five dimensions: global fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity (Smets et al., 1995).

Sleep quality was assessed using two scales. The Parkinson's Disease Sleep Scale (PDSS-2) evaluates sleep disturbances in PD patients across four dimensions: total sleep score, motor symptoms, Parkinson's-related symptoms, and disturbed sleep (Chaudhuri et al., 2002). The Epworth Sleepiness Scale (ESS), an 8-item scale, was used to measure excessive daytime sleepiness, with higher scores reflecting greater sleepiness (Johns, 1991).

For cognitive function, the Montreal Cognitive Assessment (MoCA) was administered. This widely used tool evaluates various cognitive domains, including memory, attention, language, and executive functions, providing a comprehensive overview of cognitive performance (Nasreddine et al., 2005).

Finally, mood disorders were assessed using two tools. The Hospital Anxiety and Depression Scale (HADS) is a 14-item questionnaire with two subscales measuring anxiety and depression symptoms, both scored separately (Zigmond & Snaith, 1983). Additionally, the Apathy Evaluation Scale (AES) was used to measure the presence and severity of apathy, which is common in PD and can significantly impact motivation and daily life (Marin et al., 1991).

Protocol

The experiment was conducted with PD patients in the *off* medication state, meaning they abstained from dopamine therapy or other Parkinson’s-related medications for at least 8 hours prior to the session. Participants began with one of the two FMT conditions (Direct or Indirect), immediately followed by the VAS assessment. They then completed the second condition (Direct or Indirect), followed by a second VAS assessment. After finishing both task conditions, participants completed the UPDRS-III assessment and then proceeded with the clinical scales and questionnaires. The full protocol sequence is schematized in Figure 2.

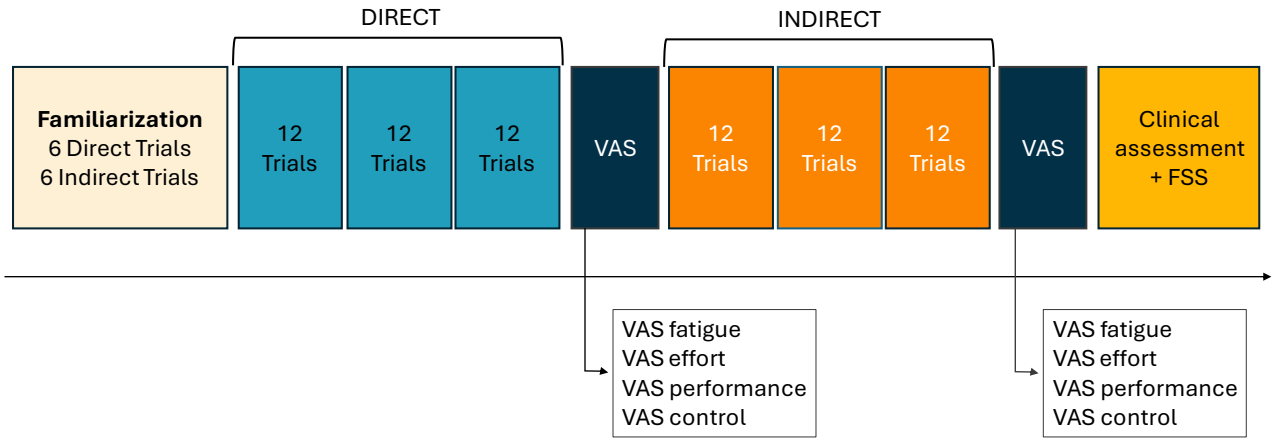

Figure 2. ***Schematic representation of the experimental protocol.*** *Participants first completed either the Direct or Indirect condition of the FMT, followed by a set of four VAS assessing state fatigue, physical effort, perceived precision, and control. This process was then repeated with the other condition (Direct or Indirect), followed by another VAS assessment. The protocol concluded with the UPDRS evaluation and completion of clinical questionnaires.*

Data analysis

Statistical analyses were conducted to investigate differences between groups, examine within-subject effects across conditions, and explore relationships between SA and clinical variables. All analyses were performed using IBM SPSS Statistics 25 and MATLAB R2023b, with significance threshold set at a p-value of < 0.05. Where appropriate, Bonferroni corrections for multiple comparisons were applied.

To evaluate differences in SA between groups, a repeated measures ANOVA (rmANOVA) was performed on the SA indices. The within-subject factors were Target Force (1N, 2N, 3N) and Condition (Direct, Indirect), while the between-subject factor was Group (PD_NoFatigue, PD_Fatigue, HC). This analysis allowed us to assess how SA varied across different force levels and conditions in each group. Additionally, a one-sample t-test was performed against a reference value of 1 for the Mean SA index in each condition This analysis assessed whether the reproduced force significantly deviated from the target force and clarified the direction of the deviation. Specifically, it identified whether participants overestimated the target force (value greater than 1), as typically observed in the Direct condition, underestimated it (value lower than 1), or were accurated in the reproduction, showing no significant difference between matched and target force (no significant difference from 1), as expected in the Indirect condition.

To explore deeper the group-specific differences in SA, a one-way ANOVA was performed with Group (PD_Fatigue, PD_NoFatigue, and HC) as the between-subject factor, focusing on Delta SA. Unlike the rmANOVA, which evaluates condition-specific effects, this

analysis isolates the magnitude of the difference between Direct and Indirect conditions to determine whether it varies systematically across groups. Additionally, to further confirm SA effects, a one-sample t-test was conducted on Delta SA values against 0, where 0 indicated the absence of difference between direct and indirect values.

Given the ordinal nature of the VAS ratings, non-parametric tests were used to analyze perceived fatigue, effort, performance, and control ratings across groups and conditions. Kruskal-Wallis tests were conducted to compare VAS scores between groups (PD_Fatigue, PD_NoFatigue, HC) for each condition (Direct, Indirect). Mann-Whitney U and Wilcoxon signed-rank tests were used for post-hoc comparisons between groups and to assess within-subject differences between Direct and Indirect conditions.

To explore relationships between SA and clinical measures, Spearman's rank-order correlation analyses were conducted to assess the association between Mean SA index and Delta SA with a range of clinical scores, including measures of fatigue severity, sleep quality, cognitive function, and mood disturbances. Spearman's method was selected due to violations of normality observed in several key variables, including the SA indices and various clinical scales, as determined by Shapiro-Wilk tests. Correlations were calculated for the entire sample, as well as within each group (PD_Fatigue, PD_NoFatigue, HC), to identify potential group-specific patterns. Additionally, exploratory correlations were conducted between SA measures (Mean SA index and Delta SA) and disease-specific variables, including UPDRS-III scores, H&Y, LEDD, and disease duration, to assess potential relationships between SA and PD severity.

Results

Outliers were identified based on the Mean SA index, defined as scores more than 2.5 standard deviations above the group mean. Three participants—one from each group (PD_Fatigue, PD_NoFatigue, and HC)—were excluded to ensure robust findings without the influence of extreme values. Following the removal of outliers, the updated sample size characteristics are provided in the following table, detailing each group demographic data (Table 1) and clinical assessment scores (Table 2).

Table 1. ***Demographic and clinical characteristics after removal of outliers.*** *Values are presented as means, standard deviations (SD) and number of cases (n). Significant differences between groups are marked with *(=p<0.05).*

	PD_Fatigue			**PD_NoFatigue**			**HC**		
	Mean	SD	n	Mean	SD	n	Mean	SD	n

Sex	Male			10			14			14
	Female			9			5			6
Age	Years	66.37	11.29		62.74	8.67		64.60	7.90	
Education	Years	11.06	4.08		11.39	3.31		13.40	2.84	
Handedness	Left			0			0			1
	Right			19			19			19
Age onset	Years	61.47	11.77		58.11	8.57				
Disease Duration	Years	4.92	3.44		4.66	2.85				
Affected Side	Left			12			9			-
	Right			7			10			-
PD subtype	Akinetic-Rigid			1			0			-
	Tremor-Dominant			12			11			-
	Bradykinetic-Rigid			6			8			-
LEDD		469.53	260.32		445.74	245.61		-	-	
UPDRS-III		20.63	10.84		18.42	6.33		-	-	
H&Y		1.92	0.42		1.87	0.50		-	-	

FSS: Fatigue Severity Scale; LEDD: Levodopa Equivalent Daily Dose; UPDRS-III: Unified Parkinson's Disease Rating Scale, Part III; H&Y: Hoehn and Yahr stage.

Table 2. ***Clinical and cognitive assessments for the revised sample across four dimensions: fatigue severity, sleep quality, cognitive function, and mood disorders.*** *Scores are presented for each group (PD_Fatigue, PD_NoFatigue, and HC) with mean values and standard deviations (SD). Significant differences between groups are marked with *(=p<0.05).*

		PD_Fatigue		**PD_NoFatigue**		**HC**	
Fatigue Severity		Mean	SD	Mean	SD	Mean	SD
FSS		46.95*	6.46	21.72	7.81	21.50	6.82
PFS		3.57 *	0.68	2.11	0.80	1.56	0.58
MFI	Global Fatigue	13.53*	3.88	9.89	3.88	8.60	3.45
	Physical Fatigue	13.26*	4.21	9.89	3.69	7.50	2.93
	Mental Fatigue	11.11	4.15	8.78	2.92	8.90	2.65
	Reduced Motivation	8.68	4.20	7.89	3.45	8.05	3.56
	Reduced Activity	10.58	4.29	8.83	3.70	8.90	4.48
Sleep Quality							

PDSS-2	Total Sleep	17.58*	7.73	11.68	7.64	11.85	5.71
	Motor Symptoms	4.53 *	3.44	1.95	2.55	2.05	2.09
	Parkison's Symptoms	3.84	2.99	2.11	2.90	2.05	2.24
	Disturbed Sleep	9.21	3.66	7.63	4.37	7.75	3.34
ESS		7.05	4.26	6.42	3.36	5.55	4.11
Cognitive Function							
MoCA		26.16	3.82	26.11	2.99	27.30	1.75
Mood Disorders							
HADS	Anxiety	5.95	3.58	4.16	2.48	6.00	4.23
	Depression	5.74	2.60	4.05	3.12	3.75	2.97
AES		31.37	6.95	29.74	5.61	28.95	7.04

FSS: Fatigue Severity Scale; PFS: Parkinson Fatigue Scale; MFI: Multidimensional Fatigue Inventory; PDSS-2: Parkinson's Disease Sleep Scale; ESS: Epworth Sleepiness Scale; MoCA: Montreal Cognitive Assessment; HADS: Hospital Anxiety and Depression Scale: AES: Apathy Evaluation Scale.

Analysis of SA using rmANOVA revealed a significant main effect of Condition [$F_{(1, 55)}$ =25.331, $p < 0.001$], with higher SA indices values in the Direct condition (Mean $\pm$ SD: 1.325 $\pm$ 0.442) than in the Indirect condition (1.048 $\pm$ 0.206), indicating greater SA for self-generated forces. This main effect confirms the reliability of our protocol in eliciting SA, aligning with prior research that establishes the FMT as a reliable paradigm for assessing SA (Pareés et al., 2014; Shergill et al., 2003). Additionally, our analysis revealed a significant main effect of Target Force [$F_{(2, 54)}$ =24.513, $p < 0.001$], with SA index values showing a decreasing pattern across force levels (1N > 2N > 3N), suggesting that SA was more pronounced for lower target forces, consistent with previous studies showing that SA decreases as force magnitude increases, possibly due to greater reliance on external feedback at higher forces (Palmer et al., 2016). Furthermore, a significant interaction between Target Force and Condition [$F_{(2, 54)}$ =36.627, $p < 0.001$] was observed, with all target forces in the Direct condition displaying higher SA index values than in the Indirect condition across groups.

More interestingly, the primary findings of our study emerged from the significant interaction between Group and Condition [$F_{(2, 55)}$ =3.507, $p = 0.037$] (Figure 3). Specifically, the HC group exhibited a significant difference between conditions [$F_{(1, 55)}$ =18.023, $p < 0.001$], with higher SA index values in the Direct (1.379 ± 0.509) compared to the Indirect condition (0.981 ± 0.148). In the same way, the PD_NoFatigue group showed the same significant pattern between conditions [$F_{(1, 55)}$ =14.167, $p < 0.001$], overshooting target forces in the Direct (1.380 ± 0.406) compared to Indirect condition (1.018 ± 0.145). In contrast, the PD_Fatigue group displayed no significant difference between Direct (1.217 ± 0.386) and Indirect conditions

(1.145 ± 0.294) [$F_{(1, 55)}$ =0.552, p = 0.461], indicating similar SA levels in both conditions. These results suggest that while the HC and PD_NoFatigue groups were able to discriminate between Direct and Indirect, the PD_Fatigue group did not, suggesting an alteration in sensory processing in fatigued PD patients.

Comparisons of the SA index to the reference value of 1 (Figure 3), through one-sample t-tests, revealed that the Direct condition SA index values for both the HC, and PD_NoFatigue groups were significantly different from 1 (HC: $t_{(19)}$ =3.328, p=0.004; PD_NoFatigue: $t_{(18)}$ =4,082, p= 0.001), indicating overestimation in force reproduction for self-generated forces. Conversely, in the PD_Fatigue group, both Direct and Indirect conditions were significantly different from 1 (Direct: $t_{(18)}$ =2.448, p=0.025; Indirect: $t_{(18)}$ =2.154, p=0.045), suggesting an altered SA pattern in this group characterized by a significant overshooting of forces in both Direct and Indirect conditions.

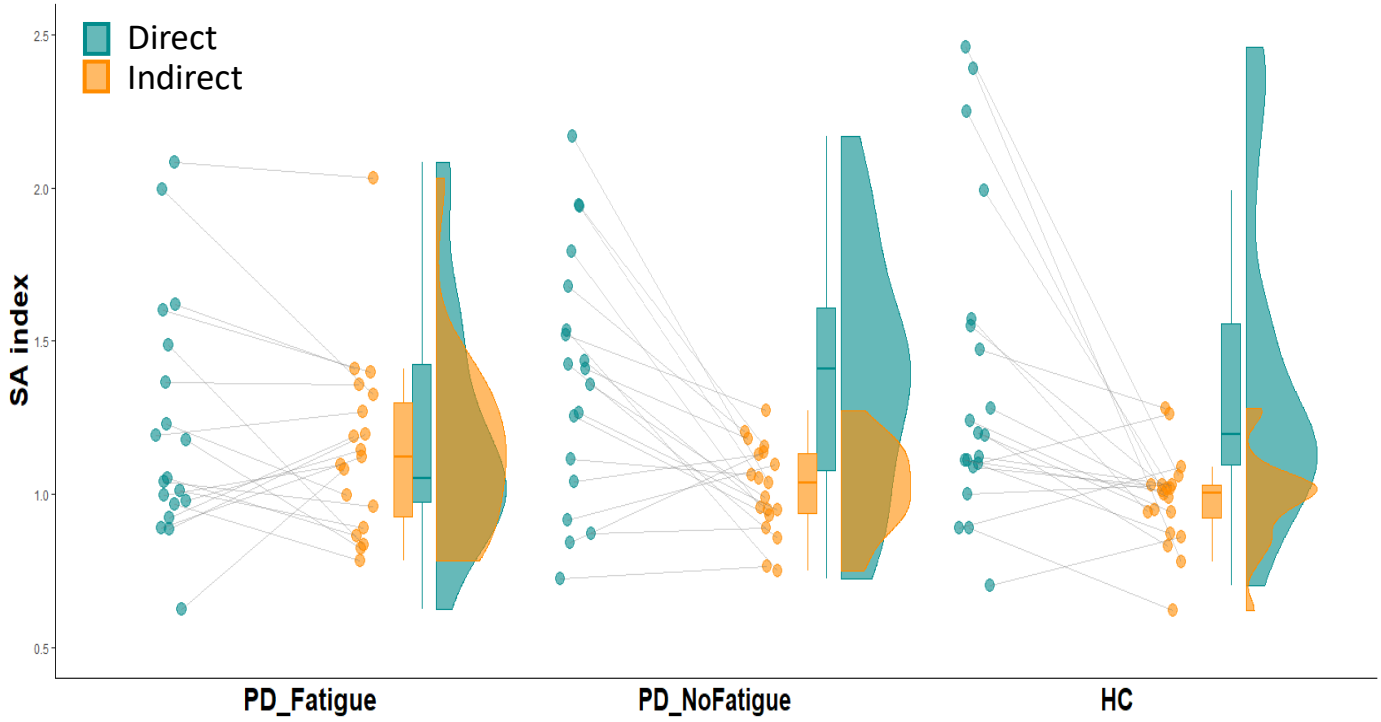

Figure 3. ***Distribution of SA Index Across Groups and Conditions.*** *The violin plots illustrate the SA index for Direct (blue) and Indirect (orange) conditions across the PD_Fatigue, PD_NoFatigue, and HC groups. The overlaid boxplots display the median and interquartile ranges for each condition, while individual data points (connected by gray lines) represent changes between Direct and Indirect conditions within participants. HC and PD_NoFatigue groups show higher SA index values in the Direct condition compared to the Indirect condition, consistent with preserved SA. In contrast, the PD_Fatigue group exhibits minimal differences between Direct and Indirect conditions, suggesting altered sensory processing.*

Figure 4 shows the results of Delta SA analysis. Delta SA was significantly greater than 0 in both the HC (0.398 ± 0.521) and PD_NoFatigue groups (0.362 ± 0.401), confirming a

distinct difference in force reproduction between Direct and Indirect conditions. In the PD_Fatigue group (0.07 ± 0.299), however, Delta SA was not significantly different from 0, suggesting no distinction between Direct and Indirect conditions.

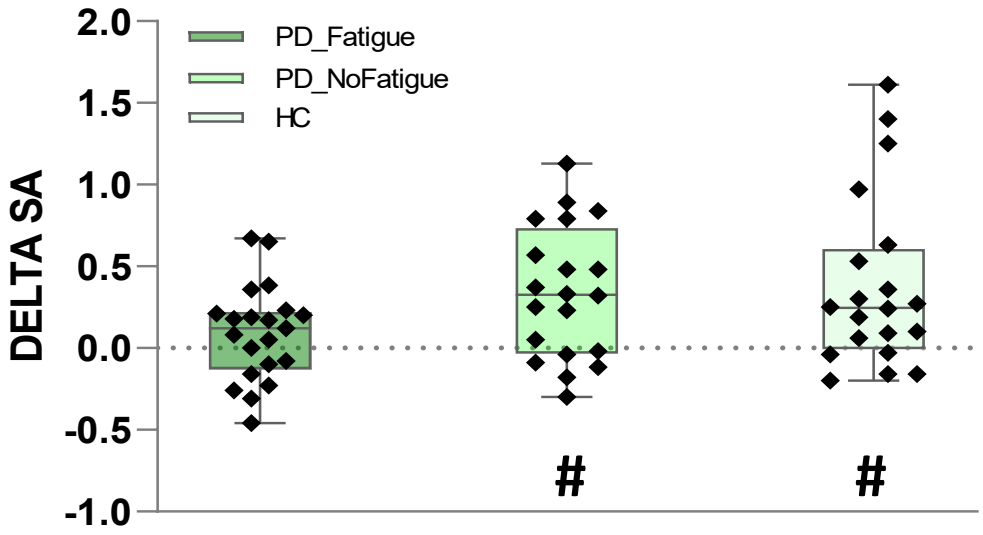

Figure 4. ***Delta SA Index Across Groups****. Boxplots display the Delta SA index for PD_Fatigue (dark green), PD_NoFatigue (green), and HC (light green) groups. Individual data points represent participants' Delta SA values. Delta SA values are significantly greater than zero in both the HC and PD_NoFatigue groups (#), indicating a pronounced distinction between Direct and Indirect conditions. Conversely, the PD_Fatigue group shows Delta SA values not significantly different from zero, suggesting no differentiation between conditions*

.

The VAS analysis revealed significant differences only in VAS Fatigue and VAS Effort scores (Figure 5). We used the mean VAS scores across Direct and Indirect conditions, as there were no significant differences between these conditions in any group for either VAS Fatigue or VAS Effort. Averaging across conditions provided a more stable and comprehensive measure of perceived fatigue and effort, reducing variability and emphasizing overall group differences. Kruskal-Wallis tests revealed a significant effect of Group for both VAS Fatigue ($H_{(2)}$ =7.687, p = 0.021) and VAS Effort ($H_{(2)}$ =7.607, p = 0.022). Post-hoc Mann-Whitney U tests showed no significant differences between HC and PD_NoFatigue for either measure. However, both VAS Fatigue and VAS Effort scores were significantly higher in the PD_Fatigue group compared to the HC group (VAS Fatigue: U = 103.5, Z= -2.431, p = 0.014; VAS Effort: U = 100.0, Z= -2.534, p = 0.011) and the PD_NoFatigue group (VAS Fatigue: U = 101.5, Z= -2.307, p = 0.021; VAS Effort: U = 106.0, Z= - 2.178, p = 0.030). These results suggest that the fatigue symptoms in the PD_Fatigue group may heighten perceived fatigue and effort during the task.

