

Il ruolo dell'Interocezione nella Sclerosi Multipla: Evidenze Cliniche e Implicazioni Riabilitative

The Role of Interoception in Multiple Sclerosis: Clinical Evidence and Rehabilitation Implications

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Abstract

La sclerosi multipla (SM) è una malattia demielinizzante cronica del sistema nervoso centrale che colpisce le aree motorie, cognitive ed emotive, e la fatica è tra i sintomi più debilitanti. Recenti evidenze suggeriscono che un'alterata interocezione – la capacità di percepire e interpretare i segnali corporei interni – possa svolgere un ruolo chiave nella fisiopatologia della fatica nella SM. Questo articolo offre una revisione integrata dei processi interocettivi nella SM, concentrandosi sulle loro basi neuroanatomiche, sui correlati cognitivi e sulle implicazioni per la sintomatologia. Infine, è stato esplorato il potenziale terapeutico di nuovi interventi, tra cui approcci basati sull'embodiment, la stimolazione transcranica a corrente continua (tDCS) e la realtà virtuale (VR), incentrati sull'elaborazione interocettiva e sensomotoria per supportare la riabilitazione nella SM. Queste intuizioni sottolineano la necessità di considerare l'interocezione come un ambito promettente per la valutazione clinica e l'intervento nella sclerosi multipla.

Parole chiave

Sclerosi Multipla, Interocezione, fatica, metacognizione, riabilitazione.

Abstract

Multiple Sclerosis (MS) is a chronic demyelinating disease of the central nervous system that affects motor, cognitive, and emotional domains, with fatigue being among the most debilitating symptoms. Recent evidence suggests that altered interoception—the ability to sense and interpret internal bodily signals—may play a key role in the pathophysiology of fatigue in MS. This article offers an integrative review of interoceptive processes in MS, focusing on their neuroanatomical bases, cognitive correlates, and implications for symptomatology. Finally, has been explore the therapeutic potential of novel interventions—including embodiment-based approaches, transcranial direct current stimulation (tDCS), and virtual reality (VR) focusing on interoceptive and sensorimotor processing to support rehabilitation in MS.

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These insights underscore the need to consider interoception as a promising domain for clinical assessment and intervention in multiple sclerosis.

Keywords

Multiple sclerosis, interoception, fatigue, metacognition, rehabilitation.

Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS), characterized by inflammation, widespread primary demyelination, and progressive neurodegeneration. A widely accepted concept of MS pathogenesis suggests that tissue injury in the brain and spinal cord is initiated by T cell-mediated inflammation. Subsequent demyelination and neurodegeneration are then driven by heterogeneous mechanisms involving both the adaptive and innate immune systems (Lassmann et al., 2007). Numerous studies have proposed that microglial activation, the production of reactive oxygen species, and oxidative damage are key mechanisms underlying demyelination and neurodegeneration, particularly during the progressive stages of the disease (Haider et al., 2011, 2016; Fischer et al., 2013). Clinically, MS presents a wide spectrum of symptoms, including motor impairments, fatigue, pain, and cognitive dysfunction. As an inflammatory disease, MS leads to widespread white matter damage and disrupts neural networks involved in emotional regulation, particularly in subcortical and cortical structures such as the frontal lobe, the cingulate gyrus, and the insula. These alterations impair self-regulation and emotion processing (Giurgola et al., 2022; Boron et al., 2019). Consequently, emotional disturbances - depression, irritability, anhedonia, inappropriate affect (e.g., uncontrollable crying or laughing), severe mood swings, and emotional dysregulation -are frequently reported,

regardless of disease severity or executive functioning abilities (Prakash et al., 2019).

At a deeper level, emotion regulation involves a coherent relationship with the self, specifically effective communication between body, thoughts, and feelings. It requires tolerance and understanding of signals from the body and the related cognitive attributes (Price et al., 2018).

In the last decade, interoception —the sensing and interpretation of internal bodily signals—has gained increasing recognition in psychological and neuroscientific research.

This growing interest has been especially fueled by the foundational work of Antonio Damasio (1999) and Craig (2009), who highlighted the central role of interoception in self-awareness and emotional regulation.

Dysfunction of interoception is increasingly recognized as an important component of different mental health conditions, including anxiety disorders, mood disorders, eating disorders, addictive disorders, and somatic symptom disorders (Khalsa et al., 2024). Therefore, determining whether interoceptive processes are a cause or consequence of developmental psychopathology—and understanding the factors such as early-life stress or chronic pain which factors —will be an important area for future research.

This article provides an overview of the role of interoception in Multiple Sclerosis, exploring its clinical and rehabilitative implications and

proposing future directions for research and treatment.

