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THESIS TITLE

Rehabilitation paradigms in congenital and acquired neurological disorders: quantitative and cognitive assessments, and prospective rehabilitative interventions

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Abstract

Sensorimotor integration is central to all the activities we distractedly perform daily: getting dressed, eating, moving around, interacting with people, learning and working. Furthermore, it is crucial in the perceptual and cognitive experience of our body. Alterations in the sensorimotor integration processes can arise from countless conditions affecting the central and peripheral nervous systems as well as from physiological ageing. Thus, the relevance of a deeper understanding of the multisensory integration mechanisms is a fundamental clinical and research goal in treating these conditions. In this thesis, three different clinical conditions sharing a sensorimotor integration impairment and the lack of a therapeutic gold standard are presented and discussed with a double purpose: first, to better characterize their sensorimotor integration impairments and etiopathogenetic processes; second, to propose new multidisciplinary rehabilitation approaches targeting each of them with particular focus on the bidirectional cognitive-motor interplay. As a result of this thesis, the sensorimotor integration mechanisms and the resulting body schema should be conceived as emergent properties of multiple brain circuits working synergically. As such, sensorimotor integration disorders require tailored, multidisciplinary intervention. Finally, the current most updated techniques to deal with sensorimotor integration disorders (e.g., robotic technologies) are presented alongside a new protocol proposal.

Chapter 1.

Background: from sensorimotor integration to body representations

Every action of daily living, from the more straightforward to the most complex and articulated, is highly dependent on our brain's capacity to select task-relevant somatosensory information and integrate them to guide effective motor outputs. This process is known as sensorimotor integration. Sensorimotor integration allows us to know where our body and body parts are in the space, where the objects are with regard to our body, and, consequently, to interact successfully with the environment. On the other hand, sensorimotor integration is the foundation of constructing internal coherent and plastic body representations. A reduced ability to efficiently interact with the environment or an altered body representation can arise from several dysfunctions in the sensorimotor integration process. Significantly different clinical conditions, such as the ones presented in this thesis, give evidence of the many forms sensorimotor integration deficits can assume and how difficult it can be to assess and treat them. Before getting to the heart of the thesis' hypotheses and experimental paradigms, this brief introduction aims to summarize the basic principles of the neural mechanisms of sensorimotor integration and their link with body representations.

1.1 The Sensorimotor Integration System

Sensorimotor integration is the complex process by which multiple sensory information from the periphery is integrated into the central nervous system (CNS) to inform motor output [1]. Different structures functionally contribute to this process. Indeed, sensorimotor integration occurs at various hierarchically organized levels, comprising both subcortical and cortical associative areas [1], [2]. Before introducing the brain mechanisms of sensorimotor integration, it is worth recalling some basic notions about the organization of the somatosensory system.

The somatosensory system provides four input modalities: touch, proprioception, nociception, and temperature. Each of these modalities has specific receptors in the skin, muscles and joints whose

activation determine the evoked sensation. Ganglion neurons innervating peripheral receptors form the first level of signal transmission of the dorsal column-medial lemniscus pathway (DCML), (see **Fig. 1**). Their axons ascend ipsilaterally inside the spinal cord at the level of the posterior (dorsal) columns till they reach the dorsal column nuclei in the caudal medulla, respectively: cuneate nucleus (upper body inputs) and gracile nucleus (lower body inputs). At this level, the axons cross the midline to travel in the medial lemniscus pathway. The second synapsis is located in the thalamus, particularly in the ventral posterolateral nucleus (VPL) and ventral posteromedial nucleus (VPM). VPL receives afferent projections from the DCML pathway and projects to the primary somatosensory cortex (S1) in a somatotopic manner. On the other side, VPM receives information on tactile, thermal, and noxious stimuli from the face area through the fifth cranial nerve.

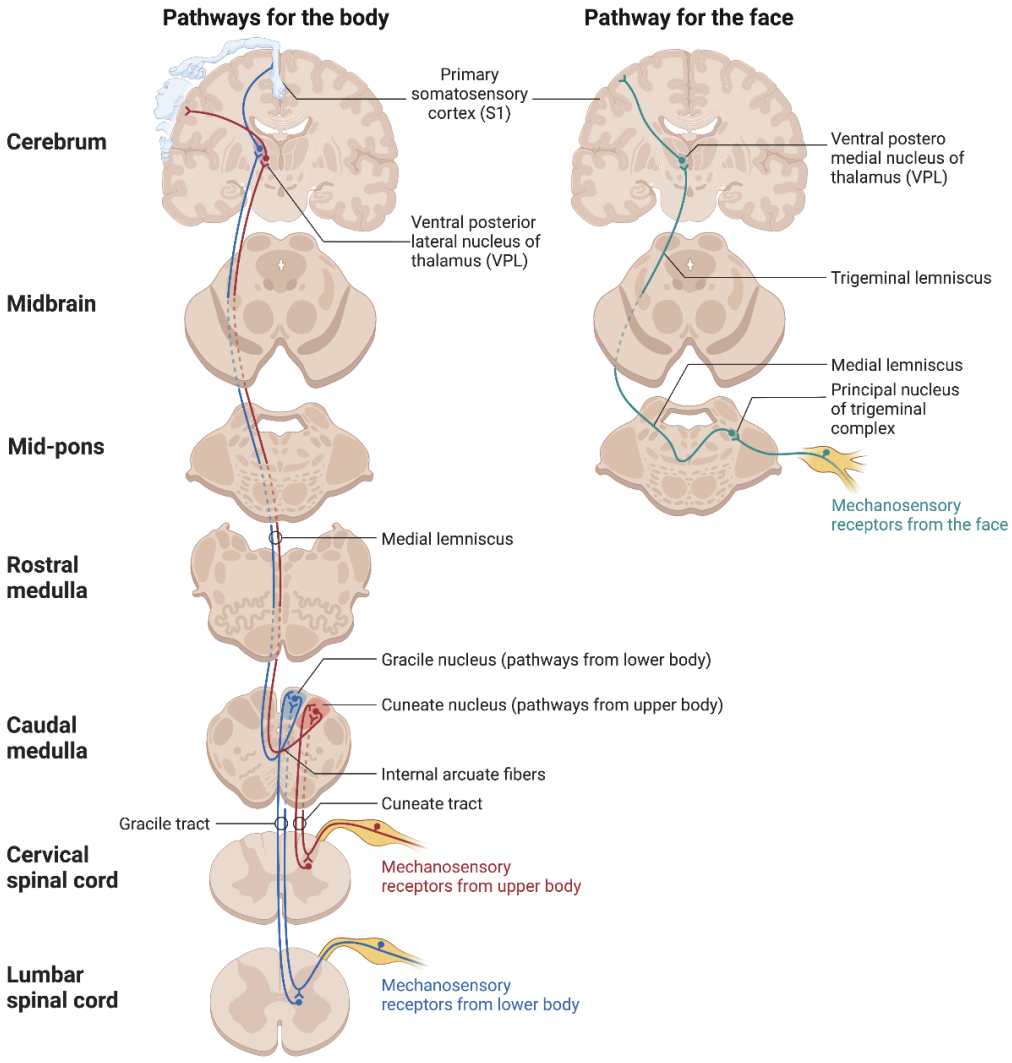

Fig. 1 *Dorsal Column-Medial Lemniscus pathway:* schematic representation of the sensory pathways from the spinal cord to the primary somatosensory cortex for the body (on the left) and the face (on the right). *Created with Biorender.com*

A fundamental question at this point is how and where the different sensory signals from the periphery are integrated into the brain between them and with other modality signals (e.g., visual, auditory…) to form a unified percept guiding our interactions with the world and construction of body representation. Three hierarchically organized levels of sensory signal integration can be described: spinal cord, subcortical, and cortical levels. The spinal cord is considered the most primitive level of signal integration: here, sensory signals from the skin, muscles and joints are integrated and used to generate reflex motor outputs such as the withdrawal reflex and automatic locomotor patterns [1]. Subcortical structures represent the second level of sensorimotor integration. Among these, vestibular nuclei, reticular formation and superior colliculus are essential for the generation of compensatory reactions to disturbances of the postural axis and anticipatory postural adjustments to voluntary movements [1]. The higher level of sensorimotor integration consists of the cerebellar and cortical associative areas. For the aims of this thesis, particular emphasis will be put on the posterior parietal cortex (PPC) and cerebellar contributions to sensorimotor integration.

1.1.1 Posterior Parietal Cortex

From an anatomical perspective, the parietal lobe has four main components: the postcentral gyrus (posteriorly to the central sulcus), the inferior parietal lobe (IPL), the superior parietal lobe (SPL), and on the medial surface, the praecuneus, which extends from the supramarginal sulcus to the parieto-occipital sulcus [3] (see **Fig. 2**).

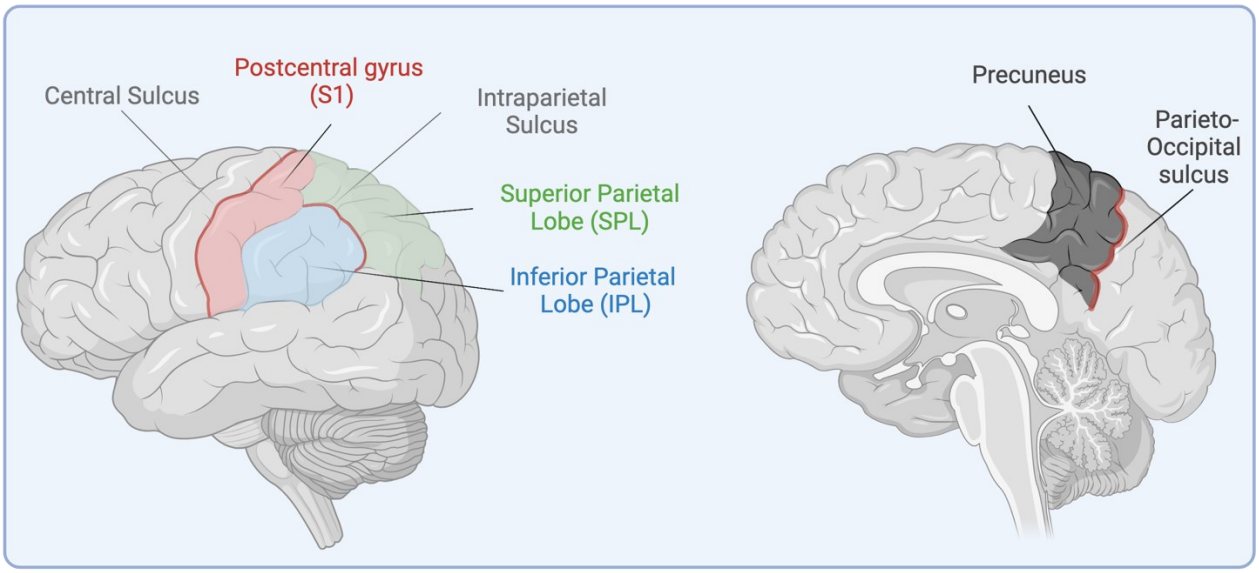

Fig. 2 Parietal lobe: lateral view of the parietal cortex (on the left) and sagittal section of the parietal lobe (on the right). Created with Biorender.com

The postcentral gyrus forms the primary somatosensory cortex (S1), which is so-called because it receives the information from all the sensory receptors (i.e., the dorsal column pathway and spinothalamic pathway). Indeed, this area presents a prevalent granular-type histology, with layers II and IV much more pronounced than the motor layers III and V (i.e., pyramidal cells). The sensory signals in S1 are organized in a somatotopic manner, referred to as the cortical sensory homunculus [4]. The homunculus consists of a disproportionate representation of the human body whose proportions reflect the extent of the cortical areas controlling different parts of the body. Posteriorly to S1 lies the PPC comprising both the SPL and IPL, divided by the intraparietal sulcus (IPS). The PPC has been traditionally considered one of the three main associative regions of the brain, along with the temporal and prefrontal cortices. It is located between the occipital lobe and the somatosensory cortex, identified by Brodmann's areas 5, 7, 39, and 40 [5]. Its associative nature lies in the different afferents it receives, including somatosensory, auditory, visual, motor, cingulate and prefrontal cortices signals, and proprioceptive and vestibular signals from subcortical areas. Indeed, contrary to S1, PPC cytoarchitecture equally expresses all the six cell layers of the cortex. The variety of connections speaks to the variety of behaviours and cognitive functions it subserved, including but not limited to: sensorimotor integration, spatial attention, spatial navigation, decision making,

working memory, early motor planning, others' actions understanding, representation of real and imagined spatial relationships as well as mathematical quantities representation, and mathematical abilities [5]. Lesions studies provided the first insights on PPC functions: in 1909, the case of a patient with concomitant bilateral stroke damage to PPC and parietal-visual border areas was first described. The resulting syndrome, subsequently named *Bàlint syndrome,* is characterized by three major symptoms: simultagnosia (i.e., inability to perceive more than one item at a time in the visual field), oculomotor apraxia (i.e., inability to make targeted eye movements), and optic ataxia (i.e., inability to make visually guided arm and hand movements) [5], [6]. These observations first disclosed the major role of PPC in the construction of peri-personal space maps and its involvement in coordinating actions within them. Other clinical observations in the same years highlighted that PPC damages were often associated with a lack of awareness of body posture and/or limb positions [7]. For instance, strokes in the PPC can be associated with so-called hemispatial neglect. In this condition, usually following right PPC stroke, patients can still see both hemifields but cannot direct their attention toward the visual hemifield contralateral to the lesion side [8]. As a result, they can be unaware of their body position in that hemifield (i.e., personal neglect) or be unable to plan and perform motor actions in it (i.e., motor neglect). Notably, these patients can ignore any of these problems (i.e., anosognosia), denying any motor or perceptual impairment [8]. Observing these deficits led to the concept of a PPC "body schema", a somatosensory map of the body informing about the position of our limbs in space and aiming to guide motion execution (see section 1.2 for a detailed description). After these preliminary observations, several models were developed to explain PPC involvement in sensorimotor integration processes responsible for body schema formation. The model of Dijkerman & de Haan is probably the most famous one [9] (see **Fig. 3**). Their model proposed two separate cortical processing streams: one composed of the anterior parietal cortex (APC/S1) projecting to the secondary somatosensory cortex (SII) and finally to the posterior insula, whereas the other terminates in the PPC. While the former seems to be mainly involved in somatosensory processes for recognition and perception, the second involves somatosensory processes for action.

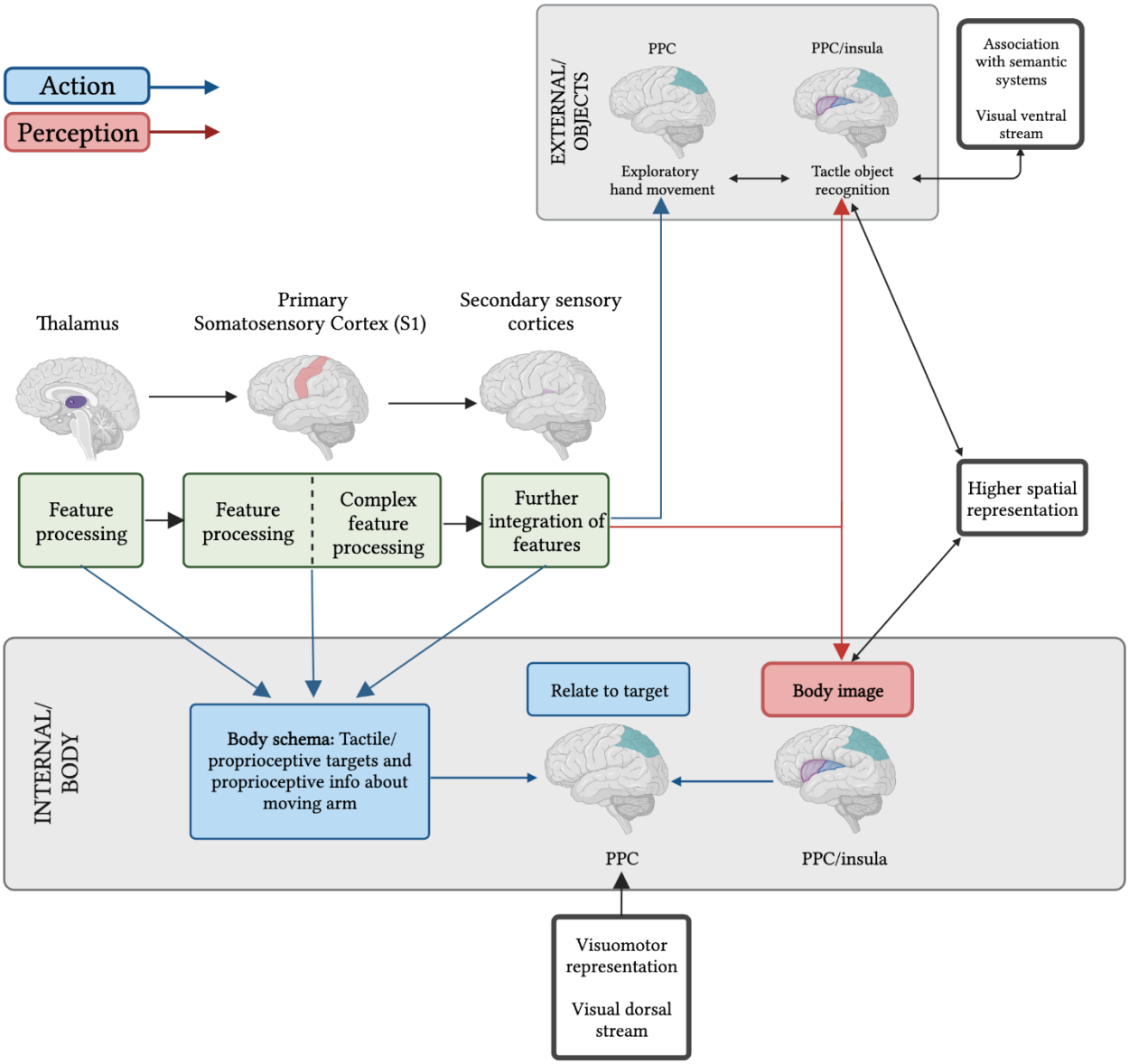

Fig. 3 Dijkerman & de Haan model: re-adaptation of the model proposed by Dijkerman & de Haan. Blue boxes and arrows indicate areas involved in somatosensory processing for action. Red boxes and arrows show areas involved in somatosensory processing for perceptual recognition. The regions and pathways engaged in body processing are grouped at the bottom of the figure. In contrast, those concerning external stimuli processing are represented on the top. Created with Biorender.com

This idea was confirmed by neuropsychological studies, which demonstrated the possibility of double dissociations between the two routes. It is the case of *numbsense* patients, unable to identify a touch over the affected insensible area but still able to guide actions toward the touched zone [9]. The model additionally distinguishes between the processes pertaining to the body and those about the objects. The former includes a first route projecting from SII to the insula, responsible for body image representation and a second route projecting from SII to PPC involved in body schema formation [9]

(see **Fig. 3**). The object-related route projects from SII to both the insula and the PPC and seems involved in tactile recognition of objects and exploratory hand movements for their recognition [9]. The hypothesized PPC body-related and environment-related routes were recently reframed and enriched in light of the optimal feedback control theory (OFC) [10]. According to the OFC framework, the brain must continuously estimate the state of the environment and the body and integrate these two states to elicit proper motor behaviours [11]. The brain integrates sensory inputs with the predictions made by internal forward models representing the mapping between motor and sensory commands to estimate body state. The integration between forward models and sensory feedback allowing state estimation seems to be mainly carried on by the PPC [11]. The model proposes a rostral-to-caudal gradient of state estimation in PPC, explaining the PPC body-related vs environment-related distinction previously described. Particularly, caudal parts of PPC would be involved in representing environmental states and thus projecting the body in the external environment, while rostral parts would be body-centred [11]. This gradient arises from the anatomical contiguity of the rostral part of PPC with somatosensory areas and the caudal part with visual ones. In summary, PPC caudal area is supposed to be predominantly visual (i.e., eye-centred coding) and committed to external space processing. This, in turn, allows the creation of an allocentric representation of the external space in which the body is projected. Finally, caudal PPC reflects the expected visual consequences of planned movement, including body-related movements [11]. Rostral PPC, on the contrary, seems to predominantly process somatosensory information (i.e., touch, proprioception, and vestibular signals), thus has been related to body state representation (body-centred coding). fMRI studies proved the role of rostral PPC in body state estimation in the context of sensorimotor tasks [12]. In summary, caudal and rostral PPC parts employ different perspectives but with the same final aim to relate the body and the environment.

1.1.2 Cerebellum

The cerebellum is a critical structure in sensorimotor integration. Its involvement in this process lies in its highly organized and functionally specific connections with the spinal cord, brainstem, and

cerebral cortex. Traditionally, the cerebellum was divided into three main functional areas [13] (see **Fig. 4**):

1. The *vestibulocerebellum* (or flocculonodular lobe) is the phylogenetically oldest part of the cerebellum, receiving inputs mainly from vestibular nuclei in the brainstem and visual centres, suggesting its role in balance/posture and eye movement control. Lesions to the vestibulocerebellum lead to conditions such as nystagmus, strabismus, oscillopsia and smooth pursuit deficits.

2. The *spinocerebellum* occupies the cerebellar hemispheres' median (i.e., vermis) and paramedian zones. It receives proprioceptive, visual, and auditory input directly from the spinal cord (spinocerebellar tract). Its outputs to rubrospinal, vestibulospinal and reticulospinal tracts are responsible for body limbs' gross movement regulation and sensorimotor integration. Indeed, lesions to this area result in coordination deficits of gait and posture as well as speech, hand, and eye movements.

3. The *cerebrocerebellum* is the phylogenetically newest region of the cerebellum, receiving signals from the cerebral lobes. It is the largest part of the cerebellum, especially well-developed in primates. Functionally, the cerebrocerebellum regulates highly skilled movements, particularly the planning and execution of complex spatial and temporal movement sequences, including speech.

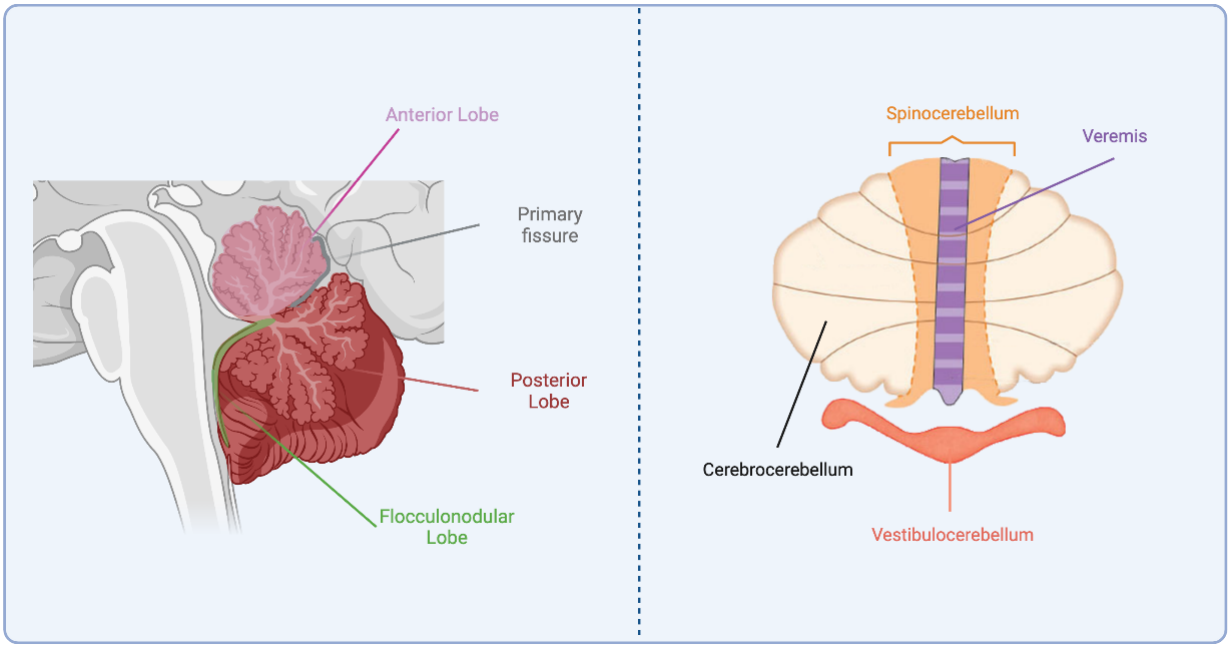

Fig. 4 Cerebellar functional anatomy: midsagittal section of the cerebellum (on the left); Superior view of a "flattened" cerebellum. Created with Biorender.com

The anatomical inputs to the cerebellar cortex come mainly from the mossy fibres and climbing fibres [14]. Mossy fibres originate from the spinal cord and several brainstem nuclei, conveying interoceptive, proprioceptive and exteroceptive information from limbs, trunk and face [14]. This information is then integrated by granule cells in the cerebellum, which, in turn, excite Purkinje cells, the principal output of the cerebellar cortex [15]. Climbing fibres inputs generate exclusively from the inferior olive of the brainstem, which receives information from a wide range of brain structures funnelling data from the periphery (i.e., spinal cord, dorsal column nuclei, trigeminal and vestibular nuclei, and the nucleus of the solitary tract) and brain structures (i.e., red nucleus, superior colliculus, pretectal area, and cerebral cortex) [14]. Like the mossy fibres, the climbing ones terminate in numerous synaptic contacts with Purkinje cells [15]. The output system of the cerebellum is formed by the deep cerebellar nuclei, namely fastigial, interposed, and dentate, receiving massive inhibitory (GABAergic) inputs from the Purkinje cells [16]. Thus, increased activity of the Purkinje cells reduces the excitatory (glutamatergic) cerebellar output [16].

It is thus clear that the cerebellum receives multiple multisensory information from both the periphery and the brain. The notions by which the cerebellum can affect the planning, initiation, and coordination of motor responses, and many cognitive functions, come mainly from studies of patients with cerebellar damage. Central deficits arising following cerebellar lesions better clarify cerebellar involvement in sensorimotor integration processes.