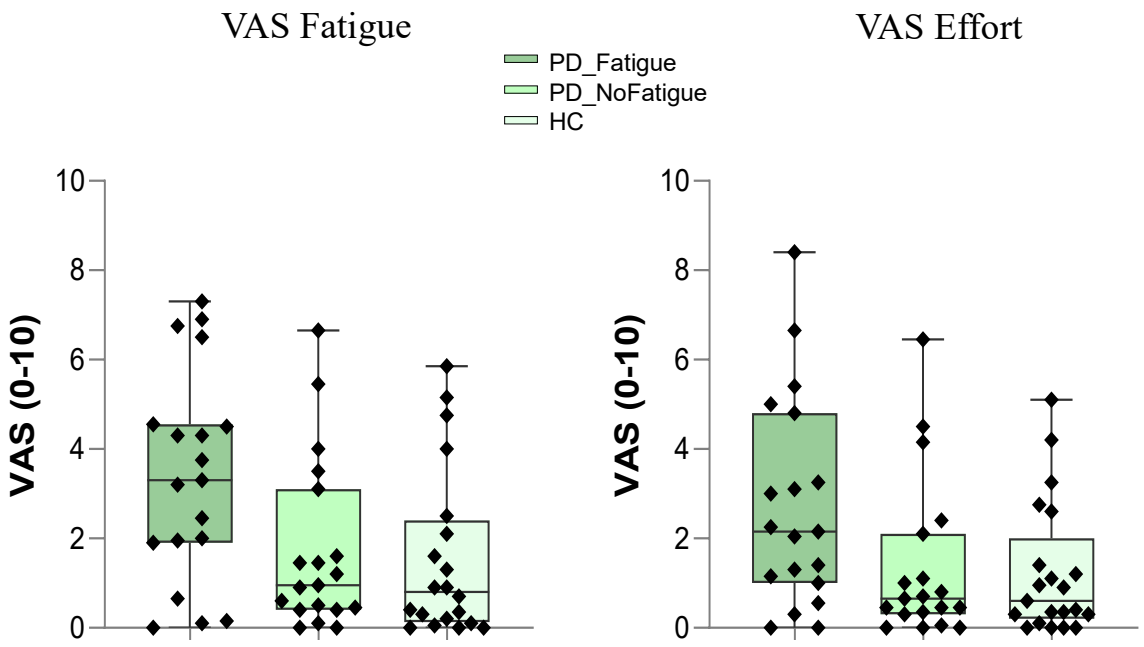

Figure 5. ***VAS Fatigue and VAS Effort Scores Across Groups.*** *Boxplots represent VAS ratings for perceived fatigue (left) and effort (right) in the PD_Fatigue, PD_NoFatigue, and HC groups. Individual data points represent participant-level scores. The PD_Fatigue group reported significantly higher fatigue and effort ratings compared to the PD_NoFatigue and HC groups.*

Correlation analyses between SA measures and clinical assessment scores for the entire sample revealed no significant associations. However, group-specific correlations revealed significant relationships between Mean SA index and clinical measures of fatigue and sleep quality, as shown in Table 3. In the PD_Fatigue group, higher levels of fatigue (MFI) and sleep problems (PDSS-2) were linked to lower force output in both the Direct and Indirect conditions. This negative correlation suggests that as fatigue and sleep disturbances increase, the ability to exert force decreases, indicating a potential disruption in sensorimotor processing.

Conversely, in the HC group, higher MFI and PDSS-2 scores correlated with greater force output in the Indirect condition. This positive correlation implies that in healthy individuals, fatigue and sleep disturbances might lead to an overcompensation in force exertion when the action is mediated externally. No significant correlations were found in the PD_NoFatigue group.

Exploratory correlations with disease-specific characteristics, including UPDRS-III scores, Hoehn & Yahr stage (H&Y), LEDD, and disease duration, revealed no significant associations with SA measurements for either patient group ($p > 0.05$). This indicates that SA was not directly related to these markers of disease severity in our sample.

Table 3. ***Group-specific correlation analysis between sensory attenuation measure and clinical assessment.*** *Significant correlations are presented for the Multidimensional Fatigue Inventory (MFI) and the Parkinson's Disease Sleep Scale (PDSS-2) subscales across the PD_Fatigue and HC groups. Significant correlations (p <*

0.05) are indicated alongside Spearman's correlation coefficient (ρ). The specific condition involved in the correlation is also included.

		PD_Fatigue		HC	
		p value	Correlation Coefficient (r)	p value	Correlation Coefficient (r)
MFI	Global Fatigue	p =.043	ρ =-.469 (Direct)		
				p=.038	ρ =.466 (Indirect)
PDSS-2	Total Sleep	p < 0.001	ρ =-.783 (Indirect)	p=.008	ρ = .576 (Indirect)
	Motor Symptom			p =.025	ρ =.499 (Indirect)
	Parkinson's Symptom	p =.002	ρ =-.657 (Indirect)	p =.046	ρ =.452 (Indirect)
	Disturbed Sleep	p =.001	r=-.684 (Indirect)		

Discussion

Our study provides valuable insights into the understanding of SA in Parkinson's Disease patients with and without fatigue symptoms, as well as in healthy controls, using the Force Matching Task (Shergill et al., 2003; Pareés et al., 2014).

The key finding of our study was the significant interaction effect between Condition and Group, which revealed distinct SA patterns among fatigued PD patients, non-fatigued PD patients, and healthy controls. In healthy controls and PD patients without fatigue, typical SA effects were clearly observed, with participants consistently overestimating forces in the Direct condition compared to the Indirect condition. This is consistent with the concept that self-generated actions are perceived as less intense than externally generated ones due to the brain's internal prediction processes, which reduce the salience of expected sensations (Blakemore et al., 1998). In contrast, PD patients with fatigue demonstrated no significant difference between Direct and Indirect conditions. This result supports the hypothesis that pathological fatigue may arise from disturbances in sensorimotor prediction processes, as proposed by the SAF model (Kuppuswamy 2017). Normally, SA enables accurate predictions about movement outcomes, modulating the perceived effort required to execute the motor plan. However, in the PD_Fatigue group, the reduced ability to discriminate between Direct and Indirect conditions may reflect an alteration in SA. Specifically, PD fatigued patients demonstrated predictive processes that functioned similarly across both conditions. This impaired differentiation suggests selective difficulties distinguish between actions where the individual has full control over the outcome (Direct condition) and those where control is diminished because the outcome is mediated by an external device and perceived as externally generated (Indirect condition). Typically, the external mediation introduces greater unpredictability since the tactile sensation is not directly

produced, like in the Direct condition, but is ultimately generated by an external motor not perceived as a part of the self or an extension of the body (Kilteni et al., 2017). However, this distinction appears to be lost in PD patients with fatigue. One possible interpretation is that these patients may have predicted the sensory consequences even in the Indirect condition, resulting in attenuation across both conditions. While this interpretation may appear to contradict the SAF model, we argue it is, in fact, consistent with it and, potentially, reveals a deeper disruption in predictive processing. According to the SAF model, fatigue reflects a failure in the precision of sensorimotor predictions (Kuppuswamy, 2017). In healthy individuals, predictions are flexibly engaged: self-generated actions (Direct condition) trigger attenuation, while externally generated ones (Indirect) do not. However, in the PD_Fatigue group, the predictive system may be impaired not in its strength but in its specificity, applying predictive suppression even when it is inappropriate. This pattern suggests a form of overgeneralized or context-insensitive prediction, where the system fails to adjust its predictive models to distinguish between internally and externally generated stimuli. Such a dysfunction is consistent with the SAF's core premise: that fatigue arises from an inability to generate accurate or appropriately timed predictions, leading to effort misestimation and sensory misprocessing. In this light, the attenuation observed in the Indirect condition should not be seen as successful prediction, but rather as a marker of impaired sensory differentiation, specifically a sign that the system is unable to gate predictions correctly based on the action context. This pattern was further corroborated by VAS results, which showed that PD_Fatigue patients reported significantly higher subjective fatigue and effort compared to both HC and PD_NoFatigue groups. This heightened perception of effort and fatigue partially aligns with prior findings of impaired decision-making related to physical activity in PD, where patients struggle to accurately assess the effort needed for tasks, contributing to greater perceived effort (Sáez-Francàs et al., 2014; Kostić et al., 2016). Together, these findings suggest that fatigue in PD affects not only objective sensory processing but also the subjective experience of effort, supporting the SAF model (Kuppuswamy, 2017) and providing a potential mechanism for how fatigue manifests as a heightened sense of effort in daily activities.

Supporting evidence of a potential link between pathological fatigue and altered prediction in the sensorimotor domain also comes from neuroimaging studies. A critical link lies in the shared involvement of the basal ganglia-thalamus-prefrontal cortex (BG-Thalamus-PFC) network, a key circuit to both sensorimotor prediction and the regulation of effort perception (Capone et al., 2020; Chaudhuri & Behan, 2004; Wylie et al., 2020). Dysfunction in this network is well-documented in PD patients (Caligiore et al., 2016; Kearney & Brittain, 2021; Pavese et al., 2010) and has been linked to pathological fatigue in multiple clinical conditions (Pardini et al., 2010; Roelcke et al., 1997). Specifically, disruptions in the basal

ganglia's non-motor functions—particularly its role in integrating sensory, motor, and affective signals—are thought to underpin the heightened perception of effort seen in fatigue (Chaudhuri & Behan, 2004; Dobryakova et al., 2013). Alterations in this network may impair the processing of efference copies, thereby reducing the precision of internal predictions. This impaired predictive capacity may manifest as a heightened sense of effort, providing a mechanistic explanation for the relationship between pathological fatigue and abnormal sensorimotor prediction (Blakemore et al., 1998; Kuppuswamy, 2017; Redinbaugh & Saalmann, 2024). Together, these findings highlight the shared neural basis of sensorimotor prediction and fatigue, providing a mechanistic bridge between them.

Our study builds upon previous research, such as the work by Wolpe et al. (2018), who used the FMT to examine SA in medicated PD patients and found no significant differences between HC and PD patients. However, Wolpe et al. did not include fatigue as a potential distinguishing factor and therefore did not differentiate between fatigued and non-fatigued patients. Moreover, their study tested participants exclusively during the "on-medication" state, which limits the ability to isolate the effects of dopaminergic medication on sensory processing. By focusing on unmedicated PD patients -testing participants during the "off-medication" state to control for the potential confounding effects of dopamine treatment- and differentiating between those with and without fatigue, our study provides new evidence that fatigue interact with SA in PD, possibly due to disruptions in efference copy processing, which plays a critical role in distinguishing self- from externally generated actions (Harrison et al., 2023; McNaughton et al., 2022).

Beyond group-level differences in sensory attenuation, our correlation analyses revealed distinct relationships between SA measures and clinical symptoms that further clarify how fatigue and fatigue-related symptoms interact with sensorimotor processes. In the PD_Fatigue group, higher levels of fatigue and sleep disturbance were associated with lower force output in both Direct and Indirect conditions. This suggests that patients with more severe symptoms may have a reduced ability to engage predictive mechanisms, leading to a blunting of motor responses even when actions are self-generated. Rather than showing normal sensory attenuation, these patients may struggle to properly adjust their actions based on internal predictions, supporting the idea proposed by the SAF that fatigue reflects a disruption in predictive processing (Kuppuswamy, 2017; 2022). Conversely, in healthy individuals, higher fatigue and sleep disturbances correlated with increased force output in the Indirect condition. This may reflect a compensatory mechanism where, in the face of reduced alertness or increased effort perception, healthy individuals amplify their motor output to maintain performance levels (Lorcery et al., 2024). The contrasting patterns underscore how fatigue and sleep disturbances can differentially affect sensorimotor processing depending on neural integrity and symptom

severity. In PD_Fatigue patients, pathological symptoms may amplify existing deficits, resulting in predictive disengagement and under-modulation of force. In healthy controls, subclinical symptoms may instead trigger adaptive compensatory strategies that maintain performance despite increased internal strain.

Interestingly, no significant correlations were found between SA measurements and traditional markers of PD disease severity, such as UPDRS-III scores, Hoehn & Yahr stage, LEDD, and disease duration. This lack of association suggests that SA in PD operates independently of motor symptom severity or disease progression, emphasizing the distinct and specific interaction between fatigue and SA. This finding contrasts with Wolpe et al. (2018), who found that SA was negatively related to motor severity in PD and positively associated with dopamine dosage but aligns with previous studies indicating that fatigue in PD does not correlate with disease duration or motor severity (Kostić et al., 2016; Friedman et al., 2007; Havlikova et al., 2008).

The main limitation of our study is the cross-sectional design, which limits the possibility of making causal inferences. In this sense, longitudinal studies are needed to examine whether changes in SA precede or follow the development of fatigue symptoms in PD. Additionally, while our sample size was adequate for exploratory analyses, larger cohorts are needed to confirm these findings and would allow robust subgroup analyses, such as examining this interaction in different PD subtypes (e.g., tremor-dominant, akinetic-rigid, postural instability and gait difficulty and mixed subtype) or explored the influence of the levels of fatigue severity on SA. Given the high variability typically associated with SA (Blakemore et al., 2000), increasing the sample size could also help mitigate the impact of this variability, enhancing the clarity and reliability of the observed phenomena. Future research should also include neuroimaging studies that could provide insight into the neural underpinnings of altered sensory attenuation in fatigued PD patients, identifying the specific brain networks involved in sensory processing and motor control in these individuals.

Expanding our understanding of the relationship between fatigue and SA could aid in developing personalized treatment plans, as fatigue management may be essential not only for addressing motor symptoms but also for improving sensory processing in PD.

Conclusion

In conclusion, this study highlights the interplay between sensory attenuation and fatigue in Parkinson's Disease. While HC and PD_NoFatigue groups demonstrated preserved SA, the PD_Fatigue group showed altered sensory processing, evidenced by reduced differentiation between self-generated and externally generated forces. These findings offer

empirical support for the Sensory Attenuation model of fatigue, demonstrating that fatigue in Parkinson's Disease extends beyond a subjective experience and involves measurable interactions with sensory mechanisms, potentially rooted in impaired SA. This underscores the potential of SA as a reliable and objective tool for assessing fatigue, addressing a critical gap in current methodologies that predominantly rely on subjective self-report measures.

Assessing SA in fatigued PD patients could provide valuable insights into individual differences in sensory-motor processing, identifying patients who may benefit from targeted interventions. For instance, therapies aimed at enhancing sensory feedback processing or sensorimotor predictive abilities may improve motor performance and quality of life in this clinical population.

By enhancing our understanding of the sensory-motor deficits associated with fatigue in PD, this study lays the groundwork for future research aimed at developing targeted interventions to improve sensory-motor integration and quality of life in this vulnerable patient population.

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Chapter 3: The interplay between sensory attenuation and fatigue in Functional Movement Disorder: A Preliminary Study

This chapter presents work based on a study currently in progress, with data collection still ongoing. A manuscript based on this research is planned for future submission.

Introduction

Functional Movement Disorder (FMD) is a neurological condition characterized by abnormal movements, such as tremors, spasms, or gait abnormalities, that are inconsistent with known neurological disease and are often incompatible with traditional pathophysiological patterns (Edwards & Bhatia, 2012). Clinically, FMD patients may exhibit functional tremor, dystonia, or other movement patterns that fluctuate and lack the regularity or predictability seen in organic movement disorders (Věchetová et al., 2018). These movements are usually reported to be involuntary by the patient despite exhibiting characteristics more commonly associated with voluntary movement, such as distractibility, variability, and modulation by attention or emotional states (Edwards et al., 2013; Macerollo et al., 2015).

Fatigue is highly prevalent in FMD (Di Vico et al., 2021; Gelauff et al., 2018), with studies indicating that it affects approximately 78% of this clinical population, a notably higher rate than the 53% prevalence observed in Parkison's Disease (PD) (Di Vico et al., 2021). This high prevalence underscores the role of fatigue as a core feature of FMD, significantly diminishing patients' quality of life and often leading to reduced functional independence (Gelauff et al., 2018). Despite its high prevalence and impact, the mechanisms underlying fatigue in FMD remain poorly understood, limiting the development of effective treatment options (Gelauff et al., 2018)

Within the theoretical framework of the SAF model presented previously (Chapter 1 and 2), a potential explanation for pathological fatigue across different neurological conditions lies in impaired SA. When SA functions normally, the brain accurately predicts the sensory consequences and effort required for self-generated actions. However, when SA is disrupted, predictive abilities are compromised, leading to a heightened perception of effort and a corresponding increase in fatigue (Kuppuswamy, 2017; 2022).

Applying the SAF model to FMD extends its relevance beyond PD and highlights its potential as a transdiagnostic approach. Investigating SA in FMD offers the opportunity to explore whether SA could serve as a universal biomarker of pathological fatigue, independent of the specific neurological condition. Such evidence would pave the way for the use of SA as an objective tool for assessing fatigue, addressing the limitations of current diagnostic approaches that rely primarily on subjective self-reports (Kluger et al., 2013).

Previous studies have examined SA in FMD without accounting for fatigue as a potential modulating factor. For instance, Pareés et al. (2014) investigated SA using a behavioral protocol (Force Matching Task) and found reduced SA in FMD patients relative to healthy controls. On the same line, Macerollo et al. (2015) used neuroimaging techniques to investigate SA neurophysiological pattern in FMD patients during self-paced movements. The results suggest

an alteration of SA in FMD patients, showing that patients lacked the normal sensory evoked potentials (SEPs) attenuation observed in healthy controls at movement onset (Chapter 1- Electrophysiological and Neuroimaging Techniques). Considering the high prevalence of fatigue symptom in FMD, is possible that the results reported in these studies were guided by fatigued patients. However, neither study examined in a systematic way the interaction between the symptom of fatigue and SA in FMD, leaving a gap in our understanding about sensory processing in this clinical population.

To address this gap, our study aims to explore SA in FMD patients with and without fatigue by utilizing a Force Matching Task paradigm described in Chapter 2. This paradigm provides a direct measure of the sensory processing involved in distinguishing between self-generated and externally generated stimuli, offering insight into SA mechanisms. Specifically, we aim to determine whether SA deficits —conceptualized as reduced overestimation of target forces in the Direct condition and/or reduced or absent significant difference between Direct and Indirect conditions, as observed in PD patients (Chapter 2)— are more pronounced in fatigued FMD patients than in non-fatigued FMD patients and healthy controls. This study seeks to replicate findings from our PD study, extending them to another neurological condition.

Given the exploratory nature of our study and the small sample size collected so far, this research serves as a preliminary investigation to explore if fatigue interacts with sensory processing mechanisms in FMD. Based on the SAF model and our previous finding in PD, we hypothesized that fatigued FMD patients would exhibit reduced SA. Additionally, we anticipated that fatigued FMD patients would report higher subjective perceptions of fatigue and effort, consistent with our previous observations in PD, where effort perception deficits were specific to fatigued patients.

Through this study, we seek to contribute to the understanding of the mechanisms underlying fatigue in neurological disorders. By documenting the role of SA in fatigue across multiple conditions, we can advance our understanding of its underlying mechanisms and move closer to developing reliable, objective measures and potential biomarkers for pathological fatigue, ultimately improving diagnostic and therapeutic approaches.

Materials and Methods

Participants

To date, the study has included 10 patients diagnosed with Functional Movement Disorder (FMD), each evaluated and diagnosed by a consultant neurologist with expertise in Functional Disorders. Diagnoses were made following established clinical criteria (Gupta & Lang, 2009) to ensure consistency and accuracy. Motor symptom severity and duration were

assessed using the Simplified Functional Movement Disorders Rating Scale (S-FMDRS), a standardized, objective measure where higher scores (range: 0–54) indicate more severe motor symptoms (Nielsen et al., 2017).

Participants met specific inclusion and exclusion criteria to ensure the sample was both representative and able to complete the study requirements. Inclusion criteria required an established diagnosis of FMD by a specialist neurologist, age of 18 years or older, and acceptance and understanding of the diagnosis. Exclusion criteria were designed to rule out confounding factors and included prominent dissociative seizures, significant cognitive or physical impairments that could interfere with informed consent or study participation, and incomplete assessments or difficulty completing questionnaires due to language comprehension issues.

To address the aims of our study, patients were categorized into subgroups based on fatigue severity, as measured by the Fatigue Severity Scale (FSS; Krupp et al., 1989). For a detailed description of the FSS and its structr, refer to Chapter 2. A threshold score of 36 was used to classify patients into two subgroups: those with significant fatigue symptoms (FMD_Fatigue) and those without (FMD_NoFatigue). We recruited 5 patients in each subgroup, along with a control group of 5 healthy individuals (HC) matched for age, sex, and handedness. Demographic and clinical characteristics of each group are summarized in Table 4, with detailed individual profiles for patients in Table 5. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee (Comitato Etico per la Sperimentazione Clinica - CESC), with written informed consent obtained from all participants.

Table 4. ***Demographic and Clinical Characteristics of Each Group (n=15).*** *Summary of demographic and clinical characteristics for the three groups: FMD_Fatigue (n=5), FMD_NoFatigue (n=5), and Healthy Controls (HC; n=5). Data include mean and standard deviation (SD) for age, Fatigue Severity Scale scores (FSS), disease duration, and Simplified Functional Movement Disorders Rating Scale (S-FMDRS) scores, as well as counts (n) for sex and handedness.*

		FMD_Fatigue			**FMD_NoFatigue**			**HC**		
		Mean	SD	n	Mean	SD	n	Mean	SD	n
Sex	Male			1			1			1
	Female			4			4			4
Age	Years	45.60	13.58		47,60	7.89		45.00	9.57	
Handedness	Left			0			0			0
	Right			5			5			5
FSS		49.40	5.13		24.80	5.54		18.80	5.72	

Disease Duration	Years	55.60	40.26		39.00	31.61				
S-FMDRS		5.80	5.22		8.20	5.85				

Table 5. ***Clinical Profiles and Symptomatology of FMD Patients with and without Fatigue.*** *Clinical characteristics for each FMD patient in the FMD_Fatigue and FMD_NoFatigue groups, including Fatigue Severity Scale (FSS) scores, symptoms phenomenology, disease duration (in months), and Simplified Functional Movement Disorders Rating Scale (S-FMDRS) scores.*

GROUP	FSS	PHENOMENOLOGY	DISEASE DURATION (MONTHS)	S- FMDRS
FMD_Fatigue	51	Tremor, hyposthenia, myoclonus	50	2
FMD_Fatigue	55	Tremor, dystonia, swallowing disorders, gait disorders	12	8
FMD_Fatigue	44	Tremor, hyposthenia, dystonia, parkinsonism	60	2
FMD_Fatigue	53	Hyposthenia, dystonia bradykinesia, gait disorders	36	14
FMD_Fatigue	44	Hyposthenia	120	3
FMD_NoFatigue	26	Tremor, hyposthenia, dystonia, gait disorders	84	9
FMD_NoFatigue	21	Tremor, speech disorders	15	4
FMD_NoFatigue	34	Hyposthenia, myoclonus, dystonia, gait disorders, facial expression disorders	60	30
FMD_NoFatigue	22	Hyposthenia, gait disorders	24	4
FMD_NoFatigue	21	Tremor, hyposthenia, dystonia, myoclonus, gait disorders	12	18

Sensory Attenuation evaluation

The evaluation of SA followed the protocol outlined in detail in Chapter 2. Briefly, participants performed the Force Matching Task, which involved reproducing a target force in two different conditions: by directly pressing on their left index finger (Direct condition) or by pressing a button on an external device that controlled the lever's movement (Indirect condition). The procedures for data collection and calculation of SA indices were consistent with those outlined in the previous study. Specifically, SA index for each target force was calculated as the ratio between the matched force and the target force. Considering the high variability given by the small sample size, we focused our analysis on the Mean SA index for each condition. For a comprehensive description of the paradigm, including FMT graphical representations and details of SA indices, please refer to Chapter 2.