Overview of the Interoception

The concept of bodily awareness is a puzzle in the cognitive sciences and is rooted in the idea that humans possess a conscious awareness not only of the external world but also of their psychological state, as well as our feelings, thoughts, and perceptions and that this is something peculiar in humans. However, the body can also be perceived from the inside, such as several mechanisms such as proprioception, (i.e., the processing of the position and movement of limbs), balance, and interoception (Parma et al., 2024). Interoception has garnered attention in the last two decades has been described by Khalsa and collaborators (2018) as it “refers collectively to the processing of internal bodily stimuli by the nervous system”.

According to Garfinkel et al. (2015), interoception is a multidimensional construct, encompassing: Interoceptive accuracy (IAcc): the objective ability to detect internal bodily signals, such as heartbeats or hunger, typically assessed via behavioral tasks. Interoceptive sensibility (IS): the subjective tendency to report or attend to bodily sensations (e.g., muscle tension, dry mouth). Interoceptive awareness (IA): the metacognitive insight into one's interoceptive accuracy, that is, the confidence in one's ability to perceive internal signals. Interoceptive evaluation (IE): the affective and interpretative dimension of bodily sensations, which plays a crucial role in emotion formation and regulation (Herbert et al., 2021).

These dimensions can be measured using different objective and subjective tools. For example, heartbeat detection tasks —the most widely used method for assessing interoceptive accuracy— (Fermin et al., 2023). Although these

tasks are limited in scope —focusing only on cardiac signals — it offers the advantage of being relatively resistant to voluntary control, unlike respiratory measures.

Beyond behavioral tasks, several self-report instruments are used to assess bodily awareness and interoception. Among these, the Functional Body Sensation Questionnaire (FBSQ) and the Multidimensional Assessment of Interoception (MAIA) are two of the most prominent. While both tools assess various aspects of bodily awareness, they differ in focus:

- The FBSQ measures perception, differentiation, and emotion regulation.

- The MAIA evaluates attention to bodily signals, as well as one's attitudes and reactions towards emotional and non-emotional-related body sensations (Parma et al., 2024).

Considering its multidimensional nature, interoception has become a key target for empirical research. A deeper understanding of the neural circuits underpinning interoceptive processing is essential to elucidate how internal bodily states are represented in the brain and how they interact with emotion, cognition and self-awareness.

Neuroanatomical Basis of Interoceptive Processing

Craig's work (Strigo et al., 2016) on the central anatomy of interoceptive processing describes a hierarchical organization of interoceptive pathways, characterized by the convergence of afferent signals from the spinal cord and vagus nerve toward cortical representations within the insular cortex. Primary interoceptive signals are transmitted from the ventromedial nucleus of the thalamus to the posterior insula, where initial representations of bodily states occur. Integration with exteroceptive, sensorimotor, and proprioceptive information is thought to

take place primarily within the posterior and central insular regions. The anterior insular cortex (AIC), which is densely connected to paralimbic cortical areas such as the orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC), is believed to play a key role in integrating interoceptive information with emotional and cognitive states (Herbert et al., 2020). Furthermore, different portions of the insula appear to be involved in different and successive stages of neural processing: raw interoceptive signals from visceral changes and pain first project to the posterior insula and integrate with motivational and hedonic information as they progress to the anterior insula (Parma et al., 2024). In the last decade, an interesting approach has emerged from neuroscientific research and computational theories. The Embodied Predictive Interoception Coding (EPIC) model proposes that the brain actively generates explanations for the stimuli it encounters (Barrett et al., 2015). In this framework, the brain constructs a generative model of bodily sensations, combining predictive mappings (from hidden bodily states to interoceptive sensations) with prior beliefs or expectations about those bodily states, represented as probability under the same computational principles through Bayesian inference mechanisms (Khalsa et al., 2022, Barrett et al., 2015). This provides a conceptual foundation for a taxonomy of disease processes thoughts the active inference model and corticocortical connectivity structures, thereby extending earlier predictive-coding accounts of interoception.

A substantial body of evidence links interoception to the activity of the insular cortex. A functional MRI studies have demonstrated differences in the hypoactivation in various insula regions in individuals with major depressive disorder (MDD) whilst non-

psychiatric participants and patients in remission from MDD show the same neural activity - during interoceptive attention tasks - in insula subregions implying a possible state marker for MDD (Wiebking et al., 2015).

In the context of multiple sclerosis (MS) interoceptive alterations have been corroborated by connectivity findings. Salamone et al (2018) demonstrated altered neural signature of interoception in patients using 128-channel EEG system during a heartbeat detection task (HEP) (Study 1) and fMRI recoding (study 2). Patients exhibited greater HEP modulation during the interoceptive condition, and they presented atrophy in the left insula, the posterior part of the right insula and neuroanatomical patterns. Sagliano et al., (2019) using double-blind study, investigated the role of insula in interoception through transcranial direct current stimulation (tDCS). Their results showed a significant improvement of participants' performance on the heartbeat counting task after the sham stimulation, indicating the importance of insular activity in interoceptive accuracy.