Cerebellum has been historically considered part of the motor system as the main symptoms arising from focal cerebellar lesions are motor. However, damage to the cerebellum does not result in a lack of movement but rather in poor motor coordination and accuracy [17]. Clinical cerebellar motor deficits can be grouped into four main categories: oculomotor disturbances, dysarthria, ataxia of limbs and ataxia of stance and gait [17]. Oculomotor disturbances encompass conditions such as instability of gaze, nystagmus (i.e., rhythmic or oscillatory movements of one or both eyes, with a fast and a slow component in opposite directions [17]), ocular hypermetria (i.e., inaccurate saccade with

overshooting of the target), and vestibulo-ocular reflexes (VOR) alterations [17]. VOR allows us to maintain gaze on an object when the head is rotated: vestibular detection of head movements is sent to the cerebellum, which recalibrates eye muscles output taking into account the head rotation [17]. Cerebellar dysarthria or ataxic dysarthria is characterized by severe temporal dysregulation of the muscles involved in speech production leading to unintelligible word production, and altered rhythm and speech fluency [17]. Lesions of both cerebellar hemispheres have been associated with this condition [17]. Finally, ataxia, including ataxia of limbs, stance, and gait, is probably the most known condition associated with cerebellar disorders. Ataxia of limbs is defined as unsteadiness or incoordination of limbs, including impairment in muscle force control and timing [17]. It leads to deficits such as dysmetria (i.e., errors in the movement trajectory), dysdiadochokinesia (i.e., inability to perform rapid successive movements), postural and kinetic tremor (i.e., low-frequency tremor occurring respectively during postural or limbs motor tasks, produced by voluntarily muscles contractions) and decomposition of movements (i.e., lack of synergy between joints resulting in lack of motion fluidity) [17]. Ataxia of stance refers to the inability to maintain the body in a stationary posture, resulting in a broad-based stance and increased body sway [17]. Distorted postural anticipatory adjustments and responses to external forces have also been described [18]. Likewise, ataxia of gait is characterized by broad-base unstable walking associated with a distorted walking rhythm manifesting in high spatiotemporal and kinematic parameters variability [17]. In addition, cerebellar motor abnormalities have been associated with an altered ability to use predictive information of perturbations to implement anticipatory postural adjustments [19]. To sum up, cerebellar involvement in motor control seems to manifest in complex tasks requiring the integration of multisensory information to form the perception of environmental stimuli and guide motor output consequently [20].

Contrary to previous beliefs, the cerebellum plays a fundamental role also in cognition. Indeed it is now acknowledged that cerebellar mechanisms in play in sensorimotor control and vestibular control are the same explaining a broad set of non-motor functions associated with cerebellar lesions, namely

cognitive, emotional and autonomic deficits [21]. The first insights on this came from resting state functional connectivity MRI studies showing a large number of reciprocal connections between associative brain areas, including primary and associative motor areas, as well as frontal, parietal and limbic areas with the cerebellum [21]. Notably, these functional networks project to the cerebellum with topographic specificity, with the motor network mapping onto the cerebellar anterior lobe and VIII lobule, while attention networks and frontoparietal networks mapping onto the posterior cerebellar lobe [21]. This gave rise to the hypothesis of a cerebellar sensorimotor-cognitive dichotomy: motor tasks were associated with cerebellar anterior lobe activation and adjacent VIII lobule, while cognitive tasks (e.g., language, working memory, spatial attention, executive functions) activated topologically distinct regions of the posterior cerebellar lobe [22]. Indeed, observations of patients with focal brain injuries secondary to stroke episodes proved the development of entirely different symptoms depending on the anterior or posterior cerebellar involvement: anterior lobe damages were associated with gait ataxia, limb dysmetria, and dysarthria, while posterior lesions led to little or no ataxia and a set of non-motor symptoms [21]. Based on these and other clinical observations [23], the well-known cerebellar cognitive affective syndrome (CCAS) was eventually defined. CCAS is characterized by clinically relevant deficits in executive functions, visuospatial processing, language and dysregulation of affect usually associated with posterior cerebellar lobe and/or vermis lesions [24]. J.D. Schmahmann then conceptualised the *dysmetria of thought theory* to explain how the cerebellum may be involved in all these higher-order brain functions. According to this theory, the exact mechanisms of cerebellar motor regulation of rate, rhythm, force, and movement accuracy occur when the cerebellum is involved in cognitive processes regulation. This principle would arise from the cerebellar anatomy per se. Indeed, as the microscopic anatomy of the cerebellum is relatively uniform in front of the numerous pathways linking the cerebellum with autonomic, limbic, and associative regions of the cerebral cortex, it is conceivable that the same cerebellar mechanisms of action can apply to all of them [21]. This mechanism, called the universal cerebellar transform (UCT), implies the integration of multiple internal representations with the external stimuli

and self-generated outputs to maintain a homeostatic baseline serving as an oscillation dampener to optimize performance in relation to the context [21]. Cerebellar abnormalities in this mechanism lead to “dysmetria”, which can manifest as a motor symptom or cognitive/limbic syndrome [21].

The mechanisms of action of the cerebellum have been later associated with those of a control system [25]. In a feedback control system, the desired output is constantly compared with the actual output, and modifications are made to minimize the eventual errors between actual and desired outputs. However, these systems are slow, requiring sensory feedback to reach the comparator, which in turn needs to send a new command to the effector. Thus, feedback control systems can work well only when the sensory feedback about the actual output is faster than the actual output *per se*. This implies that feedback control in the cerebellum can be effective just for slow movements, like postural adjustments. Taking this into account, the feedforward cerebellar model was proposed to explain cerebellar online control of fast movements [26]. In a feedforward control system, the controller evaluates sensory information about the environment and the system before generating the output commands. Therefore, the cerebellum would use current motor commands and past sensory information to predict the consequences of the current motor action. This *a priori* prediction would avoid the waiting time for the sensory feedback to correct itself [27]. According to this model, a copy of the motor command (i.e., efference copy) is generated before the execution of a voluntary movement to predict the sensory consequences of a forthcoming action. The cerebellum is thought to integrate the efference copy and the actual sensory feedback and, possibly, use the mismatch between the two to adjust the output and minimize the errors [28]. See **Fig. 5** for a schematic representation of the cerebellar feedforward model.

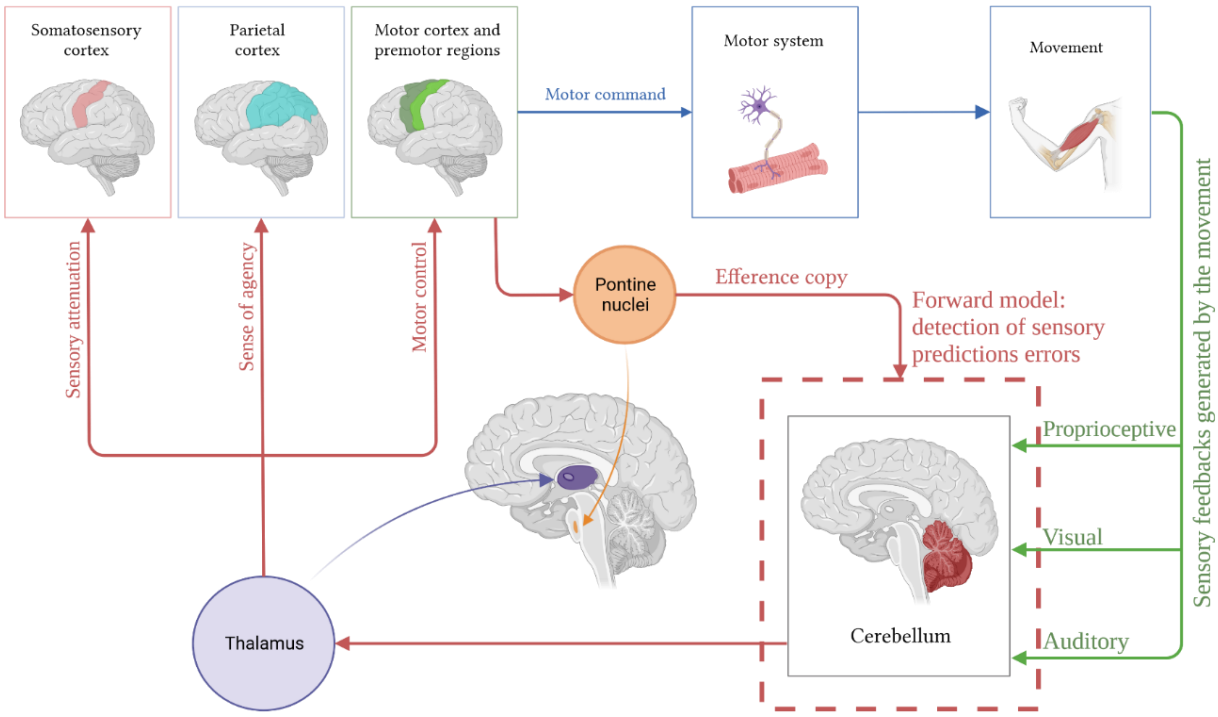

Fig. 5 *Cerebellar feedforward model:* The cerebellum receives sensory feedback (green lines) from the periphery, which provide information about the actual movement (the "feedback" part of the model). The feedback signal is compared with the desired one generated before the execution of the voluntary movement ((i.e., efference copy, the "forward" part of the model). The eventual mismatch between the actual and desired output would be detected in the cerebellum. The error is then sent to different cortical areas for different functions: sensory attenuation (i.e., the phenomenon by which voluntary actions elicit smaller cortical responses as compared to externally generated sensory signals), sense of agency (i.e., the experience of controlling one's own action), and motor control. *Created with Biorender.com*

1.2 Dyadic Model of Body Representation

Our body is essential to our sense of self, identity, and interactions with the world. The way we represent our body has thus become an increasing focus of research in many fields ranging from psychology, neuroscience, and psychiatry. Several different models have been suggested to explain the mechanisms underlying the construction of a coherent and stable representation of our body. Although many type of body representations have been proposed, there is general agreement on the existence of at least two types of them: body image and body schema. In short, the body schema consists of the sensorimotor representations of the body, guiding actions, while the body image groups all the other representations of the body not action-related (i.e., perceptual, conceptual, and affective)[29]. Definitions of body image and body schema change from model to model, but a general aspect on which almost all the taxonomies agree is the different functional role of these

representations, with body schema guiding actions and body image perceptual identification and recognition [29]. This fundamental distinction is founded on the well-known perception-action model of vision, consisting of a ventral stream (i.e., occipitotemporal cortex) and a dorsal stream (occipitoparietal cortex) [30] (see **Fig. 6**).

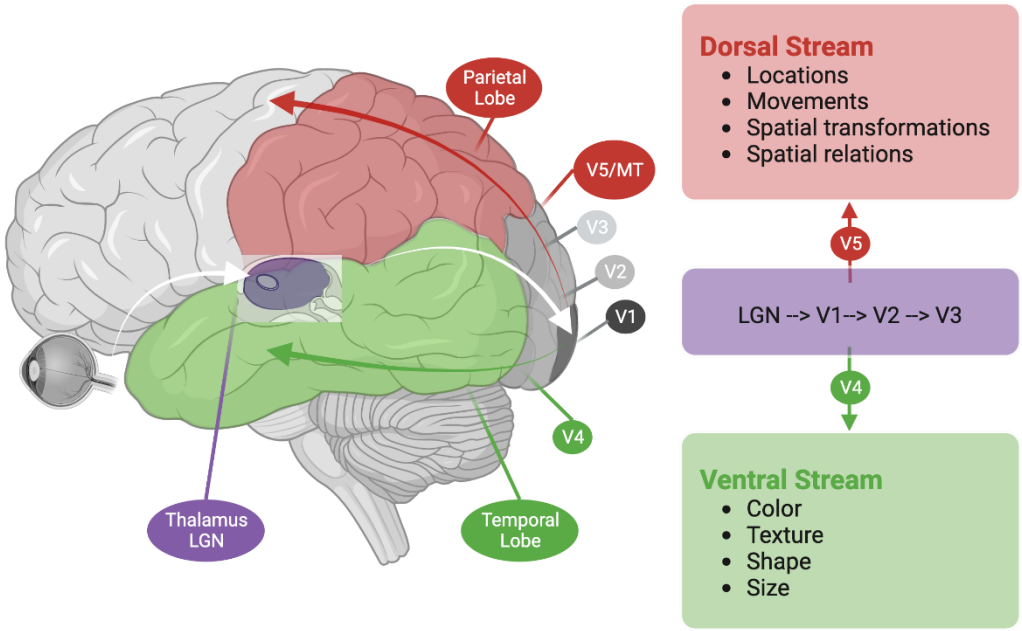

Fig. 6 *Two visual streams hypothesis:* Schematic representation of the two visual stream hypothesis. The visual signal is first processed in the thalamus's lateral geniculate nucleus (LGN). Then, it reaches the primary visual cortex (V1) and the secondary visual cortices (V2; V3), where simple objects' properties such as orientation and spatial frequency are processed. The dorsal stream (red) is proposed to be involved in processing objects' spatial properties and movement, as well as in the guidance of actions. The posterior parietal cortex is essential for the perception and interpretation of spatial relationships, body schema formation, and learning tasks involving the coordination of the body in space. The ventral stream (green) is involved in objects' recognition, shape, and color processing. *Created with Biorender.com*

The ventral stream is involved in object feature processing (e.g., colour, shape) and contributes to their recognition, whilst the dorsal elaborates objects' spatial locations, thus contributing to action planning. The two-route model suggested for the first time that the same sensory information could be processed in different ways by different brain structures, depending on the individual's aim. Further support for this model came from lesion studies, showing dissociations between object discrimination and localization deficits following inferior temporal and posterior parietal lesions [31]. Gradually the interpretation of these deficits led to the conclusion that both the colour/shape and the location features of an object are always parallelly elaborated by the two routes, no matter the

individual intentions. The model was later transported into auditory [32], touch and proprioception domains [9] and applied to the study of body representations [33]. This resulted in the body image (body for perception) vs schema (body for action) dichotomy. Other than their different functions, body image and body schema can be distinguished based on two other dimensions: consciousness and temporal dynamic [34]. The body schema is mainly an unconscious representation, which can possibly become conscious under certain circumstances. Indeed, it does not need awareness to be updated, but the result of the update can reach consciousness and be verbalized and elaborated (e.g., motor imagery tasks) [34]. On the other side, body image is always accessible to consciousness and is involved in perceptual tasks where body information is processed (e.g., verbal localization) [34]. Finally, although both body schema and body image are susceptible to changes in time, body schema is considered a short-term representation, while body image is a long-term one. The reason for this difference grounds again in their different functions: body schema needs to be continuously updated during movement execution to serve action performance efficiently. Consequently, the actual state of the body needs to be stored just for a very short time [34]. However, information such as body parts' size is more constant over time but still part of the body schema. Therefore, some authors suggested that short-term and long-term bodily information co-exists in the body schema [34]. On the other side, body image is a long-term representation, carrying the off-line properties of our body (i.e., perceptual characteristics, memory, cognitive and emotional associated states) [34].

Proves of the existence of different body representations rely mainly on neurological and neuropsychological clinical conditions (further discussed in section 1.3) and on experimental manipulations of sensory inputs leading to the emergence of multisensory illusions. Two very well-known paradigms altering body schema by creating multisensory incongruences are the Rubber Hand Illusion (RHI) [35], and the Pinocchio illusion [36]. In the classic RHI paradigm, participants sit with one of their arms resting on a table, hidden behind a screen, while looking at a rubber hand in front of them. In the meantime, the experimenter simultaneously strokes the real and rubber hands with a paintbrush. After a short while, participants report feeling the touch on the rubber hand and feeling

the rubber hand as their hand. The proprioceptive drift is ensured by the simultaneous touching of the real and rubber hand, which lead to a temporal matching between the visual input (the touched rubber hand) and the proprioceptive one (the real hand touched behind the screen) [35]. On the other side, in the Pinocchio illusion, participants are blindfolded, holding their noses while undergoing vibration to the ipsilateral biceps tendon. The vibration applied to the tendon creates the illusion of arm extension and, consequently, the perception of an elongating nose. The perceived long nose stems from a resolution of multisensory conflicts: the perception of arm elongation, not actually moving and nose simultaneous touching.

1.2.1 Body schema: operational definition

Body schema is traditionally defined as a sensorimotor representation of the body based on afferent and efferent information directed at motor actions. It is mainly unconscious and continuously updated by proprioceptive, vestibular and motor signals to maintain accurate spatial representations [37]. Besides the classical definition provided in the literature, an in-depth definition of the concept of body schema needs to consider its intrinsic properties [38]:

1. *Spatially coded*: body schema represents positions and configurations of the body in the space. This is allowed by integrating proprioceptive information about limb configuration in the space and tactile information on the body surface. The integration of multiple signals drives, in turn, the spatial localization of the body in the external space and the stimuli on the body itself.

2. *Modular:* the brain represents different body parts in different neural modules. Therefore, the body schema is modular, with each body part bearing spatial and categorial relations with the others (e.g., fingers are parts of the hand). Consequently, each module of the body schema can selectively be affected.

3. *Updated with movement:* as body schema is used for action execution, continuous tracking of the positions of the moving body parts is necessary. This updating process allows the body schema to set effective motor outputs towards targets in the external space.

4. *Adaptable:* the body schema updates and adapts to body changes occurring during the lifespan, as the result of body growth (e.g., changes in body parts dimensions), but also when using tools. Indeed, body schema can change after tool use on a short time scale to incorporate additional objects as new body segments, thus allowing effective tool-performed actions.

5. *Supra-modal:* as previously stated, the body schema is the result of the integration of inputs from multiple sensory modalities: visual, tactile, auditory, and proprioceptive information.

6. *Coherent:* body schema maintains a coherent representation of the body in space and time. This continuity is believed to be at the base of individual self-consciousness. Alterations of body coherence give rise to pathologies such as anosognosia and somatoparaphrenia.

7. *Interpersonal:* body schema is used to represent one's body and others' bodies. Several experiments proved this in that the observed and self-generated actions are co-represented within a single modular body schema.

Another important caveat to consider when defining the body schema is its conceptual overlapping with the notion of peri-personal space. The peri-personal space is defined as the space immediately surrounding our bodies, constituting a privileged window for the body to interact with the environment. It is also defined as the *reaching space* because functionally defined as the area around the body where objects can be reached by hand [37], [39]. It has been proved that peri-personal space representation depends on the activity of multisensory neurons (i.e., neurons of frontoparietal networks and PPC) responding to tactile stimuli on the body and visual and auditory stimuli signals near the body [40]. Given the similarities between these two concepts (i.e., plastic, multisensory, action-related representations), some authors not surprisingly raised the possibility that peri-personal space and body schema are different ways to express the same concept [39]. According to others, although body schema and peri-personal space can be distinguished, they cannot, however, be separately considered [37]:

"… the 'body schema' and 'peri-personal space' are emergent properties of a network of interacting cortical and subcortical centres. Each centre processes multisensory information in a reference

frame appropriate to the body part concerning which it receives information, and with which responses are to be made."

1.3 Linking body schema and motor disorders

Accurate movement execution requires fine processing and integration of sensory information from the environment and the body [41]. All the sensory systems contribute to movement control: visual, auditory, and somatosensory signals reach the PPC, where multisensory integration allows the emergence of the body schema [41]. The integration of multisensory signals comprises internal sources of information from the body (e.g., somatosensory, vestibular signals) and external sources from the environment (e.g., visual and auditory systems). External and internal signals are complementary to building our body awareness and self-consciousness as well as a coherent multimodal representation of the world [41]. These two representations (i.e., body and world) must be integrated to perform efficient goal-directed movements. Lastly, PPC modulates the motor output through its connections with premotor (PM), supplementary motor (SMA) and cerebellar areas. These areas send, in turn, feedback to the PPC and modulate M1 output. (See **Fig. 7** for a schematic representation of the primary brain networks involved in the sensorimotor integration process).

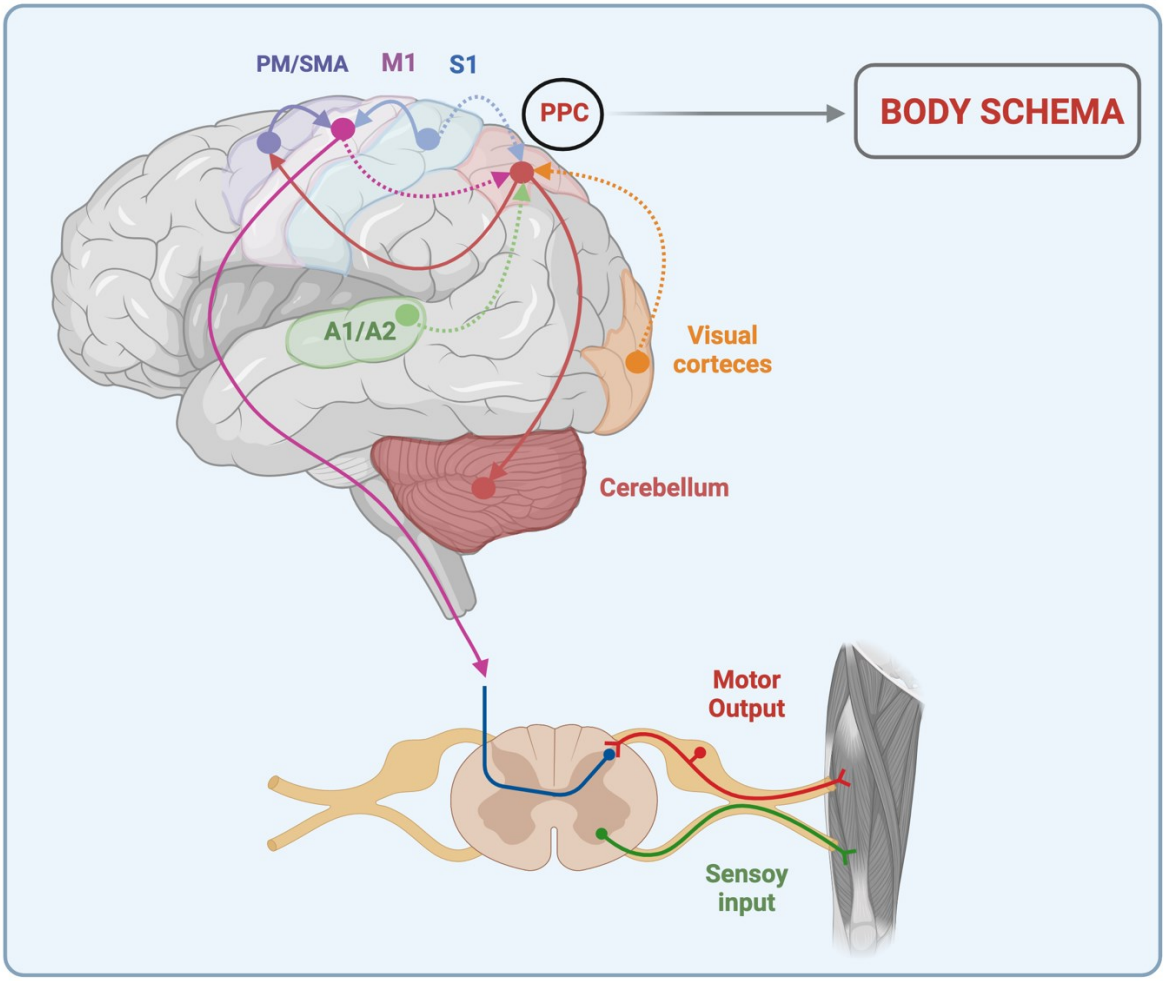

Fig. *7 Sensorimotor integration circuits:* representation of the complex brain network involved in sensorimotor integration and body schema formation. Dashed lines represent the input signals to the posterior parietal cortex (PPC). Continuous lines represent the output signals. PPC receives and integrates multisensory information [e.g., visual, and auditory (A1/A2)] and feedback information from motor (M1) and sensory (S1) cortices. Integrating the different signals allows body schema formation, which guides motor execution through PPC output connections to the cerebellum, premotor (PM) and supplementary motor (SMA) cortices. *Created with Biorender.com*

The visuomotor integration tasks give one of the most evident examples of multisensory signals and movement interaction: visual information about an object or the environment needs to be converted from allocentric coordinates to egocentric coordinates (body-centred) to plan effective goal-directed actions [41]. The somatosensory system, providing information on touch and proprioception, also plays a fundamental role in motor control. This is demonstrated in clinical conditions where motor pathways are preserved, but afferent information about the body is lacking (e.g., deafferented patients), leading to altered movement execution [41]. From this evidence, motor control can also be defective when sensory information is deficient, or the central processes of multisensory integration are impaired. The resulting body schema deficits affect motor planning and execution processes thus

promoting motor deficits (e.g., hypometric movements [42], postural malalignments) and non-motor changes (e.g., increased nociceptive sensitivity, altered mental imagery abilities) [43]. Below are summarized just a few of the many well-known conditions referred to in the literature as body schema disorders. Notably, these disorders often occur after damage to the parietal lobe, but the specific locus associated with each functional impairment has not been clearly identified for many of them.

1.3.1 Neurological disorders body schema-related

Deafferentation and Phantom limb phenomenon: the deafferentation is a clinical condition characterized by the loss of somatosensory information related to a specific body part [38]. It can arise both by a central lesion in the cortical/subcortical areas involved in sensorimotor processing (i.e., central deafferentation) or because of peripheral nerve lesions (i.e., peripheral deafferentation, amputees). In both cases, the affected patients become unable to locate the position of the affected body part in the space without relying on constant visual feedback [38]. Therefore, these patients' motor control heavily relays on visual feedback and is highly attention demanding. In contrast, blind people can reach an accurate sensorimotor control with a lower attentional cost [38]. This proves the principal role proprioceptive and tactile inputs play over visual inputs on body schema construction. The lack of proprioception and the associated motor control deficits make this condition an interesting model to study the body schema. A famous study [44] described the clinical features of a patient that, following a lesion to the left PPC, reported alterations in her right-hand position sense and ability to detect stimuli on it. The patient could not consciously feel the stimulation on the deafferented hand nor report it verbally but could still localize tactile stimulation above chance, making pointing movements with the spared hand. This proved the possible dissociation between the presence of a body schema still available to perform motor tasks and impaired conscious perception of the body.