Subjective measures

As in the previous study on PD, participants in this procedure also rated their subjective experiences after completing each condition using four 10- cm VAS. The first VAS measured state fatigue perception, while the second assessed perceived physical effort. The third VAS evaluated perceived precision, where participants rated the accuracy of their performance. Lastly, the fourth VAS assessed the perception of control over the task. A detailed description of these VAS measures is provided in Chapter 2.

Wilcoxon signed-rank tests confirmed no significant differences between the Direct and Indirect conditions within any group for these subjective measures. Consequently, the mean VAS scores across conditions were used for subsequent analyses.

Protocol

The experiment was conducted with FMD patients during hospitalization, following a protocol visually summarized in Figure 7. The design closely resembles the protocol used in the PD study, with a few notable differences concerning clinical assessment. Participants first familiarized themselves with the FMT, then completed one of the two FMT conditions (Direct or Indirect), followed by a VAS assessment. They subsequently performed the second condition (Direct or Indirect), followed by a second VAS assessment.

Unlike the PD study, participants completed only the FSS after finishing both task conditions, providing a focused assessment of fatigue. No other clinical symptoms were collected at the end of the experiment. Motor symptom severity was evaluated prior to the experiment by a specialized neurologist.

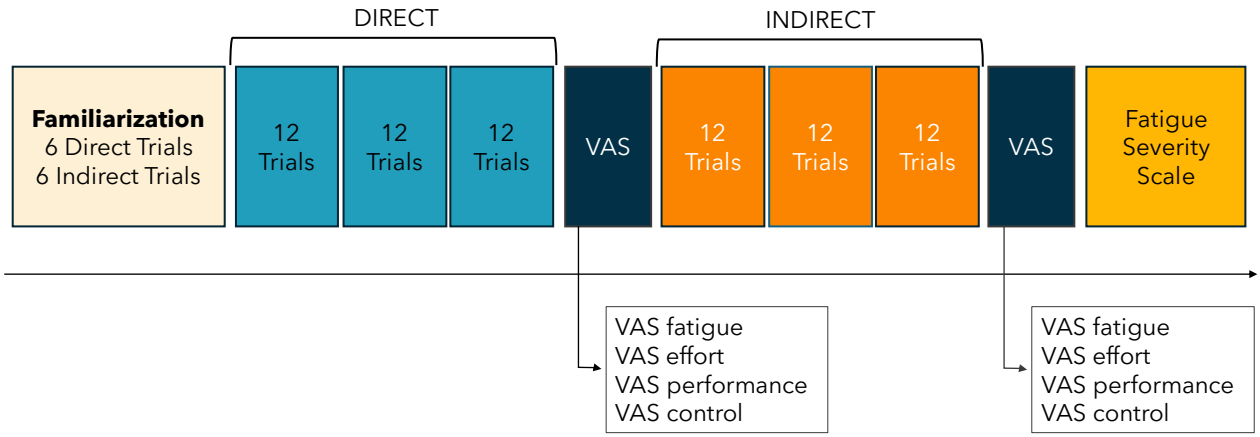

Figure 7. ***Experimental protocol****. Participants began with a familiarization phase, followed by three blocks of 12 trials in either the Direct or Indirect condition (counterbalanced order), VAS assessments after each condition, covering fatigue, effort, performance, and control, and concluding with the Fatigue Severity Scale (FSS) to assess fatigue severity.*

Data Analysis

All analyses were performed using SPSS Statistics 25 and MATLAB R2023b, with significance set at a p-value of < 0.05. Given the small sample size and the exploratory nature of this study, non-parametric tests were employed to accommodate the mixed design structure.

Mean SA indices were analyzed separately for the Direct and Indirect conditions. To assess group differences, Kruskal-Wallis Tests were conducted independently for each condition, followed by pairwise Mann-Whitney U Tests to identify significant group contrasts. In addition, Wilcoxon Signed-Rank Tests were conducted to compare the Mean SA indices against the reference value of 1 within each group (FMD_Fatigue, FMD_NoFatigue, and HC) and condition (Direct, Indirect). These tests assessed whether participants exhibited significant overestimation (value > 1, typically seen in the Direct condition), underestimation (value < 1), or no difference between the reproduced and target forces (value $= 1$). Notably, patterns of underestimation or absence of overestimation may indicate potential alterations in SA mechanisms.

VAS scores were analyzed using Kruskal-Wallis Tests to compare group differences and Mann-Whitney U Test for post-hoc comparisons. Finally, Spearman Correlation analyses were conducted to explore relationships between FSS scores, Mean SA indices, and clinical characteristics (disease duration S-FMDRS) across the entire sample.

Results

Descriptive analyses confirmed that demographic factors, including age, sex, handedness, were well matched between the three groups. Analysis of clinical characteristics

also revealed no significant differences in disease duration and symptoms severity (S-FMDRS) in FMD_NoFatigue, and FMD_Fatigue groups (Table 5). FSS scores showed significant differences in fatigue levels. The FMD_Fatigue group reported notably higher FSS scores (Mean ± SD: 49.40 ± 5.13) compared to both the FMD_NoFatigue (24.80 ± 5.54) and HC groups (18.80 ± 5.72). Pairwise comparisons highlighted significant differences between the FMD_Fatigue group and both the HC and FMD_NoFatigue groups ($p < 0.001$), emphasizing the higher fatigue severity in the FMD_Fatigue group.

Kruskal-Wallis tests revealed significant group differences for Mean SA in the Direct condition ($H_{(2)} = 10.820$, $p = 0.004$), with pairwise Mann-Whitney U tests showing significant differences between FMD_Fatigue (0.821 ± 0.120) and HC (1.545 ± 0.281) [$U = 0.000$, $Z = -2.611$, $p = 0.008$] and between FMD_Fatigue and FMD_NoFatigue (1.204 ± 0.305) [$U = 0.000$, $Z = -2.611$, $p = 0.008$]. Both HC and FMD_NoFatigue groups showed higher SA index values in the Direct condition compared to the FMD_Fatigue group. These preliminary results suggests that while the HC and FMD_NoFatigue group maintained typical SA patterns (with a higher Direct condition), the FMD_Fatigue group showed a marked reduction in SA, as evidenced by lower SA index values in the Direct condition. No significant difference between FMD_NoFatigue and HC was found [$U = 4.000$, $Z = -1.776$, $p = 0.095$], suggesting that SA in the FMD_NoFatigue group was similar to that of the HC. No significant group differences were found in the Indirect condition, indicating that the potential impairment in SA was specific to the self-generated force condition in the FMD_Fatigue group. A schematic representation of this result is presented in Figure 8.

Comparisons of Mean SA against the reference value of 1 provided insight into group-specific patterns of SA (Figure 8). In the HC group, the SA index for both Direct and Indirect conditions was significantly different from 1 (Direct: $Z = -2.023$, $p = 0.043$; Indirect: $Z = -2.023$, $p = 0.043$), with the Direct condition showing overestimation (SA index > 1) and the Indirect condition underestimation (SA index < 1). In the FMD_Fatigue group and FMD_NoFatigue group, only the Direct condition was significantly different from 1 (FMD_Fatigue: $Z = -2.023$, $p = 0.043$; FMD_NoFatigue: $Z = -2.023$, $p = 0.043$), however, the direction of the effect differed between the two groups. In the FMD_NoFatigue group, the Direct condition mirrored the overestimation pattern observed in the HC group (SA index > 1), suggesting relatively preserved SA. In contrast, the FMD_Fatigue group exhibited an SA index < 1 in the Direct condition, indicating significant underestimation of the target forces. This finding points to potential alterations in sensory processing mechanisms uniquely associated with fatigue in FMD patients.

Figure 9a illustrates single subject scores in the Direct condition. In general, a higher percentage of HC participants displayed SA index values above 1, consistent with the typical

overestimation associated with self-generated actions. In contrast, both FMD groups showed values closer to or below 1, indicating a possible alteration in SA specifically in the Direct condition. In the Indirect condition, depicted in Figure 9b, no clear group differences were observed, with SA indices clustering closer to 1 across all groups. This pattern supports the notion that potential SA impairments are specific to self-generated actions.

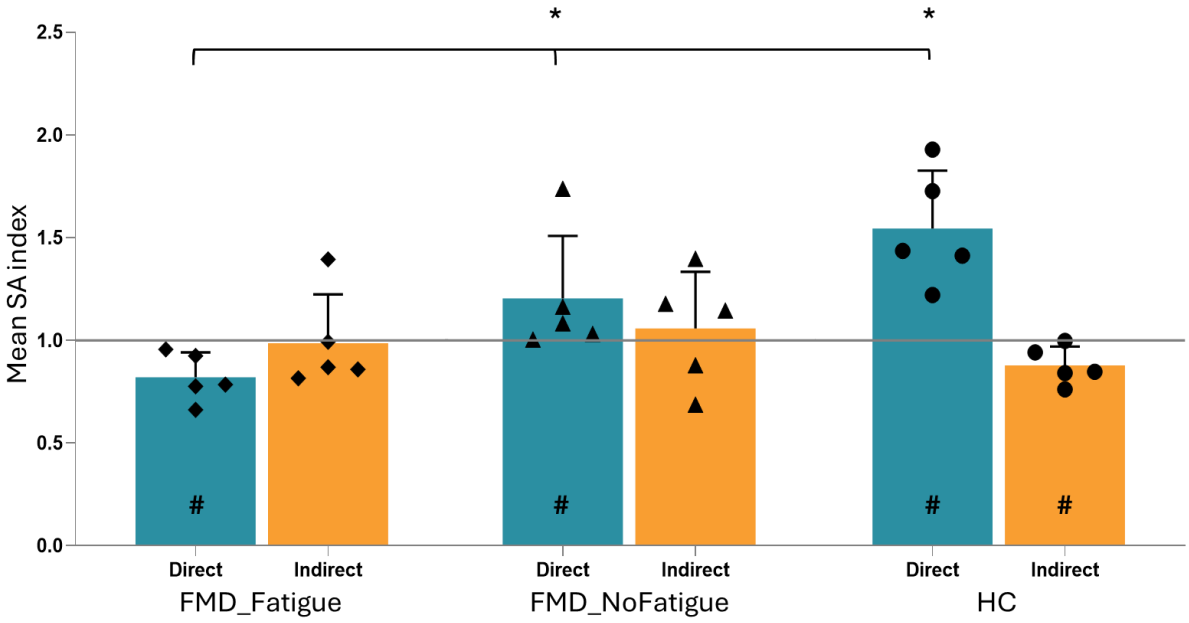

Figure 8. ***Mean SA index for Direct (blue) and Indirect (orange) conditions across PD_Fatigue, PD_NoFatigue, and Healthy Control (HC) groups.*** *A significant interaction effect is observed, with the HC Direct condition significantly differing from the PD_Fatigue Direct condition. The horizontal line at SA index = 1.0 represents accurate force matching; values above 1.0 indicate overestimation, and values below 1.0 indicate underestimation. HC participants exhibit overestimation in the Direct condition, while PD_Fatigue participants show underestimation. The PD_NoFatigue group displays a pattern qualitatively similar to that of HC. (*= p<0.05; #= significant deviations from 1.0 within groups)*

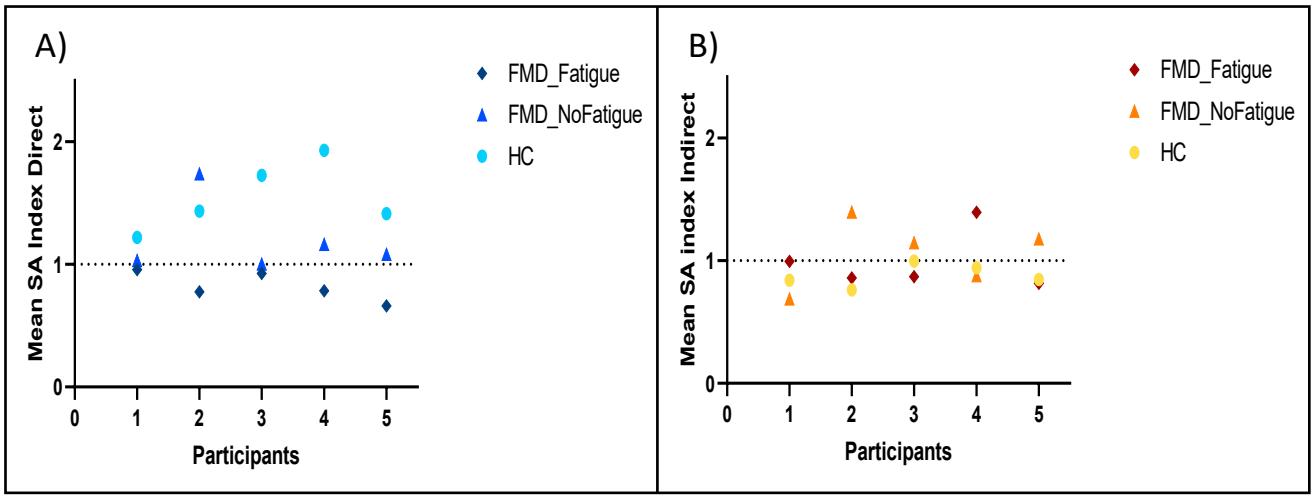

Figure 9. ***Mean SA Index for Each Participant Across Conditions.*** *A) Mean SA Index for the Direct condition across individual participants in each group: FMD_Fatigue, FMD_NoFatigue, and HC. On the y axis, the dotted line at 1 represents an reproduction of the target force (Target force=matched force), with values above 1 indicating overestimation (typical SA). In general, more HC than FMD showed an SA index above 1. B) Mean SA Index for the Indirect condition across individual participants in each group. Here, SA indices are closer to the target value of 1 across all groups, with no significant differences observed between groups.*

For the VAS analysis, Wilcoxon signed-rank tests confirmed no significant differences between Direct and Indirect conditions for any VAS scores within any group, allowing the use of mean VAS scores across conditions. Kruskal-Wallis tests revealed significant group effects for VAS fatigue [$H_{(2)} = 8.195$, $p = 0.017$] and VAS effort [$H_{(2)} = 8.195$, $p = 0.017$]. Post-hoc Mann-Whitney U tests showed that the FMD_Fatigue group reported significantly higher mean VAS fatigue and effort scores compared to both the HC [VAS Fatigue: $U = 2.000$, $Z=-.2.200$ $p = 0.032$; VAS effort: $U = 1.000$, $Z= -2.402$, $p = 0.016$] and FMD_NoFatigue groups [VAS Fatigue: $U =0.000$, $Z= -2.619$, $p = 0.008$; VAS effort: $U = 1.000$, $Z= -2.410$, $p = 0.016$]. These findings indicate that subjective perceptions of fatigue and effort were notably heightened in FMD patients with fatigue.

Finally, Spearman correlation analysis across the entire sample showed significant negative correlations between Mean SA index in the Direct condition and FSS scores ($\rho = -0.830$, $p < 0.001$). These results suggest that higher fatigue severity is associated with reduced SA, supporting the hypothesis of a potential relationship between fatigue and impaired sensorimotor predictive mechanisms. No significant correlations were found between FSS and Indirect Mean SA or between Mean SA and clinical characteristics (e.g., disease duration, S_FMDRS).

Discussion

Our study provides preliminary evidence that SA deficits in FMD patients may interact with fatigue. Using the Force Matching Task, we observed distinct SA patterns between healthy controls, FMD patients without fatigue, and FMD patients with fatigue. Specifically, the FMD_Fatigue group displayed significantly reduced SA index values in the Direct condition compared to both HC and FMD_NoFatigue, potentially indicative of compromised SA. Further analysis of Mean SA indices against the reference value of 1 reinforced these findings: while HC and FMD_NoFatigue participants demonstrated significant overestimation in the Direct condition, the FMD_Fatigue group showed a significant underestimation. These results further suggest significant alterations in SA within the FMD_Fatigue group and highlight how fatigue

may exacerbate sensory processing impairments in FMD, aligning with our results in PD patients (Chapter 2).

Specifically, our results regarding individual subject data showed that FMD patients generally exhibit SA indices closer to 1 in the Direct condition, corroborating prior research (Pareés et al., 2014; Macerollo et al., 2015). However, unlike prior studies, our study extends these findings by specifically addressing the interaction between fatigue and SA. Our preliminary results suggest that fatigue intensifies SA deficits, as fatigued FMD patients displayed more pronounced attenuation impairments compared to both non-fatigued FMD patients and HC participants. These results align with the hypothesis that fatigue may interact with sensory processing, potentially leading to an altered perception of self-generated actions (Kuppuswamy, 2017; Maurer et al., 2016) and suggest alterations in sensory prediction and comparison mechanisms (Baek et al., 2017; Edwards et al., 2013; Voon et al., 2010).

Moreover, our results lend additional support to the SAF model (Kuppuswamy 2017; 2022), which posits that fatigue arises from disruptions in SA, impairing an individual's ability to predict the sensory consequences of self-generated actions accurately, including the effort required. Under typical conditions, intact SA allows for accurate predictions, assuring normal perception of effort. However, when SA is altered, as seen in our FMD_Fatigue group, the prediction process is compromised, leading to a heightened perception of effort and subsequent fatigue. Our data align with this model: the FMD_Fatigue group's subjective ratings on the VAS scales showed significantly higher perceptions of fatigue and effort than those of the FMD_NoFatigue and HC groups, implying that disruptions in sensory prediction mechanisms may directly influence the subjective experience of fatigue and effort in FMD patients with fatigue.

The negative correlations observed between fatigue severity (as measured by FSS scores) and the Mean SA index in the Direct condition, further reinforce this interpretation. These correlations suggest that higher FSS scores are associated with reduced SA, supporting the hypothesis that as fatigue severity increases, the brain's capacity to attenuate self-generated sensory signals diminishes. This aligns with the SAF model's suggestion that impaired SA contributes to a distorted sense of effort and fatigue (Kuppuswamy, 2017).

The similarity in SA deficits observed in fatigued FMD and PD patients suggests that abnormal SA may be a transdiagnostic marker of fatigue across neurological disorders. Abnormal SA may be a common feature associated with fatigue, independently of the specific neurological disease. Such parallels raise questions about the potential mechanisms underlying fatigue's interaction with SA. One plausible explanation, as previously outlined in Chapter 2, involves the basal ganglia–cortex–cerebellum network, which is involved in motor control, sensorimotor prediction, and effort estimation (Bostan et al., 2018; Baladron et al., 2023;

Blakemore & Sirigu, 2003) and may be affected in both PD (Caligiore et al., 2016) and FMD (Maurer et al., 2016; Roelofs et al., 2019). Dysfunction within this network could disrupt the comparison process between actual sensory feedback and predicted sensory signals (efference copy; Blakemore et al., 1998), leading to an impaired ability to predict the sensory consequences of actions, thereby heightening perceived effort (Kuppuswamy, 2017). This neural circuitry may be a common substrate for the observed SA deficits in fatigued FMD and PD patients.

Considering the transdiagnostic nature of fatigue as a symptom across numerous neurological conditions, including PD, multiple sclerosis, FMD, and post-stroke syndromes (Di Vico et al., 2021; Kuppuswamy, 2022), SA has the potential to serve as an objective marker of fatigue. Current diagnostic tools for fatigue rely heavily on subjective self-reports, which are prone to variability and bias (Kluger et al., 2013). If the relationship between SA and fatigue is confirmed through further research involving larger, more diverse patient populations, SA could emerge as a reliable biomarker for pathological fatigue. This would represent a significant advancement, offering an objective tool to assess a symptom that is currently challenging to quantify.

While promising, our findings are preliminary and should be interpreted with caution given certain limitations, most notably the small sample size. Importantly, this study is part of an ongoing larger project aimed at identifying biomarkers of FMD, and data collection is continuing. Future studies would benefit from employing neuroimaging techniques, such as functional MRI or EEG, to identify the neural substrates of SA alterations in fatigued FMD patients, providing insight into the brain networks involved in this sensory impairment. Additionally, longitudinal research would be essential to determine whether SA deficits precede or develop as a consequence of fatigue in FMD, providing clarity on the temporal relationship between the two factors. These approaches could help clarify the mechanisms underlying fatigue's role in sensory processing and potentially inform therapeutic strategies for addressing fatigue in FMD and related conditions.

Conclusion

In summary, our preliminary findings suggest that fatigue symptom in FMD is associated with reduced SA, which may underlie an increased perception of effort and fatigue in this population. By offering preliminary support for the SAF model, this study contributes to a growing body of evidence on the role of sensorimotor prediction mechanisms in fatigue and opens new doors for understanding and managing fatigue-related symptoms in FMD.

Larger sample sizes, neuroimaging studies, and longitudinal approaches will be critical for validating these results and advancing our understanding of fatigue's interaction with sensory attenuation in FMD.