Additionally, it has been demonstrated that the efficacy of real-time fMRI (rt-fMRI) neurofeedback (NF) training of a novel regulation strategy based on interoceptive processing in up-regulating anterior insula (IA) activity (Zhang et al., 2023).

Overall, this body of evidence underscores the importance of assessing interoception in MS through multidimensional results and integrative approach.

Interoception in Multiple Sclerosis

Multidimensional disruptions of interoception have been observed in patients with multiple sclerosis (MS), including deficits in taste and temperature perception alongside altered pain sensitivity and persistent fatigue. MS

patients exhibit reduced structural neural responses, and aberrant brain-wise connectivity patterns during cardiac interoception tasks. Nevertheless, further research is needed to link causally hypothesized interoceptive deficits to fatigue in MS (Bonaz et al., 2021). Notably, most of the literature has investigated interoception specifically in relation to fatigue – one of the most frequent and disabling symptoms in MS – with a prevalence of up to 83% of patients (Kluger et al., 2013). Among all symptoms in MS, fatigue exerts a particularly profound impact on quality of life and represents a critical challenge for clinical management.

According to Manjaly et al (2019) several factors contribute to pathophysiology of fatigue: Structural damage of white matter (WM) and grey matter (GM), inflammatory processes (within or outside the central nervous system, CNS), maladaptive network recruitment due to distributed lesions or inflammation, metacognition (self-monitoring) of interoception of dyshomeostatic states. Most studies to date have predominantly focused on neuroanatomical correlates, examining how damage to brain regions involved in interoceptive processing relates to fatigue in MS patients (Ware et al., 2023). However, some research has also reported difficulties in the awareness of emotions and their bodily correlates, as well as excessive concern about bodily symptoms, which are often linked to anxiety and impaired self-regulation in individuals with MS (Eboni et al., 2018). A promising and more recent and framework to understand fatigue in MS is offered by the Allostatic Self-Efficacy (ASE) theory (Petzschner et al., 2017). This theory is grounded in computational models of brain-body interaction and highlights the interplay between interoception and metacognition - broadly defined as “cognition about cognition”

encompasses evaluative processes by which the brain monitors and assesses its own operations (Fleming, 2012)- as key cognitive mechanisms. Within this framework, fatigue is reconceptualized as the experience of low allostatic self-efficacy (ASE) a subjective state arising when the brain perceives regulatory failure, that is, an inability to minimize interoceptive prediction errors (PEs). Fatigue, in this view, becomes a signal to suspend ongoing actions and prioritize rest to restore homeostasis (Stephan et al., 2016).

Abundant indirect evidence suggests that subjective fatigue in MS could reflect a disruption of interoceptive mechanisms. For instance, Rouault et al. (2023) hypothesized that variability in fatigue levels among individuals with Multiple Sclerosis (MS) would be associated with individual differences in interoception, metacognition, and automatic regulation. Their results support the theoretical framework in which interoception plays a key role in fatigue and demonstrates the feasibility of predicting individual fatigue levels based on these variables. Similarly, Gonzalez et al. (2020) investigated whether fatigue in MS patients is associated with specific behavioral, structural, and functional alterations within the interoceptive domain. Using a modified fatigue scale to classify fatigue levels and a heartbeat detection task to assess interoceptive accuracy, they found that only fatigued MS patients exhibited decreased interoceptive accuracy. This was accompanied by reduced gray matter volume and increased functional connectivity in core interoceptive regions such as the insula and anterior cingulate cortex (ACC). Each of these neural changes was positively correlated with fatigue levels. More recently, Danciut et al. (2024) employed behavioral tasks and quantitative MRI to investigate the neural correlations of interoception and metacognition in relation to

cognitive fatigue in MS. Their findings demonstrated that interoceptive insight—defined as the metacognitive ability to track one's internal bodily signals—is selectively associated with cognitive fatigue. This relationship appears to be mediated by microstructural damage to white matter pathways. The interaction between cognitive fatigue and interoceptive tracking insight (divided into two levels) was found to be significant for fractional anisotropy (FA) within a bilaterally distributed network, including the superior longitudinal fasciculus, medial and inferior longitudinal fasciculi, arcuate fasciculus, uncinate fasciculus, inferior fronto-occipital fasciculus, external capsule, cingulum (including parietal connections), corpus callosum (rostrum, genu, body, splenium), callosal radiations, forceps major and minor, fornix, hippocampal commissure, posterior thalamic radiations, genu of the internal capsule, optic radiations, U-fibers (frontal, parietal, and temporal), and orbitomedial prefrontal connecting fibers. Alterations of functional connections (between insula and posterior cingulate gyrus and between the right thalamus and right precentral gyrus) as well as correlated with cognitive fatigue severity (Stefancin et al., 2019).