The *phantom limb* is a well-known phenomenon occurring in amputated patients who still feel the amputated body part as present and painful. It is generally considered an example of maladaptive brain plasticity resulting from the cortical reorganization of the deafferented brain region [45]. The

cortical areas surrounding the deafferented one project to it and consequently alter the body schema neural representation [45]. There is a clear link between the phantom limb condition and the altered body schema representation: amputees often experience their missing limb as heavy, shorter, swollen or stuck in a position [46]. One commonly experienced phenomenon is the feeling of telescoping: patients experience their affected limbs as shrunken, with the more distal portions attached to the stump. This has been explained as the result of the disparity in the brain representation of different brain segments, with the distal parts (e.g., hand, fingers) overrepresented compared to the proximal ones [46].

Chronic pain disorders: Pain and body perception are inextricably linked. Neuroimaging studies proved that body representation and pain share at least partially the same networks of brain areas (i.e., pain matrix and body matrix). The pain matrix (extensively discussed in chapter 2.3.2) is defined as a network of brain areas comprising brainstem and thalamic nuclei, primary and secondary somatosensory areas, and insular and anterior cingulate cortices [46], [47]. On the other side, the body matrix includes a network of multisensory regions processing bodily-related inputs, such as the posterior parietal cortex, the somatosensory cortices, and the insula [46]. Their link is supported by behavioural evidence in patients affected by chronic pain syndromes. Patients affected by complex regional pain syndrome (CRPS) tend to experience body perception disturbances in the area affected by the pain. Misperception can include size (e.g., perception of a larger dimension of the affected body part), shape (e.g., perception of missing segments in the affected body part), and spatial representation distortions (e.g., reduced ability to determine laterality) [46]. Notably, the degree of misperception seems to correlate with pain intensity.

1.3.2. Neuropsychological disorders body schema-related

Personal neglect: the personal neglect is a specific type of neglect, typically occurring following right parietal lesions. This neuropsychological condition can be characterized by inattention toward one specific part or an entire half of the body, leading to a lack of awareness of the stimuli located in the

contralesional side of space [48]. It has been conceived as an attention deficit or a specific body representation disorder. In the latter case, it is explained as a pathology of the body schema coherence, in which patients unaware of their condition do not report the unattended body part missing from their body representation.

Autotopagnosia: the autotopagnosia is a disorder of body schema usually occurring after left parietal lesions [38]. These patients make mislocation errors when asked to point to a specific body location. Typically, the pattern of errors relates to adjacent body parts (e.g., pointing to the elbow when asked to point to the shoulder) [38]. This disorder seems to involve higher-level cognitive representation of the body rather than primary sensorimotor representations, as the errors can transfer to others' bodies [49]. Additionally, the naming of body parts is usually preserved, indicating a speared knowledge of body parts categories. This suggests that autotopagnosia is an example of incorrect segmentation of the modular parts of the body constituting the body schema [38].

Heterotopagnosia: this rare condition usually follows a left parietal lesion and affects the interpersonal mapping function associated with body schema [38]. When asked to point to body parts of the examiner, these patients tend to point to the correct body part but on their bodies. This disorder has been explained as selective damage to the processing stage at which body parts are assigned to different persons [38].

1.4 Rehabilitation of body schema disorders

Research on developing rehabilitation paradigms to restore body representation and, consequently, motor abilities is still in its infancy. Most of it has faced the problem from the opposite perspective, using motor rehabilitation to positively impact body representation alterations. Among the proposed paradigms, the so-called cross-modal illusions have been used in neurorehabilitation to modulate altered body representations resulting from brain damage. Cross-modal illusions occur when one sensory modality influences the experience of another sensory modality, as in the above-described case of the Rubber Hand Illusion (see section 1.2). Multisensory integration mechanisms and higher-

level cognitive processes mediate these illusions. It is worth mentioning, for instance, the mirror visual feedback therapy (MVFT) [50]. MVFT is especially used to rehabilitate amputee patients suffering from phantom limb syndrome. In this technique, the patient's healthy limb is reflected in a mirror and visually superimposed on the location of the affected limb (see **Fig. 8**).

Fig. 8 *Mirror therapy*: Picture of the mirror box from: *Brain*, Volume 132, Issue 7, July 2009, Pages 1693–1710, https://doi.org/10.1093/brain/awp135

The visual feedback in the mirror gives the patient the illusion of moving the affected limb, restoring congruence between vision and action, and relieving the pain [51]. Several theories tried to explain this phenomenon, among which the mirror neurons theory is leading. Mirror neurons are multimodal neurons (i.e., vision, motor commands, proprioception) firing in response to action execution and observation, localized especially in frontal and parietal lobes [52]. MVFT would activate these multimodal neurons through visual feedback, temporarily reestablishing coherence between proprioception, vision, and motion of the affected body part [50]. This technique was effective even in treating stroke patients, as it helps re-learn motor patterns and correct body representation derangements. Indeed, motor impairments after stroke prevent the active use of the affected limb,

leading to decrease cortical representation of the affected area in the somatosensory cortices. This phenomenon leads to the progressive cortical reorganization of the adjacent body parts, resulting in increased disability of the affected limb and enhanced motor impairment [53]. It was proved that after performing MVFT, stroke patients significantly improved their movements and performances in forearm bisection tasks specifically designed to test the metric representation of the arm [53].

Secondly, virtual reality paradigms are currently adopted with the same aims and theoretical principles of the MVFT. In these paradigms, it is possible to induce the embodiment of a full virtual body observed from a first-person perspective to modulate pain perception and improve motor performance [50].

Conversely, a few paradigms target body schema rehabilitation to improve motor deficits. Mental imagery paradigms seem promising in this regard. Mental imagery is the cognitive process of simulating sensations, actions and other experiences through the generation and use of mental images, including one's own body[43]. Mental imagery is believed to activate body-schema-related brain pathways. Thus, body schema can be modified by mental imagery tasks [54]. Among the various types of mental imagery paradigms, dynamic neuro-cognitive imagery (DNI) stands out [43]. The DNI is a systematized mental rehearsal for motor and cognitive retraining, using mental imagery from different categories and modalities. It is often combined with the actual movement execution of basic and advanced activities [54]. One example of the clinical application of the DNI to enhance body schema is provided by Parkinson's disease (PD) rehabilitation research [43]. PD patients experience sensory/perceptual deficits, including proprioception and kinesthesia alterations. This often leads to physical misperception and inaccurate body schema [54] further exacerbating PD's motor and cognitive deficits. Mental imagery protocols in PD patients seem to positively affect body schema representation and, consequently, the related motor deficits [54]. Notably, this approach relies on adequate cognitive capacity to perform mental imagery tasks; therefore, it is not recommended for all types of patients.

Despite the attempts to plan efficient rehabilitation paradigms to act on body schema and improve motor outcomes, there is still not enough literature on this subject. Given the acknowledged role of body schema in perception and action, this thesis focuses on the need to develop new rehabilitation paradigms specifically targeting this dimension.

Chapter 2.

Thesis' Overall Aim

There is a close link between motor and cognitive processes. This connection is especially evident in the tasks involving sensorimotor integration, where different sources of information are combined to produce precise motor outputs but also to create a coherent cognitive representation of the environment and the body acting within it. As the same neural circuits subserve both functions, not surprisingly, targeting one among motor or cognitive-related aspects of the sensorimotor integration also positively affects the other. To date, rehabilitation paradigms mainly focused on the motor part of the bidirectional relation between motor and cognitive dimensions, observing the positive effects of motor rehabilitation on cognition (e.g., improvement in body representation, spatial cognition, and executive functions [55]). However, there is a need to increase the research exploring the reverse effect, implying cognitive-related rehabilitation impact on motor and sensorimotor functions. The overall hypothesis guiding the experimental paradigms described below is that by better understanding and characterizing each condition's different patterns of sensorimotor integration deficit, it will be possible: (1) to better understand the close relationship between motor and cognitive processes; (2) to apply that knowledge to the development of tailored rehabilitation paradigms targeting specific motor or cognitive-related aspect of sensorimotor integration.

The final aim is to provide a theoretical rationale to boost the development of new cognitive-related sensorimotor rehabilitation paradigms to improve motor symptoms.

This thesis focuses on the study of three clinical conditions differently involving the sensorimotor integration system and characterized by a not yet completely understood aetiopathogenesis: Dravet syndrome (DS), Adolescent Idiopathic Scoliosis (AIS) and Fibromyalgia Syndrome (FMS). Since a gold standard to treat these conditions is still lacking, this thesis aims to enrich the knowledge of their pathological mechanisms to develop new therapeutic and rehabilitative interventions. With this proposes, the research lines have been developed:

1. DS cognitive and behavioural profile highlighted a predominant impairment of sensorimotor integration and cerebellar circuits. However, the overlapping between these circuits' functions and the associated deficits stressed the need to develop new screening tools to disentangle their relative contribution in determining the final DS phenotype. This with the final goal of developing personalized programs targeting each subject's specific pool of symptoms. Thus, the first study aimed at identifying specific motor and cognitive parameters to distinguish PPC and cerebellar involvement in two sensorimotor-related functions: gait and body schema. Toward this aim, a repetitive Transcranial Magnetic Stimulation (rTMS) paradigm was developed to simulate a selective cerebellar or PPC lesion in a group of healthy subjects. The hypothesis is that a double dissociation exists between specific gait parameters and body schema alterations among groups, particularly: (1) PPC would be more involved in body schema formation and kinematic-related aspects of gait, tightly associated with body schema; (2) cerebellum would participate more in the determination of gait spatiotemporal and kinematic variability, and less on body schema representation. The results of this study may provide additional quantitative parameters to help differential diagnosis between a prevalent PPC or cerebellar phenotype in DS to better direct their rehabilitation. Particularly in a patient with PPC-related motor deficits, rehabilitation targeting the body schema would probably help the overall outcome of motor symptoms. On the contrary, a cerebellar phenotype would probably benefit less from this type of intervention.

2. The second reach line is driven by AIS representational abnormalities and hypotheses of a central sensorimotor impairment reported in literature. The paucity of studies on body schema alterations in this clinical condition, and the evidence of abnormal central sensorimotor integration mechanisms led to the second study aims: better characterize central mechanisms of altered sensorimotor integration in AIS and to relate them with body schema deficits. For this purpose, the EEG activity of a group of girls with AIS was recorded and compared to that of a control group while executing postural tasks. In parallel, a new method to assess AIS body schema representation was employed. Particularly, the hypotheses driving this research were the following: (1) AIS girls display altered

brain activation of the sensorimotor network compared to controls; (2) AIS girls have a less efficient balance control on the plane with the larger scoliotic deformity; (3) the altered body schema reflects the altered activation of the sensorimotor network. The results of this study may provide a new valuable biomarker of AIS progression and consequently offer a new therapeutic target.

3. The third aim was motivated by FMS theories on pain matrix. According to this theory, pain is just one of the possible outputs of a complex and extensive brain circuit involving several cortical and subcortical structures, among which sensorimotor areas play a crucial role [56]. As abnormal central activation of the pain matrix in FMS was postulated in literature, we aimed to manipulate a promising biomarker of this abnormal central activity (i.e., EEG abnormal oscillatory activity) to test the efficacy of a new tailored treatment approach [i.e., Transcranial Alternating Current Stimulation (tACS)]. The hypothesis is that tACS delivered over the cortical areas showing the greatest EEG abnormal oscillatory activity (i.e., sensorimotor areas) may improve pain and cognitive symptoms by shifting the EEG activity toward the physiological frequency. See **Fig. 9** for a schematic representation of the thesis main hypotheses.

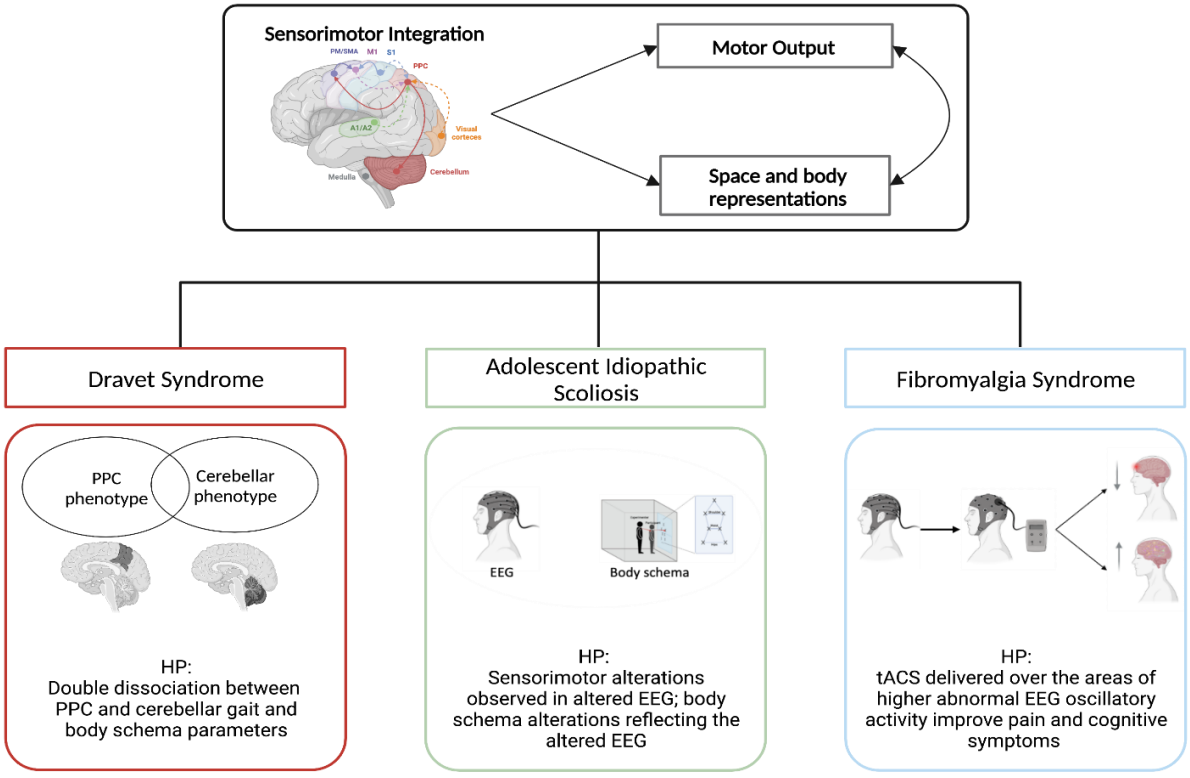

Fig. 9 *Schematic representation of the thesis hypothesis. Created with Biorender.com*

In the following chapter, the main clinical features of the three conditions of interest are presented to better understand each experimental paradigm' underneath rationale. Notably, their link with sensorimotor integration abnormalities is emphasized by two literature reviews on DS and AIS and a summary of the main theories explaining the deficits in FMS.

Chapter 3.

Three pathological models of body schema and sensorimotor integration deficits

This chapter presents the three pathologies of interest of this thesis, namely Dravet Syndrome (DS), Adolescent Idiopathic Scoliosis (AIS), and Fibromyalgia Syndrome (FMS). Although apparently wholly different, these conditions have something in common: a not yet completely understood aetiology, sensorimotor integration alterations and the need for developing new effective therapeutic strategies.

3.1 Dravet Syndrome

3.1.1 Clinical features

Dravet syndrome, or severe myoclonic epilepsy in infancy (SMEI) was historically first described by Charlotte Dravet in 1978, after which it is named. It is a rare and severe developmental epileptic encephalopathy affecting children since their first year of life [57]. DS estimated incidence varies between 1/15.000 to 1/40.000, affecting males twice as often as females [58], [59]. The following factor should co-occur to make a DS diagnosis:

1. Seizure onset within the first year of life (at four to eight months in most cases) [60]. The first seizures are typically clonic, generalized, or unilateral and generally triggered by hyperthermia (fever, hot bath ...), but afebrile onset seizures have been reported as well [60], [61]. At the onset, seizures tend to be prolonged, lasting longer than 20 minutes, and sometimes evolving to status epilepticus [62], [63]. The EEG activity is usually regular at the beginning, both during awake and sleep [60], but can progressively become abnormal (e.g., generalized and multifocal epileptiform discharges) [63]. Within the first years of life, other drug-resistant seizure types appear, such as focal, myoclonic, and absence seizures with frequent occurrence of convulsive and nonconvulsive status epilepticus.

The frequency of seizure episodes increases during the first ten years of life, then slowly decreases into adolescence and adulthood [64].

2. Genetic confirmed mutation in the gene coding for the alpha-1 subunit of the sodium channel (SCN1A): genetic mutations are observed in 75-80% of individuals with DS [65]. Mutations can be of several types (e.g., truncating, missense, spice-site changes), mainly de novo, but familial ones have also been observed in up to 10% of cases [65]. SCN1A mutation has been associated with DS pathophysiology: experimental studies on mouse genetic models of DS highlighted the association between the reduced inhibition of GABAergic inhibitory interneurons caused by the mutation and the resulting excessive excitation. This, in turn, can explain some of the clinical signs of the syndrome such as ataxia, poor motor coordination, autistic-like behaviour and cognitive impairment [66].

3. Cognitive, psychomotor, and behavioural disorders. Developmental motor retardation becomes evident from 2nd year onward [60]. Neuropsychological phenotypes in DS are heterogeneous, but early visual function impairments (i.e., acuity, fixation shift) are often reported, preceding subsequent development of abnormalities in hand-eye coordination and gross motor functions [67], [68]. These early disorders are usually associated with later higher-order executive dysfunctions: motor inhibition, visual and auditory attention, planning, set-shifting and working memory. This pool of cognitive deficits following early visual abnormalities made some authors propose a possible bottom-up causal relationship between visual impairment and cognitive decline [69]. Studies reporting Intelligent Quotients (IQ) show variable degrees of intellectual disability ranging from low average IQ to severe impairment. Non-verbal Wechsler IQ scores are generally lower than the verbal ones [70], [71], but language can be affected as well, mostly in motor speech production (i.e., dysarthria, speech planning difficulties, and expressive language deficit) compared to a relatively spared semantic processing [67]. Autistic-like traits (e.g., poor eye contact, ritualistic behaviours, narrow interests, speech delay, adherence to routine, low ability to express emotions), and attention-hyperactivity disorders, are often reported as well [67], [72].

4. Gait disorders: as a rule, children younger than six years old generally show a typical gait pattern which becomes increasingly impaired with age leading many patients in their adolescence and adulthood to lose completely their ability to walk [73]. Indeed, a recent literature review reported that up to 15%-30% of patients need support to walk outside the house, and 20% need a wheelchair [74]. The most observed abnormal gait pattern in DS is pseudo crouch gait, characterized by excessive ankle dorsiflexion and excessive hip and knee flexion on the sagittal plane during the stance phase [73], [74].

The cause of crouch gait is still not completely understood, but multiple factors have been proposed, including muscle weakness, spasticity, contractures and lever arm dysfunction [74]. Additionally, cerebellar gait ataxia and parkinsonism have been observed in patients affected by DS, but their manifestations are less consistently reported [74].

The long-term outcome is dominated by premature death. According to a recent literature review, the mean age at death occurs before 20 years in 93% of the reported cases [75]. The leading cause of death is the sudden unexpected death in epilepsy (SUDEP), causing nearly half of deaths in this condition. Other common causes include status epilepticus, drowning, accidents and infections [75]. Treatment options are focused on seizure management, especially in young children, with valproic acid and clobazam as first-line treatment options (responder rate of 48% with 40% seizure reduction) [76]. However, neither of these medications controls seizures completely most of the time. Thus, they are combined with other drugs [76]. There is no gold standard in managing DS comorbidities, but multi-disciplinary treatment considerations are recommended (i.e., behavioural therapies, physical therapy, sleep specialists …) [76].

3.1.2 DS and sensorimotor integration

The pathophysiology underlying the broad spectrum of DS neurophysiological and neuropsychological manifestations is still largely debated. Several theories have been proposed, among which the sensorimotor integration hypothesis, the dorsal stream vulnerability, and the

cerebellar-like pattern are the most represented. These theories have been reviewed in this thesis, considering current literature in favour or against each hypothesis to propose a unified theoretical framework.

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CRITICAL REVIEW – INVITED COMMENTARY

Deconstructing Dravet syndrome neurocognitive development: A scoping review

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Abstract

Dravet syndrome (DS) is a rare severe epilepsy syndrome associated with slowed psychomotor development and behavioral disorders from the second year onward in a previously seemingly normal child.

Among cognitive impairments, visuospatial, sensorimotor integration, and expressive language deficits are consistently reported. There have been independent hypotheses to deconstruct the typical cognitive development in DS (dorsal stream vulnerability, cerebellar-like pattern, sensorimotor integration deficit), but an encompassing framework is still lacking. We performed a scoping review of existing evidence to map the current understanding of DS cognitive and behavioral developmental profiles and to summarize the evidence on suggested frameworks. We searched PubMed, Scopus, PsycInfo, and MEDLINE to identify reports focusing on cognitive deficits and/or behavioral abnormalities in DS published between 1978 and March 15, 2020. We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines. Twenty-one reports were selected and tabulated by three independent reviewers based on predefined data extraction and eligibility forms. Eighteen reports provided assessments of global intelligence quotients with variable degrees of cognitive impairment. Eleven reports analyzed single subitems contribution to global cognitive scores: these reports showed consistently larger impairment in performance scales compared to verbal ones. Studies assessing specific cognitive functions demonstrated deterioration of

early visual processing, fine and gross motor abilities, visuomotor and auditory-motor integration, spatial processing, visuo-attentive abilities, executive functions, and expressive language. Behavioral abnormalities, reported from 14 studies, highlighted autistic-like traits and attention and hyperactivity disorders, slightly improving with age. The cognitive profile in DS and some behavioral and motor abnormalities may be enclosed within a unified theoretical framework of the three main hypotheses advanced: a pervasive sensorimotor integration deficit, encompassing an occipito-parietofrontal circuit (dorsal stream) dysfunction and a coexistent cerebellar deficit.

KEYWORDS

cerebellar impairment, cognition, dorsal stream, sensorimotor integration, severe myoclonic epilepsy in infancy

1 | INTRODUCTION

Dravet syndrome (DS) is a complex and rare epileptic developmental encephalopathy, with an estimated prevalence between 1/15 000 and 1/40 000,[1,2] first described by Dravet in 1978.[3] DS manifests with drug-resistant "febrile and afebrile generalized and unilateral, clonic or tonic-clonic seizures, occurring in the first year of life in an otherwise apparently normal infant,"[4] and later on associated with myoclonic and absence seizures and the occurrence of status epilepticus. Based on seizure semiology, two forms are currently recognized: typical DS and atypical DS, characterized by a lack of myoclonic seizures.[5]

At least 80% of people with DS carry familial or de novo mutations of the sodium channel α1 subunit (*SCN1A*) gene.[6] From the second year of life, cognitive stagnation, associated with neurological signs, gait abnormalities,[7,8] and behavioral disorders becomes evident, leading to a progressive ubiquitous developmental delay.[8]

Several neuropsychological phenotypes are reported, ranging from mild specific deficits to severe global impairment. Visual impairments and visuomotor deficits in DS usually manifest early. They may anticipate higher-order cognitive-developmental abnormalities, such as impaired visuoconstructive abilities, attention, language production, and executive functions. This contrasts with better preservation of visual object recognition, memory, and language comprehension,[8–10] in line with a dorsal-ventral cognitive dissociation, suggesting an involvement of the dorsal-stream pathway (see Table 1).

Behavioral disorders are common and often characterized by hyperactivity, attention deficit, autistic traits, aggressiveness, and opposition.[11]

The pathophysiology underlying such a broad spectrum of neuropsychological features is not fully understood. Three main theoretical frameworks have been independently proposed to explain the DS cognitive and behavioral profile: the dorsal stream vulnerability hypothesis,[12] the cerebellar-like pattern,[13] and the sensorimotor integration deficit[14,15] (see Table 2).

Key Points

- Dravet syndrome (DS) is a complex developmental encephalopathy characterized, among other symptoms, by cognitive stagnation and behavioral disorders
- A comprehensive framework facilitating the understanding of cognitive/behavioral issues in DS to guide future research is still lacking
- A sensorimotor-integration impairment encompassing a visuo-dorsal-stream dysfunction and a coexistent cerebellar deficit may explain DS cognitive outcomes
- Future work should concentrate on these aspects and disentangle their relative contributions to the disease

According to the dorsal-stream vulnerability hypothesis (based on the cognitive dual-stream hypothesis[16]), slight visual deficits precede the decline of visuomotor dorsal pathway skills. The asymmetric involvement of the so-called visual "dorsal pathway" functions, opposed to the "ventral" ones, is consistently reported. A similar asymmetry in the involvement of the two cognitive pathways has been described in other genetic syndromes (Williams, Prader-Willi, fragile-X), leading to the concept of genetic involvement as the determinant for the cognitive pattern as well as for the seizures.[8,12] A recent study found a high degree of expression of some genes, including *SCN1A*, along the brain's visuomotor integration network, connecting its malfunctioning with the genetic mutations.[17]

TABLE 1 Cognitive dual-stream theory

	Dorsal visual stream	Ventral visual stream
Brain pathways	Occipito-parietal network	Occipito-temporal network
Functional properties	Visually guided reaching/grasping Visual motion processing Spatial location coding Spatial working memory Sensorimotor integration Visuo-attentive abilities	Recognition of visual shapes/objects Long-/short-term memory Learning processes Emotional processes Reward system
	Dorsal language stream	**Ventral language stream**
Brain pathways	From inferior-parietal regions to posterior-frontal regions	From posterior-superior temporal sulcus to middle-temporal gyrus
Functional properties	Auditory-motor integration (verbal repetition/verbal production)	Auditory conceptual mapping (auditory comprehension)

The cerebellar-like pattern hypothesis also links the cognitive impairments and *SCN1A* mutations. Experimental studies on a DS model in mice[18] showed decreased excitability of inhibitory cerebellar Purkinje neurons likely to explain some of the motor and cognitive deficits observed[13,19]: ataxia, poor motor coordination, and performance impairments in executive functions, spatial cognition, language abilities and autistic-like behaviors.[20]

Lastly, the sensorimotor-integration hypothesis refers to the complex process at the central nervous system level that allows the accomplishment of specific motor responses based on integrating multiple sources of sensory information.[21]

These integrative processes, especially visuomotor and auditory-motor integrations, are frequently impaired in children with DS, suggesting the sensorimotor integration deficit as a likely framework. According to this model, an integration deficit can explain the observed visuomotor and visuo-constructive impairments and the productive language dysfunctions consequent to an auditory-motor deficit.[13–15] Conversely, the frequently observed gait and postural abnormalities[7] may be interpreted as the result of abnormal proprioceptive and vestibular integration.[15] Behavioral abnormalities are associated with earlier visuomotor integration deficits limiting social learning abilities and communication efficacy.[22,23]

We aim to summarize cognitive and behavioral findings in DS to collate evidence in favor or against the three proposed hypothesis and to propose a unified theoretical framework. Future research, as well as clinical practice, could benefit from this understanding to aid the design of new practical rehabilitative approaches.