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Chapter 4: Sensory attenuation and fatigue in a healthy population

This chapter is based on the manuscript entitled: *'The Interplay Between Sense of Agency and Fatigue: New Insights from Sensory Attenuation'*, currently in preparation for submission.

Introduction

In previous chapter (2 and 3) we provided clinical evidence in support of the SAF model, demonstrating that SA is selectively impaired in PD and FMD patients with pathological

fatigue. These finding suggests that reduced SA may serve as a potential biomarker for fatigue in clinical settings. However, as outlined in Chapter 1, fatigue exists on a spectrum that extends beyond pathological conditions, ranging from exacerbated clinical symptoms to a common physiological experience with both subjective and objective dimensions (Echteld et al., 2007; de Raaf et al., 2012). Despite is universality, the mechanisms underlying physiological fatigue remain poorly understood.

To bridge this gap, it is essential to revisit the distinction between subjective and objective dimensions of fatigue, discussed in Chapter 1. Subjective fatigue, or perceived fatigue, refers to the personal experience of exhaustion and a lack of energy, which individuals can verbally report (Enoka and Duchateau, 2016; Kowalski et al., 2021). Subjective fatigue can be further divided into trait fatigue and state fatigue (Kowalski et al., 2021). Trait fatigue reflects an individual's predisposition to feeling tired, which can occur independently of intense physical or mental exertion (Guillemin et al., 2022; Malloy et al., 2021; Möller et al., 2019; Wylie & Flashman, 2017). In contrast, state fatigue is a transient, immediate response to intense or prolonged exertion, whether physical or mental (Kowalski et al., 2021; Guillemin et al., 2022). This temporary state of fatigue often coincides with the objective fatigue component: performance fatigability, which refers to a measurable decline in physical or cognitive performance over time (Ream & Richardson, 1997; Chaudhuri & Behan, 2004). Moving beyond the pathological framework of fatigue to understand how its various dimensions—subjective and objective—interact with sensory processing, and specifically SA, is critical for a comprehensive understanding of this phenomenon.

This study investigates whether the SAF model extends to physiological fatigue. To tackle the complexity of fatigue, we examine both subjective and objective components of this experience. Specifically, we explore whether SA: 1) differs between individuals with high and low trait fatigue; 2) interacts with state fatigue and performance fatiguability. To this aim, we measured sensory attenuation in individuals with high and low fatigue traits, both with and without exposure to a fatiguing task. Based on previous findings (De Doncker et al., 2020; Kuppuswamy, 2022), we hypothesize that healthy individuals with higher trait fatigue will exhibit lower SA than those with lower trait fatigue. This pattern would mirror the SA deficits observed in fatigued clinical populations, suggesting that the SAF model may encompass both pathological and physiological fatigue. Our hypothesis regarding the interplay between SA, fatiguability, and state fatigue is less clear-cut. We anticipate that the fatiguing task will induce increased state fatigue and fatigability across all participants. Furthermore, we predict this increase in state fatigue and fatiguability will be more pronounced in individuals with higher trait fatigue and lower SA. This would suggest that those predisposed to fatigue and reduced

SA may be more susceptible to fatiguability and subjective experience of state fatigue after exertion.

This study seeks to deepen our understanding of physiological fatigue and its interplay with sensory processing, potentially providing new evidence to support an extension of the SAF model to encompass a broader spectrum of fatigue experiences.

Materials and methods

Participants

Computation of the sample size was performed with GPower 3.1 (Faul et al., 2007), assuming an anticipated effect size f of .25 (considered as medium according to Cohen, 1988), an alpha error probability of .05, a power of .80, a correlation among repeated measures of .5, and a non-sphericity correction ε of 1. For our experimental design (two groups and two sessions, see below for details), the resulting sample size was 34. We recruited more participants to prevent a reduction in statistical power due to dropouts.

A total of 45 naïve healthy participants (21 women, mean age ± (SD): 23.24 ± 3.62 years) with no history of neurological or psychiatric illness were recruited from the student population of the University of Verona (Italy). All participants but two were right-handed (Edinburgh Handedness Inventory: 68.15 ±26.11) (Oldfield, 1971).

The study received approval from the ethical committee of the University of Verona (CARP) and was conducted in accordance with the Declaration of Helsinki. Written, informed consent was obtained from all participants.

Trait fatigue

To categorize participants into the two groups, one with high predisposition to fatigue and one with low predisposition to fatigue, we assessed trait fatigue, with the Fatigue Severity Scale (FSS; Krupp et Participants were categorized into two groups—those with a high predisposition to fatigue and those with a low predisposition to fatigue—based on their trait fatigue levels, assessed using the Fatigue Severity Scale (FSS; Krupp et al., 1989; Ottonello et al., 2016). A comprehensive description of the FSS is provided in Chapter 2. The FSS has been used in previous studies to assess trait fatigue in healthy participants (Laerdal et al., 2005; Schneider, 2004), and to measure the severity of pathological fatigue in clinical populations (cut-off score of ≥36) (Krupp et al., 1989). Based on trait fatigue levels, we utilized a data-driven approach employing a K-means cluster analysis on their FSS scores. This method, supported by previous research (Siciliano et al., 2017), allows for robust grouping based on

individual differences in self-reported fatigue, particularly crucial given the absence of an established FSS cutoff score for healthy populations. The analysis identified an optimal two-cluster solution (K=2), with a silhouette coefficient of 0.5980 and a BIC index of 91.8112, indicating good cluster separation. To further ensure robust grouping, we adopted a conservative approach by retaining only participants consistently assigned to the same cluster across multiple iterations of the analysis. This led to the exclusion of two participants with unstable cluster assignments. This procedure yielded two distinct groups: High-FSS group (n=22, 13 women, 9 men, mean age = 23.64 ± 4.20 years); Low-FSS group (n=21, 8 women, 13 men, mean age = 22.95 ± 2.87 years). The High-FSS and the Low-FSS groups were matched for age, gender distribution and education level.

This approach allowed us to establish a reliable cutoff for trait fatigue within our healthy participant sample and ensure a meaningful analysis of the relationship between fatigue and SA.

The fatiguing task.

The fatiguing task consisted of a sustained maximal isometric handgrip contraction. Participants first performed two 4-second maximal voluntary contractions (MVC) with their right hand using a handgrip dynamometer. The two MVC attempts were separated by a 30-second rest interval. The highest MVC value was considered the baseline ($MVC_{baseline}$) and used to calculate the stopping criterion (i.e., 20 % $MVC_{baseline}$) for the fatiguing task. During the fatiguing task, participants were instructed to squeeze the handgrip as hard as possible and to maintain this maximal contraction. The experimenter stopped the participant when the force production was reduced to 20% of the $MVC_{baseline}$ and maintained that level for at least 10 seconds (Figure 10). The participants were unaware of the stopping criteria. This procedure has been previously validated as an effective method for inducing fatigability, defined as a reduction in the maximal capacity to generate force or power output (Kennedy et al., 2013; Vøllestad, 1997). The fatiguing task was repeated four times, with SA assessed after each repetition (see below *Protocol*).

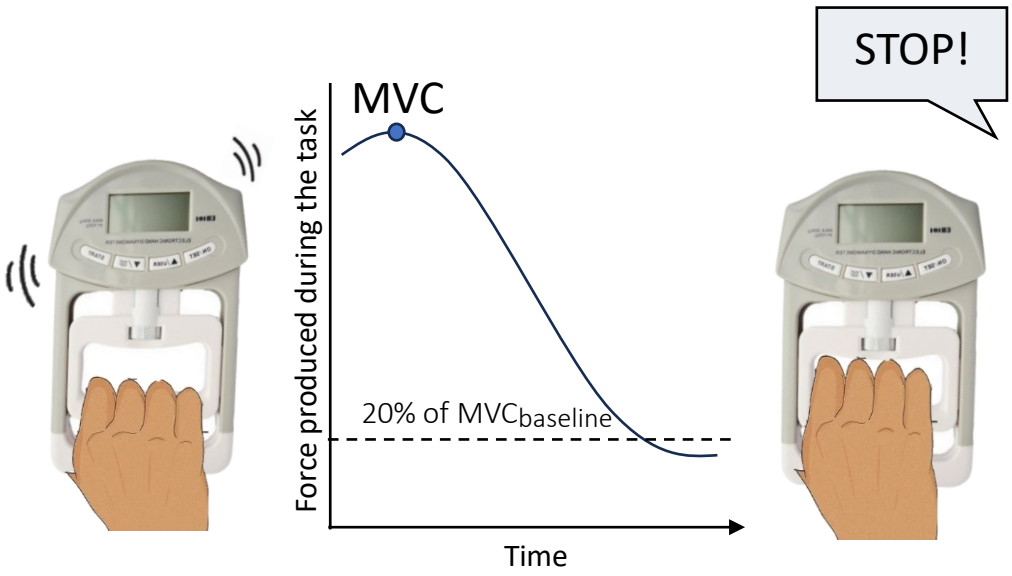

Figure 10. ***Fatiguing task protocol.*** *Participants performed a sustained maximal isometric handgrip contraction using a handgrip dynamometer. The baseline maximal voluntary contraction ($MVC_{baseline}$) was established from the highest of two 4-second MVC attempts. During the task, participants were instructed to maintain maximal contraction until the force output decreased to 20% of the MVC baseline and remained at that level for at least 10 seconds. The stopping criterion was not disclosed to participants.*

To objectively quantify fatiguability, we calculated normalized MVC for each participant during each repetition of the fatiguing task, using the following equation:

$$MVC_Tj_{norm} = \frac{MVC_j}{MVC_{baseline}} * 100$$

where MVC_Tj_{norm} is the MVC recorded during repetition j and normalized at the baseline; MVCj is the MVC recorded during the repetition j (Figure 10); $MVC_{baseline}$ is the MVC recorded at the baseline. Following this procedure we calculated four MVC_Tj_{norm} (MVC_T1_{norm}, MVC_T2_{norm}, MVC_T3_{norm}, MVC_T4_{norm}), reflecting the decline in maximal force production over repetitions of the fatiguing task (i.e., fatiguability).

Sensory Attenuation evaluation

The evaluation of SA followed a similar procedure to the one detailed in Chapter 2. Participants completed the Force Matching Task (FMT; Shergill et al., 2003; Pareés et al., 2014; Palmer et al., 2016), which required reproducing a target force under two conditions: by directly pressing on their left index finger (Direct condition) or by using an external device to control the lever's movement (Indirect condition).

Unlike the procedures employed in studies on PD and FMD, the current study included two blocks of 18 trials for each FMT condition, with 6 trials per target force presented in random

order. Between blocks participants performed the fatiguing task (see Protocol below). Additionally, participants were familiarized with the FMT through a 12-trial training session for each condition to ensure adequate understanding and practice.

Data collection and SA index calculation procedures were consistent with those described in previous chapters. The SA index for each target force was calculated as the ratio between the matched force and the target force. The Mean SA index for each condition was then derived by averaging the SA indices across all target forces. Additionally, Delta SA was computed as the difference between the Mean SA index for the Direct and Indirect conditions. For a comprehensive description of the paradigm, including graphical representations of the FMT and detailed calculations of SA indices, please refer to Chapter 2.

Subjective measure

As in the studies detailed in the previous chapter, participants completed a series of 10-cm VAS at the end of each condition. The first VAS assessed their perception of state fatigue. Additional VAS were used to evaluate perceived effort, the subjective quality of task performance, and the sense of control experienced during the task. These measures provided insights into participants' subjective experiences related to fatigue and task engagement.

Protocol

To investigate the interplay between SA and perceived state fatigue in High and Low FSS groups, participants underwent two experimental sessions (Fatigability and No-Fatigability, Figure 11), separated by one-week intervals. In one of the two sessions, together with the assessment of SA, participants were required to perform the fatiguing task (Fatigability session). The order of sessions and conditions was counterbalanced across participants. To rule out any effect of physical activity on fatigue, subjects were asked not to perform medium- or high-intensity physical activities in the 12 hours preceding the experimental sessions. In addition, the sessions were distributed so that female participants were not in the menstrual phase during the experiment.

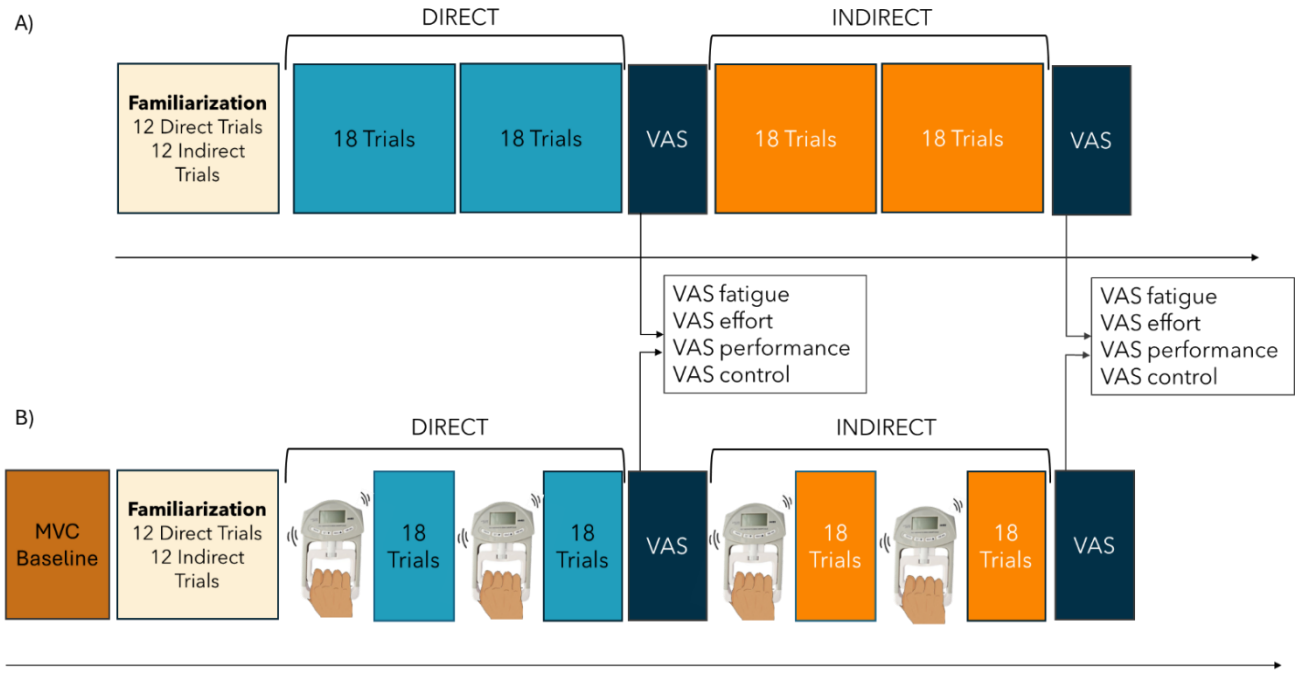

Figure 11. ***Protocol for the No-Fatigability (A) and Fatigability (B) sessions.*** *Session A (No-Fatigability): participants started with familiarization trials for FMT. They then performed the first condition of the SA task (Direct or Indirect) and rated their perception using VAS. After a brief rest, they completed the second SA condition, followed by additional VAS ratings. In Session B (Fatigability), participants began with a baseline measurement of MVC using a handgrip dynamometer, followed by FMT familiarization. Before each block of either the Direct or Indirect condition, participants completed a fatiguing task. At the end of each condition, participants provided VAS ratings. At the conclusion of both sessions, participants completed the FSS. The sessions were counterbalanced across participants and conducted one week apart to minimize carryover effects.*

Data Analysis

SPSS Statistics (version 25.0.0) and Matlab (version R2023b) were used for the analysis.

To analyze fatiguability, the MVC_{norm} recorded in all the repetitions of the fatigability task was entered in a 2 × 4 rmANOVA with Group (High-FSS, Low-FSS) as the between-subjects factor and Time (T1, T2, T3, T4) as the within-subjects factor.

The Mean SA_{index} was analyzed with a 2×2×2 rmANOVA with Group (High-FSS, Low-FSS) as a between-subjects factor and Condition (Direct, Indirect) and Session (Fatigability, No-Fatigability) as within-subjects factors. To verify whether participants significantly overestimate the target force, Mean SA indices were compared against 1, where 1 indicates total accuracy in the reproduction of the target force, using a one-sample t-test. To explore deeper the group-specific differences in SA, a rmANOVA was performed with Session (Fatigability, No-Fatigability) as a within factor and Group (High-FSS, Low-FSS) as the between-subject factor, focusing on Delta SA. Unlike the rmANOVA, which evaluates condition-specific effects, this analysis isolates the magnitude of the difference between Direct and Indirect

conditions to determine whether it varies systematically across groups. Additionally, to further confirm SA effects, a one-sample t-test was conducted on Delta SA values against 0, where 0 indicated the absence of difference between direct and indirect values.

Subjective feelings of state fatigue, effort, precision, and control were analyzed through non-parametric tests (Wilcoxon signed rank test and Mann-Whitney U test) to investigate statistically significant differences in the subjective judgments reported in each session and condition in both groups.

Results

Fatiguability

The rmANOVA showed a significant main effect of Time [$F_{(3, 39)}$= 61.443, $p < 0.001$], driven by significantly different MVC values at timepoints 2, 3, and 4 compared to timepoint 1 (Figure 12). Specifically, pairwise comparisons revealed a consistent decline in force production across consecutive timepoints (1 > 2 > 3 > 4), emphasizing the progressive nature of the fatigability induced by the task. These results validate our experimental manipulation and confirm that the fatiguing task was effective in inducing and maintaining motor fatigability over time. Neither the main effect of Group [$F_{(1,41)}$= 1.773, p= 0.190] nor the Time x Group interaction [$F_{(3,39)}$= 0.132; p= 0.941] reached statistical significance, indicating that the performance during the fatiguing task did not differ between the High-FSS and Low-FSS groups. This suggests that trait fatigue does not affect performance in this context, as both groups—despite differing levels of trait fatigue—exhibited similar reductions in force during the fatigue induction task.

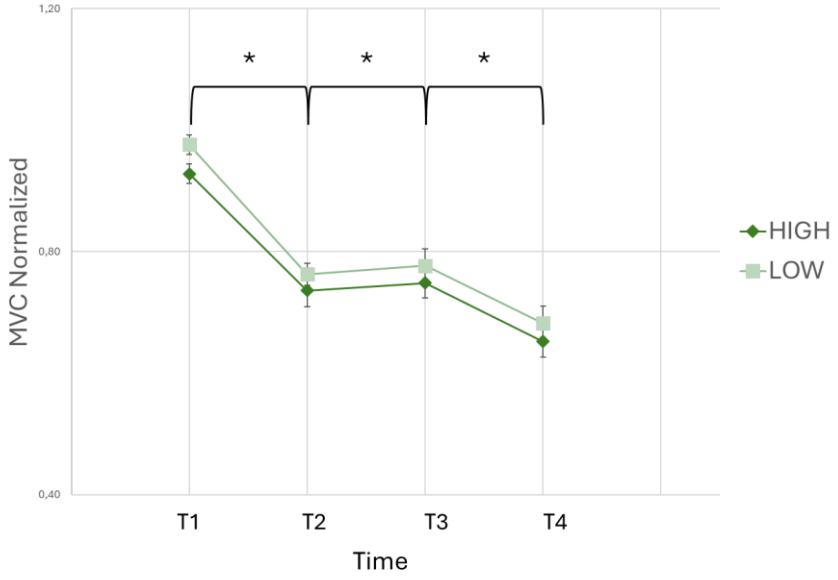

Figure 12. ***Normalized MVC decline across timepoints for High-FSS and Low-FSS groups.*** *Both groups show a significant reduction in MVC from Time 1 to subsequent timepoints (Time 2, 3, and 4), confirming the*

effectiveness of the fatiguing task in inducing fatigability. The absence of significant differences between the groups indicates that trait fatigue (High-FSS vs. Low-FSS) does not influence the rate of force decline during the fatiguing task.

Sensory attenuation in high and low fatigue groups

The rmANOVA showed a significant main effect of the Condition [$F_{(1,41)}$= 75.226, p < 0.001], due to a higher Mean SA index in the Direct (mean ± SD = 1.308 ± 0.295) compared to Indirect condition (0.919 ± 0.022) across all groups. This finding confirms the expected pattern of overestimation in the Direct condition, typically seen in healthy subjects (Shergill et al., 2003).

Interestingly, a significant Group × Condition interaction was observed [$F_{(1,41)}$ = 9.981, p = 0.003] (Figure 13). Specifically, the High-FSS group showed a significantly lower Mean SA index in the Direct condition (1.205 ± 0.295) compared with the Low-FSS group (1.410 ± 0.293) [$F_{(1,41)}$=5.240, p = 0.027]. This finding suggests that individuals with higher trait fatigue exhibit reduced overestimation of the target force in the Direct condition, reflecting a diminished SA. Conversely, in the Indirect condition, no significant difference between the groups was found [$F_{(1,41)}$ = 3.162, p = 0.083], as both groups exhibited similar Mean SA indices. The reduced SA observed in the High-FSS group indicates that individuals with a more pronounced fatigue trait tend to be more precise in reproducing force in the Direct condition and exhibit less overestimation of the target force compared to the Low-FSS group, suggesting that trait fatigue may interact with SA in healthy subjects and alters the perception of self-generated actions. No main effects of Session [$F_{(1,41)}$= 0.282, p = 0.598], Session × Condition [$F_{(1,41)}$= 0.263, p = 0.611] or Condition × Session × Group [$F_{(1,41)}$= 0.005, p = 0.942] were found, indicating that the pattern of SA was consistent across the two experimental sessions (Fatigability and No-Fatigability).

Comparisons of SA indices against the reference value of 1 provided additional insights into the dynamics of SA. In the Direct condition, both High-FSS group [$t_{(21)}$= 3.516, p = 0.002] and Low-FSS groups [t(20)= 6.007, p < 0.001] significantly overestimated the target force, confirming the presence of sensory attenuation. However, in the Indirect condition, the Low-

FSS group exhibited significant underestimation of the target force [$t_{(20)}$ = -3.475, p=0.002), with an average Mean SA index below 1 (0.879 ± 0.158).