These findings underscore the existence of a widespread structural network within the white matter that is specifically linked to cognitive fatigue in MS.

Given the neurodegenerative nature of MS, and its impact on cognition, it is reasonable to hypothesize the disruption of multisensory integration, with potential implications for interoception and associated neuropsychological deficits. Giurgola et al. (2022) reported impaired multisensory integration in relapsing-remitting MS patients, indicating a significant impact on interoceptive processing. One relevant construct is the Temporal Binding Window (TBW) -index

of deficit multisensory integration process—reflecting the time interval within which sensory inputs from different modalities are perceived as belonging to the same event. TBW alterations have been reported in some neurological and neuropsychiatric disorders and seem to negatively affect cognition and behavior. However, it remains unclear whether MS is characterized by abnormal TBW, and to what extent disruptions are linked to interoceptive processing mechanisms, particularly in relation to autonomic information monitoring.

Relevance for Therapeutic Applications

Rehabilitation, including psychotherapy, symptomatic treatment, and physical activity, represents one of the most effective approaches for managing symptoms of multiple sclerosis (MS) and improving motor performance and quality of life. Conventional rehabilitation for MS patients primarily relies on physical therapy and therapeutic exercise, aiming to help individuals develop strategies to cope with various disabilities and regain the highest possible level of independence in Activities of Daily Living (ADLs) and return to work (Duan et al., 2023). The overarching goal of rehabilitation is to minimize motor impairments and promote the activation of neural pathways to support long-term recovery, especially in walking. While traditional rehabilitation techniques remain the standard of care, innovative technologies are emerging to enhance the management of disabling symptoms. One such innovation is transcranial direct current stimulation (tDCS), a neurorehabilitation technique that modulates cortical excitability and cortico-spinal circuits by inducing subthreshold changes in neuronal resting membrane potentials. tDCS has shown promise in improving movement disorders such as

dystonia, tremor, and Parkinson's disease, as well as degenerative cerebellar ataxia. In MS, tDCS has produced short-term improvements in gait and balance, suggesting that its benefits may be maximized when combined with conventional rehabilitation therapies (Marotta et al., 2022). Most recently, interventions focused on embodiment and body awareness have shown promise in MS rehabilitation (Price et al., 2021). The term embodied refers to a novel therapeutic approach in which the physiotherapist consistently guides the patient's attention toward bodily sensations and movement awareness. This method emphasizes the relationship between interoceptive awareness (IA), body sense, posture, and action (Paolucci et al., 2022). In parallel, technological innovations such as computer-based tools, robotics, and virtual reality (VR) have demonstrated efficacy in addressing motor and cognitive impairments in neurological populations, including those with MS (Pinilla et al., 2021; Parma et al., 2024; Maggio et al., 2019). VR-based interventions enhance sensory feedback and improve specific cognitive domains such as attention, problem-solving, working memory, praxis, and information processing speed (Kalron et al., 2016). VR has also been shown to foster neuroplasticity, leading to improvements in both cognitive and motor functions in MS patients. For example, semi-immersive VR training using systems like BTS Nirvana allows patients to engage in realistic, multisensory experiences that provide enhanced visual and auditory feedback. This sensory engagement facilitates motor and cognitive rehabilitation in MS (Maggio et al., 2022). Given the complexity and variability of MS symptoms and their associated complications, as well as the high likelihood of relapses, further research is needed to refine and expand clinical and rehabilitative approaches.

Conclusions

In recent years, interoception has emerged as a fundamental construct for understanding the complex symptomatology of multiple sclerosis (MS), particularly in relation to fatigue, cognitive dysfunction and emotional regulation. From a neuroanatomical point of view, these findings highlight the insula and related cortical and subcortical networks as key regions involved in the modulation of interoceptive signals. Despite promising developments, longitudinal studies combining neuroimaging, physiological and behavioral measures are still needed to track the progression of interoceptive alterations and their clinical implications over time. Moreover, the development of standardized, multidimensional tools for assessing interoception in MS will be essential for both research and clinical practice. Interventions targeting interoceptive awareness – such as neurofeedback, mindfulness-based therapies and virtual reality-based training – should be systematically evaluated for their efficacy and feasibility in diverse MS populations. Finally, incorporating interoceptive dimensions into personalized rehabilitation programs may help optimize therapeutic outcomes and improve quality of life for individuals living with MS.

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