Toward this aim, the following research question was formulated: *Is the evidence favoring or contradicting the main hypotheses to deconstruct DS neurocognitive developmental phenotype?*

2 | METHODS

We used the PRISMA-ScR checklist for Preferred Reporting Items for Systematic reviews and Meta-Analysis extension for Scoping Reviews.[24] After data extraction and in light of the extreme heterogeneity of the assessed cognitive domains and neuropsychological test, we opted for a scoping review.[25,26]

2.1 | Eligibility criteria

Inclusion criteria were the following: full-length items, peer-reviewed, original research articles in English, and published between 1978 (when DS was initially described)[3] and March 15, 2020. Included items reported on individuals meeting the International League Against Epilepsy (ILAE) diagnostic criteria for DS[27] and assessed to have behavioral disorders or at least one of the following cognitive dysfunctions: visual processing, phonological processing, visuo-motor processing, visuospatial abilities, visuo-attentive abilities, working memory, executive functions, language, measures of general development besides intelligence quotients (IQs). Cognitive evaluations had to be carried out using standardized neuropsychological tests. Single case studies, animal studies, and articles not meeting the inclusion criteria were excluded.

2.2 | Information sources

A systematic search on DS neuropsychological characterization was conducted by one author (MB). The databases Scopus, PubMed, PsycInfo, and MEDLINE were searched by adapting the following keywords to meet each database's search

TABLE 2 Three theoretical frameworks for Dravet syndrome

1. Dorsal-stream vulnerability	
Brain pathways	Occipito-parietofrontal network
Hypothesis	Precocious visual impairment preceding the decline of visuomotor dorsal pathway functions vs relatively preserved ventral stream functions
2. Cerebellar-like pattern	
Brain pathways	Cerebellar-cortical loops
Hypothesis	Decreased excitability of cerebellar Purkinje neurons leading to: 1. Motor alterations: ataxia, poor motor coordination 2. Cognitive deficits: executive functions, spatial cognition, language 3. Behavioral abnormalities: autistic-like behaviours
3. Sensorimotor-integration deficit	
Brain pathways	Sensory input parietofrontal pathway
Hypothesis	Deficit in the process of integration of multiple sources of information, leading to: Visuomotor deficits Auditory-motor deficits Gait and postural abnormalities Impaired social learning abilities

features: Dravet syndrome, severe myoclonic epilepsy in infancy, cognition, neuropsychology, neuropsychological phenotypes, autistic features, autism spectrum disorder. Detailed search queries for PubMed are provided in Appendix 1.

The electronic database search was supplemented by screening the reference lists of retrieved articles and scanning relevant reviews. Final search results were exported into the MENDELEY bibliographic software package to keep and organize finding and apply deduplication procedures.

2.3 | Selection of sources of evidence

To increase consistency in the selection, three reviewers (MB, AH, KV) independently evaluated the identified articles. A fourth reviewer (ADF) revised articles in cases of disagreement on data extraction or inclusion. (See Figure 1 for the full selection procedure.)

2.4 | Data charting process and data items

Reviewers jointly designed an *ad hoc* data extraction form covering relevant variables to address the research question by adapting one proposed in the Cochrane handbook for systematic reviews[28] (see Appendix 1).

The first part of the extraction form identifies general article information and organizational aspects: reviewer identity, date of review, article title, first author's name, publication year, country of origin, journal, publication type, and a short article description.

The second part includes eligibility criteria and reasons for exclusion. Articles were selected as eligible based on type of publication, sample characteristics, assessment method, and outcomes of interest.

Eligible items were eventually tabulated by extracting the variables of interest: sample characteristics (e.g., sample size, age of participants, diagnostic criteria, treatments), type of study design (e.g., longitudinal, cross-sectional, and so on), cognitive domains assessed and assessment procedures (specific neuropsychological tests, test batteries, questionnaires, and so on).

Cognitive and behavioral data were summarized and discussed in light of the three hypotheses.

3 | RESULTS

3.1 | Synthesis of the results

A first screening based on titles and abstracts led to identification of 36 articles, which underwent full-text examination.

Of these, 15 were excluded: 3 were not full-length original research articles (editorials and internal progress reports); 7 were reviews used to screen for missing items of potential interest; 2 did not assess outcomes of interest; and 3 did not use standardized neuropsychological assessment tools.

Lastly, the outcomes of the 21 included articles were grouped according to cognitive domain assessed (see Table S1): general intellectual/developmental quotient; lower-order cognitive functions (visual processing, phonological processing, fine and gross motor functions); sensory-motor integration (visuo-motor and auditory-motor integration); higher-order cognitive functions (visuospatial abilities, language comprehension, attention, executive functions); and behavioral outcomes. For each domain, we reported the assessment method and the main findings.

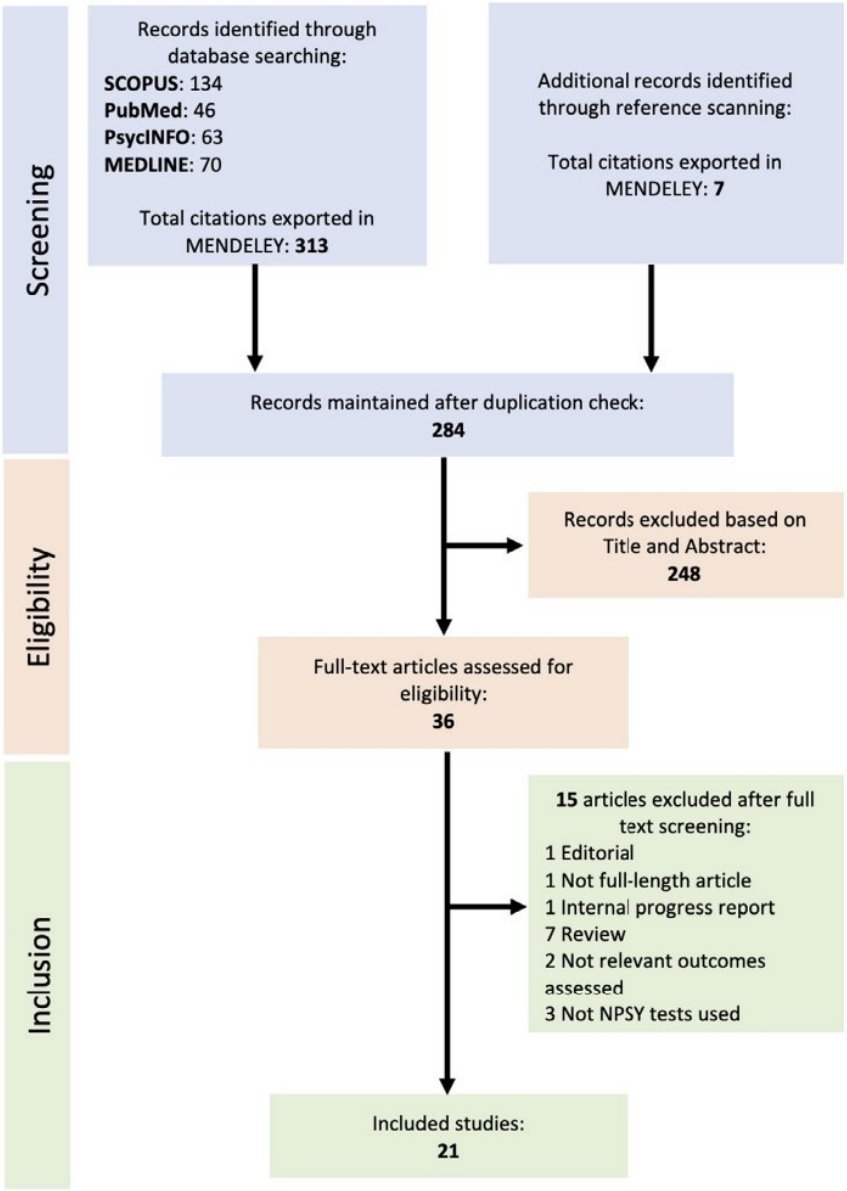

FIGURE 1 Flow chart of the systematic search. Preferred Reporting Items of Systematic Review and Meta-Analysis (PRISMA) flow chart showing the process of systematic article search and selection

3.1.1 | Study characteristics

Studies included were heterogeneous in study design (7 cross-sectional, 3 longitudinal retrospective studies, 10 prospective longitudinal studies, and one family cohort study), participant age (≥6 months to 60 years), assessment tools, and assessed domains. Multiple tests were administered in the same study (see Table S2).

3.1.2 | Global cognitive assessment

General intellectual/developmental quotients were assessed in 18 of 21 studies. The following scales were used: Wechsler Intelligence Scales, adapted to the age at testing (13 studies); Griffiths Mental Development Scales (nine studies); Brunet-Lézine Scale (four studies); Gesell Developmental Schedules (one study); McCarthy Scales of Children's Abilities (one study); Psychoeducational Profile, Third Edition (PEP- 3) (one study). In two studies, Raven's Coloured Progressive Matrices were used as an alternative measure of intelligence when children were not fully cooperative (see Table S3).

All 18 studies reported a variable degree of developmental delay/intellectual disability, ranging from low average IQ to profound intellectual disability. In the studies that reported them, the tests' sub-item analysis showed a more significant contribution of the performance IQ (PIQ), than the verbal IQ (VIQ) in determining the global intellectual disability. In particular, 11 of 18 reports highlighted severe impairment in

visual, fine motor, gross motor, visuomotor, visuospatial, and receptive language functions. The remaining seven studies did not report single subitem scores.

Of seven studies investigating the relationship between epilepsy features (semiology and frequency of seizures) and intellectual disability, three highlighted the relationship between myoclonic plus absence seizures with a worse cognitive outcome.[29–31] Two studies found a correlation between higher seizure frequency and worse cognitive development,[10,32] whereas another two did not find any clear association.[12,33]

Two studies examining the relationship between autism and IQ found a significantly higher proportion of profound intellectual disability in children who were also diagnosed with autism.[34,35]

3.1.3 | Behavioral assessment

Behavioral abnormalities were evaluated in 14 of 21 included studies using the following scales: Child Behaviour Checklist (eight studies); Vineland Adaptive Behavior Scales (five studies); Autism Diagnostic Interview (ADI) (two studies); The Autism Diagnostic Observation Schedule (ADOS) (two studies); Conners Comprehensive Behavior Rating Scales (Conners CBRS), Pervasive Developmental Disorder in Mental Retardation Scale - Revised (AVZ-R), Maladaptive Behavior Scale for the Mentally Retarded (SGZ), Temperamental scale for individuals with ID (TVZ), Autism Behaviour Checklist (ABC), Childhood Autism Rating Scale (CARS), and Diagnostic Interview for Social and Communication Disorders (DISCO), each in one study (see Table S4).

Of the 14 articles, 7 reported autistic-like traits, 6 attention deficit, and 6 hyperactivity disorders. Externalizing behaviors, especially hyperactivity, impulsivity, and aggressiveness, were more often observed than internalizing behaviors (anxiety, depressive-traits, and over-controlled behaviors), with the exception of two studies finding the opposite pattern.[13,31]

Two studies reporting the longitudinal evolution of behavioral abnormalities found a gradual decrease in behavioral disorders from adolescence to adulthood[29] and from the first evaluation (mean age: 21.7 months) to the last follow-up (mean age: 6 years 6 months),[33] especially related to hyperactivity traits.

Three studies investigating comorbidity between DS and autism spectrum disorder (ASD) found between 23% and 62% of people with DS additionally diagnosed with ASD.[34–36] Another eight studies reported the presence of pervasive autistic-like traits such as poor eye contact, ritualistic behaviors, narrow interests, speech delay, adherence to routine, and low ability to express emotions. In some of these studies, however, authors emphasized relative preservation of socialization capacity and excessive familiarity with strangers, which contrasts with the typical autistic pattern.[9,36]

3.1.4 | Specific perceptual and cognitive functions assessment

Low-level cognitive and perceptual functions (visual processing; phonological processing; gross/fine motor abilities)

Seven of 21 articles reported evaluations of visual processing (four studies), phonological processing (two studies), and fine/gross motor abilities (two studies) (see Table S5).

Two of the four articles assessing visual processing abilities emphasized variable degrees of impairment in the different sub-scores tested, ranging from abnormal to average scores.[12,37] Two items reported general pervasive visual perceptual impairment in all assessed children.[13,33]

Two studies examining phonological processing abilities emphasized impairments in phonological perception and detection, particularly near chance correctness (54%) in a same-different judgement paradigm, persistent with age, in contrast with 100% correctness of healthy age-matched controls[14] and abnormal scores in the phonological accuracy subitem of the Testa (TPL) (5 of 10 evaluated children, mean Z score = −2.53, standard deviation [SD] = 0.45).[15]

The two studies assessing fine and gross motor abilities show delayed motor development in most children older than 2 years. In the first study, gross motor delay was reported in 7 of 7 and fine motor delay in 11 of 13 individuals,[38] whereas in the other, abnormal fine motor abilities were observed in 75% and abnormal gross motor abnormalities in 37.5%.[13]

Sensorimotor integration (visuo-motor integration; auditory-motor integration)

Seven articles analyzed sensorimotor integration abilities in DS. Of these, five examined visuo-motor integration abilities and five auditory-motor integration abilities (see Table S6).

All five articles investigating visuomotor integration abilities reported inferior performances. Four reports assessing visuomotor development using the Beery-Buktenica Developmental Test of Visual-Motor Integration reported mean Z scores of 2 SD below the mean.[12,13,33,38] In one study, a finger tapping task's performance showed fewer taps and higher inter-tap latencies than in healthy age-matched controls.[14]

All five studies assessing language-production abilities reported dysfunctions in naming and repetition, related to oral sensorimotor impairment rather than semantic dysfunctions, resulting in imprecise articulation,

omission errors, and low phonological and morphosyntactic accuracy.[13-15,33,39]

High-level cognitive functions (language comprehension; attention; working memory; executive functions)

Seven studies reported the assessment of language comprehension, attention, memory, and executive functions. Language-comprehension abilities investigated in three studies showed results mainly in the normal range, with few exceptions showing a borderline impairment level. Visual-attention abilities as well as executive functions, assessed in four studies, showed impaired skills. In detail, the results of the Teddy Bear Cancellation Test and the Bells on average lower than 2 SD below the mean, with a few borderline scores (see Table S7).

Significantly worst performance was reported in DS than in controls in a go/no-go task, in terms of correct action execution (% of correct responses in DS Group: mean = 30.1, SD = 13.2, vs Control group: mean = 94.6, SD = 4.6) and inhibitory capacity ($P < .001$).[14] The performance on the Tower of London test, as assessed by three studies, also showed impairments.

Verbal working memory (digit/word span, forward and backward) and spatial working memory (Corsi Block-tapping Test, forward and backwards) tasks appeared to be impaired.[13,33] In contrast, a visual memory task[14] did not find any significant differences between controls and the DS group.

4 | DISCUSSION

This review highlights the lack of evidence within this topic, characterized by methodological and clinical heterogeneity and small cohort sample size.

We associated each of our finding with the three main hypotheses to deconstruct DS neurocognitive developmental phenotype: the dorsal-stream vulnerability premise, the sensorimotor-integration deficit theory, and the cerebellar-like configuration (see Table 3). We discuss our findings accordingly.

4.1 | Findings fitting with all three hypotheses

Variable degrees of global cognitive impairment, ranging from mild to profound as assessed by general developmental/intelligence scales, emerged. No unequivocal relationship between the degree of global cognitive impairment and seizure type or frequency could be recognized.[10,29-32] Therefore, the assumption of a purely epileptic etiology of cognitive deterioration in DS should be reconsidered.[29,30]

The relative contribution of the test subitems in determining the global intellectual retardation displayed significantly worse scores in Wechsler's performance subscales and in the hand-eye coordination and gross motor subscales (Griffiths' and Brunet Lézine developmental scales) compared to verbal comprehension and memory abilities.

The verbal-performance cognitive asymmetry is also confirmed by the assessment of specific cognitive function. Low-level cognitive functions including visual processing, as well as fine and gross motor abilities, showed impairment from a young age,[12-14,37,38,40] and often heralded a progressively abnormal development of higher order cognitive functions,[14,37] motor inhibition, planning, set-shifting, verbal fluency, and working memory.[12-15,33,39] These findings seamlessly match the dorsal-stream vulnerability model and the sensorimotor-integration deficit hypothesis, suggesting an early visual deficit preceding the decline of visuomotor dorsal pathway skills leaving the ventral ones relatively preserved.

The cerebellar-like pattern may also account for this: low fine and gross motor abilities and impairment of executive functions including poor planning, set-shifting, verbal fluency and spatial working memory are often referred to as part of the so-called "cerebellar cognitive-affective syndrome."[41]

4.2 | Dissociation between the three hypotheses

Sensorimotor-integration abilities showed inferior results,[12,13,33,38] which are not limited to the visual dorsal-stream functions.

In the language domain[42] the motor aspects of speech production (dorsal-temporofrontal sensorimotor mapping of sound into articulation) are significantly more affected than the semantic processing (ventral-temporofrontal-lexical semantic pathway).[8,14] Functional abnormalities of this sensory-motor loop in the dorsal stream may also account for observed verbal working-memory deficits.[14] According to Baddeley's model of working memory,[43] keeping an active trace of auditory-based representation relays on the continuous rehearsal of information through articulatory-based processes.[43]

These poor performances in visuo-motor and auditory-motor integration manifest from the first developmental stages, rather than maturing later as a consequence of an abnormal developmental process and seem responsible for cognitive and motor disharmonic development.[15]

Abnormalities in visual and language sensorimotor systems have been observed in other genetically based clinical pictures, such as Williams syndrome, fragile-X syndrome, and Prader-Willi syndrome, leading to a genetic hypothesis in the determination of the cognitive outcome.[13,15] A study investigating the contribution of the *SCN1A* mutation to the

TABLE 3 Evidence in favour of the main hypotheses

Results	Dorsal-stream vulnerability	Sensorimotor-integration deficit	Cerebellar-like pattern
Global cognitive outcomes (see Table S3)	Greater impairment in PIQ sub-items than VIQ sub-items (11/18 studies)	Greater impairment in PIQ sub-items than VIQ sub-items (11/18 studies)	Greater impairment in PIQ sub-items than VIQ sub-items (11/18 studies)
Behavioral outcomes (see Table S4)	—	Attention and hyperactivity disorders (6/14 studies)	Attention and hyperactivity disorders (6/14 studies)
	—	Comorbidity with ASD (3/14 studies)	Comorbidity with ASD (3/14 studies)
	—	Autistic-like traits (7/14 studies): - Poor eye contact - Speech delay - Adherence to routine - Poor ability to express emotions	Autistic-like traits (7/14 studies): - Poor eye contact - Speech delay - Adherence to routine - Poor ability to express emotions
Low-level cognitive and perceptual functions (See Table S5)	Pervasive visual perceptual impairments (2/4 articles)	Pervasive visual perceptual impairments (2/4 articles)	—
	Abnormal eye movements (1/1 article): ocular motility, stereopsis, fixation shift	Abnormal eye movements (1/1 article): ocular motility, stereopsis, fixation shift	Abnormal eye movements (1/1 article): ocular motility, stereopsis, fixation shift
	Abnormal fine motor abilities (2/2 articles)	Abnormal fine motor abilities (2/2 articles)	Abnormal fine motor abilities (2/2 articles)
	—	Abnormal gross motor abilities (2/2 articles): - Delayed independent walking (1/1 article) - Delayed independent sitting (1/1 article) - Coordination problems during locomotion (2/2 articles)	Abnormal gross motor abilities (2/2 articles): - Delayed independent sitting (1/1 article) - Balance problems (2/2 articles) - Coordination problems during locomotion (2/2) - Muscle strength anomalies (2/2)
	—	Abnormal phonological perception and detection (2/2 articles)	—
	—	—	Dysarthric speech (5/5 articles) - Imprecise articulation - Abnormal nasal resonance, voice and pitch - Prosody errors
Sensorimotor integration (see Table S6)	visuo-motor integration deficits (5/5 articles)	visuo-motor integration deficits (5/5 articles)	Visuomotor integration deficits: - Dysrhythmic tapping of finger (1/1 article)
	—	Auditory-motor integration deficits leading to expressive language deficits in (5/5 articles): Repetition Articulation Phonological accuracy Morphosyntactic accuracy Omissions errors Agrammatism Naming	—
High-level cognitive functions (see Table S7)	Visual attention impairments (4/4 studies)	Visual attention impairments (4/4 studies)	—
	Impaired working memory: Spatial WM (1/1 articles)	Impaired working memory: Verbal WM (3/3 articles) Spatial WM (1/1 articles)	Impaired working memory: Spatial WM (1/1 articles)

(Continues)

TABLE 3 (Continued)

Results	Dorsal-stream vulnerability	Sensorimotor-integration deficit	Cerebellar-like pattern
	Executive function impairments (4/4 studies): Motor inhibition Planning Set-shifting Verbal fluency	Executive function impairments (4/4 studies): Motor inhibition Planning Set-shifting Verbal fluency	Executive function impairments (4/4 studies): Motor inhibition Planning Set-shifting Verbal fluency
Total No Cognitive/ Behavioral outcomes explained by each hypothesis	8	14	11

DS neuropsychological phenotype in a family showed variable involvement of visuo-motor abilities among three generations of mutation carriers, despite the great heterogeneity in seizure severity and global neuropsychological functioning observed.[44]

Some of the reported language-production abnormalities, however, such as dysarthric speech characterized by imprecise articulation, abnormal nasal resonance, voice, and pitch, fit better with the cerebellar-like pattern than with the sensorimotor model.[41] Thus a cerebellar parallel contribution to the language profile should be taken into account.

Sensorimotor impairment is reported as a causative factor in the development and maintenance of autistic-like traits.[22,23] In particular, an early deficit in visuo-motor integration can limit social learning abilities and communication efficacy, leading to unusual motor processing and poor coordination of eye contact with speech and gesture.[22,45] Conversely, anatomical, clinical, and neuroimaging studies strongly claim a vital role of the cerebellum as one of the neural underpinnings of ASD and attention-deficit/hyperactivity disorder (ADHD).[41] The affective component of the cerebellar cognitive, affective syndrome comprises impairment in attentional and emotional control, psychosis, autism spectrum signs, and social impairment.[20] This has been interpreted in light of the cerebellar interconnections with limbic structures, and with its function in error-driven automatic and implicit learning processes, which are at the base of social cognition development.[46]

Another feature characterizing DS neurocognitive development concerns fine and gross motor abnormalities. Some neurological cerebellar signs, such as ataxia and hypotonia, are frequently reported and linked with the *SCN1A* genetic mutation thought to affect Purkinje cerebellar neuron excitability.[33]

Accumulating evidence suggests the sensory integration process's fundamental role in determining the final gait output,[47] whereas other define gait as a sensorimotor function per se.[48] One of the reports reviewed suggests the disruption of the sensorimotor integration of vision, proprioception, and vestibular inputs as the core process leading to later emergence of DS gait abnormalities and postural instability.[15]

Even if the sensorimotor-integration deficit hypothesis and the cerebellar-like pattern may account for motor deficits, it is clear that they may explain complementary but not overlapping aspects of the final motor profile. The two systems have different roles in motor control. Although parietal lobes integrate information of other sensory modalities to build an internal model of the outside world and the body to set proper motor programs, the cerebellar system provides additional control over the incoming sensory information quality and movements' accuracy.

None of the three hypotheses alone can account for the heterogeneity of the described symptoms affecting motor, cognitive, and behavioral domains. We believe that a unified sensorimotor-cerebellar framework may explain the coexistence of most of the signs and symptoms. This model may promote a syndrome-specific assessment tool, which addresses domains prevalent in DS rather than testing all of them.

We stress the need and potential advantage of designing new assessment tools that are sensitive enough to detect the different contribution of sensorimotor integration deficits and cerebellar ones.

4.3 | Limitations

Our review has limitations. The overall number of reports on this subject was small. The reports' methodological heterogeneity and the small amount of evidence within this topic prevent a precise DS cognitive profile extraction. Because most studies also reported only global intelligence scores, we could not analyze single subitem contribution in the included material. These limitations, however, do not detract from our view of a unifying framework for the cognitive profile of people with DS.

5 | CONCLUSION

The sensorimotor-integration deficit hypothesis supports the dorsal-stream vulnerability hypothesis. It may account for the majority of the cognitive/behavioral disabilities in DS and the autistic-like traits and gait abnormalities.