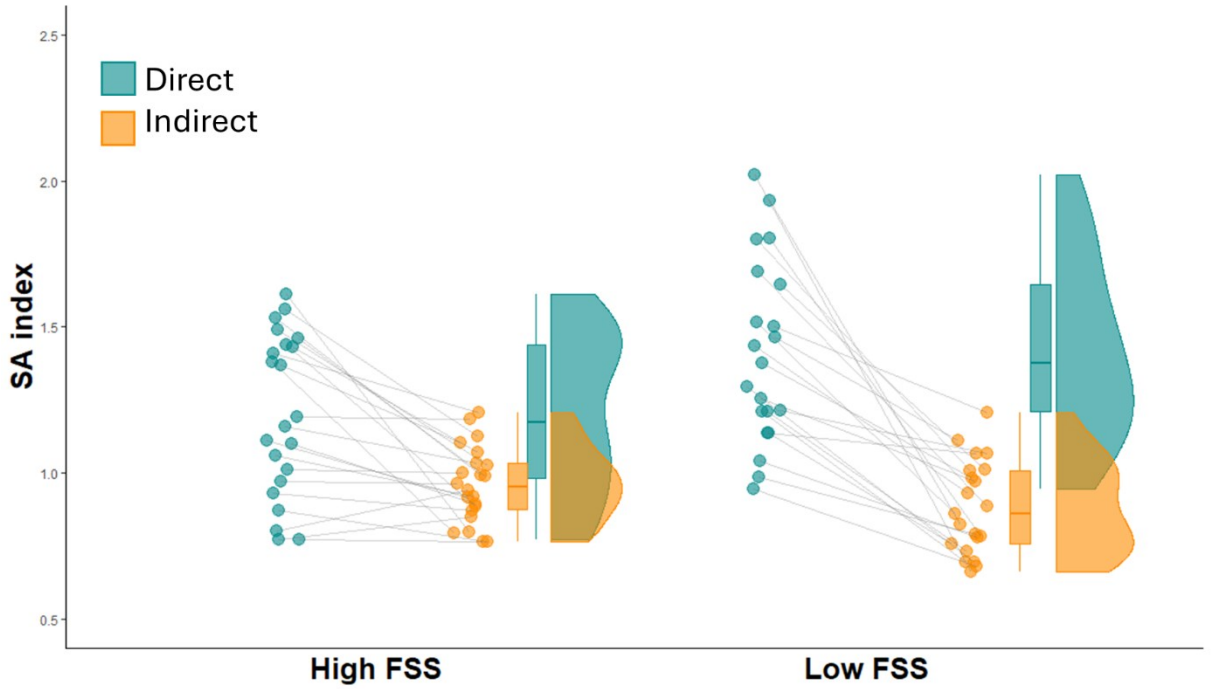

Figure 13. ***Mean SA indices in Direct and Indirect conditions across High-FSS and Low-FSS groups****. Raincloud plots depict individual SA indices, group means, and distributions for both the Direct (blue) and Indirect (orange) conditions. The High-FSS group shows significantly lower SA indices in the Direct condition compared to the Low-FSS group. Both groups exhibit similar SA indices in the Indirect condition, suggesting that the observed group differences are specific to the Direct condition. Box plots and density curves illustrate central tendencies and data distribution.*

Analysis of Delta SA via rmANOVA revealed a significant effect of Group [$F_{(1,41)}$ = 9.981, p = 0.003], with High-FSS group that displayed a significant smaller difference between Direct and Indirect (0.247 ± 0.295) compared to the Low-FSS group (0.530 ± 0.293) (Figure 14). No significant main effects of Session or interaction effects involving Session were found. Given the lack of session-related differences [$F_{(1,41)}$= 0.263, p= 0.611] Delta SA values were averaged across sessions for further analysis. A one-sample t-test against zero revealed that both groups exhibited significant differences from zero the [High-FSS $t_{(21)}$= 4.672, p < 0.001; Low-FSS $t_{(20)}$= 7.251, p < 0.001], his confirms that the difference between the Direct and Indirect conditions was significant in both groups, indicating that SA was preserved to some extent in both High-FSS and Low-FSS groups, albeit with marked reductions in the High-FSS group.

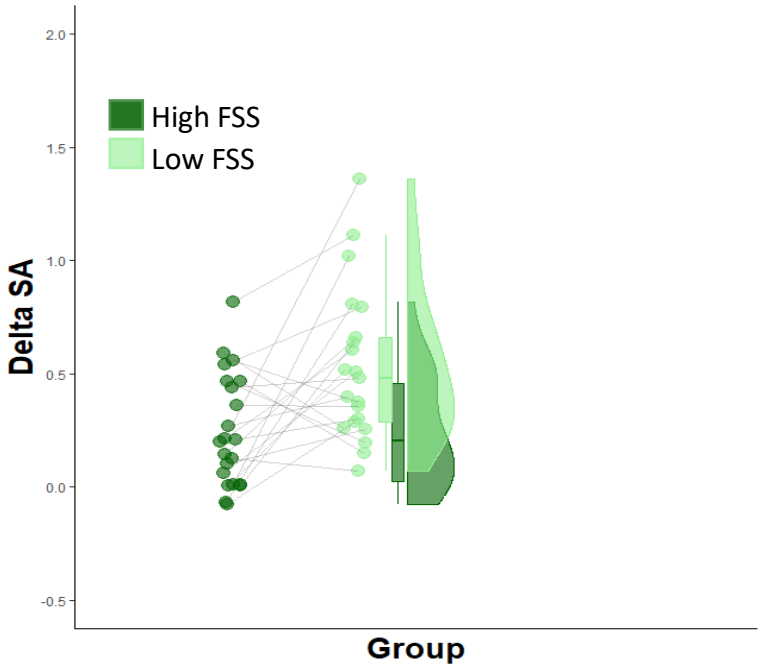

Figure 14. ***Delta SA values across High-FSS and Low-FSS groups****. Raincloud plot illustrating individual Delta SA values (for the High-FSS and Low-FSS groups. The plot includes individual data points, group means, and distribution curves. The High-FSS group shows significantly lower Delta SA values compared to the Low-FSS group, indicating a reduced difference between Direct and Indirect conditions. Box plots and density distributions highlight group differences and variability, emphasizing reduced Delta SA in the High-FSS group.*

Subjective measure

Participants from both groups reported higher levels of perceived state fatigue in the Fatigability session compared to the No-Fatigability session, in both Direct [High-FSS: Z=-2.760, p= 0.006; Low-FSS: Z=-3.268, p=0.001] and Indirect conditions [High-FSS: Z=-2.833, p= 0.005; Low-FSS: Z=-3.423, p= 0.001] (Figure 15a). These results further validate the effectiveness of the fatiguing task in inducing state fatigue. Notably, no significant differences were found between the two groups in terms of perceived state fatigue, reinforcing the idea that trait fatigue does not significantly influence the subjective experience of state fatigue induced by the fatiguing task.

Both groups also reported greater perceived effort during the Fatigability session compared to the No-Fatigability session (figure 15b). This increase was evident in both Direct (High-FSS: Z=-2.330, p= 0.020; Low-FSS: Z=-2.189, p= 0.029) and Indirect conditions (High-FSS: Z=-2.842, p= 0.004; Low-FSS: Z=-2.856, p= 0.004), suggesting that the fatiguing task successfully increased perceived exertion. However, perceived performance and control ratings remained stable across sessions and conditions, indicating that fatigue induction affected state fatigue and effort perception, but did not influence participants' subjective evaluation of task performance or control.

Interestingly, Mann-Whitney tests revealed significant differences in perceived effort between the the High-FSS and Low-FSS groups. The High-FSS group consistently reported greater exertion than the Low-FSS group in several conditions (Figure 15b). Specifically, in the No-Fatigability session, the High-FSS group reported greater perceived effort in both the Direct (High-FSS: 1.854 ± 1.828; Low-FSS: 1.043 ± 1.714; U=137.000, Z= -2.295, p=0.022) and Indirect conditions (High-FSS: 1.395 ± 1.180; Low-FSS: 0.890 ± 1.403, U=138.500, Z= -2.258, p=0.024). Similarly, in the Fatigability session, the High-FSS group reported significantly higher perceived effort in the Direct condition (High-FSS: 1.832 ± 2.063; Low-FSS: 1.814 ± 2.256, U=149.500, Z= -1.982, p=0.047). These findings suggest that trait fatigue influences the perception of effort, with individuals in the High-FSS group consistently reporting greater exertion than those in the Low-FSS group. Importantly, this effect was observed even in the No-Fatigability session, indicating that the heightened effort perception in the High-FSS group may reflect a predisposition associated with trait fatigue, independent of the fatiguing task. In the Fatigability session, this heightened perception of effort persisted, suggesting that individuals with higher trait fatigue are more susceptible to perceiving greater exertion during demanding tasks.

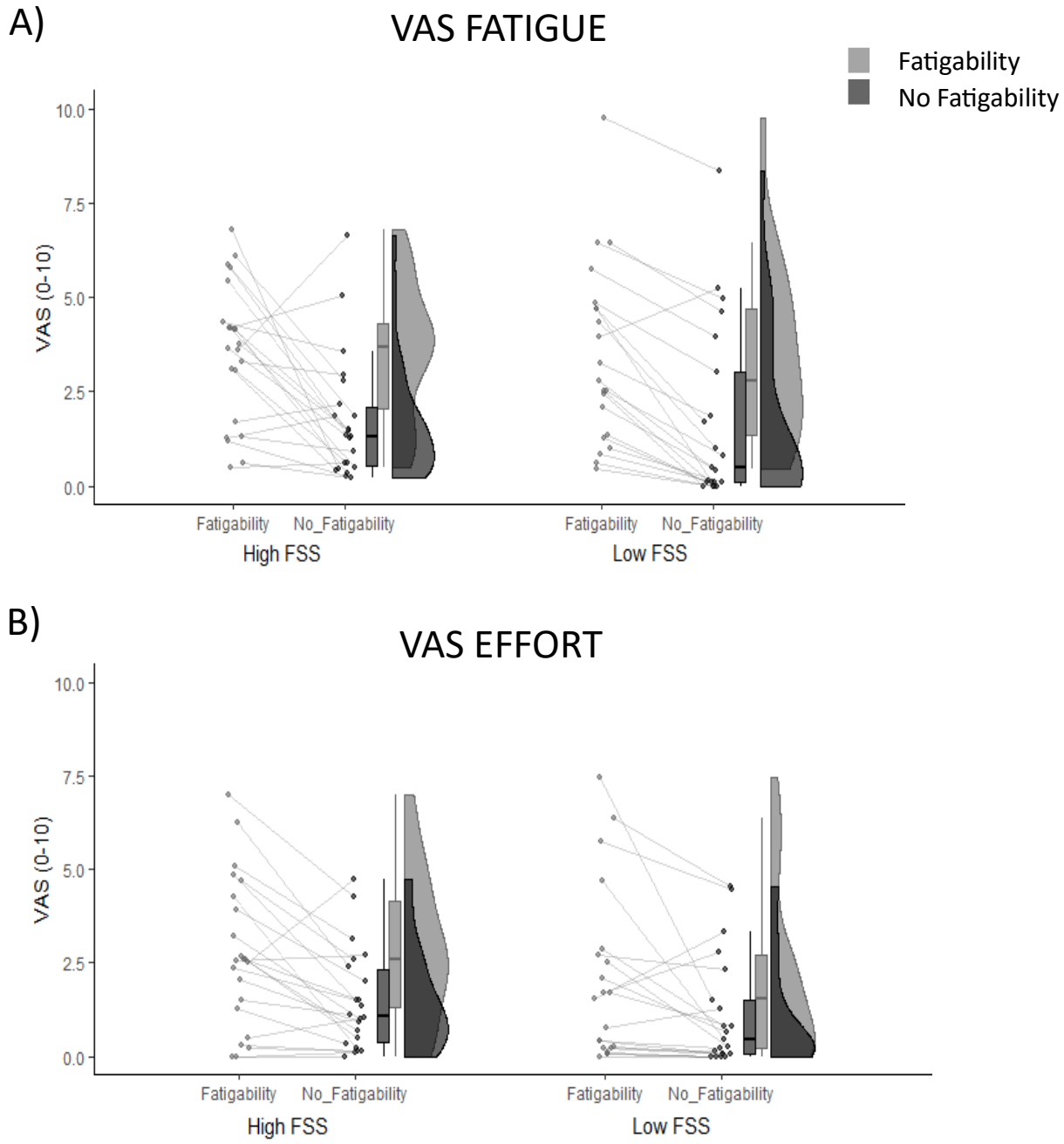

Figure 15. ***Perceived fatigue and effort across Fatigability and No-Fatigability sessions for High-FSS and Low-FSS groups.*** *A) Participants' VAS scores for perceived state fatigue. B) VAS scores for perceived effort. Both High-FSS and Low-FSS groups reported significantly higher levels of perceived fatigue and effort during the Fatigability session compared to the No-Fatigability session, confirming the effectiveness of the fatigue induction task. The High-FSS group consistently reported greater perceived effort across sessions, particularly in the Fatigability session, compared to the Low-FSS group. Shaded areas represent distribution density.*

Discussion

Our study aimed to investigate the interplay between SA and physiological fatigue, with a particular focus on differentiating the roles of trait fatigue and state fatigue. Using the Force Matching Task, previously applied in clinical populations (Chapter 2 and 3), we first tested the

robustness of this paradigm in a healthy sample. The paradigm effectively captured behavioral evidence of SA in healthy participants, replicating prior findings. Participants overestimated the target force in the Direct condition while maintaining accuracy in the Indirect condition, a clear demonstration of the sensory attenuation phenomenon. These results align with earlier studies employing the FMT as an implicit measure of SA in healthy participants (Shergill et al., 2003; Teufel et al., 2010).

We also validated the reliability of our protocol to induce fatigability and consequent state fatigue. The progressive reduction in force output (as measured by $MVC_{normalized}$) during the fatiguing task confirmed the effectiveness of our protocol in inducing fatigability (Kennedy et al., 2013). Similarly, ratings of perceived fatigue (VAS fatigue) and effort (VAS effort) were significantly higher in the Fatigability session compared to the No-Fatigability session. With these validations, we established the reliability and robustness of our methodology.

The central finding of our study is that trait fatigue, but not state fatigue, significantly affects SA mechanisms. Individuals with higher trait fatigue (High-FSS group) are more precise and exhibited reduced force overestimation in the Direct condition compared to those with lower trait fatigue (Low-FSS group). This reduction suggests a diminished ability to attenuate sensory input from self-generated actions, suggesting that trait fatigue has a significant impact on SA.

This finding aligns with the SAF model, which posits that reduced SA impairs the brain's ability to predict the sensory consequences of self-generated actions, leading to an increased perception of effort and, consequently, fatigue (Kuppuswamy, 2017; 2022). Supporting the model association between reduced SA and increased effort perception, we found that the High-FSS group reported greater perceived effort in both the Fatigability and No-Fatigability sessions compared to the Low-FSS group. Interestingly, differences in perceived effort were more pronounced in the No-Fatigability session, where the High-FSS group experienced heightened exertion even in the absence of external fatigue induction. This finding might reflect a ceiling effect in the Fatigability session, where the exertion levels were universally high due to the fatiguing task.

On the other hand, the absence of an interaction effect of Session (Fatigability vs. No-Fatigability) on Mean SA indices suggests that state fatigue, induced by the fatiguing task, does not influence SA. Participants maintained similar SA performance regardless of whether they were in a fatigued state or not, indicating that SA mechanisms are not influenced by transient fatigue. This dissociation between trait and state fatigue aligns with previous research, which distinguishes between state fatigue —characterized as a temporary perception of effort not affected by general SA — and trait fatigue a more stable predisposition to fatigue (DeDonker et al., 2020; Kowalski et al., 2021). While state fatigue may depend more on explicit effort (i.e.,

task-specific exertion), trait fatigue appears to reflect a deeper interaction with implicit sensory mechanisms like SA (De Doncker et a., 2020; Kuppuswamy, 2022).

Further supporting this dissociation between trait fatigue and other fatigue related dimensions, like fatigability and state fatigue, our results found no significant differences in performance on the fatiguing task between the High-FSS and Low-FSS groups. Both groups exhibited similar reductions in force output during the fatiguing task, indicating that trait fatigue does not influence fatigability. Moreover, the absence of significant differences in perceived state fatigue between the two groups further suggests that trait fatigue does not affect the experience of induced state fatigue.

Our findings contribute to the growing body of evidence suggesting that SA could serve as a potential biomarker for trait fatigue (Di Vico et al., 2021). The selective reduction of SA in individuals with high susceptibility to fatigue indicates that SA measurements could provide an objective assessment of fatigue predisposition in both pathological and physiological context (Di Vico et al., 2021; Kuppuswamy, 2022). The link between trait fatigue and SA observed in our study mirrors findings in clinical populations, such PD (Chapter 2) and FMD (Chapter 3), in which the interplay between fatigue symptom and sensory processing alteration drastically affects patients' quality of life (Elbers et al., 2014; Barone et al., 2009). However, our results present a milder perspective in a healthy population. Both High-FSS and Low-FSS groups demonstrated significant overestimation of the target force in the Direct condition, confirming the persistence of SA regardless of fatigue trait levels. Even in individuals with a predisposition to fatigue, SA was preserved, indicating that SA deficits in a healthy population do not reach the severity observed in pathological conditions (Di Vico et al., 2021; Macerollo et al., 2015; Pareés et al., 2014).

Conclusion

The current study gathered new evidence on the role of sensory attenuation as potential mechanisms underlying fatigue. The current study demonstrated that the high susceptibility to fatigue, but not transiently induced fatigue state, can affect sensory attenuation.

These findings not only extend the SAF model beyond pathological fatigue, offering insights into how SA mechanisms operate in physiological fatigue, but also highlights the potential of SA as an objective marker for fatigue, applicable across a spectrum of conditions. Despite these promising findings, the study has limitations. To assess trait fatigue, we employed the Fatigue Severity Scale, one of the most widely used tools to evaluate fatigue in both healthy and clinical populations. However, the FSS lacks a clear cut-off score for detecting different levels of fatigue in healthy populations, limiting the classification of participants based on

perceived trait fatigue. To address this limitation, we utilized a k-means clustering approach, which allowed us to group participants into high- and low-fatigue susceptibility clusters. This methodological choice enabled us to explore variations in SA based on trait fatigue levels. Further research with larger, more diverse populations is needed to confirm these findings. Additionally, neuroimaging studies could provide insights into the neural substrates of the interaction between SA and fatigue, identifying potential brain networks involved in these processes. Longitudinal studies could help clarify the temporal relationship between SA deficits and fatigue, determining whether reduced SA precedes or results from heightened trait fatigue.

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PART 2

Expanding Perspectives on Fatigue and Sensory Attenuation: Insights from Body Perception and Vestibular Modulation

(Studies conducted in collaboration with Birkbeck University of London)

Introduction

In Part 1 of this thesis, I explored the interplay between fatigue and SA primarily within the sensorimotor domain, focusing on how impaired prediction mechanisms might underlie both pathological and physiological manifestations of fatigue. These studies demonstrated that alterations in SA, reflecting dysfunction in the brain's ability to predict the sensory consequences of self-generated movements, are consistently associated with increased perceived effort and fatigue across healthy and clinical populations. However, the human body does not exist in isolation as an object of motor control. Our experience of the body and our sense of self extend far beyond simple sensorimotor mechanisms.

The sense of body ownership, action agency, and body representation result from the continuous integration of multiple sensory channels—including tactile, proprioceptive, interoceptive, vestibular, and visual information. While SA mechanisms are essential for distinguishing self-generated from externally generated sensations and thus contribute to action ownership and agency (Blakemore et al., 2000; Haggard, 2017), they represent only one component of a broader network of processes shaping our body experience Recent studies have begun to investigate how external manipulations, such as fatiguing tasks or altered vestibular input, can influence body and action perception. For instance, physical fatigue has been shown to distort body representation, including perceived limb weight (Ferrè et al., 2023), while vestibular manipulations have been found to influence implicit measures of body ownership and agency through predictive mechanisms (Ponzo et al., 2018). However, given the novelty of this research area, many fundamental questions remain unanswered.

The aim of this section is to explore some of these open questions across two experimental chapters. Chapter 5 investigates whether mental fatigue, a cognitive rather than physical phenomenon, influences body perception, specifically hand weight estimation. While physical fatigue has been shown to reduce the typical underestimation bias in perceived hand weight (Ferrè et al., 2023), the effects of mental fatigue remain unknown. Using a recently developed weight judgment paradigm, this study explores whether cognitive load similarly alters body perception, offering insight into the shared or distinct mechanisms underlying physical and mental fatigue.

Chapter 6 examines whether vestibular inputs, which provide critical interoceptive information about body position and movement, contribute to SA processes. Although SA has been studied primarily in the somatosensory and motor domains, recent work highlights the vestibular system as an integral player in multisensory integration (Ferrè and Haggard, 2016; Britton and Arshad, 2019). Using stochastic Galvanic Vestibular Stimulation (sGVS) to transiently disrupt vestibular signals, this study tests whether altered vestibular input modifies auditory SA in a tone comparison task adapted from the protocol by Reznik et al. (2015).

Together, these studies extend the investigation of fatigue and SA beyond classical sensorimotor paradigms, evaluating how fatigue (both physical and cognitive) and altered multisensory integration modulate the predictive mechanisms underlying body and sensory perception.

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Chapter 5: Distinct Impacts of Mental and Physical Fatigue on Hand Weight Perception

This chapter is based on the manuscript entitled *'No Effect of Mental Fatigue on Perceived Hand Weight'*, currently under review at *Quarterly Journal of Experimental Psychology.*

Introduction

After a long day at work, we may feel as though our eyelids are heavier than usual; similarly, after a marathon, our legs might feel like they're made of lead. These sensations are not merely anecdotal but may reflect a critical interaction between fatigue and the perception of our own body.

As described in Chapter 1, fatigue is a universal experience, encompassing both physical fatigue and mental fatigue, which differ in their origins and impacts. Physical fatigue arises from prolonged or intense physical activity, typically involving muscle exertion and peripheral sensory changes (Billones et al., 2021; Pattyn et al., 2018). In contrast, mental fatigue results from sustained cognitive effort, characterized by declines in attention, executive function, and motivation due to the depletion of cognitive resources (Linnhoff et al., 2019; Solomon & Manea, 2022).

Fatigue is known to influence a range of sensory and perceptual processes. For example, physical fatigue has been shown to alter time perception (Goudini et al., 2024; Tonelli et al., 2022), distance perception (Witt et al., 2004), and the perceived weight of external objects (Burgess & Jones, 2009; McCloskey et al., 1974). Recent evidence has also demonstrated its effects on body weight perception, particularly in relation to a newly identified perceptual bias: the underestimation of hand weight. This phenomenon, first quantified by Ferrè et al. (2023), refers to the systematic tendency to perceive one's hand as significantly lighter than its actual physical weight, often by as much as 50% (Cadete et al., 2024; Ferrè et al., 2023). This perceptual bias is thought to serve an adaptive function by reducing the perceived effort required for movement, thereby facilitating physical engagement.

Physical fatigue has been shown to significantly modulate this perceptual bias. After physically fatiguing tasks, individuals demonstrate a reduced degree of hand weight underestimation (Ferrè et al., 2023), suggesting that physical fatigue alters body perception by increasing the perceived effort required to move a fatigued limb. However, the impact of mental fatigue on hand weight perception remains unexplored, leaving a critical gap in our understanding of how fatigue influences body-related perceptual processes.

Mental fatigue, like physical fatigue, is known to increase perceived effort, leading to alteration in physical and cognitive task performance, such as reduced endurance and longer task completion times (MacMahon et al., 2014; Marcora et al., 2009; McMorris et al., 2018). This heightened effort perception acts as a motivational signal, reducing drive and willingness to act to conserve cognitive resources (Schiphof-Godart et al., 2018). Unlike physical fatigue, however, the higher effort perception associated with mental fatigue is generalized rather than limb- or body-specific (Domine et al., 2022; Schiphof-Godart et al., 2018). This distinction

raises an important question: does mental fatigue influence body weight perception in a manner similar to physical fatigue, or do its effects remain confined to cognitive and motivational domains?

One hypothesis is that mental fatigue, while not directly altering sensory peripheral mechanisms like physical fatigue, could indirectly affect weight perception by increasing the cognitive burden of engaging with physical tasks. This heightened cognitive demand might lead to weights being perceived as heavier, resembling the effects observed with physical fatigue. Alternatively, mental fatigue may act through mechanisms distinct from those of physical fatigue, potentially leaving sensory processes such as hand weight perception unaffected.

The present study aimed to investigate the impact of mental fatigue on hand weight perception. By employing a validated mental fatigue induction task and comparing hand weight perception before and after fatigue, we aim to determine whether mental fatigue would reduce the degree of hand weight underestimation, as observed with physical fatigue in previous research. We hypothesized that participants would replicate the established hand weight underestimation bias in the pre-fatigue condition and that mental fatigue would reduce the degree of underestimation in the post-fatigue condition, mirroring the effects of physical fatigue. By addressing these hypotheses, this study aims to fill this gap in the literature, advancing our understanding of how mental fatigue influences body weight perception.

Materials and methods

Participants

To determine the minimum sample size required for this study, we conducted a priori power analysis using G*Power version 3.1.9.7 (Faul et al., 2007). Based on parameters derived from a similar experiment (Ferrè et al., 2023, Exp 2), we calculated that a sample size of 24 participants would provide sufficient to detect meaningful effects, ensuring the robustness of our findings power [power: 0.90, effect size: 0.693, significance level: 0.05]. Consequently, we recruited twenty-four healthy participants (15 females, Mean age ± SD = 33.88 ± 11.97 years), all of whom provided informed consent prior to the study. Participants were recruited from the university community and were compensated with either payment or course credit. Eligibility criteria included an absence of neurological or physical impairments that could impact cognitive, sensory, or motor function.

Procedures were approved by the School of Psychological Sciences Research Ethics Committee at Birkbeck, University of London, ensuring adherence to the ethical principles outlined in the Declaration of Helsinki.

Stimuli

The stimuli for the hand weight judgment task were identical to those used in a previous study using this paradigm (Ferrè et al., 2023). Weighted stimuli consisted of plastic bags filled with rice, set to 16 weight levels logarithmically spaced between 100 g and 600 g, and rounded to the nearest gram. The specific weights used were: 100, 113, 127, 143, 161, 182, 205, 231, 260, 293, 330, 372, 419, 472, 532, and 600 g. This weight range was chosen to include values both below and above the typical weight of a human hand (approximately 335 g), thereby allowing participants to engage in a challenging comparison of the experimental weights relative to their perceived hand weight. In each experimental trial, one of the stimuli was hung to a hook attached to a wristband (Senshi Japan; 5 cm in width) secured around the participant's wrist. The wristband and hook together weighed 76.5 g. Each bag weight was adjusted to achieve the total target weight, accounting for both the wristband and hook.

Mental Fatiguing Task

The Mental Fatiguing Task (MFT) employed was the standard version of the TloadDback, as proposed by O'Keeffe et al. (2020) and inspired by Borragán et al. (2017). This task is a 16-minute dual-task paradigm requiring participants to perform two simultaneous cognitive tasks. One of the two tasks is a parity judgment test, where participants distinguished between odd and even numbers - when an even number was presented, the participant must press the number 2, and when an odd number was presented, participants must press the number 3. This task was performed using the right hand. The second task followed the classic n-back paradigm (Kirchner, 1958; Lawlor-Savage & Goghari, 2016) presenting a sequence of letters. Participants pressed the space bar with their left hand when the currently presented letter matched the one immediately preceding it. Familiarization trials were provided for each task individually, followed by a combined practice to ensure participants understood the dual-task requirements. Once familiarized, participants completed the full 16-minute task, during which letters and numbers alternated in a single continuous sequence (Figure 16).

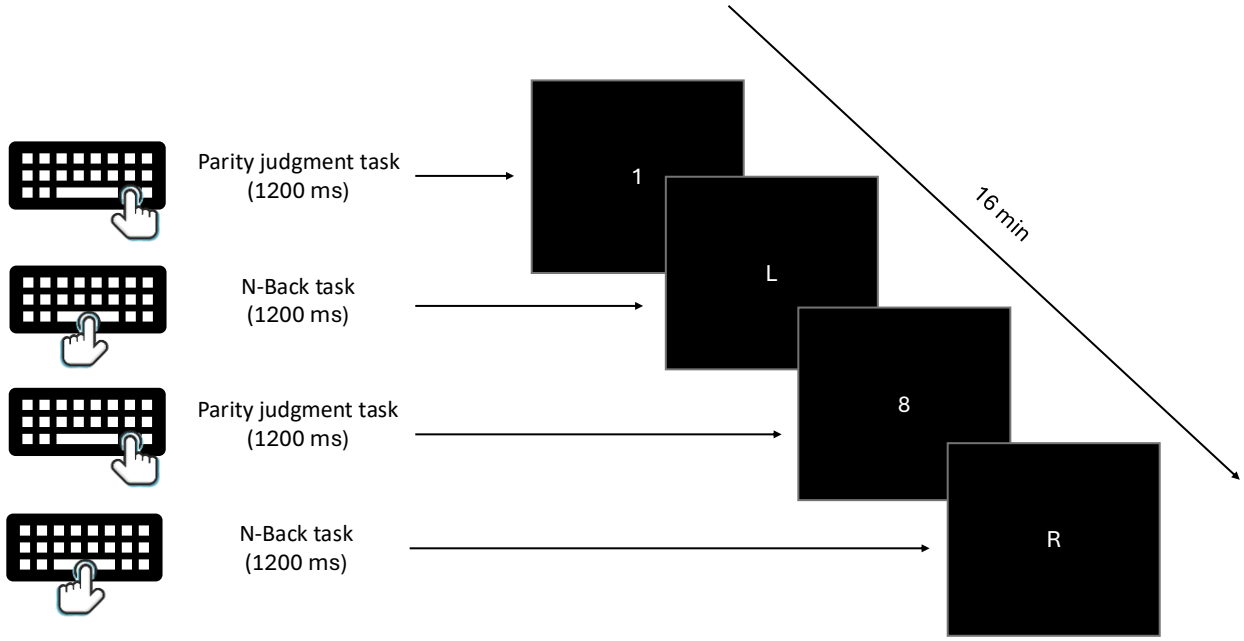

*Figure 16. **Mental Fatiguing Task (MFT).** The 16-minute TloadDback task was designed to induce mental fatigue by alternating between a parity judgment task and an N-Back task, with each trial lasting 1200ms. During the parity judgment task, participants classified numbers as odd or even by pressing "2" or "3" on the keyboard with their right hand. In the N-Back task, participants determined whether the current letter matched the one presented in the previous trial by pressing the space bar with their left hand. These tasks were performed continuously in an alternating sequence.*

Protocol

The experimental procedure for measurement of hand weight, presented in Figure 17, was similar to that used in Experiment 2 described in Ferrè et al. (2023). The protocol was divided into two sessions: a pre-session conducted before the MFT and a post-session conducted afterward. In both sessions, participants sat comfortably on a chair, with their left arm hidden behind a wooden panel and resting on a cushion. At the beginning of each session, participants were instructed to let their left hand hang freely for 30 seconds, with their forearm resting on the cushion. During this period, they were asked to focus on the perception of the weight of their hand.

Following this phase, participants placed their arm across two cushions, supporting both the forearm and hand, with a gap at the wrist to allow weights to be hung. On each trial, one of the weighted stimuli was attached to the wristband, and the participant was asked to compare it to the weight of their perceived hand weight from the beginning of the session. Each session included 30 trials of this weight judgment task. Trials followed two interleaved psychophysical staircases implemented using the QUEST algorithm in PsychToolbox for MATLAB, which,

using Bayesian analyses of the responses on the previous trials, systematically estimated the most informative stimulus in each trial (Ferrè et al., 2023).

Between the pre- and post-sessions, participants completed the MFT to induce mental fatigue (Fatigue intervention), which was assessed using a 10-cm VAS before and after the fatiguing task. Fatigue evaluation was described to participants as follows:

"Please rate the level of mental fatigue you are experiencing. By mental fatigue, we mean the ability to concentrate and the presence or absence of mental fogginess."

At the end of the experiment, trait fatigue was also assessed using the FSS (see Chapter 2 for a comprehensive description of the scale). Finally, hand volume measurements were collected using a water displacement method (Ferrè et al., 2023). Participants submerged their left hand (up to, but not including, the ulnar styloid process) in a beaker of water placed on a digital scale (AMPUT APTP457A 7500 g, Shenzhen Amput Electronic Technology Co. Ltd). Three consecutive measures of hand volume were collected and averaged. Additionally, participants' overall body weight was measured using a standard commercial scale. On average, participants' hands weighed 335.11 g ± 80.61 g, and their body weight was 73.9 ± 17.46 kg.

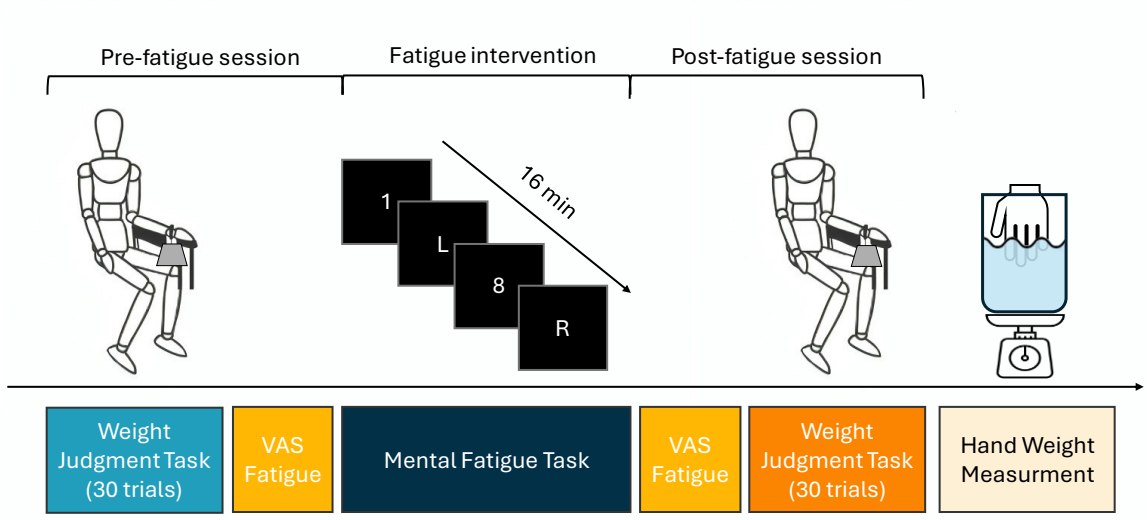

*Figure 17. **Protocol**. The study consisted of a pre-fatigue session, a fatigue intervention, and a post-fatigue session. In the pre-fatigue session, participants performed 30 trials of the weight judgment task, followed by a subjective fatigue assessment using a visual analog scale (VAS). The fatigue intervention involved the 16-minute TloadDback, In the post-fatigue session, participants repeated the VAS fatigue assessment and the weight judgment task (30 trials). Finally, hand weight measurements were collected using a water displacement method to quantify actual hand weight.*

Data Analysis

Data were analyzed using a combination of frequentist and Bayesian statistical approaches to examine the effects of mental fatigue on hand weight perception. Frequentist analyses were performed using IBM SPSS Statistics 25, with an alpha threshold of $p < 0.05$ for significance.

To confirm the effectiveness of the fatiguing intervention, VAS ratings of mental fatigue were analyzed. Paired-samples t-tests were conducted to compare ratings before and after the MFT. This ensured that the intervention successfully induced the intended level of mental fatigue.

One-sample t-tests were conducted for both the pre- and post-fatigue sessions to determine whether the perceived weight differed significantly from the actual hand weight.

To examine the effect of mental fatigue on hand weight perception, we use the percentage of overestimation of the perceived hand weight, that was quantified as:

$$Overstimation\% = \frac{Weigh\ Estimation - Actual\ Weigh}{Actual\ Weight} * 100$$

A paired-samples t-test compared the percentage of overestimation between the pre- and post-fatigue sessions.

To further explore whether mental fatigue affected weight perception in a manner similar to physical fatigue, a Bayesian paired-samples t-test was conducted using JASP 0.19.1.0. A Cauchy prior distribution was used for the parameter of interest, defined as Cauchy (0,0.707), where the location parameter is 0 and the scale parameter is 0.707 (Rouder et al., 2009; Wagenmakers et al., 2018). The null hypothesis (H0) posited no change in the degree of underestimation between the pre- and post-fatigue sessions, while the alternative hypothesis (H1) was based on previous results on physical fatigue and specified a reduction in underestimation in the post-fatigue session. Bayes Factors (BF10) were calculated to quantify evidence for H0 relative to H1. Credible intervals and error percentages associated with the Bayes Factor were also reported.

To investigate the relationship between subjective mental fatigue, trait fatigue and weight perception, Pearson correlation analyses were conducted between VAS scores, FSS score and the degree of hand weight underestimation in both pre- and post-fatigue sessions. These analyses explored whether state and/or trait fatigue predicted changes in hand weight perception. Prior to analysis, the assumption of normality was tested using the Shapiro-Wilk test and was confirmed for all relevant variables, supporting the use of Pearson correlations.

Results

VAS ratings of mental fatigue showed a significant increase following the MFT (Figure 18). Before the task, fatigue ratings averaged 2.54 ± 1.87, whereas post-task ratings increased to 5.84 ± 2.53. This difference was statistically significant [$t_{(23)}$ = -6.909, $p < 0.001$, d_z: 1.41], confirming the effectiveness of the fatiguing intervention in inducing mental fatigue. Notably, the magnitude of this effect aligns with findings from O'Keeffe et al. (2020), further validating the use of this paradigm as a reliable method for inducing mental fatigue and demonstrating its consistency across studies.

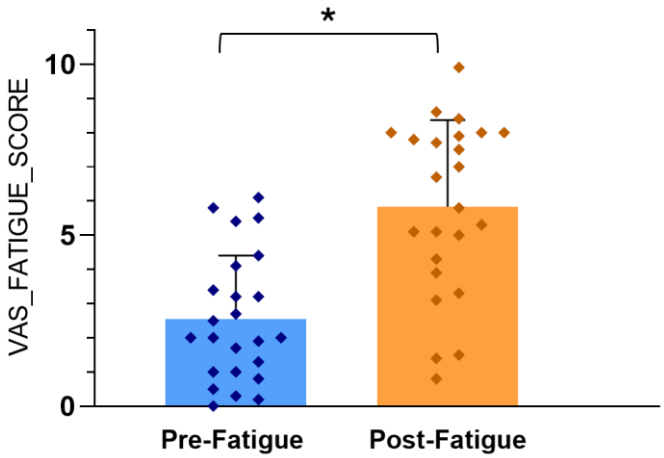

*Figure 18.**VAS ratings of fatigue before and after the MFT.** Fatigue ratings significantly increased following the TloadDback task, with higher VAS scores observed in the post-fatigue session (orange) compared to the pre-fatigue session (blue). Individual data points (diamonds) represent ratings from each participant. (*=p < 0.05).*

The reliability of hand weight perception was confirmed by strong correlations between the high and low weight estimates from the two interleaved psychophysical staircases. In the pre-fatigue session, a robust correlation was observed [$r_{(22)}$ = 0.935, $p < 0.001$], and this reliability persisted in the post-fatigue session [$r_{(22)}$ = 0.959, $p < 0.0001$], demonstrating consistent hand weight estimates across sessions. Average psychophysical staircases starting from low (200 g) and high (600 g) weight initial estimates quickly converged on a common estimate of perceived hand weight, both before and after the MFT (Figure 19a).

Our results confirmed that participants significantly underestimated the weight of their own hand in both the pre- and post-fatigue sessions (Figure 19a), consistent with prior findings on physical fatigue (Ferrè et al., 2023). The results of the one-sample t-tests comparing perceived hand weight to the actual hand weight found significant underestimation in both pre-session (overestimation percentage: 32.119 ± 28.408) [$t_{(23)}$ = 5.683, $p < 0.001$, d = 1.16] and post-session (overestimation percentage: 39.877 ± 33.966) [$t_{(23)}$ = 5.690, $p < 0.001$, d = 1.16], suggesting a consisted bias in hand weight estimation that replicate previous finding (Ferrè et al., 2023)

More interestingly, although the observed slight increase, no significant difference was found in the overestimation percentage between pre- and post-fatigue sessions [$t_{(23)} = 1.325$, $p = 0.198$, $d_z = 0.27$] (Figure 19b), suggesting the absence of influence of mental fatigue on hand weight perception.

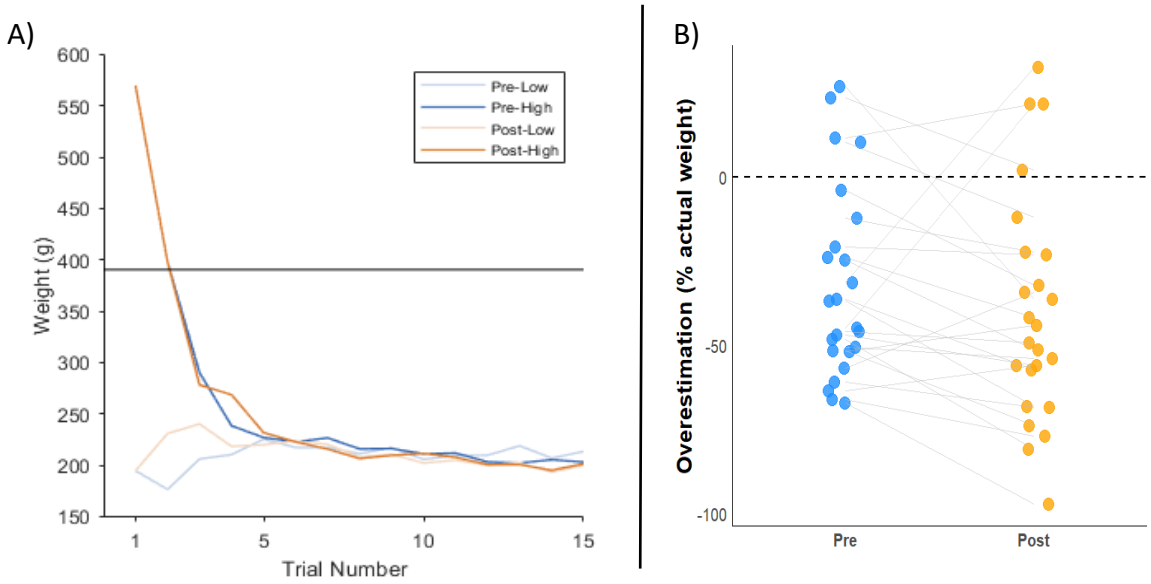

Figure 19. **Hand Weight Underestimation in pre- and post- fatigue session**. A) Convergence of weight estimates over 15 trials in both pre- and post-fatigue sessions, shown separately for high and low staircases. The curves illustrate the reliability of the hand weight judgment task across conditions, with estimates stabilizing by the first 5 to 10 trials. The horizontal line represents the average of the actual hand weight. B) Overestimation percentage (% actual weight) in pre- and post-fatigue sessions. Each point represents an individual participant, with connecting lines illustrating paired pre- and post-session data. The dashed line at 0% indicates accurate weight estimation.