The cerebellar disorder is likely to play a role in determining impairments that are different and complementary to the ones explained by the sensorimotor-integration deficit. In fact, given the complexity of the clinical manifestations, we cannot exclude neocortical and subcortical areas other than the cerebellum.

A unified sensorimotor-cerebellar framework may explain most of the behavioral, motor, and language disorders seen, which if taken in isolation provide only a fragmentary picture of the complex signs and symptoms in DS. Figure 2 summarizes the unified framework we propose.

Future work should specifically address the sensorimotor-integration deficit and the cerebellar signs to disentangle their relative contribution in determining the final cognitive/behavioural phenotype. People with DS present mainly a set of sensorimotor-integration deficits or more cerebellar signs. Conversely, one set of symptoms may be more predominant in a specific developmental period or precede the other's onset. Future research should focus on developing new screening tools able to grasp and distinguish these aspects during the diagnostic phase. This, in turn, will lead to cognitive and motor rehabilitation programs targeting each subject' specific pool of symptom.

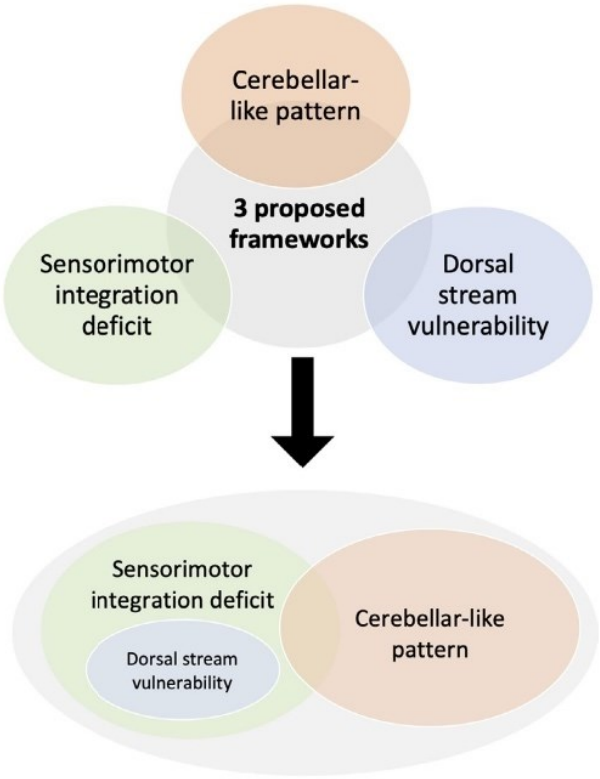

FIGURE 2 Unified theoretical framework. Three main theoretical frameworks to explain DS cognitive and behavioural profile have been independently suggested. This review offers a unified literature-based theoretical framework to understand DS cognitive characterization better and guide future research

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CONFLICT OF INTEREST

None of the authors has conflicts of interest to disclose concerning this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

AUTHOR CONTRIBUTIONS

No undisclosed groups or persons have had a primary role in the study or in manuscript preparation. All co-authors have seen and approved the final submission of the manuscript and accept responsibility for its content.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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APPENDIX 1

1. PUBMED SEARCH STRATEGY

Queries PubMed		
Search	**Query**	**Items found**
#6	#4 OR #5	46
#5	#1 AND #3 Filters: Humans, English	46
#4	#1 AND #2 Filters: Humans, English	28
#3	("cognition"[MeSH Terms]) OR "neuropsychology"[MeSH Terms])	143 187
#2	("autism spectrum disorder"[MeSH Terms]) OR "autistic features"[MeSH Terms])	27489
#1	("epilepsies, myoclonic" [MeSH Terms] OR ("epilepsies" [All Fields] AND "myoclonic" [All Fields]) OR "myoclonic epilepsies" [All Fields] OR ("dravet" [All Fields] AND "syndrome" [All Fields]) OR "dravet syndrome" [All Fields]) OR (severe[All Fields] AND ("epilepsies, myoclonic" [MeSH Terms] OR ("epilepsies" [All Fields] AND "myoclonic" [All Fields]) OR "myoclonic epilepsies" [All Fields] OR ("myoclonic" [All Fields] AND "epilepsy" [All Fields]) OR "myoclonic epilepsy" [All Fields]))))	4585

2. DATA EXTRACTION FORM

Organizational aspects		**EX**	**IN**
Ref Id	**Reviewer, date**	**Checked by**	
Author, Year			
Journal/Source		Study ID	NR /
Title			
Country of origin			
Publication type	Full-text / Abstract / Book chapter / Other (please specify)		
Fate	Decision pending / Check references / Use for discussion /Excluded/Other (please specify)		
Notes / Short description			
CURRENT STATUS: *(NAME OF REVIEWER + DATE)*			
Question to author Status verified with study investigators or sponsors: Yes/No Enter name of the source (e.g. PI, sponsor, etc.)————			

3.2 Adolescent Idiopathic Scoliosis

3.2.1 Clinical features

Scoliosis is a three-dimensional morphological spinal deformity characterized by the spine lateral deviation in the frontal plane (10 Cobb degrees or higher), concurrent axial rotation of the affected vertebral bodies and reduction of the physiological curves of the rachis in the sagittal plane[77] (see **Fig. 10**).

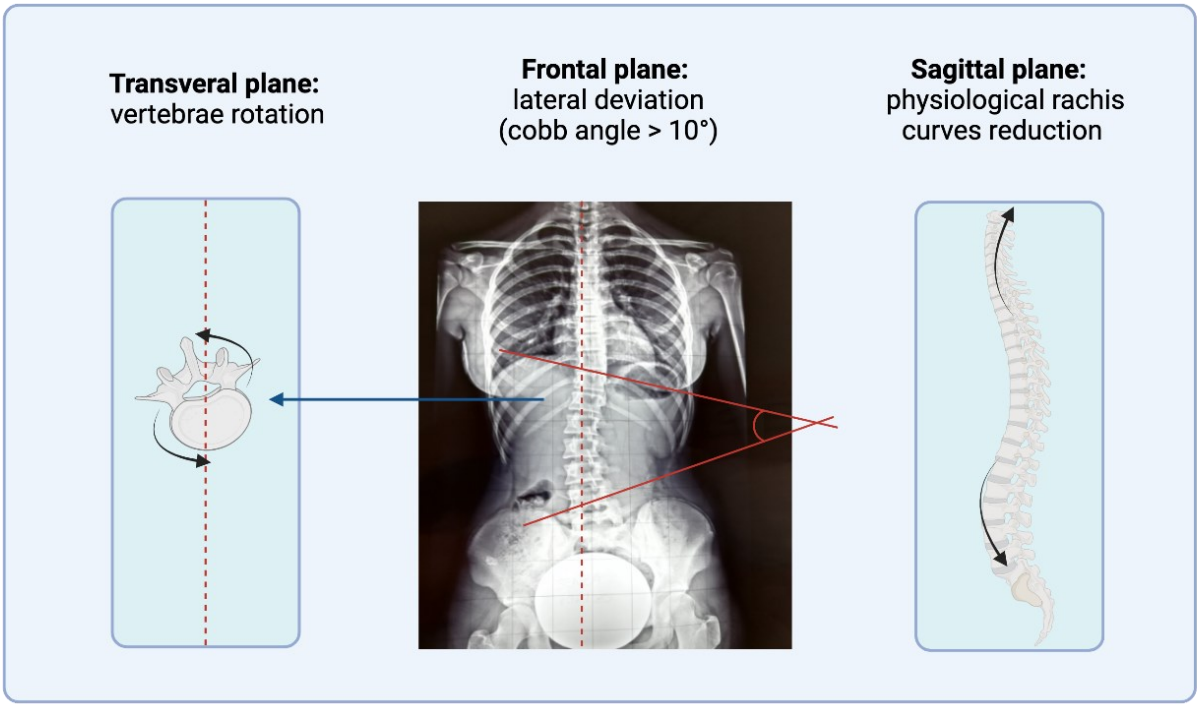

Fig. 10 *Scoliosis clinical characteristics. Created with Biorender.com*

The term idiopathic scoliosis was introduced in 1922 [78] to describe all the scoliosis cases in which it was impossible to find a specific cause of the deformity. 80% of scoliosis cases are considered idiopathic [77]. Idiopathic scoliosis is 1.5 to 3 times more prevalent among girls than among males and more recurrent in the adolescent population (i.e., 12-18 years old) compared to young children [79]. The etiopathogenesis of AIS is still largely unknown, but a multifactorial origin is the most acknowledged. Six significant factors have been addressed in the literature [80]:

1. Genetic factors: genetic predisposition has been one of the most studied factors of AIS. Research on this topic highlighted several mutations frequently associated with AIS development (e.g., Vang-

like protein-1 and calmodulin-1) [81]. However, genetics alone does not entirely account for AIS pathological development, as underlined by studies on twins, showing a concordance rate between 0.10–0.70 in monozygotic twins and between −0.05 to 0.15 in dizygotic ones [82]

2. Hormones and metabolic dysfunctions: several hormones appear to be involved in AIS development and progression. Growth hormone (GH) and insulin-like growth factors (IGH) levels seem higher in the AIS population notably from 7 to 12 years and in the pubertal stage [83], [84]. However, further studies are still needed to clarify their role better. Other involved hormones are the sex hormones (abnormal levels of estrogen and testosterone [85], [86]), melatonin (e.g., pinealectomized animal studies show the role of melatonin in scoliosis development [87], [88]), calmodulin (e.g., increased calmodulin levels in platelets have been associated with progression of AIS [89]), and leptin (e.g., lower circulating leptin reported [90]).

3. Nervous system alterations (i.e., visual, vestibular, and proprioceptive system deficits, postural control alterations and brain structural abnormalities): there is increasing agreement on CNS involvement in scoliosis development. Brain structural abnormalities were detected with MRI in regional brain volumes, the white matter of the corpus callosum, and internal capsule, as well as in pontine and hindbrain regions [91], [92]. Neurophysiological studies focused instead on the possibility of a defective CNS control of the growing spine, postulating an asymmetric timing of maturation of the CNS as compared to the skeletal system (i.e., neuro-osseous theory of scoliosis [93]).

4. Skeletal growth (i.e., spinal, extraspinal, and skull): rapid skeletal growth in AIS has been observed, producing skeletal sizes beyond the capacity of the somatic nervous system to control for the initiating deformity (e.g., higher growth velocity during puberty in girls with moderate to severe scoliosis [94]).

5. Biomechanical factors: according to some authors, the initiating scoliosis deformity provokes asymmetrical loading of the skeletally immature spine, which in turn activates mechano-transduction biological processes affecting skeletal tissue, muscles tendons and ligaments [95].

6. Environmental and lifestyle factors: diet, vitamin D, calcium intake, and exercise levels, have been reported in some studies to be associated with AIS [96].

Current treatment options for AIS are typically divided into conservative treatment (i.e., observation, physiotherapy exercises and bracing) and surgery for severer cases (i.e., 40 Cobb degrees or higher) [77]. Patient compliance is fundamental to ensure conservative treatment efficacy. Thus, education, psychotherapy and periodical assessment are deemed crucial elements of treatment success.

The psychological component is another relevant point to consider when dealing with AIS. In 1986 it was first reported that around 20% of adolescent girls with scoliosis suffer psychological disturbances [97]: body image alterations are the ones more frequently reported. The relevance and the pervasiveness of body representational alterations in AIS and their role in AIS etiopathogenesis have been highlighted in a literature review.

Adolescent Research Review
https://doi.org/10.1007/s40894-022-00187-4

QUALITATIVE REVIEW

Body Image and Body Schema in Adolescents with Idiopathic Scoliosis: A Scoping Review

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Abstract

Alterations in body representations (i.e., body image and body schema) are increasingly getting attention in clinical practice. Adolescents affected by idiopathic scoliosis experience body image dissatisfaction, and alterations in body schema have been suggested to be a consequence of the disease development. Although research has recognized the predisposing role of body representation disorders to psychopathologies, these aspects have been largely overlooked in this clinical population. This scoping review aims to establish the state of the art on the widely neglected aspects of body image and body schema disorders in adolescents affected by idiopathic scoliosis. PubMed, Scopus, PsycInfo, and MEDLINE were consulted to select articles published between 2000 and 2021. Three independent reviewers identified 27 articles by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping review guidelines. Body image was assessed in 24 of the 27 studies. Body image disorders were reported, with more severe scoliosis cases showing higher body image dissatisfaction. Surgery seems to be the best approach to improve body image outcomes, but studies did not reveal clear associations between clinical measures of scoliosis severity (e.g., Cobb angle, hump height) and body image. Disorders of body schema have been reported, but the finding might have been biased by the paucity of studies on this aspect of body representations (4/27). This review highlighted the wide prevalence of psychological distress and body schema alterations among adolescents affected by idiopathic scoliosis; but it also revealed that both are disregarded and not properly evaluated.

Keywords Body representation · Body image · Body schema · Adolescents · Idiopathic scoliosis

Introduction

Alterations of body representations are commonly encountered conditions among different clinical and non-clinical settings. Many psychiatric diseases such as eating disorders or body dysmorphic disorders are characterized by body image misperceptions and dysfunctional beliefs about the body. Neurological conditions affecting somatosensation also can eventually lead to disorders of body representations (e.g., somatoparaphrenia, personal neglect, phantom limbs) (Case et al., 2019). However, alterations of body representations can be observed even in unlooked-for clinical conditions. Among them, the adolescent girls affected by idiopathic scoliosis (Carrasco & Ruiz, 2014). Because of adolescent idiopathic scoliosis disease characteristics, this condition can be used as a model to study the concurrent impairment of dual aspects of body representation: body image and body schema. To date, these facets of idiopathic scoliosis have been largely neglected compared to their clinical and genetic determinants. This study addresses the need

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to systematically review literature on body representation disorders (i.e., body image and body schema) in adolescents affected by idiopathic scoliosis to better understand its multifactorial nature and improve these patients' care. Moreover, it seeks to advance a better theoretical comprehension of body image and body schema' interaction.

Literature disagrees on how many brain representations of the human body exists, but at least two are always mentioned: body image and body schema. Body image is a complex psychological construct involving the subjective perception of body appearance and its associated feelings, beliefs and thoughts (de Vignemont, 2010). Body image disorders can manifest as alterations of each of these components, resulting in different pathological conditions. Thus, perceptual and cognitive disorders of body image are associated with eating disorders (Sattler et al., 2020), while dysfunctional feelings on physical appearance can lead to depression (Soares Filho et al., 2020). Body schema is a different aspect of body representation. It is defined as a continuously updated and largely unaware sensorimotor representation of the body in the space and of the configurations of all its parts in relation between each other and the world (de Vignemont, 2010; Head & Holmes, 1912). Hence, body schema has a fundamental role in setting body movements and in posture control mechanisms (Picelli et al., 2016).

Adolescents affected by idiopathic scoliosis display concurrent alterations of both of these aspects of body representation. Indeed, adolescent idiopathic scoliosis presents as a noticeable three-dimensional spinal deformity, characterized by frontal plane deviation, rotation of the affected vertebral bodies and reduction of the physiological curves on the sagittal plane (Negrini et al., 2018). The disfiguring appearance caused by the scoliotic curve and the related brace treatments has notable effects on adolescents' mental health. Not surprisingly, body image dissatisfaction in this clinical population has been largely described as having detrimental effects on both quality of life and adherence to treatment (Auerbach et al., 2014; Tones et al., 2006).

Adolescent idiopathic scoliosis etiopathogenesis is largely unknown, but a central nervous system (CNS) involvement has been postulated. Many studies have reported visual, vestibular, and proprioceptive system deficits, postural control alterations and brain structural abnormalities (Burwell & Dangerfield, 2002; Burwell et al., 2008; Chu et al., 2011). Starting from these findings, some authors have suggested the so-called "double neuro-osseous theory" of scoliosis, positing an imbalance between peripheral skeletal/body maturation and posterior parietal cortex (PPC) sensory-motor integration processes (Assaiante et al., 2014; Burwell et al., 2006). These abnormalities in sensory-motor adaptation of the brain to the growing bodies of adolescents corroborate the hypothesis of an altered body schema in this clinical population.

Current Study

Scoliosis-associated disorders of body representations among adolescents have been inadequately studied compared to the other determinants of this condition, regardless of their clinical relevance. The present scoping review aims to summarize literature findings on disorders of body representations in adolescents affected by idiopathic scoliosis, including studies on body schema alterations and body image distortions. Toward this aim, three research questions were formulated. Do adolescents affected by idiopathic scoliosis have altered body image and/or body schema (Question 1)? Are there any correlations between altered body representations and clinical parameters of scoliosis severity (Question 2)? Do different treatment approaches have a different impact on body representations (Question 3)?

Method

Considering the high heterogeneity of the assessment instruments adopted to evaluate body representations and different study designs, a scoping review was deemed the best-suited tool to answer the research questions.

The Preferred Reporting Items for Systematic reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) guidelines were followed (Tricco et al., 2018).

Eligibility Criteria

The included articles were full-length, peer-reviewed, original research articles written in English and published between 2000 and 15th June 2020. Participants included in the studies should be diagnosed with Adolescent Idiopathic Scoliosis by an expert clinician, according to Scoliosis Research Society criteria (Negrini et al., 2018), and additionally assessed for at least one of our measures of interest: body image alterations or body schema alterations. Clinical and psychological (body image) evaluations had to be carried out using standardized assessment tools. As body schema is often indirectly assessed manipulating sensory and proprioceptive information, articles adopting innovative experimental paradigms were included as well if provided with adequate control groups. Studies not matching the inclusion criteria, single case studies, validation studies and literature reviews were excluded (See Supplementary Material).

Information Sources

A comprehensive systematic search on body representations in adolescent idiopathic scoliosis was performed

independently by two authors (MB, FC). The following keywords were chosen to search on SCOPUS, PubMed, PsycINFO and MEDLINE databases: (*Adolescent idiopathic scoliosis OR scoliosis), AND (body representation OR body schema OR body schema alterations OR body image OR body image alterations)*. See Appendix for detailed search queries in PubMed. Authors additionally screened reference lists of retrieved articles and relevant reviews.

The final search results were exported in MENDELEY where duplicates were removed by the dedicated tool.

Selection of Sources of Evidence

To increase consistency in article inclusion and data extraction, two reviewers (MB, FC) screened the same 42 publications. Eventual disagreements during the whole selection procedure were mediated by a third reviewer (SM). See Fig. 1 for the full selection procedure.

Quality Assessment

As no agreed form exist to evaluate the methodological quality of articles for scoping reviews, the three reviewers jointly established six quality criteria by adapting already published ones of a systematic (Taborri et al., 2018) and a scoping review (Rubega et al., 2021):

1. Aim/s of the study was/were clearly stated.
2. Selection Bias: inclusion and exclusion criteria were clearly described.
3. Performance Bias: the process of data collection was precisely detailed and reliable; a control group was present.
4. Detection Bias: the outcomes reported were relevant to answer the research question.
5. Results presentation: the tests and questionnaires scores were correctly and completely reported (i.e., mean/median, and standard deviation).
6. Statistical approach: statistics performed was appropriated and clearly described; enough subjects were included (power analysis).

For each criterium was assigned a score ranging from 0 to 2 (0 = not meeting, 1 = partially meeting, 2 = fully meeting the criteria). Scores were finally added for each article resulting in a final quality score ranging from 0 to 12. An arbitrary cut-off of at least 60% (> 7) of the maximum possible score (12) was established for articles inclusion (See Appendix, Table 5, Articles quality assessment).

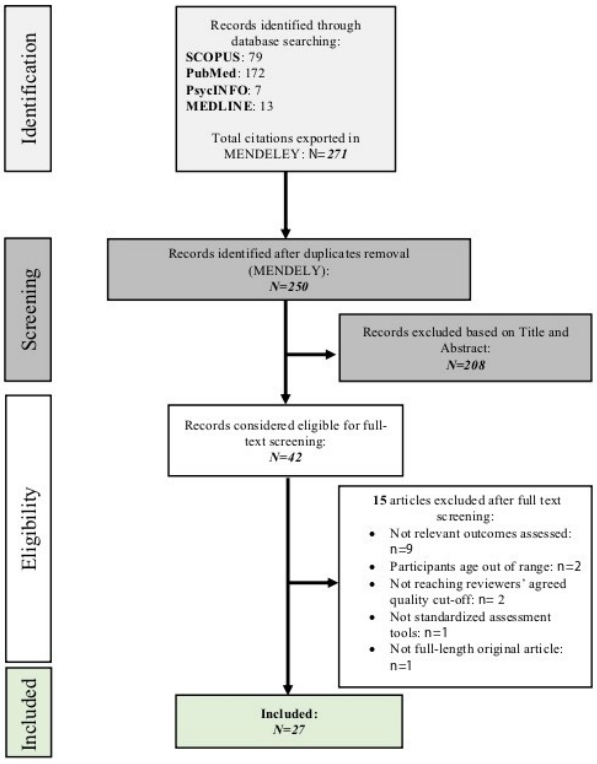

Fig. 1 Flow chart of the systematic search. Preferred Reporting Items of Systematic Review and Meta-Analysis (PRISMA) flow chart showing the process of systematic article search and selection

Data Charting Process and Data Items

A data charting form was jointly designed by the three reviewers adapting the one proposed by the Cochrane handbook for systematic reviews (Higgins & Green, 2011), (see Supplementary Material). Two reviewers (MB, FC) independently charted the data, discussed the results, and cross-checked their forms. The third reviewer (SM) revised articles in cases of disagreement on data extraction or inclusion. The charting form comprises an initial part including general articles' information (title, first author name, Journal, year of publication, type of publication, short article description) and organizational information (date of revision and reviewer identity). The second part includes the eligibility form based on articles' general characteristics (e.g., date of publication, language) participants' characteristics (age, diagnosis), assessment instruments and outcomes. In the last part reports study-specific information (study design, sample characteristics, assessment tools) and the findings of interest. Data on body image and body schema alterations in adolescent idiopathic scoliosis were summarized and placed in relation to clinical indices of scoliosis and treatment approaches.

Results

An initial literature screening based on titles and abstracts led to the identification of 42 articles, which underwent full-text screening. Of these, a total of 15 were excluded for the following reasons: 9 didn't report outcomes of interest to answer the research question; in two of them, subjects age was out of the inclusion range; two did not reach the estimated cut-off of quality; one used non-standardized assessment tools; one was not a full-length original article.

The twenty-seven articles eventually included were grouped according to the type of body representation assessed: body image and body schema. For each domain, the assessment tools, the main findings related to body representational alterations, their correlation with clinically relevant variables, and the effects of different scoliosis treatment approaches on body representation changes were reported.

Study Characteristics

Studies were heterogeneous in terms of study design with a higher prevalence of cross-sectional (10/27) and longitudinal prospective trials (8/27). A minor number of articles were retrospective (4/27), case-controlled (3/27) and randomized controlled (2/27) trials (see Table 1).

Most of the included studies assessed body image alterations (24/27) while body schema was assessed in just four articles (See Table 2).

The Scoliosis research society questionnaire (SRS), (Asher et al., 2003) emerged as the preferred assessment tool to evaluate body image alterations (19/24), specifically the SRS-22 (15/19), SRS-23 (Asher et al., 2003), (2/19), and SRS-24, (2/19), (Haher et al., 1999).

The SRS-22 questionnaire is composed of 22 items, each one scored from 1(worst) to 5 (best), and sorted in different domains (Pain, Self-Image, Function, Mental Health, Satisfaction with Management, and total score).

The other body image assessment scales were: the Spinal Appearance Questionnaire (SAQ) (Sanders et al., 2007), (4/24); the Trunk Appearance Perception Scale (TAPS), (Bago et al., 2010), (3/24); the Walter Reed Visual Assessment Scale (WRVAS)(Pineda et al., 2006) (2/24); the Body Image Disturbance Questionnaire-Scoliosis (BIDQ-S)(Auerbach et al., 2014) (2/24); the Body Shape Questionnaire (BSQ-14), (Dowson & Henderson, 2001), and the Body Cathexis Scale (BCS), (Secord & Jourard, 1953);

Body schema alterations were assessed indirectly employing the following experimental paradigms: a laser line projection task (J. Cheung et al., 2002) specifically designed to test perception of body posture; a motorized version of the wheel paradigm described by Pérennou to assess subjective

Table 1 Study designs

Study Designs	Articles	Total number
Cross-sectional	Babaee et al. (2014) Cantele et al. (2020) Cheung et al. (2002) Çolak et al (2017) Lee et al. (2016) Lendzion et al. (2018) Misterska et al. (2014) Picelli et al. (2016) Soliman (2018) Watanabe et al. (2005)	10
Longitudinal prospective	Duramaz et al. (2018) Lonner et al. (2019) Mariconda et al. (2016) Misterska et al. (2011) Misterska et al. (2013) Pérez-Prieto et al. (2014) (Multicenter) Schwieger et al. (2016) (Multicenter) Watanabe et al. (2007)	8
Retrospective studies	Asher et al. (2004) Brewer et al. (2013) Cheshire et al. (2017) Wang et al. (2014a, 2014b)	4
Case–control studies	Le Berre et al. (2019) (Multicenter) Paolucci et al. (2017) Yagci et al. (2020)	3
Randomized Controlled trials	Schwieger et al. (2017) (Multicenter) Yagci et al. (2018)	2

Table 2 Assessment tools

Assessed domain	Article	Assessment tools
Body image	Asher et al (2004)	SRS22
	Babaee et al (2014)	SRS-22 (Persian version)
	Brewer et al (2013)	SRS-22
	Cantele et al (2020)	SRS-22
	Cheshire et al (2017)	SRS-22
	Çolak et al (2017)	SRS-23, WRVAS
	Duramaz et al (2018)	BCS
	Lee et al. (2016)	SRS-22
	Lendzion et al (2018)	SRS-22 (Polish version), TAPS
	Lonner et al (2019)	SRS-22, BIDQ-S
	Mariconda et al (2016)	SRS-23
	Misterska et al (2011)	SAQ
	Misterska et al (2013)	SRS-22, TAPS
	Misterska et al. (2014)	SAQ (Poland version)
	Paolucci et al. (2017)	SRS-22, TAPS, Drawing test
	Pérez-Prieto et al. (2014)	SRS-22 (Spanish version), BSQ-14
	Schwieger et al (2016)	SAQ
	Schwieger et al (2017)	SAQ
	Soliman (2018)	SRS-22r (Arabic version), BIDQ-S
	Wang et al. (2014a, 2014b)	SRS-22 (Chinese version)
	Watanabe et al (2005)	SRS-24 (Japanese version)
	Watanabe et al (2007)	SRS-24 (Japanese version)
	Yagci et al (2018)	SRS-22, WRVAS
	Yagci et al (2020)	SRS-22
Body schema	Cheung et al (2002)	Laser line projection task
	Le Berre et al (2019)	Optokinetic stimulation (SVV), Motorized version of the wheel paradigm described by Pérennou (SPV)
	Picelli et al (2016)	Graphic table displaying pictures of progressively increasing scoliotic curves
	Yagci et al (2020)	ABC

SRS Scoliosis Research Society questionnaire, *WRVAS* Walter Reed Visual Assessment Scale, *BCS* Body Cathexis Scale, *TAPS* Trunk Appearance Perception Scale, *BIDQ-S* Body Image Disturbance Questionnaire-Scoliosis, *BSQ* Body Shape Questionnaire, *SAQ* Spinal Appearance Questionnaire, *SVV* Subjective Visual Vertical, *SPV* Subjective Postural Vertical, *ABC* Awareness-Body-Chart

postural verticality (Pérennou et al., 2008) and optokinetic visual stimulation to assess subjective visual verticality (Le Berre et al., 2019); a graphic table displaying pictures of progressively increasing scoliotic curves designed to test awareness of trunk misalignment (Picelli et al., 2016) and a measure of subjective body awareness, namely the Awareness-Body-Chart test (ABC), (Danner et al., 2017).

Adolescent Idiopathic Scoliosis and Body Image

Body image alterations were consistently reported in AIS. Tables 3 and 4 report respectively the self-image subitems median and/or mean scores assessed by the SRS questionnaires and by the other assessment instruments.

Nineteen articles report SRS self-image subitems scores (Table 3). Eight of these reported scores differences within AIS sub-groups of different scoliosis severity (3/8), (Lee et al., 2016; Soliman, 2018; Watanabe et al., 2005), under different types of treatment (3/8) (Çolak et al., 2017; Lonner et al., 2019; Mariconda et al., 2016), or compared with healthy control groups (4/8), (Cantele et al., 2020; Pérez-Prieto et al., 2014; Soliman, 2018; Watanabe et al., 2005):

Lower body image subitems scores were found in more severe scoliosis cases, compared with the mild severity cases, (Lee et al., 2016) $p = 0.031$, (Soliman, 2018) $p < 0.001$ and (Watanabe et al., 2005) $p < 0.05$. Two works did not find significant differences (Asher et al., 2004; Wang et al., 2014a, 2014b). The effects of different treatment approaches in influencing SRS self-image subitem scores are conflicting, with two studies finding improvement after surgery, namely (Lonner et al., 2019) $p < 0.001$ and (Mariconda et al., 2016) $p < 0.01$, one finding better scores in those patients treated

Table 3 Scoliosis Research Society (SRS) self-image sub-scores

First Author	Year	N° subjects by group	Age (mean years ± SD)	SRS	Self- Image Subitem (Median or mean ± SD; range = 1–5)	Group differences
Asher, M	2004	**Thoracic:** 35 **Double:** 14 **Thoracolumbar:** 11	15 ± 6	SRS-22	Mean = 3.3 ± 0.7	NS
Babaee, T	2014	**Milwaukee:**30 **TLSO:**30	**Milwaukee:** 16.6 ± 2.07 **TLSO**: 16.5 ± 2.3	SRS-22	**Milwaukee mean** = 3.04 ± 0.97 **TLSO mean** = 3.05 ± 0.58	NS
Brewer, P	2013	**Untreated patients with AIS:** 93	14.6 ± 1.8	SRS-22	Mean = 3.2 ± 0.8	NA
Cantele, F	2020	**AIS:** 139 **HC:** 134	**AIS:** 14.28 ± 1.82 **HC:** 14.75 (1.52)	SRS-22	**AIS mean** = 3.4 ± 0.72 **HC mean** = 3.8 ± 0.62	P = 0.000
Cheshire, J	2017	**Pre-operative patients:** 54	14.3 ± 1.29	SRS-22	Median = 2.65 (2.20–3.15)	NA
Çolak, T. K	2016	**Physiotherapy (P):**17 **Brace + Physiotherapy (BP):**25 **Surgery (S):**26	**P:** 14.1 ± 1.2 **BP:**13.7 ± 1.1 **S:**15.8 ± 1.2	SRS-23	**P mean** = 3.5 ± 0.5 **BP mean** = 3.7 ± 0.8 **S mean** = 4.3 ± 0.4	**P vs. S:** P = 0.000 **BP vs. S:** P = 0.000
Lee, H	2016	**Mild severity:** 52 **Moderate severity:** 46 **Severe:**12	14.2 ± 2.17 (Age by group not reported)	SRS-22	**Mild severity, median (IQR)** = 3.80 (2.20) **Moderate severity, median (IQR)** = 3.80 (3.00) **Severe, median (IQR)** = 3.00 (2.80)	**Severe vs. mild and moderate:** P = 0.031
Lendzion, M	2018	**Bracing and physiotherapy (BP):** 35 **Physiotherapy alone (P):** 55	**BP:** 16.5 ± 2.3 **P:** 16.6 ± 2.07	SRS-22	**BP mean** = 3.5 ± 0.6 **P mean** = 3.6 ± 0.6	NS
Lonner, B.S	2019	75	14.4 ± 1.6	SRS-22	**Pre-operation, mean** = 3.62 ± 0.59 **Post-operation, mean** = 4.18 ± 0.48	P < 0.001
Mariconda, M	2016	**AIS:** 87	14.8 ± 2.3	SRS-23	**Pre-operation, mean(females)** = 3.6 ± 0.3 **Post operation, mean (females)** = 3.9 ± 0.6 **Pre-operation, mean (males)** = 3.5 ± 0.2 **Post operation, mean (males)** = 4.0 ± 0.4	**Females and Males pre vs. post:** P < 0.01
Misterska, E	2012	**Conservative Treatment:** 36	13.4 ± 1.7	SRS-22	**1st evaluation, mean** = 3.7 ± 0.5 **2nd evaluation, mean** = 3.7 ± 0.5 **3rd evaluation, mean:** 3.9 ± 0.4	NS
Paolucci, T	2017	**Brace Group:** 16 **No-Brace Group:** 16	**Brace:** 14 ± 3.16 **No-Brace:** 14.14 ± 2.89	SRS-22	**Brace Group, mean** = 17.14 ± 2.93 **No-Brace mean** = 17.95 ± 2.96	NS
Pérez-Prieto, D	2014	**BMI < 18:**13 **BMI > 18:**26	**BMI < 18:** 16.38 ± 3.55 **BMI > 18:** 15.92 ± 2.24	SRS-22	**BMI < 18, mean** = 16.36 ± 1.96 **BMI > 18, mean** = 19.73 ± 3.17	P < 0.001

Table 3 (continued)

First Author	Year	N° subjects by group	Age (mean years ± SD)	SRS	Self- Image Subitem (Median or mean ± SD; range = 1–5)	Group differences
Soliman, H	2018	**Group 1 (Major curve angles of 90°-120°):** 76 **Group 2 (Major curve angles > 120°):** 61 **Group 3 (HC):** 50	**Group 1:** 15.3 ± 2.1 **Group 2:** 15.8 ± 1.8 **Group 3:** 16.1 ± 2.3	SRS-22r	**Group 1, mean** = 1.93 ± 0.3 **Group 2, mean** = 1.45 ± 0.3 **Group 3, mean** = 4.1 ± 0.6	**Overall group differences:** P < 0.001
Wang, L	2014	**One curve group:** 42 **Double curve group:** 102 **Three curve group:** 58	14.18 ± 1.42	SRS-22	**One curve group, mean** = 3.08 ± 0.52 **Double curve group, mean** = 3.07 ± 0.53 **Three curve group, mean** = 3.12 ± 0.51	NS
Watanabe, K	2005	**Mild scoliosis:** 43 **Moderate scoliosis:** 72 **Severe scoliosis:** 26 **HC:** 72	13.6	SRS-24	**Mild scoliosis, mean** = 10.5 ± 1.4 **Moderate scoliosis, mean** = 9.8 ± 1.9 **Severe scoliosis, mean** = 9.2 ± 1.8 **HC, mean** = 9.8 ± 1.7	**HC vs. AIS:** P < 0.05
Watanabe, K	2007	**Post-surgery patients:** 81	14.1	SRS-24	Mean = 3.1 ± 0.7	NA
Yagci, G	2018	**BBAT group:** 10 **TE group:** 10	**BBAT group** 14.20 ± 2.04 **TE group** 13.60 ± 1.65	SRS-22	**BBAT Pre-treatment, mean** = 3.46 ± 0.45 **BBAT Post-treatment, mean** = 3.62 ± 0.82 **TE Pre-treatment, mean** = 3.52 ± 0.53 **TE Post-treatment, mean** = 3.51 ± 0.71	NA
Yagci, G	2020	**AIS:** 96	15.9 ± 3.6	SRS-22	Self-image subitem: 3.3 ± 0.8	NA

HC healthy controls, *BMI* body mass index, *TLSO* thoraco–lumbosacral orthosis, *SRS* Scoliosis Research Society questionnaire, *IQR* interquartile range, *BBAT* basic body awareness therapy, *TE* traditional exercises, *NS* not significant, *NA* not applicable. Groups names are in bold

with surgery compared with traditional physiotherapy and brace treatments, p = 0.000 (Çolak et al., 2017) and five studies not reporting significant differences between different treatment approaches (Babaee et al., 2014; Lendzion et al., 2018; Misterska et al., 2013; Paolucci et al., 2017; Yagci et al., 2018).

Among the three articles comparing AIS and healthy control groups, lower body image subitem scores were always found in the AIS population, respectively (Cantele et al., 2020) p = 0.000, (Soliman, 2018) p < 0.00, and (Watanabe et al., 2005) p < 0.05.

In both of the two studies assessing self-image subitem scores contrasting AIS girls having normative Body Mass Index (BMI) and those with BMI values below normality-threshold score, lower values were found in the underweight girls (Cantele et al., 2020; Pérez-Prieto et al., 2014).

Body image outcomes assessed by instruments other than SRS questionnaires highlighted general body image alterations as well (See Table 4).

Two articles assessing body image perception by comparing milder and more severe scoliosis cases, found lower body image scores in the latter group, specifically: one study evaluating a group of patients with the Cobb angle of more than 40 degrees reported lower self-body, ideal-body and self-ideal subitems scores of SAQ compared with the less severe group at different evaluation intervals (see Table 4) (Schwieger et al., 2016); another study assessing body image disturbance through the BIDQ-S, found significantly higher scores (higher body image disturbance), in the group having the major curve angle (p < 0.001) (Soliman, 2018).

Table 4 Other measures of body image alterations

First author	Year	N° subjects by group	Age (mean years ± SD)	SRS	Self- image subitem (Mean ± SD/ Median)	P values
Çolak, T. K	2016	**Physiotherapy (P):**17 **Brace + Physiotherapy (BP):**25 **Surgery (S):**26	**P:** 14.1 ± 1.2 **BP:**13.7 ± 1.1 **S:**15.8 ± 1.2	WRVAS	**P mean =** 14.0 ± 5.9 **BP mean =** 14.0 ± 3.2 **S mean =** 7.0 ± 2.7	**P vs. S:** P = 0.000 **BP vs. S:** P = 0.000
Duramaz, A	2018	**AIS:** 41 **HC:** 52	**AIS:**15.3 ± 1.5 **HC:** 15.57 ± 1.46	BCS	**AIS pre-operative, mean =** 91.7 ± 24.9 **AIS post-operative, mean =** 74.2 ± 20.0 **HC:** 79.4 ± 21.3	**AIS pre vs. HC:** P = 0.010 **AIS pre vs. post:** P = 0.000
Lendzion, M	2018	**Bracing and physiotherapy (BP):** 35 **Physiotherapy alone (P):** 55	**BP:** 16.5 ± 2.3 **P:** 16.6 ± 2.07	TAPS	**Bracing and Physiotherapy mean TOT** = 3.2 ± 0.8 **Physiotherapy alone mean TOT** = 3.8 ± 0.6	**P vs. BP:** P = 0.04 (P alone better total TAPS)
Lonner, B.S	2019	75	14.4 ± 1.6	BIDQ-S	**BIDQ-S pre-operative, mean =** 1.64 ± 0.51 **BIDQ-S post-operative, mean =** 1.22 ± 0.38	**Pre vs. Post:** P < 0.0001
Misterska, E	2011	40	15 ± 31.5	SAQ	SAQ (two years post-surgery) **Median general score** = 34.48	NA
Misterska, E	2012	**Conservative Treatment:** 36	13.4 ± 1.7	TAPS	**TAPS total 1st evaluation mean** = 3.6 ± 0.6 **TAPS total 2nd evaluation mean** = 3.9 ± 0.5 **TAPS total 3rd evaluation mean** = 4.0 ± 0.4	**2nd vs. 3rd evaluations:** P = 0.005
Misterska, E	2014	41	13.60 ± 1.6	SAQ	**SAQ mean total score** = 2.7 ± 0.6	NA
Paolucci, T	2017	**Brace Group:** 16 **No-Brace Group:** 16	**Brace:** 14 ± 3.16 **No-Brace:** 14.14 ± 2.89	TAPS	**Brace Group mean** = 3.90 ± 0.44 **No-Brace mean** = 3.97 ± 0.47	NS
Perez-Prieto, D	2014	**BMI < 18:** 13 **BMI > 18:** 26	**BMI < 18:**16.38 ± 3.55 **BMI > 18:**15.92 ± 2.24	BSQ-14	**BMI < 18, mean:** 46.62 ± 8.86 **BMI > 18, mean:** 37.69 (15.15) 19 of 39: self-perception disorder (BSQ-14 > 40)	**BMI < 18 vs. BMI > 18** P = 0.05

Table 4 (continued)

First author	Year	N° subjects by group	Age (mean years ± SD)	SRS	Self- image subitem (Mean ± SD/ Median)	P values
Schwieger, T	2016	**< 40 Degree Largest Cobb Angle:** 257 **> 40 Degree Largest Cobb Angle:** 42	Range: 10–15 years	SAQ	**< 40 Degree Largest Cobb Angle:** T1 = Self-body: 16.8 (4.1) Ideal body: 19.3 (10.4) Self-ideal: 36.2 (12.7) T2 = Self-body: 17.5 (4.5) Ideal body: 19.2 (10.1) Self-ideal: 36.7 (12.6) T3 = Self-body: 17.5 (4.7) Ideal body: 19.2 (10.7) Self-ideal: 36.7 (13.2) T4 = Self-body: 17.3 (4.7) Ideal body: 19.2 (10.2) Self-ideal: 36.5 (12.7) **> 40 Degree Largest Cobb Angle:** T1 = Self-body: 19.9 (5.4) Ideal body: 21.5 (10.0) Self-ideal: 41.4 (13.0) T2 = Self-body: 21.9 (5.6) Ideal body: 22.4 (10.8) Self-ideal: 44.3 (13.9) T3 = Self-body: 20.7 (6.0) Ideal body: 19.6 (9.6) Self-ideal: 40.2 (12.9) T4 = Self-body: 21.9 (5.3) Ideal body: 22.7 (10.0) Self-ideal: 44.6 (12.9)	**< 40 Degree Largest Cobb Angle vs. > 40:** **T1:** **Self-body:** P = 0.0002 **Self -ideal:** P = 0.01 **T2** **Self-body:** P < 0.0001 **Ideal body:** P = 0.02 **Self -ideal:** P = 0.0002 **T3** **Self-body:** P = 0.0001 **Self -ideal:** P = 0.004 **T4** **Self-body:** P < 0.0001 **Self -ideal:** P < 0.0001 **Brace vs. Observation treatments:** NS
Schwieger, T	2017	**Most adherent Brace wear:** 92 **Least adherent Brace wear:** 39	**Most adherent:** 11.7 ± 1.1 **Least adherent:** 11.8 ± 1.1	SAQ	**SAQ total Baseline (Most adherent):** 36.9 ± 12.0 **SAQ total Baseline (Least adherent):** 34.8 ± 9.9	NS
Soliman, H	2018	**Group 1 (Major curve angles of 90°-120°):** 76 **Group 2 (Major curve angles > 120°):** 61	**Group 1:**15.3 ± 2.1 **Group 2:**15.8 ± 1.8	BIDQ-S	**Group 1 BIDQ-S, mean =** 3.38 ± 0.76 **Group 2 BIDQ-S, mean =** 4.5 ± 0.61	**Group 1 vs. Group2:** P < 0.001
Yagci, G	2018	**BBAT group:** 10 **TE group:** 10	**BBAT group:** 14.20 ± 2.04 **TE group:** 13.60 ± 1.65	WRVAS	**BBAT Pre-treatment, mean =** 21.00 ± 3.83 **BBAT Post-treatment, mean =** 13.30 ± 2.50 **TE Pre-treatment, mean =** 20.20 ± 2.94 **TE Post-treatment, mean =** 17.50 ± 2.68	**Pre vs. Post BBAT:** P < 0.05 **Pre vs. Post TE:** P < 0.05

WRVAS Walter Reed Visual Assessment Scale, *SAQ* Spinal Appearance Questionnaire, *BCS* Body Cathexis Scale, *TAPS* Trunk Appearance Perception Scale, *BSQ-14* Body Shape Questionnaire, *BIDQ-S* Body Image Disturbance Questionnaire-Scoliosis, *BBAT* Basic Body Awareness Therapy, *TE* Traditional Exercises, *ABC* Awareness-Body-Chart, *NS* not significant, *NA* not applicable. Groups names are in bold

Different Treatment Approaches' Impact on Body Representations

Among the eight studies evaluating the effects of different treatments on body image perception, two reported post-surgery improvements in BCS scores (Duramaz et al., 2018) $p = 0.000$ and BIDQ-S scores (Lonner et al., 2019) $p < 0.0001$ and one found a better impact of surgery over other traditional types of treatments assessed with the WRVAS $p = 0.000$ (Çolak et al., 2017). Brace effects on body image disturbances were assessed in three studies providing conflicting evidence: one reported physiotherapy-alone as a better practice than combined with brace in improving body image perception, as assessed by TAPS, ($p = 0.04$), (Lendzion et al., 2018); the other two did not find significant body image score differences between a group under orthotic treatment compared with a group not treated with brace (Paolucci et al., 2017), and comparing poor adherent and most adherent to brace treatment groups (Schwieger et al., 2017).

When compared with healthy control groups, AIS scored lower in the BCS $p = 0.010$ (Duramaz et al., 2018).

Correlations Between Altered Body Representations and Clinical Parameters of Scoliosis Severity

Fifteen of the 27 included articles considered correlations between body image scores and clinical or demographic variables (see Table S2).

Within the six studies analyzing correlations between participants' age and self-image scores (Babaee et al., 2014; Cheung et al., 2002; Çolak et al., 2017; Lendzion et al., 2018; Misterska et al., 2013; Wang et al., 2014a, 2014b), just one found a significant negative correlation, with outcomes worsening at increasing age (Lendzion et al., 2018) (TAPS, $p = 0.03$; SRS-22, $p = 0.01$).

The relation between sex and scoliosis was inquired just in two studies (Cheung et al., 2002; Lendzion et al., 2018), with one finding lower body image scores in female groups assessed with Trunk Appearance Perception Scale and SRS-22 (respectively $p = 0.027$; $p = 0.015$) (Lendzion et al., 2018).

Curve localization didn't correlate with self-image scores in any of the 8 studies investigating this relation (Asher et al., 2002; Babaee et al., 2014; Cantele et al., 2020; Cheung et al., 2002; Çolak et al., 2017; Lendzion et al., 2018; Lonner et al., 2019; Wang et al., 2014a, 2014b).

Conversely, correlations between scoliosis severity (Cobb angle) and self-image scores were significant in 7 out of 10 studies, revealing a negative correlation between scoliosis severity and satisfaction with body image as assessed by SRS questionnaires and Trunk Appearance Perception Scale (Brewer et al., 2013; Cantele et al., 2020; Cheung et al., 2002; Lendzion et al., 2018; Misterska et al., 2013; Wang et al., 2014a, 2014b; Watanabe et al., 2007), (see Table S2 of the supplementary materials for details).

Three studies explored the correlations between self-image and other radiographic measures (Risser sign, Apical Vertebral Translation and Apical Vertical Rotation). No significant relations emerged related to the Risser sign (Babaee et al., 2014; Wang et al., 2014a, 2014b) while contrasting results are reported with regards to apical vertebral rotation and translation: one study found a significant negative correlation between the apical vertical translation and SRS self-image subitem ($r = –0.290$, $p < 0.001$) but no relation with the vertebral rotation component (Wang et al., 2014a, 2014b), while another one found a significant correlation between the latter and the SRS-24 self-image domain ($r = -0.30$, $p < 0.01$), (Watanabe et al., 2007).

Nine studies explored the impact of other clinical measures (Angle of Trunk Rotation, hump height, BMI) on self-image. Most of them did not find clear relations. However, in four studies significant correlations between body image scores and the angle of trunk rotation (Lendzion et al., 2018; Misterska et al., 2011)(respectively: $r = -0.228$, $p = 0.03$ and $r = -0.91$, $p = 0.002$) and hump height (Mariconda et al., 2016; Wang et al., 2014a, 2014b) (respectively: $r = -- 0.04$, $p < 0.00$ and $r = –0.277$, $p < 0.001$) is reported.

Three studies adopting surface topography measures and asymmetry parameters revealed a weak correlation with self-image scores (Asher et al., 2002; Brewer et al., 2013; Cheshire et al., 2017).

Adolescent Idiopathic Scoliosis and Body Schema

Body schema alterations were assessed in four out of the twenty-seven included studies (See Table 2).

In two of these, perception of verticality and body posture were assessed: one study (Cheung et al., 2002) aiming to assess the perception of body employing vertical and horizontal laser line projections in darkness, failed to find significant task performance differences with a control group. However, a significant correlation between the amplitude of the angle formed by the horizontal and vertical line projections and the severity of scoliosis (Cobb angle) was observed ($r = 0.16$; $p = 0.045$). In the second study(Le Berre et al., 2019), altered perception of subjective postural and visual verticality were assessed in both static and dynamic optokinetic stimulation conditions. The scoliosis group had significantly altered perception of postural verticality compared with a matched-age control group ($p = 0.00023$) which was significantly correlated with the clinical frontal tilt ($p = 0.007$), while no differences were found for the subjective visual vertical.

Two other studies, investigating trunk misalignment awareness and general body perception awareness, found

respectively significant differences between the subjective perception of trunk curvature and the objective trunk curvature (underestimation at thoracolumbar district and overestimation at thoracic and lumbar districts, $p < 0.016$) (Picelli et al., 2016) and overall lower body awareness in AIS group compared with a matched-age control group ($p < 0.001$) (Yagci et al., 2020).

Discussion

Body representation disorders are a severe and widespread phenomenon among adolescents affected by idiopathic scoliosis. Nevertheless, literature on this topic is still in its infancy, mainly focused on detecting predisposing-genetic determinants and finding treatments for scoliosis biomechanical alterations. The lack of a general framework on the scoliosis-associated disorders of body representations led to the need of this review. This study highlighted evidence of high prevalence of body representation alterations in this clinical population, which require proper assessment and treatment. The small number of articles on this topic characterized by methodological heterogeneity, mostly adopting self-reported assessment scales, stressed the need for further studies and appropriate assessment procedures.

Body Image

The first finding of this review answers the first research question, pointing to the high prevalence of body image dissatisfaction among adolescents having idiopathic scoliosis, which always emerged regardless of assessment instruments. Adolescents with scoliosis scored consistently lower in self-image compared with healthy adolescents (Cantele et al., 2020; Yagci et al., 2020) and in those presenting a more severe degree of deformity compared with milder severity cases (Asher et al., 2004; Brewer et al., 2013; Lee et al., 2016; Lendzion et al., 2018; Schwieger et al., 2016; Soliman, 2018; Watanabe et al., 2005, 2007). However, all these studies employed questionnaires to assess body image, particularly the SRS designed to assess general aspects of quality of life more than body image. This should be considered as a general bias of all these works, giving the intrinsic limitations characterizing self-reported scales. Proper assessment procedures should be considered, such as those used in other conditions characterized by body image disorders, like in eating disorders (Caspi et al., 2017), (e.g., computerized tasks, structured clinical interviews, etc.).

The second research question aimed to explore the impact of different treatment options on body image, which was assessed in a fair number of studies (8/27). The strongest evidence of improvement in self-image is given by surgery. When interpreting these data, should be considered that patients undergoing surgery present more severe scoliosis deformations (mean degree Cobb angles > 50° Duramaz et al., 2018; Lonner et al., 2019; Mariconda et al., 2016)) if compared with those treated with less invasive interventions. Post-surgery body aesthetic changes are more easily detectable and thus more capable to influence the self-reported measure of body image perceptions. However, it was found that severity of deformity does not necessarily correlate with patients' decision to undergo surgery, which suggests again possible discrepancies between psychological beliefs/attitudes on body image and objective measures of physical appearance (Borges et al., 2017). This is even more evident when considering the effects of brace and physiotherapy on body image, with brace-wearing found not to affect body image per se, regardless of its esthetic impact (Cantele et al., 2020; Schwieger et al., 2016).