Bayesian analysis further reinforced these findings. The Bayesian paired-samples t-test yielded a Bayes Factor (BF10) of 0.102, demonstrating that the data were approximately 9.8 times more likely under the null hypothesis (H0: no difference in underestimation between sessions) than under the alternative hypothesis (H1: reduced underestimation in the post-session). This result strongly supports the null hypothesis (95% credible interval). The error percentage associated with the Bayes Factor was minimal (< 4.154×10−4%), indicating high robustness of this conclusion.

Correlation analyses between subjective fatigue ratings and hand weight perception revealed no significant relationships. In the pre-session, the correlation between VAS mental fatigue scores and the degree of hand weight underestimation was not significant [$r = 0.004$, $p = 0.986$]. Similarly, in the post-fatigue session, the correlation remained non-significant [$r = 0.266$, $p= 0.210$]. Furthermore, trait fatigue, as measured by FSS scores, did not significantly correlate with hand weight estimation in either the pre-fatigue [$r = -0.063$, $p = 0.772$] or post-

fatigue sessions [r = -0.252, p = 0.234]. These results suggest that subjective ratings of mental fatigue and trait fatigue do not predict changes in hand weight perception.

Discussion

Our study aimed to investigate the impact of mental fatigue on hand weight perception. The systematic underestimation of hand weight is a recently discovered perceptual bias, with individuals perceiving their hands to weigh significantly less than their actual physical weight. For instance, Ferrè et al. (2023) demonstrated an average underestimation of approximately 50% of actual hand weight. In this study, we successfully replicated this effect, with participants underestimating their hand weight by 30% to 40% in both pre- and post-fatigue conditions. These results reinforce the reliability of this perceptual bias and the robustness of our paradigm in detecting it.

We also validated the effectiveness of the standard TloadDBack task in inducing mental fatigue, as evidenced by a significant increase in subjective fatigue ratings following the task. This aligns with previous research establishing this paradigm as a reliable method for inducing mental fatigue by taxing working memory and attentional resources (O'Keeffe et al., 2020; Borragán et al., 2017).

Despite the confirmed induction of mental fatigue, we found no significant differences in the extent of hand weight underestimation between pre- and post-fatigue conditions. In contrast to our hypothesis, participants consistently underestimated their hand weight to a similar degree, regardless of their cognitive fatigue state. This finding stands in contrast to the effects of physical fatigue, which has been shown to alter the perceived weight both of external objects (Burgess & Jones, 2009; McCloskey et al., 1974) and body parts (Ferrè et al., 2023).

Hand weight perception is a process that likely relies on the integration of proprioceptive input, which integrates sensory feedback from muscles, tendons, and joints to provide a sense of body position in space. Physical fatigue appears to disrupt these sensory pathways (Ferrè et al., 2023), potentially altering peripheral sensory feedback or central integration mechanisms (Amann et al., 2013). This alteration may impair the brain's ability to process proprioceptive signals accurately, leading to reduced underestimation of hand weight (Ferrè et al., 2023). In contrast, mental fatigue appears to engage higher-order cognitive processes, such as decision-making (Smith et al., 2016; Verschueren et al., 2020) and attentional control (Csathó et al., 2010; Slimani et al., 2018), rather than directly influencing sensory pathways. As a result, proprioceptive inputs remain relatively unaffected in mental fatigue, which explains the lack of significant changes in hand weight perception observed in our study. This distinction

underscores the specificity of physical fatigue in altering sensory feedback mechanisms (Goudini et al., 2024; Tonelli et al., 2022; Witt et al., 2004).

This framework is line with findings showing that while mental fatigue affects endurance performance (Brown et al., 2020; Mortimer et al., 2024) and task-related effort perception (Pageaux et al., 2015; Van Cutsem et al., 2017), it does not significantly alter physiological measures such as heart rate, oxygen uptake, and blood lactate (Head et al., 2016), measures that, on the other hand, are affected by physical fatigue (Kay et al., 2001; Minder et al., 2023). Similarly, motor performance metrics like maximal voluntary contraction (Pageaux et al., 2015) or power output (Van Cutsem et al., 2017) remain unaffected by mental fatigue, further highlighting its distinct effects compared to physical fatigue.

Further evidence in favor of this interpretation is offered by studies that explored the distinction between physical and mental fatigue in the perceptual domain. For instance, Goudini et al. (2024) examined the impact of mental and physical fatigue on time perception and found that mental fatigue did not significantly alter this process, whereas physical fatigue led to time misjudgment. Specifically, under physical fatigue condition, participants underestimated time intervals during post-test and follow-up assessments, while no such effects were observed under mental fatigue or control conditions. These findings confirmed that, in contrast to physical fatigue, mental fatigue has no impact on sensory mechanisms underlying body weight awareness and temporal perception. This highlights the specificity of mental fatigue's influence on cognitive rather than sensory domains, contrasting with the effects of physical fatigue, which alters both sensory and motor function (Ferrè et al., 2023; Goudini et al., 2024; Tonelli et al., 2022). Overall, our findings extend previous results and support the notion that mental and physical fatigue interact with perceptual systems through partially independent pathways. This distinction emphasizes the need for targeted approaches that address mental and physical fatigue as separate phenomena.

While our study offers valuable insights, it is not without limitations. A notable limitation lies in the reliance on subjective measures to assess mental fatigue. Although these methods have already been used (Ferrè et al., 2023; Verschueren et al., 2020), they lack the precision and robustness that objective fatigue assessment could provide. Future research should aim to incorporate objective measures to complement subjective assessments.

Conclusion

In conclusion, our findings highlight the resistance of hand weight underestimation to mental fatigue, reinforcing the reliability of this perceptual bias and its independence from changes in cognitive state. The divergence in the effects of mental and physical fatigue

underscores the importance of distinguishing between these two types of fatigue when investigating their impact on sensory and motor processes. This study contributes to a growing understanding of fatigue's multifaceted nature and lays the groundwork for future research exploring the unique mechanisms underlying different fatigue domains.

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Chapter 6: The Role of Vestibular Input in Sensory Attenuation: Insights from Stochastic Galvanic Vestibular Stimulation

This chapter is based on the manuscript entitled *'Vestibular Contributions to Sensory Predictive Mechanisms'*, currently under review at *Experimental Brain Research*.

Introduction

This thesis has consistently emphasized the central role of SA as a neurophysiological mechanism that bridges sensory processing and interoceptive signals linked to internal conditions like fatigue. By demonstrating how pathological and trait fatigue interacts with SA, we've already provided strong evidence for the interplay between sensory, motor, and interoceptive domains. The final study extends this framework by incorporating the vestibular system—another key interoceptive pathway—into the discussion. In this Chapter we will describe how SA is not only interacting with fatigue but is also dynamically influenced by other interoceptive inputs, revealing its reliance on the integration of multiple sensory systems. The final study, therefore, serves as a natural progression of my thesis, offering a deeper and more comprehensive understanding of the nature of SA.

Traditionally, the role of the vestibular system has been associated with its ability to keep us balanced, with a constant flow of information reaching the semicircular canals and otoliths, collectively referred to as vestibular organs. These organs, which lie in our inner ear, detect varied accelerations. Specifically, rotational accelerations are processed by the semicircular canals, whilst linear and translational accelerations are detected and processed by the otoliths (Zanchi et al, 2023). Regional neural contributions have been established as being widespread, with incoming vestibular information being processed by all but the occipital regions (Eulenburg et al., 2012). Crucially, due to the distributed nature of this system, one research area of focus has been set on the role vestibular inputs have in multisensory integration (Zanchi et al, 2023; Shayman et al, 2018), i.e., the process by which the nervous system combines information from different sensory modalities, such as sight, sound, touch, smell, and taste (Holmes et al., 2009). This integration enables the formation of a coherent representation of our environment and is essential for adaptive behavior, as it enhances our ability to respond to complex stimuli and navigate our surroundings effectively (Stein & Meredith, 1993).

The integration of multiple sensory modalities, including vestibular inputs, plays a crucial role in various functions, from spatial processing (Zanchi et al., 2023; Chen et al., 2017) to the perception of self-movement (Britton & Arshad, 2019). The Comparator Model (Chapter 1), a well-established theoretical framework for sensorimotor control, explains how the brain typically uses the integration of various sensory modalities to facilitate self-monitoring and motor processing mechanisms (Blakemore et al., 2001). Briefly, the model postulates that this multisensory information is used to formulate predictions about our actions, enabling us to move in the constantly shifting environment to which we face in our everyday lives (Blakemore et al., 2001; David et al., 2008). According to this model, initiating an action begins with

conceptualizing the movement's goal and formulating a motor plan based on multisensory inputs. Simultaneously, an efference copy of the motor command is generated to predict the sensory outcomes of the planned movement. This efference copy is then compared to the actual sensory feedback during the movement, enabling the central nervous system to detect any discrepancies (Zaadnoordijk et al., 2019). When the predicted sensory feedback aligns with the internal signals, the sensory outcomes of our actions are attenuated (SA, Blakemore et al., 2000).

However, what happens when the information provided by the sensory systems are no longer reliable? Specifically, what happens when the vestibular system is altered, leading to a mismatch between our expectations and the incoming information? The crucial development of Galvanic Vestibular Stimulation (GVS) enables us to address these questions in a controlled environment on Earth. Specifically, GVS provides an effective non-invasive method to stimulate vestibular afferents, such as those from the otoliths and semicircular canals with the use of electrical currents, allowing for the mimicking of natural movement frequencies altering the normal processing of information in the vestibular system (Fitzpatrick & Day, 2004).

One form of GVS, stochastic Galvanic Vestibular Stimulation (sGVS), enables binaural stimulation to alter the vestibular system as a whole (MacDougall et al, 2006). Therefore, this technique proves to be integral in furthering our knowledge of the vestibular contributions to cognitive functions. This is exemplified by Zanchi et al.'s (2023) study, which utilised sGVS to determine the role vestibular inputs have in the efficient spatial encoding of environmental objects. The vestibular stimulation was delivered across two experiments, one looking at spatial encoding of visual targets and the other of acoustic targets. In the former, participants were required to walk toward one of three light targets after receiving either the sGVS or sham stimulation, with the experimenters measuring the difference between the target and walked distance. The latter acoustic experiment followed a similar procedure instead involving walking towards pink noise sounds at three distances. Their findings reveal that the alterations to vestibular signalling caused by the sGVS led to reduced accuracy and precision in identifying the visual targets. Importantly, this impairment was not present for acoustic targets, illustrating the vestibular systems role for spatial encoding of environmental visual targets only. These results open the door to a better understanding of the multisensory integration processes the vestibular system is a part of. The visual-vestibular interactions they evidence in the context of spatial encoding represent the involvement of fundamental multisensory components in the relationship between our body and objects within our environment. However, little is known about the role the vestibular system plays in the predictive component of multisensory integration processes. In the case of the present study, sGVS provides the opportunity to explore the vestibular system's role in this predictive processing.

In this study, we aim to explore the impact of vestibular system modulation on sensory predictive mechanisms. To do this, we investigated how sGVS influences sensory attenuation processes, through a simple auditory comparison task in which participants have to judge the loudest sound between a self-produced and an externally produced tone. Our study aims to provide new insights into the role played by the vestibular system in sensory predictive mechanisms and improve our understanding of the potential significance of this interaction in space-related studies.

Materials and Method

Participants

An a priori power analysis was conducted using G*Power 3.1 to determine the minimum sample size required for a 2 × 2 repeated-measures ANOVA. The effect size used ($f = 0.515$) was derived from partial $\eta^2 = 0.21$ reported in a study by Reznik et al. (2015), which employed a similar auditory attenuation protocol involving active and passive conditions. Using this effect size, an alpha level of 0.05, a desired power of 0.95, and a conservative nonsphericity correction ($\varepsilon = 0.75$), the analysis indicated that a minimum of 12 participants would be required to detect a significant interaction. To ensure robustness, account for potential dropouts, and increase the generalizability of our findings, we recruited a total of 20 participants. Participants were healthy adults recruited from the student body at Birkbeck University of London. The sample consisted of 12 females, (mean age ± SD) 32.7±10.5 years. All but three participants were right-handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971: 56.74 ± 60.49) and had normal or corrected-to-normal vision. None of the participants had any history of neurological disorders. All procedures were approved by the School of Psychological Sciences Research Ethics Committee at Birkbeck, University of London and were consistent with the principles of the Declaration of Helsinki.

Stochastic Galvanic Vestibular Stimulation (sGVS)

Utilising a similar procedure to Zanchi et al. (2023), we have applied the sGVS with the same dominant frequencies and maximum intensity, only changing the duration to meet our paradigm's block duration. Thereby, a commercial stimulator (Good Vibrations Engineering Ltd., Nobleton, Ontario, Canada), was controlled by Guest Vestibular Host and LabView software to deliver the vestibular stimulation. Before applying electrodes, the areas of application were cleaned with alcohol wipes. Taped carbon rubber electrodes with an area of 10 cm^2 were then placed with an electrode gel binaurally to the participants' mastoid processes (Figure 20). The stochastic Galvanic Vestibular Stimulation (sGVS) was generated by applying

an alternating sum-of-sines voltage with dominant frequencies at 0.16, 0.32, 0.43, and 0.61 Hz, enabling the alteration of vestibular signals resulting in an experience of instability (Fraser et al., 2015; MacDougall et al., 2006; Moore et al., 2006).

Importantly, the sensation of weak dizziness experienced by these disruptions only occurs within the time of stimulation (Fitzpatrick & Day, 2004). The decision for the delivery of a binaural stimulation was a purposeful one, as it avoids the compensation of a non-stimulated side relative to the stimulated one. The maximum intensity of this stimulation remained at 1 mA, with the duration lasting the length of each block (~4 minutes). A sham stimulation allowed for a control of non-vestibular specific effects. This type of stimulation was delivered via electrodes applied to the left and right side of the upper back, around 5 cm below the GVS electrodes (Ferrè et al., 2013; Lopez et al., 2010).

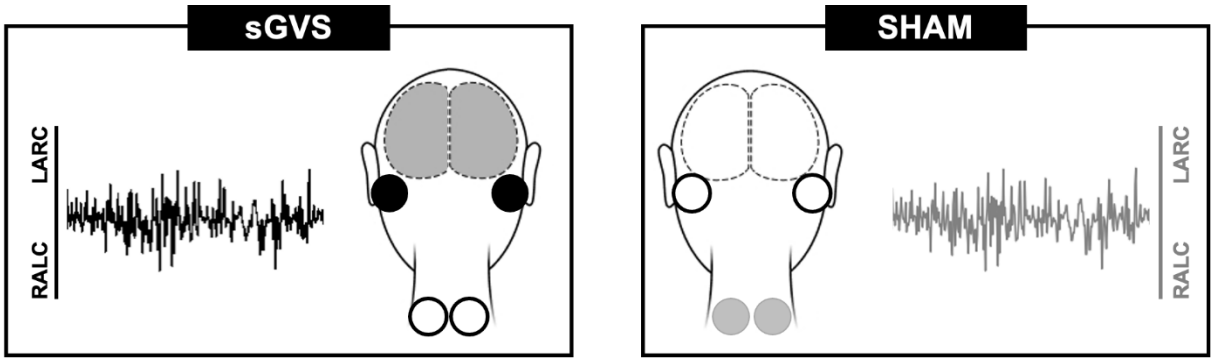

Figure 20. ***Electrode configuration for both sGVS and SHAM stimulations.*** *The image reflects the correspondence between stimulation type and regions activated. sGVS: the stimulation applied at the mastoid processes (the black regions marked in the image) generated by applying an alternating sum-of-sines voltage with frequencies of 0.16, 0.32, 0.43 and 0.61 Hz, leading to widespread alterations to the vestibular system. SHAM: the light grey areas at the base of the neck illicit no vestibular stimulation, serving as a control.*

Auditory Comparison Task (AC task)

To measure sensory attenuation, we employed a paradigm adapted from Reznik et al. (2015). Participants listened to two consecutive pure tones at 1 kHz (300 ms duration) using headphones, and they were asked to judge which tone was louder. Unbeknownst to participants, the intensity of the two tones was identical in all experimental trials, except for the oddball trials.

In the active condition, the word "PRESS" appeared on the computer screen, prompting participants to press a button with their right index finger. The first tone played 100 ms after pressing the button. After a 1000 ms interval during which a fixation cross was displayed, the word "LISTEN" appeared on the screen for 600 ms, cueing the presentation of a second identical tone generated by the computer 300 ms after the onset of the visual signal. In the passive condition, both the first and second tones were generated by the computer following the visual signal "LISTEN." After the second tone was presented, participants indicated which

tone was louder by pressing one of two corresponding buttons with their left hand (Figure 21). The percentage of trials in which the second tone was reported as louder was used as the dependent measure for each subject.

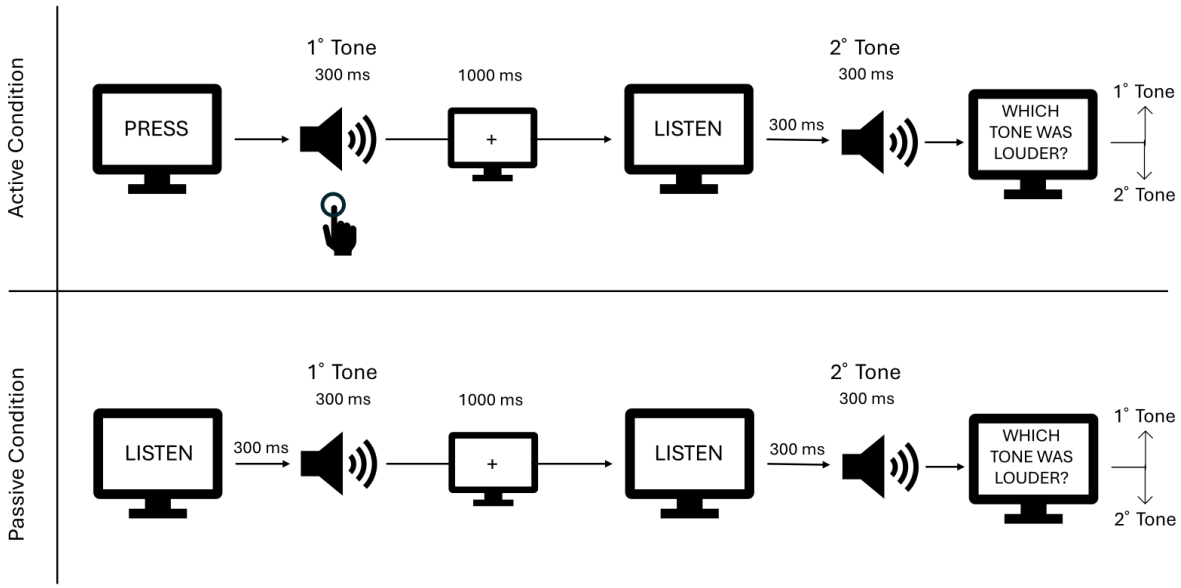

Figure 21. ***Auditory Comparison Task.*** *Active condition: the word "PRESS" appeared on the screen, prompting participants to press a button with their right index finger. The first tone played 100 ms after the button press. After a 1000 ms interval with a fixation cross, the word "LISTEN" appeared for 600 ms, cueing the second tone 300 ms later. Passive condition: both tones followed the "LISTEN" signal. After the second tone, participants indicated which tone was louder.*

Procedure

Participants, seated in a comfortable position facing 40-50 cm towards a 28-inch screen, were asked to perform the AC task in both stimulation types (sGVS and SHAM). For each stimulation type the active and passive conditions were each presented twice, arranged in two consecutive blocks consisting of 25 experimental trials, resulting in a total of four separate blocks per stimulation. To mitigate response bias, each block also included 5 randomly spaced oddball trials where the intensity of the second tone was 2 dB lower than the first tone. The order of blocks (active/passive) and stimulation type (sGVS/SHAM) was counterbalanced between subjects.

Guest Vestibular Host Software was used to upload the script needed for each stimulation type (sGVS/sham), whilst LabView enabled for the stimulation to run for the block duration. To ensure the stimulation ran throughout the entirety of the block, the stimulator was switched on one second prior to the task beginning. The Guest Vestibular Host Software was then used when it was needed to switch the stimulation type, by clearing the memory and

uploading the required script. Throughout the study, participants were asked how they were feeling, with none relaying any strong sense of dizziness or pain. Between each block, whilst the stimulation was switched off, participants were able to relax and were told they could continue 'whenever they felt ready'.

Data Analysis

The Response Bias Index (RBI), defined as the percentage of trials where participants reported the second tone as louder, served as the primary dependent variable for each subject. A higher RBI in the active condition compared to the passive condition is indicative of normal sensory attenuation, where self-produced sounds in the active condition are attenuated, leading to the external sounds being perceived as louder.

To examine the effects of the different conditions, we used a repeated measures analysis of variance (rmANOVA), incorporating two within-subject factors: condition (Active vs. Passive) and stimulation type (sGVS vs. SHAM). A significance threshold of $\alpha = 0.05$ was applied to all statistical tests.

Results

Main results are shown in Figure 22. Our analysis began by assessing whether SA occurred in the SHAM condition. In the absence of vestibular system alterations, participants exhibited a clear SA effect: they more often reported the second, externally-produced tone as louder in the active condition compared to the passive one. This finding is consistent with previous research on sensory attenuation, including the results reported by Reiznik et al. (2015), in which they found a clear SA effect when using tones with a supra-threshold intensity. Specifically in the SHAM session, the RBI was higher in the active condition (mean ± Standard Deviation: 74.80 ± 0.03%) compared to the passive condition (66.60 ± 0.03%) ($F_{(18)}$ =8.234, p = 0.010), confirming the presence of normal SA.

The main aim of this study was to determine whether sGVS interferes with this SA effect. In contrast to the SHAM condition, no significant difference between the active and passive conditions was found during the sGVS session. Participants perceived the second tone as louder at nearly the same rate in both conditions (active: 70.5 ± 0.04%, passive: 70.6 ± 0.03%; $F_{(18)}$ =0.001, p = 0.975), suggesting that sGVS disrupted the typical SA mechanism.