Finally, the third research question on the eventual associations between the perceived body image and the clinical parameters of scoliosis severity (i.e., Cobb angle, ATR, hump height) reveled not clear association between the two. Radiographic measures were found to be more often related to body image perception indices, though correlations are weak (see Table S2). Surprisingly, the relation between spinal deformity surface measures (e.g., ATR, hump height) and body image is seldom considered, even if these immediately visible aesthetic deformities may have a substantial impact on body image perception. These last two points on the lack of association between objective measures and subjective perception of body image, need to be carefully considered as they entail the necessity to regularly examine body image in the adolescents affected by idiopathic scoliosis, although apparently not needing it.

Body Schema

This review's main finding regrading body schema disorders in adolescents with idiopathic scoliosis is the big gap in literature on this topic. Indeed, only 4 studies assessing body schema alterations were identified for inclusion in this review. These works provide indirect indices of abnormal central integration mechanisms in scoliosis, specifically, altered postural perception, abnormal subjective verticality perception and a lower awareness of the body, which seem to correlate with some clinical variables of scoliosis severity (Cobb angle (Cheung et al., 2006), frontal tilt (Le Berre et al., 2019)).

The paucity of literature on this topic is surprising, given the rising number of theories trying to address the contribution of CNS abnormalities to scoliosis curvature progression (Burwell & Dangerfield, 2002; Chu et al., 2011). The etiology of idiopathic scoliosis includes sensorimotor integration deficits which lead to body schema representation abnormalities (Burwell et al., 2009). Thus, assessing

precociously body schema integrity in at risk subjects, may prevent scoliosis curvature worsening and give new insights for a better understanding of its etiopathogenesis. However, the development of new assessment instruments for body schema is mandatory to accomplish this aim.

Future Directions

In light of this review, future research on adolescents with idiopathic scoliosis should focus on the multifactorial nature of this condition, which is a spine disorder but with highly comorbid psychological consequences, and a complex etiopathogenesis. Specifically addressing body representation disorders which are both a precipitating and maintaining factor of this condition will in turn improve traditional treatments and provide new perspectives on its pathogenetic mechanisms. A theoretical comprehensive model of this is proposed in Fig. 2.

Conclusion

Body representation disorders are serious clinical conditions affecting adolescents with idiopathic scoliosis. However, up to date research on this topic is inadequate. This literature review clearly highlighted the prevalence of body image disorders and the lack of studies on body schema alterations. It also highlighted the lack of clear associations of these disorders with clinical measures of scoliosis severity as well as the absence of standardized assessments and treatment procedures. Body image dissatisfaction, negative attitudes toward perceived body appearance and body schema alterations should be considered as highly comorbid

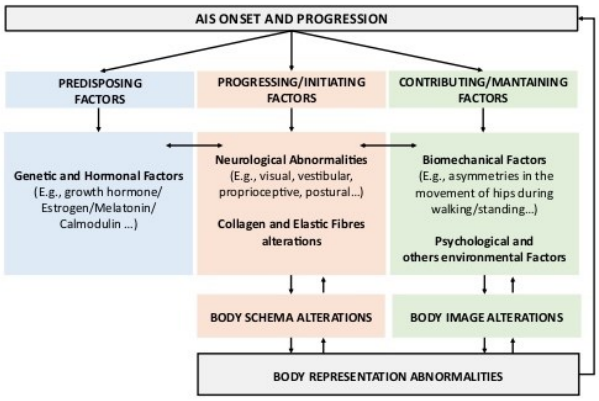

Fig. 2 Multifactorial model of AIS onset and progression. Schematic representation of the contribution of multiple factors concurring to adolescent idiopathic scoliosis onset and progression. Body schema and body image alterations are initiating and maintaining factors concurring to scoliosis progression

conditions of adolescents affected by scoliosis. Thus, when dealing with adolescents with scoliosis, clinicians should consider the multifactorial nature of this condition and set convenient assessments and treatments in association with the traditional ones (i.e., brace, surgery, and physiotherapy). Adolescent idiopathic scoliosis is a complex, multifactorial condition that would benefit from a multidisciplinary treatment approach, especially one that includes a focus on body representations.

Appendix

PubMed search strategy.

Table 5 Articles quality assessment

Articles	Aim of the work	Selection bias (inclusion/exclusion criteria)	Performance Bias (data collection/processing)	Detection bias (Outcomes)	Results presentation	Statistical approach	Quality score (Max 12)
	The research question is clearly stated	Participant's inclusion and exclusion criteria are clearly defined	1. Data collection is clearly described and reliable 2. Presence of a control group	Outcomes are relevant to answer research question	Test/questionnaires/clinical scores are clearly reported	1.Statistical procedures performed are clearly described 2. Power analysis	
Asher et al. (2004)	2	1 (exclusion criteria not defined)	1 (lack of a control group)	2	2	1	9
Babaee et al. (2014)	2	2	1 (lack of a control group)	2	2	1	10
Brewer et al. (2013)	2	2	1 (lack of a control group)	2	2	1	10
Cheshire et al. (2017)	2	2	1 (lack of a control group)	2	2	1	10
Cheung et al. (2002)	2	1 (exclusion criteria not defined)	2	2	2	1	10
Çolak et al. (2017)	2	2	1 (lack of a control group)	2	2	1	10
Danielsson et al. (2012)	2	1 (exclusion criteria not defined)	1 (lack of a control group)	0	2	1	7 EXCLUDED
Duramaz et al. (2018)	2	2	2	2	2	2	12
Duri et al. (2019)	2	1 (exclusion criteria not defined)	1 (lack of a control group)	0	1	1	6 EXCLUDED
Le Berre et al. (2019)	2	2	2	2	2	1	11
Lee et al. (2016)	2	2	1 (lack of a control group)	2	2	1	10
Lendzion et al. (2018)	2	2	1 (lack of a control group)	2	2	1	10
Lonner et al. (2019)	2	2	1 (lack of a control group)	1	2	1	9
Mariconda et al. (2016)	2	2	1 (lack of a control group)	2	2	1	10
Misterska et al. (2011)	2	2	1 (lack of a control group)	1	1	1	8
Misterska et al. (2013)	2	2	1 (lack of a control group)	1	2	1	9
Misterska et al. (2014)	2	2	2	1	2	1	10
Paolucci et al. (2017)	2	2	2	2	2	1	11
Pérez-Prieto et al. (2014)	2	2	2	2	2	1	11
Picelli et al. (2016)	2	1	1 (lack of a control group)	2	2	1	10
Schwieger et al. (2016)	2	2	1 (lack of a control group)	2	2	1	10

Table 5 (continued)

Articles	Aim of the work	Selection bias (inclusion/exclusion criteria)	Performance Bias (data collection/processing)	Detection bias (Outcomes)	Results presentation	Statistical approach	Quality score (Max 12)
	The research question is clearly stated	Participant's inclusion and exclusion criteria are clearly defined	1. Data collection is clearly described and reliable 2. Presence of a control group	Outcomes are relevant to answer research question	Test/questionnaires/clinical scores are clearly reported	1.Statistical procedures performed are clearly described 2. Power analysis	
Schwieger et al. (2017)	2	2	1 (lack of a control group)	2	2	1	10
Soliman (2018)	2	2	2	2	2	1	11
Wang et al. (2014a, 2014b)	2	2	1 (lack of a control group)	2	2	1	10
Yagci et al. (2018)	2	2	2	1	2	1	10
Yagci et al. (2020)	2	1 (exclusion criteria not defined)	2	2	2	1	10

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Declarations

Conflict of interest The authors report no conflict of interests.

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3.2.2 AIS and sensorimotor integration

Among the various theories of AIS etiopathogenesis, for the purposes of this thesis, special attention should be given to the one pointing to CNS deficits. Neurological abnormalities in AIS have been explained by considering four main models [98]:

1. Visuospatial perceptual impairment producing a motor control problem. Visuospatial perceptual impairments (i.e., altered visual and/or vestibular generated eye movements) have been reported in AIS. According to this model scoliosis would result by the attempt of the axial motor system to restore the perceptual dysfunction by implementing new axial and vestibular motor control strategies [99].
2. Body spatial orientation impairments (i.e., body schema alterations). The integration of faulty sensory information from visual, vestibular, and somatic sensors results in a faulty representation of the body spatial orientation. This, in turn, lead to motor control strategy resulting in the structural scoliotic deformity [100].
3. Neurodevelopmental theory of scoliosis (i.e., neuro-osseous theory of scoliosis). This theory postulates developmental disharmony between somatic and autonomic nervous systems expressed in spine and trunk and exacerbated by hormones producing skeletal overgrowth [93].
4. Sensorimotor integration disorder [101]

All these theories postulate an abnormal processing/integration of sensory information, resulting in improper trunk' muscles response to compensate for scoliosis. Whether these abnormalities are the result of disorders of higher integrative levels of the CNS (i.e., body schema) or peripheral sensory disorders (i.e., posterior column pathway abnormalities) is still unclear [102].

3.3 Fibromyalgia syndrome

3.3.1 FMS clinical features

The FMS is a complex chronic pain syndrome characterized by widespread musculoskeletal pain in the absence of apparent tissue damage, associated to a set of additional symptoms including fatigue,

sleep, and cognitive and affective disorders. The American College of Rheumatology (ACR) defined the diagnostic criteria of FMS [103]:

1. Generalized pain in at least four of five body regions [upper left, upper right, lower left, lower right, axial (see **Fig. 11**)].

2. Symptoms lasting for at least three months and with a similar level of intensity

3. Obtaining one of these scores' combinations in the following self-reported scales of pain evaluation: (i) Widespread Pain Index [i.e., index describing the number of body regions affected by pain (range: 0-19) during last week] score ≥ 7 and symptoms severity scale (range: 0-9) score ≥ 5; (ii) Widespread Pain Index score between 4 and 6 and severity of symptoms scale score ≥ 9

4. A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses

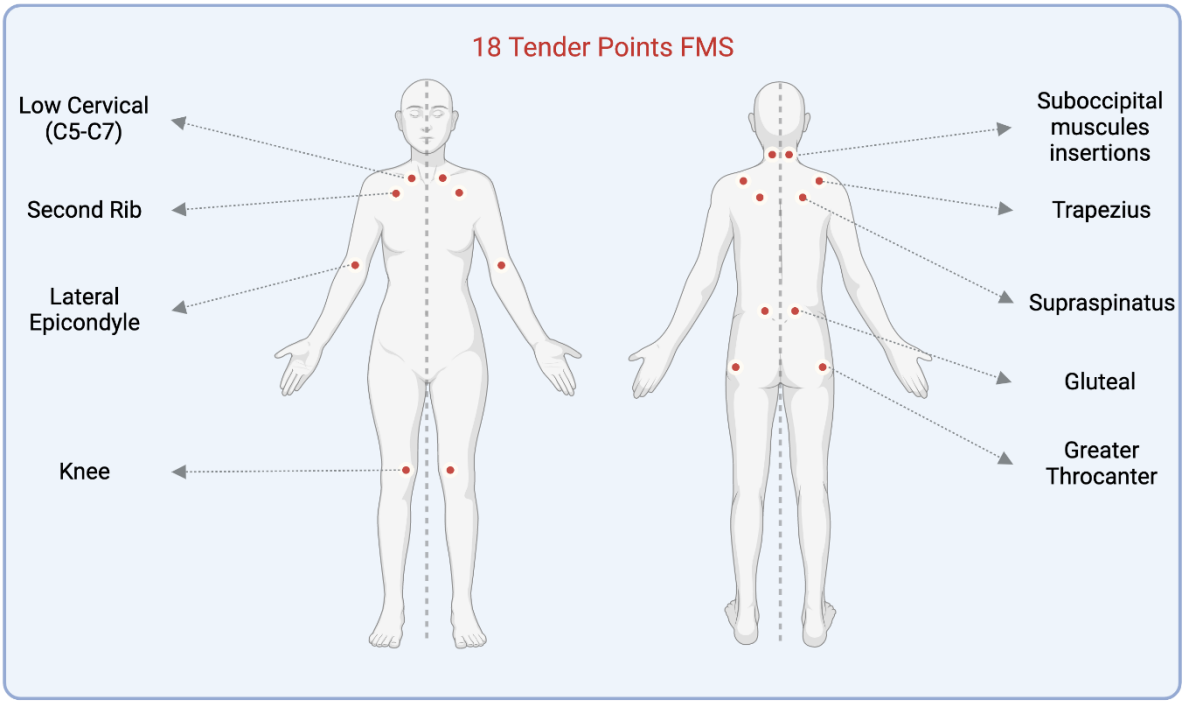

Fig. 11 *Fibromyalgia tender points. Created with Biorender.com*

The overall prevalence of FMS in the general population is estimated between 0.5-5%, affecting women 9:1 times more than males [104]. Although largely diffused, the aetiology and pathogenesis of FMS are not yet completely understood. Several factors have been proposed to interact in its determination [105]. The most reported ones are the following:

1. Genetic predisposition: several familial studies highlighted the role of genes in FMS [106]. Among the genes investigated, the most relevant seem to be those associated with neurotransmitters (e.g., anomalies in the serotonin transporter gene or the dopamine D4 receptor gene) [105].

2. Central sensitization: accumulating evidence suggests a crucial role of abnormal pain processing in the central nervous system due to sensitization processes. Central pain sensitization is defined as the increased responsiveness of nociceptive neurons of the CNS to either average (i.e., minimum tissue damage) or subthreshold inputs [107]. A relevant phenomenon observed in FMS is the excessive "windup", by which, after a painful stimulus, subsequent stimuli of the same intensity are perceived as stronger [105].

3. Neuroendocrine and autonomic hypothesis: different studies proposed the involvement of the hypothalamic-pituitary-adrenal (HPA) axis dysfunction in FMS development [108]. Elevated cortisol levels and adrenocorticotropic hormone (ACTH) have been documented, probably secondary to low serotonin levels.

4. Psychogenic hypothesis: psychiatric/psychological conditions and FMS are often comorbid. The most reported disorders are anxiety, somatization, dysthymia, panic disorders, posttraumatic stress, and depression [105].

Apart from the pain symptomatology, special attention should be given to the heterogeneous set of symptoms associated with FMS. Up to 80% of FMS patients report some form of cognitive disorder [109]. The term "fibro-fog" was coined to illustrate the pattern of concentration difficulties, forgetfulness, mental confusion, and inability to multitask complained by these patients [110]. It is unclear, however, if cognitive symptoms in FMS are part of the disease pathogenesis *per se* or, somewhat, a consequence of depression, anxiety, and sleep disorders. Indeed, given the overlapping neural networks involved in pain processing and cognitive processes, the hypothesis of cognitive impairments due to resource competition between cognitive tasks and pain processing cannot be ruled out [111], [112]. Secondly, affective disorders, including anxiety and depression, are frequently diagnosed with FMS to the extent that some authors proposed to consider this syndrome among the

"affective spectrum disorders" [113]. It is unclear if these symptoms should be considered a reaction to the chronic pain condition or, instead, a clinical manifestation of the abnormal HPA axis regulation [113].

There is currently no cure for fibromyalgia. Research shows that the most effective treatment for fibromyalgia is physical exercise. Patients benefit from physical exercise, which can be prescribed in addition to any drug treatment. However, physiotherapy alone does not provide long-lasting effects.

3.3.2 FMS and sensorimotor integration

Substantial research has investigated motor, sensory and body representation disorders in pathological pain conditions. Sensorimotor integration can be altered in several chronic pain conditions, including FMS. To better understand the link between pain and sensorimotor integration mechanisms in FMS, it is relevant to introduce the concept of "pain matrix" or "body-self neuromatrix" [56]. According to the model originally proposed by Malzack [114], [115] pain is just one of the possible outputs of a complex and extensive brain circuit involving several cortical and subcortical structures (see **Fig. 12**). Thus, pain can be triggered by sensory inputs (i.e., acute pain activated by noxious inputs) but can also be activated independently. The body-self neuromatrix concept implies input from sensory signalling systems (i.e., cutaneous, visceral, and musculoskeletal inputs), cognitive-related brain areas (e.g., memories of past experiences, attention) and emotion-related brain areas (i.e., limbic system and associated homeostatic brain mechanisms). The integration of these signals determines the experience of body-self in all its dimensions (e.g., sensory, affective, postural). The output of this matrix comprises pain perception, as well as action programs and stress-regulation programs. Several authors have thus proposed a dysfunctional activation of the pain matrix as the cause of chronic pain in FMS.

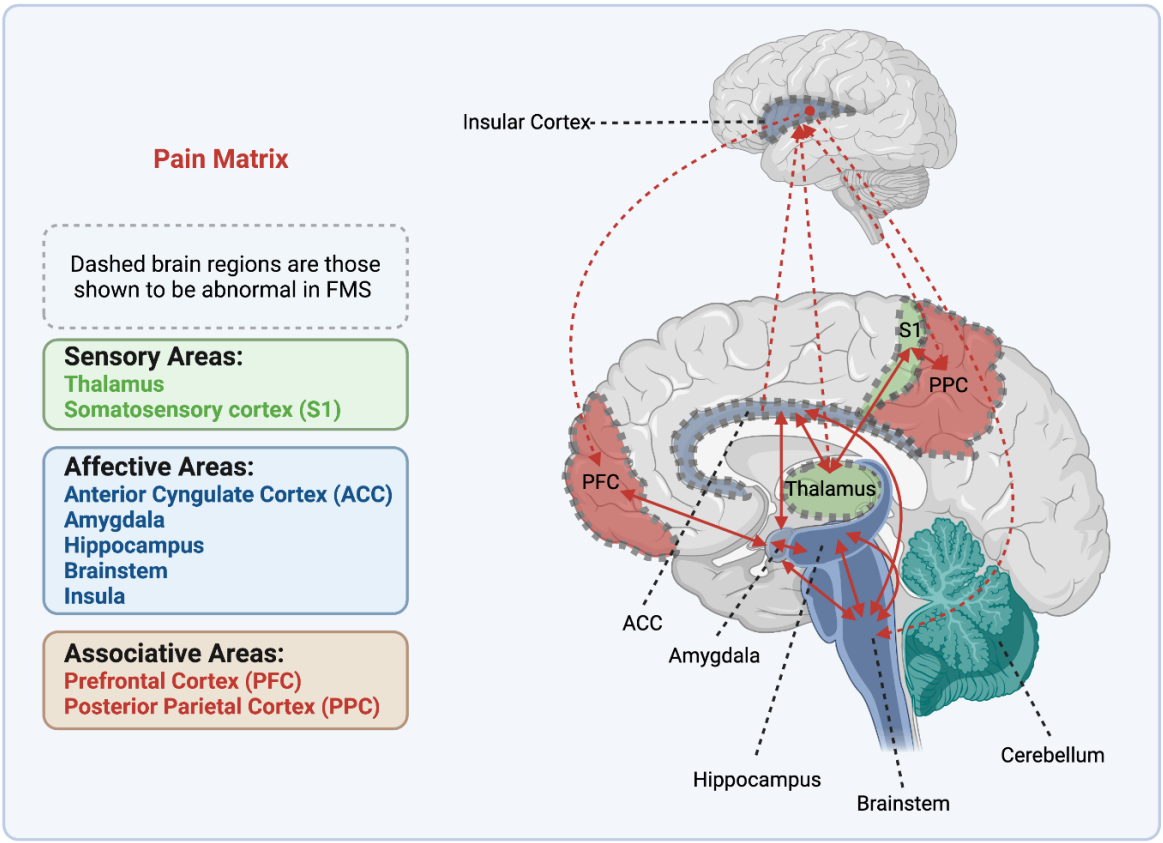

Fig. 12 *Pain Matrix:* Schematic representation of the brain circuits forming the pain matrix. On the bottom: brain sagittal view showing cortical and subcortical areas. On the top: lateral brain view showing the insular cortex. *Created with Biorender.com*

Starting from this model, several subsequent studies proved the link between sensorimotor integration deficits and pathological pain. A recent review [116] collected evidence of altered sensorimotor-related functions in people with pathological pain, particularly: motor functions, sensory feedback, cognitive representation of the body and surrounding space, and multisensory processing abnormalities. Identifying the abnormal mechanisms of the central altered sensorimotor integration in FMS may help develop new efficient treatments. Therefore, recent research on FMS has turned towards finding new biomarkers of these abnormal central mechanisms able to account for both pain processing alteration and cognitive/affective symptoms. On this ground, neuroimaging techniques have been adopted: electroencephalographic studies, for instance, revealed a shift in the typical oscillatory frequencies of the thalamocortical circuits (i.e., increased theta rhythm in frontal and anterior cingulate cortices) [117], [118]. On this ground, neuromodulation techniques have been suggested as a possible new treatment approach to restore physiological frequencies in FMS.

Chapter 4.

Methods

The current chapter briefly reviews the principles of the techniques adopted in the three central studies presented in chapters 5-7: Transcranial Magnetic Stimulation, Alternating Current Stimulation, Electroencephalography and Gait analysis.

4.1 Brain Stimulation Techniques

Non-invasive neurostimulation techniques are valuable tools for studying brain-behaviour relations in clinical and non-clinical populations and promising experimental treatment options [119]. Transcranial Magnetic Stimulation (TMS) and Transcranial Electrical Stimulation (tES) are the most employed methods: TMS activates axons via short-pulsed stimulations, leading thereby to new action potentials, while transcranial electrical stimulation is used to manipulate the membrane potential of neurons, thus modulating their spontaneous firing rate. In this thesis, both TMS and tES methods were adopted respectively in the studies*: "Disentangling cerebellar and parietal contributions to gait and body schema: an rTMS study"* (Chapter 5) and: *"Beyond physiotherapy and pharmacological treatment for fibromyalgia syndrome: tailored tACS as a new therapeutic tool"* (Chapter 7). Follow a brief description of these two techniques and their main applications.

4.1.1 Transcranial Magnetic Stimulation

TMS is a non-invasive technique exploiting principles of electromagnetic induction [119]. According to the Maxwell equations, the induction of an electrical current in a coil generates a magnetic field oriented perpendicularly to the coil. By placing the coil on a subject's scalp, the produced time-varying magnetic field induces a current in the brain cortex able to depolarize cell membranes, opening voltage-gated sodium channels and initiating action potentials. The coil geometry (i.e., size

and shape) determines the focality of the applied stimulation, with eight-shape coils being more focal than circular ones [120], (see **Fig. 13**).

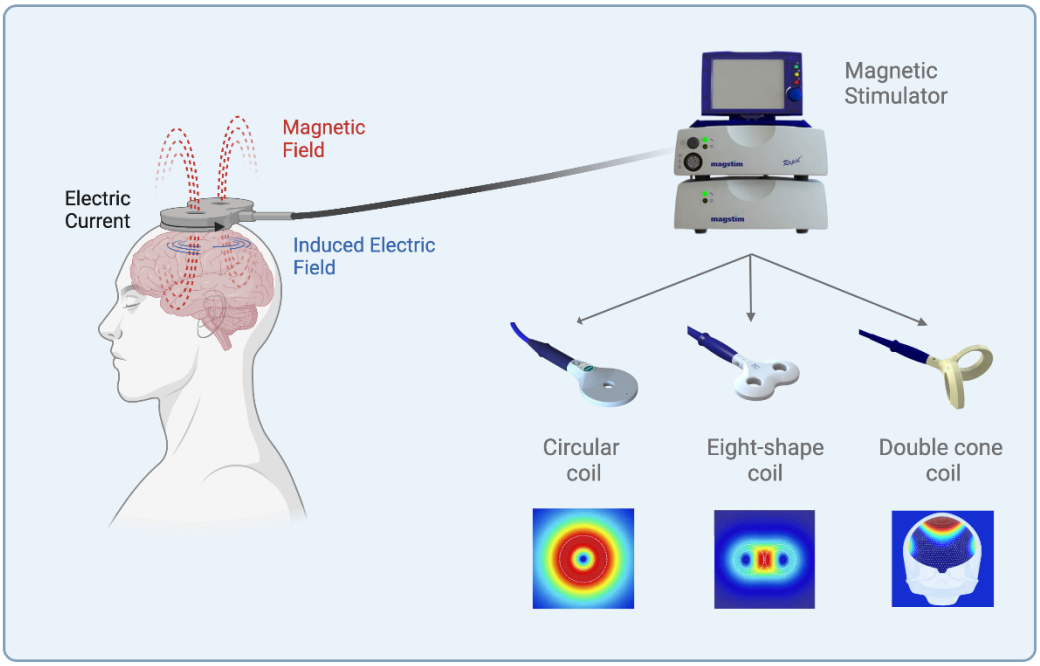

Fig. 13 *TMS mechanisms and setup:* On the left: schematic representation of the TMS working mechanisms. The pulse-delivered electric current flowing in the coil generates a varying magnetic field inducing an electric current in the brain. On the right: Magstim stimulator and the main coil types with different degrees of stimulation focality and depth. The eight-shape coil has a higher stimulation focality than the circular coil, while the double cone coil reaches deeper brain regions (e.g., cerebellum). *Created with Biorender.com*

The placement of the coil on the right stimulation site is critical: many studies utilize the international 10-20 electrode system, which does not take into account interindividual anatomo-functional variability. Stereotaxic systems, MRI and fMRI, are thus preferred when available, offering higher coil positioning accuracy over targeted areas [121]. Additionally, standardized function-guided procedures are adopted to stimulate target areas such as the primary motor cortex (M1) and the primary visual cortex (V1). These procedures imply the recording respectively of motor-evoked potentials (MEPs) or phosphenes [121] which are elicited as a direct consequence of M1 and V1 stimulation.

TMS can be applied by delivering one stimulus at a time (single-pulse TMS), in pairs of stimuli (paired-pulse), or trains of stimuli (repetitive TMS) [122]. These different approaches entail different aims: single-pulse studies are predominantly chosen to map cortical motor outputs and to inquire

about brain-behaviour interactions in causal chronometry studies. Paired-pulse studies are mainly adopted to investigate cortico-cortical interactions, while repetitive TMS (rTMS) is delivered to induce and evaluate long-lasting stimulation aftereffects [122].