Our results support the presence of a robust SA in the SHAM condition, consistent with established findings. However, when vestibular stimulation was introduced via sGVS, this effect was no longer present, suggesting that sGVS impairs perceptual processes involved in distinguishing self-generated from externally-generated sensory stimuli (Figure 22).

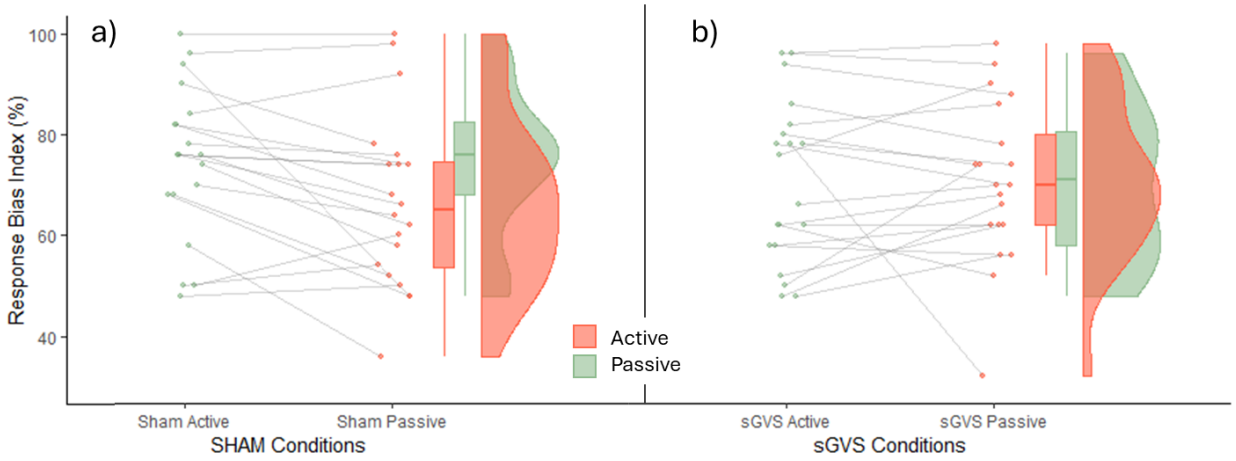

Figure 22. ***Response Bias Index (RBI) results****. a) RBI for Active (red) and Passive (green) conditions during the SHAM session. Participants in the Active SHAM condition reported significantly higher RBI scores compared to the Passive SHAM condition, indicating preserved sensory attenuation in the absence of vestibular manipulations. b) RBI for Active (red) and Passive (green) conditions during the GVS session. In contrast to the SHAM session, no significant difference was observed between Active and Passive conditions in the GVS session, suggesting an alteration in sensory attenuation.*

Additionally, there was a trend toward significance in the difference between SHAM and sGVS stimulation in the active condition ($t_{(19)}$ = 2.020, p =0.058), suggesting that participants were less likely to perceive the externally-generated tone as louder during the sGVS session compared to the SHAM session. This trend further supports the idea of a reduction in sensory attenuation under sGVS, not only because no significant difference was found between active and passive conditions in the sGVS session, but also because the active condition in the sGVS session was qualitatively lower than in the SHAM active condition. This indicates that the convergence between active and passive responses during sGVS was driven by a decrease in the active condition, rather than an increase in the passive condition. In other words, the absence of a significant difference is not due to a heightened passive response, but rather a diminished active response. This pattern hints at sGVS's influence in reducing SA by actively suppressing the normal attenuation effect in self-produced sounds (Figure 23).

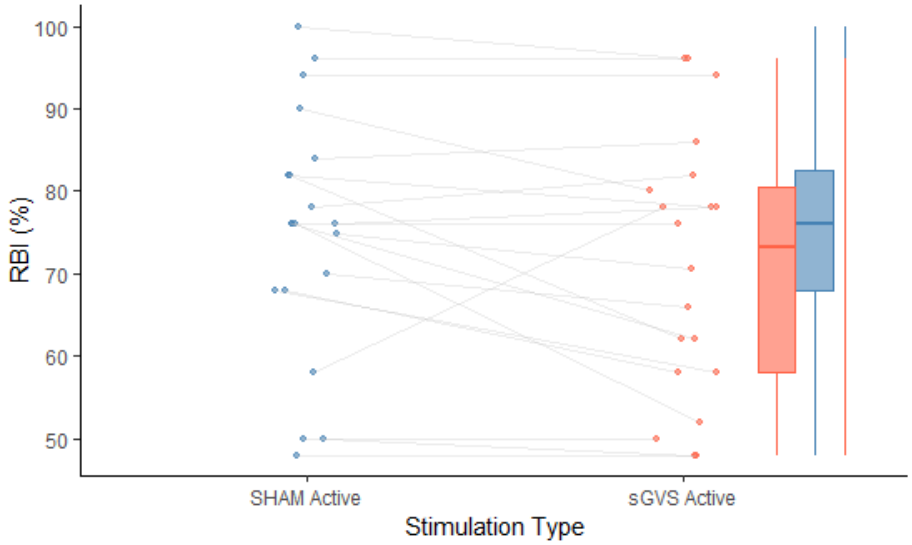

Figure 23. ***Comparison of RBI between SHAM and sGVS conditions in the active condition****. In the SHAM active condition, participants consistently reported the externally-generated tone as louder, reflecting normal SA (74.80 ± 0.03). However, during the sGVS active condition, there was a qualitative reduction in SA (70.5 ± 0.04), with participants perceiving the second tone as louder less frequently. Although the difference between SHAM and sGVS conditions did not reach statistical significance (t(19) = 2.020, p = 0.058), the trend suggests that sGVS may reduce SA by decreasing overestimation of the externally-generated tone in the active condition.*

Discussion

The primary aim of this study was to investigate the effects of stochastic Galvanic Vestibular Stimulation (sGVS) on sensory attenuation (SA), which refers to the ability to attenuate self-generated sensory stimuli, discriminating them from externally-generated ones (Blakemore et al., 2000). The ability to attenuate sensory feedback is essential for effective interaction with the environment, allowing individuals to focus on relevant stimuli while ignoring predictable sensory consequences of their own actions. Following the Comparator Model, SA is a perceptual mechanism based on predictive processes about the consequences of our actions (Blakemore et al., 2001; David et al., 2008). When action-related outcomes match predictions, sensory consequences of self-generated actions are attenuated (Kiepe et al., 2021; Blakemore et al., 1998; Shergill et al., 2003). In our study, the use of sGVS was designed to affect the vestibular system, altering interoceptive information that are crucial for formulating predictions about the sensory consequences of actions (Fitzpatrick & Day, 2004). Disrupting the reliability of vestibular inputs allowed us to examine its role in SA processes.

Our results indicate that sGVS significantly alters participants' ability to discriminate between self- and externally-generated auditory stimuli. During the SHAM session, participants perceived the externally-generated tone as louder in the active condition compared to the passive condition, reflecting the preservation of SA in absence of any vestibular alteration. This finding aligns with previous research demonstrating that self-generated actions lead to a

suppression of sensory feedback, reducing the perceived intensity of subsequent stimuli (Shergill et al., 2003; Kiepe et al., 2021). However, during the sGVS session, no significant difference was found between the active and passive conditions, suggesting that sGVS impairs the normal SA process. This lack of difference implies that participants were less able to distinguish between self-generated and externally-generated stimuli when their vestibular system does not provide reliable information. Vestibular inputs may be crucial information used by multisensory integration processing to formulate predictions and maintain a coherent perception of self-generated actions (Britton & Arshad, 2019; Zanchi et al, 2023). When the vestibular system is altered, as in the case of sGVS, the brain's predictive mechanisms may be compromised, too, due to the reduced reliability of vestibular information, leading to a diminished ability to attenuate predictable self-sensory consequences.

In addition, our results not only found that sGVS directly impacted the ability to discriminate between self- and externally-generated stimuli, but also revealed a qualitative reduction in SA during the sGVS session. Specifically, the data illustrated a near-significant trend suggesting that participants perceived the externally-generated tone as less loud during the sGVS session compared to the SHAM session in the active condition. Although this trend did not reach statistical significance, it qualitatively suggests that the reduction in SA under sGVS was primarily driven by a decrease in the active condition, with no significant change in the passive condition. This indicates that the way active and passive responses converged under sGVS was not due to an increase in the passive condition but rather a qualitative decrease in the active condition, where participants no longer overestimated the loudness of externally-generated sounds. This pattern hints at a disruption in the brain's predictive mechanisms related to sensory consequences of self-produced actions due to altered vestibular input. While the near-significant trend suggests that sGVS influences sensory attenuation, further investigation is required to explore the threshold at which vestibular modulation begins to significantly affect sensory processing and self-external discrimination.

These findings contribute to our understanding of the role of the vestibular system in predictive sensory processing and perceptual discrimination. The disruption of SA by sGVS highlights the potential for vestibular stimulation to influence cognitive processes beyond balance and spatial orientation. This suggests that the vestibular system is not only essential for maintaining balance but also plays a crucial role in predictive and perceptual functions.

Previous findings have already brought support to the vestibular contribution to multisensory integration processes. In their study of the integration of different sensory information, Shayman et al. (2018) compared patients diagnosed with vestibular hypofunction and healthy participants. Their study focused on the temporal binding window in which the sensory inputs should be presented to be integrated, finding that as a result of the vestibular

damage, patients showed a reduced ability to temporally combine sensory cues, compared to healthy controls. The authors propose that vestibular signalling, which precedes incoming visual, auditory, and proprioceptive signals, is impacted by an altered temporal alignment during the integration process.
Our results, nevertheless, expand previous findings, bringing new insight on the impact that vestibular system has in the predictive processes related to the integration of sensory information.

Examining the relationship between vestibular function and SA can significantly enhance our understanding of the challenges astronauts face during space missions. The findings from our study suggest that sGVS alters the normal sensory processing mechanisms, which may reflect the difficulties experienced by astronauts in microgravity environments. During space missions, astronauts often encounter vestibular dysfunction due to the lack of gravitational cues being received by vestibular organs, leading to impaired balance, locomotion, and sensory integration (Carriot et al., 2021).

Research indicates that nearly 70% of astronauts experience symptoms such as motion sickness, impaired gaze control, and difficulties in dynamic visual acuity shortly after entering microgravity (Lackner and Dizio, 2006; Souvestre et al., 2008). These symptoms may arise from a persistent conflict between expected and actual sensory inputs, particularly from the vestibular system.

Future research is needed to further explore the mechanisms underlying the disruption of SA by investigating different parameters of vestibular stimulation, multisensory integration, and their interaction.

Conclusion

Our study showed that sGVS can significantly influence SA, thereby affecting perceptual mechanisms related to distinguishing self- from externally-generated sensory stimuli. Our findings suggest that vestibular inputs play a crucial role in maintaining accurate internal predictions of sensory outcomes and that a reduced reliability of vestibular information can impair the brain's ability to attenuate self-produced stimuli. Our results pave the way for further research into the interplay between the vestibular system and sensory processing, providing potential implications for how astronauts' brains adapt to altered gravitational conditions and the resultant sensory conflicts.

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General Discussion

This thesis investigated how the perception of our body and movements is shaped by the interplay between interoceptive signals and sensory processing. Alterations in bodily input—whether arising from pathological fatigue, individual predisposition to fatigue, or experimental manipulations such as fatigue induction and galvanic vestibular stimulation — can significantly impact perceptual processes. Fatigue, a universal yet poorly understood phenomenon that bridges cognitive and physical domains, served as a central theme throughout this research. Across five experimental chapters, the work integrated clinical and experimental approaches, spanning clinical populations with pathological fatigue, healthy individuals with experimentally induced fatigue, and multisensory modulation. Each study provided insights into how internal states interact with sensory attenuation and body perception.

By unifying these diverse investigations under the theoretical framework of predictive coding and the Sensory Attenuation Model of Fatigue (Kuppuswamy, 2017), this thesis provides novel insights into how disruptions in sensory prediction interact with the subjective experience of fatigue and altered body perception.

In the first part of this work, we explored the interaction between fatigue and sensory attenuation in clinical populations and healthy individuals. bridging the gap between pathological and physiological fatigue. By examining individuals with Parkinson's disease and Functional Movement Disorder (Chapters 2 and 3), as well as healthy participants (Chapter 4), this work provides new evidence on how disruptions in predictive sensory processing relate to fatigue across the clinical spectrum.

In Parkinson's disease and functional movement disorders, pathological fatigue was consistently associated with impairments in sensory attenuation. Patients with fatigue showed reduced or altered pattern of sensory attenuation, reflecting a diminished capacity to predict the sensory consequences of their own movements. Importantly, a similar but subtler pattern was also observed in healthy individuals reporting high levels of trait fatigue, suggesting that sensory prediction deficits exist on a continuum from normal variability to clinical dysfunction. These results bring new experimental evidence in support of the Sensory Attenuation Model of Fatigue, which posits that fatigue arises from disruptions in sensory predictive mechanisms. Specifically, our research extends the model, by demonstrating its applicability in describing not only pathological fatigue but also non- pathological fatigue susceptibility.

A second key refinement contributed by this work is the differentiation between state and trait fatigue. While stable, trait-like fatigue states were reliably associated with changes in sensory attenuation, transient state fatigue induced experimentally did not consistently impact

sensory attenuation in healthy individuals. This distinction has significant theoretical and clinical relevance: trait fatigue may reflect a more chronic disruption of internal predictive models, whereas state fatigue may represent a temporary mismatch between prediction and feedback that the system can rapidly adapt to. Our results showed that stable individual differences in fatigue susceptibility may be linked to chronic maladaptation in sensory prediction systems. The distinction between state and trait fatigue challenges conventional assumptions that all fatigue dimensions are equal, highlighting the importance of distinguishing between fatigue as a state and fatigue as a trait in research and clinical practice.

Importantly, the association between sensory attenuation and fatigue explore in this first part was not related to general motor disability or disease severity, as indicated by the absence of correlations with UPDRS scores or disease duration in Parkinson's disease patients. This suggests that sensory attenuation alterations represent a distinct neurophysiological signature of fatigue, potentially providing a novel objective biomarker in both clinical and research settings. This has significant implications for clinical practice, paving the way toward objective and quantifiable assessments of fatigue, which is currently evaluated primarily through subjective self-report scales. Such advancements could lead to more precise diagnostics and targeted therapeutic interventions.

The second part of this thesis broadened the investigation of fatigue and sensory attenuation, exploring how these phenomena interact with fundamental body-brain related processes, such as body perception and multisensory integration. Our study on mental fatigue (Chapter 5) revealed a striking dissociation between cognitive and sensory domains. While mental fatigue increased perceived effort, it did not significantly affect perceptual biases such the systematic underestimation in hand weight perception. In contrast, physical fatigue has been shown to impact body representation, altering perceptual processes like body weight estimation (Ferrè et al., 2023). This suggests that mental fatigue influences higher-order cognitive systems without disrupting sensory pathways to the same extent as physical fatigue. These findings emphasize the distinct pathways through which physical and mental fatigue interact with sensory and perceptual systems.

Finally, the last study (Chapter 6) on stochastic galvanic vestibular stimulation further demonstrated how interoceptive signals, in this case from the vestibular system, modulate sensory attenuation. The results demonstrated that stochastic galvanic vestibular stimulation disrupted normal auditory sensory attenuation. This finding highlights a novel contribution of vestibular input to predictive mechanisms. Traditionally considered as primarily motor and postural, the vestibular system has now been recognized as a key interoceptive signal integrated into body ownership and self-motion processing (Ferrè & Haggard, 2016; Britton & Arshad, 2019). Our results suggest that altering vestibular reliability compromises internal predictions

about self-produced actions, diminishing sensory attenuation. These findings align with growing evidence that vestibular signals modulate sensory processes like the one related to body ownership (Ponzo et al., 2018) and reinforce the idea that sensory attenuation emerges from a distributed, multisensory predictive network, including vestibular, proprioceptive, and somatosensory cues.

Taken together, the findings from both parts of this thesis reinforce the conceptualization of fatigue and body perception as multisystem, predictive phenomena. In line with predictive coding theories (Friston, 2010), our results demostrated that under normal conditions (temporary induced state fatigue or healthy controls), the brain minimizes prediction errors across sensory and interoceptive channels to maintain coherent perception and action. However, when sensory reliability is compromised —whether by pathological fatigue, high trait fatigue, or vestibular disruption—the predictive system becomes impaired, leading to increased sensory uncertainty and disrupted sensory attenuation.

This research holds significant implications for our understanding of fatigue and sensory attenuation, with relevance across both theoretical and clinical domains. Our work contributes to the emerging recognition that fatigue is not merely a symptom of motor dysfunction, but a fundamental disorder of prediction and perception. By elucidating the predictive sensory mechanisms underlying fatigue, we facilitate the developing of targeted interventions aimed at better understanding fatigue-related symptoms in conditions like Parkinson's Disease and Functional Movement Disorder. Additionally, our findings highlight the need for personalized approaches to fatigue assessment and treatment, recognizing the distinct contributions of trait fatigue levels versus acute fatigue states, physical and mental fatigue on sensory processes.

Limitations

While the findings of this thesis provide new and important insights into the relationship between fatigue and sensory attenuation, some limitations must be acknowledged.

First, both Parkinson's disease and Functional Movement Disorder patients present motor symptoms that could have potentially influenced performance in the Force Matching Task. Specifically, concerns could be raised that fatigue-related motor slowness or incoordination may have contributed to the group differences in force reproduction. Although all participants had equal maximum trial durations (six seconds) with consistent protocol timing (see Chapter 2, Materials and Methods), we did not perform a dedicated analysis of movement speed or reaction time variability between groups. However, two key considerations argue against this being a primary confound. Firstly, we analyzed only the final 500 ms of each trial, where the participant was stable and force output had plateaued. Secondly, patients were well-matched in clinical motor severity using validated scales such as UPDRS III and Hoehn and

Yahr, which include key motor features like bradykinesia, rigidity, and coordination. Additionally, no significant differences were found between groups in the variability of force output, as indexed by the standard deviation of the SA index. Taken together, while this remains a theoretical limitation, the available evidence suggests that motor symptoms did not differentially bias our findings.

A more substantial limitation concerns the absence of somatosensory-only testing. We did not measure basic tactile or force discrimination thresholds in patients or controls in the absence of movement. As a result, we cannot completely rule out the possibility that group differences in somatosensory detection capacities contributed to the observed differences in the Force Matching Task. However, several procedural steps were taken to minimize this risk. Familiarization trials were performed prior to data collection to ensure that all participants could reliably perceive the three target forces and were able to perform the task accurately. If any participant expressed uncertainty or inconsistency during familiarization, the trials were repeated to reinforce task understanding and tactile differentiation. Additionally, participants were closely matched for disease severity and motor function, reducing the likelihood that general disease progression or motor deficits confounded the somatosensory aspects of task performance. However, no formal psychophysical evaluation of passive touch sensitivity or force perception was conducted. Future work should address this by incorporating control tasks assessing somatosensory discrimination independently of active force reproduction.

Another limitation concerns the study design used to explore the effect of mental versus physical fatigue on body weight perception. We tested the effects of mental fatigue in a separate sample from the original study by Ferrè et al. (2023), which investigated physical fatigue. Although both studies used identical protocols and materials within the same laboratory group, testing both conditions within the same participants would have enabled stronger direct conclusions. This was not feasible due to high variability in individual recovery times from fatigue manipulations and the risk of excessive participant burden or dropout in a multi-session design. Nonetheless, the integration of physical and mental fatigue paradigms remains an important and valuable direction for future research.

A further consideration relates to age matching. In Part 1, the sample of healthy controls in the physiological trait fatigue study was significantly younger than the patient groups tested in other studies. This compromises strict comparability across all datasets. However, both patient studies in PD and FMD incorporated age-matched control groups to control for any age-related effects. The primary goal of the younger trait fatigue cohort was to explore whether SA alterations could be detected in healthy individuals reporting higher subjective fatigue, rather than to directly compare across groups. Future studies with larger, age-homogeneous samples will be important to confirm the generalizability of these findings across the lifespan.

In conclusion, although these limitations constrain certain aspects of the interpretations, they do not undermine the central contributions of this thesis. The work offers a robust empirical demonstration that fatigue and sensory attenuation are closely linked and extend to processes of body representation and multisensory integration, providing a solid foundation for future research in this emerging field.

Future directions

The work presented in this thesis provides new evidence for the role of predictive mechanisms in fatigue and sensory attenuation. However, as with all emerging research areas, the findings also raise important new questions that warrant further exploration. A critical next step is to clarify the causal relationship between fatigue and sensory attenuation. Longitudinal research designs are needed to determine whether altered sensory prediction acts as a precursor to the experience of fatigue, or whether the onset of fatigue itself leads to disruptions in internal prediction systems. Resolving this temporal relationship could significantly advance our understanding of the mechanisms driving the fatigue–sensory attenuation interplay.

Additionally, integrating neuroimaging and physiological measures into future research could help identify the neural substrates underlying the interaction between fatigue and sensory attenuation. Understanding the brain networks involved, particularly those linking interoceptive signals with sensory prediction, is critical to help refine theoretical models.

Finally, expanding this research to include more diverse populations and experimental paradigms would enhance its generalizability and applicability.

Conclusion

Our research advances our understanding of fatigue interaction with sensory attenuation, revealing their interplay and advancing both theoretical frameworks and clinical approaches. By investigating the dynamic interactions between sensory attenuation and fatigue, this research not only enhances our understanding of fatigue-related dimensions but also lays the foundation for using sensory attenuation as an objective biomarker for fatigue, offering a much-needed tool to assess and address this debilitating symptom across a wide spectrum of conditions. Beyond fatigue, the findings underscore the dynamic nature of sensory prediction processes and their reliance on multisensory integration, offering new insight into the brain-body relationship.

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