Stimulation parameters selection (i.e., frequency and duration) has a crucial role in the determination of TMS aftereffects: low-frequency stimulations (< 1Hz) can depress cortical excitability leading to inhibitory effects [123]. This process has been linked to the well-known phenomenon of long-term depression (LTD), in which by electrically stimulating neurons in the 1 Hz range, a stable decrease in excitatory synaptic transmission is induced [123], [124]. High-frequency stimulations (> 5 Hz), on the contrary, can facilitate cortical excitability and have been associated with the phenomenon of long-term potentiation (LTP) [124], [125]. However, rTMS influence on cortical excitability is highly variable between subjects, as well as the duration of the aftereffects. The duration of stimulation seems, however, to vary in parallel with the length of the stimulation, with more prolonged stimulation inducing longest aftereffects [125].

4.1.2 Transcranial Electrical Stimulations

TES is a non-invasive stimulation technique by which an electrical current is delivered through the brain's cortex to alter its functioning. The electrical current is usually applied by two or more conductive electrodes in contact with a conductive solution and fixed over the scalp with elastic straps. The active electrode is located on the site overlying the cortical target, while the return electrode can be placed in extracephalic locations or cephalic areas unrelated to the examined function (commonly the contralateral supraorbital area) [126]. Contrarily to TMS, this technique cannot induce neuron polarization *per se* but can alter the ongoing neuronal electrical activity by modulating neuronal membrane potentials. Indeed, the intensity of the delivered current is subthreshold, meaning that its effect can bring the underlying neurons closer to their firing threshold without eliciting action potentials [126]. See **Fig. 14**.

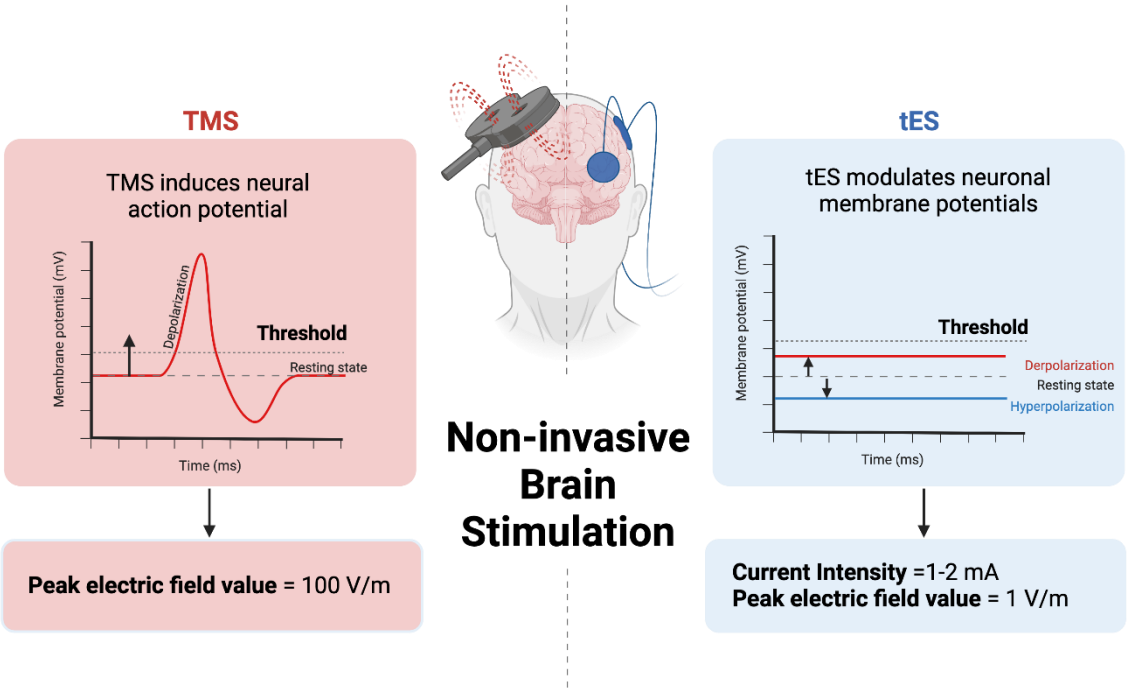

Fig. 14 *TMS vs TES mechanisms of action:* Schematic representation of TMS and TES effects on the stimulated neurons. *Created with Biorender.com*

TES comprises different application techniques among which transcranial direct current stimulation (tDCS), alternating current stimulation (tACS) and random noise stimulation (tRNS), (see **Fig. 15**). Although working on the same principles, the different electrical stimulation patterns characterizing these techniques determine different neuronal and behavioural outcomes.

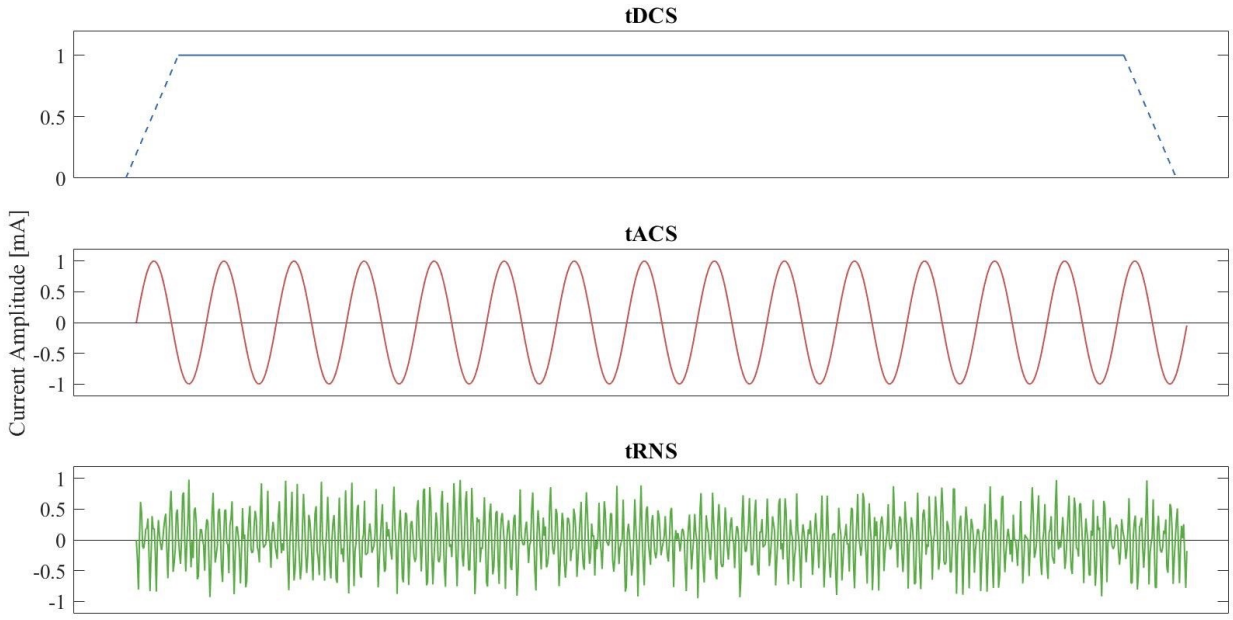

Fig. 15 *TES stimulation waveforms. Created with MATLAB_R2021b*

1. tDCS implies using constant direct current delivered at low intensities (i.e., 0.5- 2.0 mA) through one or more active electrodes. The current then propagates through the head and is returned via the reference electrode [126]. The current flow modulates cortical excitability by increasing (depolarization) or decreasing it (hyperpolarization). This phenomenon has been extensively demonstrated in literature: anodal tDCS over M1 increases the amplitude of MEPs while cathodal tDCS decreases them [127]. By modulating axonal membrane potential, tDCS can interact with endogenous neural network features such as ion channel dynamics, spike timing, firing rate, synaptic transmission and brain responses to external stimuli [128]. This technique has been widely adopted in clinical research for several conditions: drug addiction, major depressive disorder, Alzheimer's disease, schizophrenia, attention deficit hyperactivity disorder (ADHD) and disorder of consciousness [129].

2. tACS applies a low intensity alternating electrical current delivered in a sinusoidal way at a particular oscillation frequency. The physiological mechanisms underlying tACS effects are still under debate. Unlike tDCS, tACS can entrain the neuronal firing of the underlying neurons to the exogenously applied stimulation frequency [126]. Two main effects are associated respectively with online and offline tACS: Entrainment and neuroplasticity Entrainment is the phenomenon by which an external rhythmic system affects another naturally occurring, forcing it to follow its own oscillating frequency. Thus, tACS can entrain endogenous brain oscillations. Neuroplasticity, on the other side, occurs because of the spike-timing-dependent plasticity (i.e., long-term potentiation or depotentiation) induced by tACS increasing or decreasing neural synchronization [130]. Because of its properties, tACS has been proposed as a promising treatment for the so-called oscillopathies [131]: neurological and psychiatric conditions characterized by abnormalities in brain oscillatory activity (e.g., Parkinson's Disease and Fibromyalgia). This specific technique has been adopted in the study: *"Beyond physiotherapy and pharmacological treatment for fibromyalgia syndrome: tailored tACS as a new therapeutic tool"* (Chapter 7).

3. tRNS implies the application of an alternate current, which, instead of being delivered at a fixed frequency, alternates frequency and amplitude randomly within a specific range [126]. Generally, the stimulation frequency range varies between 0.1 and 650 Hz [132] but has also been delivered dividing into either low (0.1-100 Hz) or high (101-670 Hz) frequencies of stimulation [133]. Literature proved that tRNS increases cortical excitability; however, it has been suggested that low and high-frequency stimulations may have opposite effects [134]. According to others, excitability changes induced by tRNS may be intensity-dependent rather than frequency depended, with lower intensities associated with cortical inhibition and higher intensities with excitation [135]. Several theories on tRNS mechanisms of action have been suggested. One of them is the stochastic resonance theory, whereby tRNS induces random activity (noise) on the stimulated neurons, boosting their sensitivity to further external inputs [136]. Other theories proposed that tRNS repeated subthreshold stimulation can, in turn, alter homeostatic mechanisms of the stimulated system leading to the potentiation of task-related neuronal activity [133].

4.2 Electroencephalography (EEG)

The EEG is a non-invasive brain imaging technique adopted mainly in clinical and research practice. EEG signal arises from the synchronized synaptic activity of large populations of cortical neurons, with the main contribution of pyramidal cells [137]. At a cellular level, the excitation of postsynaptic neurons generates a negative extracellular voltage at the dendrites level, making the neuron a dipole. EEG electrodes on the scalp detect the sum of negative and positive charges of a large number of underneath dipoles [137]. EEG electrodes measure the sum of many individual dipoles in an area as a single dipole whose magnitude depends on the number of neurons whose dipoles are summing together [137]. As electrodes sum both positive and negative ends of dipoles, neurons must be parallelly arranged and synchronously active to detect a nonzero signal [137]. To obtain a high-quality EEG signal, the EEG system should consist of the following [138]: *(1)Electrodes with conductive media:* commonly used scalp electrodes are formed by Ag- Ag-Cl disks of 1-3 mm diameter.

Electrodes are usually arranged in standardized positions within caps. In 1958 the International Federation in Electroencephalography and Clinical Neurophysiology developed the so-called 10-20 electrode placement system (see **Fig. 16**) [139]. Electrodes are labelled according to the underneath brain area (i.e., frontal (F), central (C), temporal (T), parietal (P), and occipital (O). Each letter is then associated with a number, standing for the distance of the electrode from the midline, with odd numbers identifying the left side and even numbers the right side. The number of electrodes within a cap can vary from 32 active electrodes to high-density systems of 256 active electrodes (see **Fig. 16**). Any of these electrodes can be selected as a reference in EEG acquisition [138]. (*2) Amplifiers with filters:* EEG signal needs to be amplified to maximize the signal-to-noise ratio of the measured voltage and to increase the size of the signal above the noise that later elements of the circuit may introduce. *(3) Analog to digital (A/D) converter*. *(4) Recording device*.

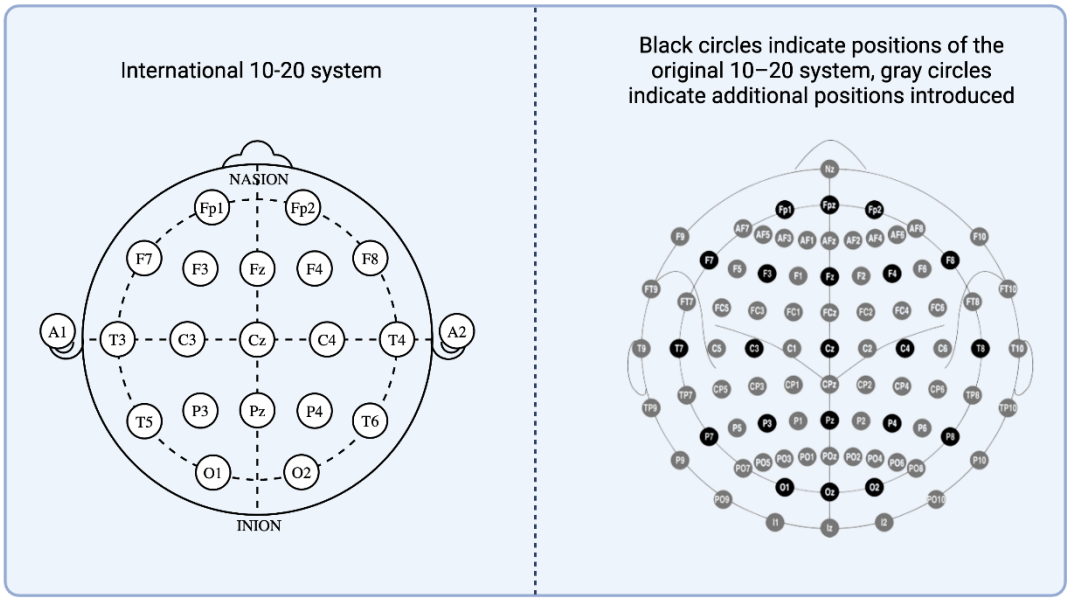

Fig. 16 *EEG 10-20 and high-density systems. Created with Biorender.com*

When dealing with EEG signals, identifying signal artefacts is of utmost importance. EEG artefacts may be either subject-related (i.e., physiological) or technical [140]. The most common subject-related artefacts comprise: *(1) Ocular activity*: the eyes can be considered as magnetic dipoles whose movement alters the surrounding electric field. Any eye movement, including blinking itself, gives rise to this kind of artefact primarily picked up by frontal electrodes. A reference electrooculogram

(EOG) measured simultaneously with the EEG is highly advantageous for ocular artefact cancellation. However, the amplitude of EOG artefacts is generally much larger than the background EEG activity, reaching values around 100-200 microvolts [140]. *(2) Muscular artefacts:* when contracted, muscles produce electrical activity. Activity such as neck and shoulder muscles contractions, swallowing, chewing, talking, sucking, sniffing etc., can lead to this artefact. It manifests as a high-frequency signal overlapping the EEG beta and gamma bands, whose amplitude correlates with muscle contraction intensity. Compared with other biological artefacts, it is thus more challenging to characterize [140]. *(3) Cardiac activity*: the electrocardiogram (ECG) measures the heart's electrical activity. Although its amplitude is low on the scalp, it can sometimes cause EEG distortions, depending on the participants' body type and electrode positions. The ECG has a regular, repetitive electrical pattern, whose frequency component overlaps with the EEG band frequencies and thus can be challenging to detect [140].

Conversely, the most common technical artefacts include power line noise (50/60 Hz), impedance fluctuation and cable movements.

4.2.1 EEG rhythms

EEG activity is typically classified according to the frequency brand. Five main frequency bands have been identified, each characterized by a specific distribution over the scalp and a particular physiological and cognitive significance (see **Fig. 17**).

1. Delta (δ, 0.5–4 Hz): Delta rhythm is physiologically observed during deep sleep (non-REM) and is prominent in frontocentral head regions. Delta activity is increased in pathological brain disturbances associated with awake states in the case of generalized encephalopathy and focal cerebral dysfunctions [141]. Intermittent rhythmic delta activity is a typical pathological EEG pattern classified according to the affected area in frontal, temporal and occipital intermittent delta activity [141]. Studies inquiring about the relation between delta rhythms and cognitive processes highlighted delta activity changes with task difficulty. Specifically, delta activity seems to increase in tasks

requiring attention to mental processes (e.g., mathematical tasks, semantic tasks, working memory) [142], whereas there is a decrease in tasks which demand attention to the external environment.

2. Theta (θ, 4–8 Hz): This rhythm has been associated with drowsiness and early stages of sleep (i.e., N1, N2). It is most prevalent in frontal-central head regions (i.e., frontal-midline theta) and hippocampus (i.e., hippocampal theta) [143]. Functionally, it has been associated with several cognitive processes: memory encoding and retrieval [144], working memory, focused and selective attention processes (midline-frontal theta) [145], spatial navigation and position coding (medial-temporal lobe – associated with encoding and retrieval of spatial information [146]) .

3. Alpha (α, 8–13 Hz): Alpha rhythm is the typical background rhythm of the adult EEG recording, usually present during awake in occipital regions. It is best observed with closed eyes and during mental relaxation while attenuating with eye-opening and mental effort tasks [141]. Indeed, event-related desynchronization of alpha rhythm (reduced alpha) is considered a sign of cortical excitation. In contrast, alpha activity increasing in specific regions during a task has been interpreted as a sign of not-involvement of that area in the task [147].

4. Beta (β, 13–30 Hz): beta rhythms are more often observed in frontal or central areas compared to posterior cortex regions and have been mainly associated with motor functions [148]. The best-known beta rhythm in the brain has been associated with basal ganglia oscillations in the high beta frequency band synchronous with beta oscillations in cortical motor areas [148]. Experimental evidence suggests that voluntary motor actions are correlated with decreased beta oscillations in the basal ganglia-thalamocortical motor loop. Indeed, conditions such as Parkinson's disease are characterized by high beta oscillations in basal ganglia, correlated with bradykinesia and rigidity [148]. Increased beta power correlates with holding periods following movements and steady contractions [149]. Notably, beta rhythm is also inhibited by motor imagery [149]. Recent hypotheses suggested that beta may signal the tendency of the sensorimotor system to maintain the status quo, more than just reflecting a lack of movement [149]. Frontal-parietal beta rhythms have also been documented and associated with top-down attentional processes [149].

5. 5. Gamma (γ, > 30 Hz): gamma rhythm has been associated with many cognitive tasks, but an unequivocal interpretation of its meaning is still lacking. Generally, increased gamma is positively correlated with complex cognitive tasks concurrently involving more brain areas: parallel increased and decreased gamma power is observed respectively in those areas necessary or not to the task execution [150].

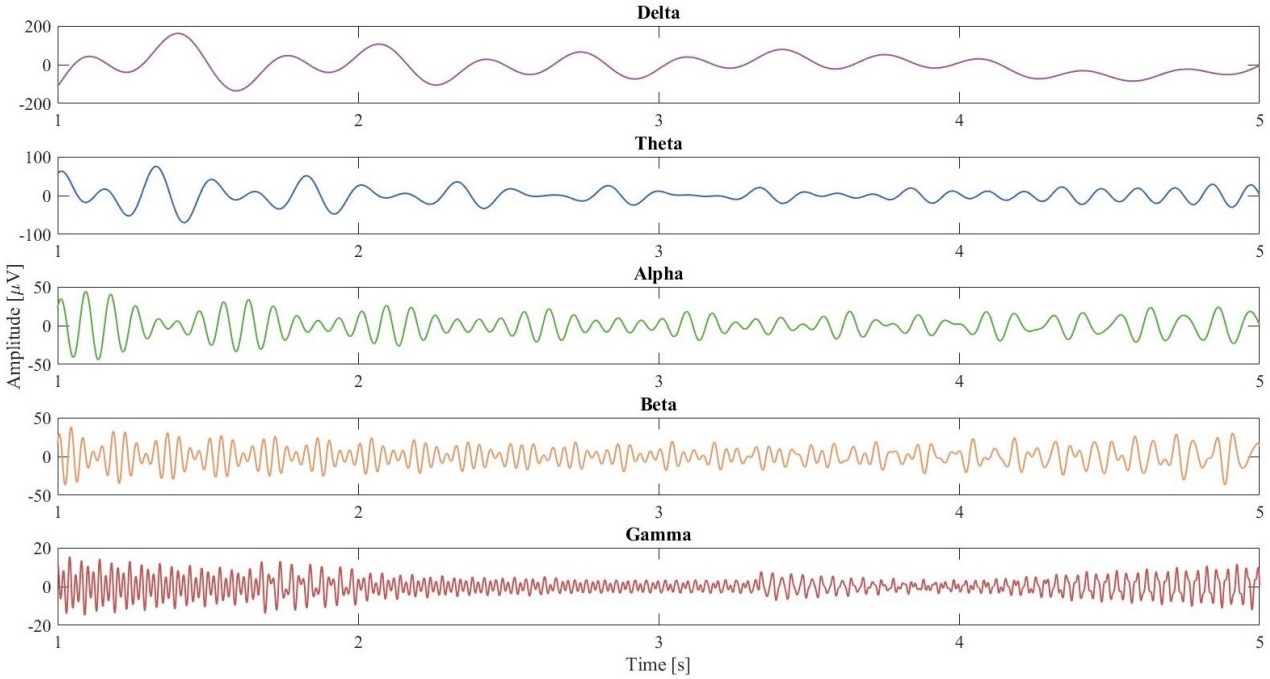

Fig. 17 *EEG frequency bands. Created with MATLAB_R2021b*

4.2.2 EEG spectral analysis

Power spectral analysis is a well-established method for the analysis of EEG signals, which quantifies the amount of oscillatory activity of different frequencies in the signal through the Fast Fourier Transform (FFT) method [151]. Two main factors are mainly considered in traditional EEG spectral analysis: the amount of a specific frequency band (i.e., power) and its spatial distribution [151]. The power represents the amount of a specific frequency band within the signal. Both increases and decreases in the EEG power carry meaningful information to understand the inquired brain function. Power can change in different brain areas, so spectral powers are usually represented as topological

distributions on the scalp (see **Fig. 18**). These maps allow for intuitive comparisons among different populations or conditions.

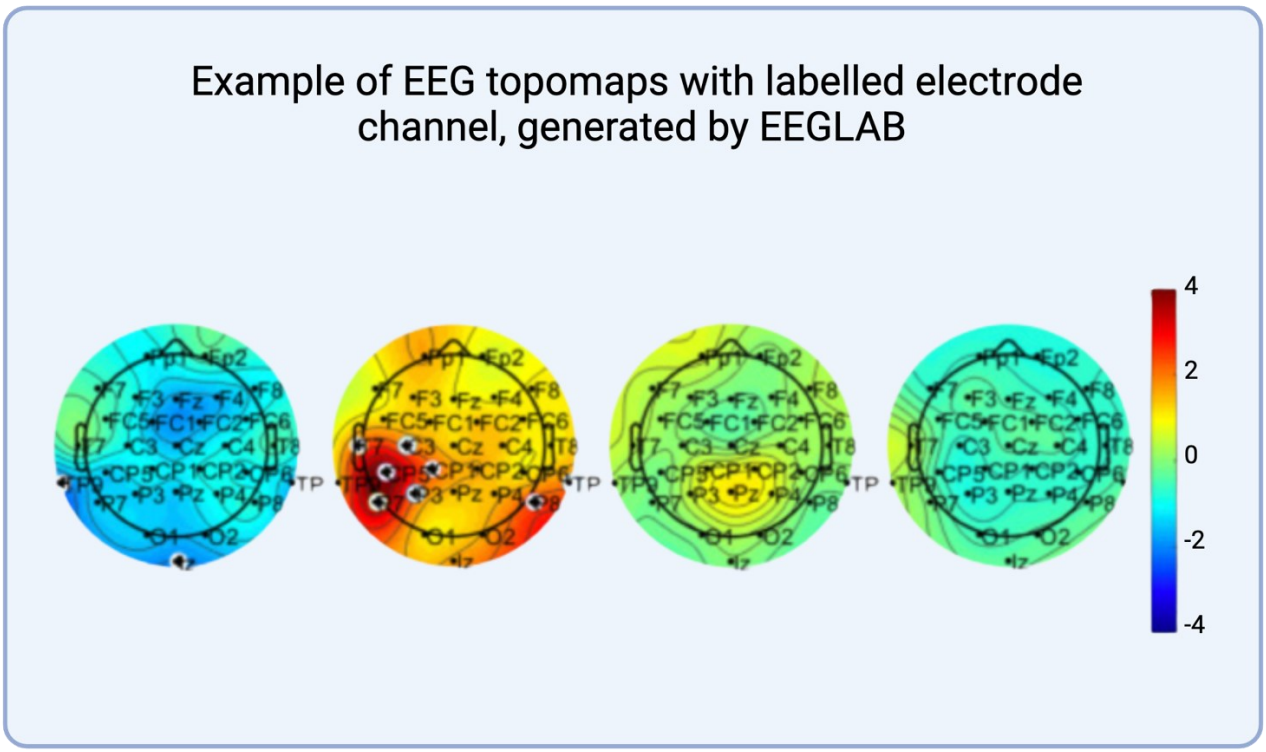

Fig. 18 *EEG topographic maps from* [152]. *Created with Biorender.com*

Spectral power in these maps is usually converted in z-scores highlighting whether the spectral powers of the EEG channels are enhanced or reduced compared with the normative data. Spectral estimation based on the FFT method has intrinsic properties, namely, aliasing and leakage, both to be carefully considered [151] (see **Fig. 19**). The aliasing effect manifests when the sampling frequency of a signal is too low, thus biasing the signal reconstruction. The resulting undersampling creates an activation in a different frequency. To avoid this, an anti-aliasing filter should be applied before signal digitalization [151].

The spectral leakage phenomenon. The FFT assumes that the input signal is a period of a periodic signal. Choosing the proper length of the measuring "window" of the signal is thus fundamental to avoid discontinuities in the time domain. Indeed, discontinuities cause the power to spread out around the original frequency, resulting in an attenuated frequency spectrum. The leakage effect can be reduced by using an appropriate windowing function [151].

Power spectral analysis of the EEG signal was applied in the studies reported in chapters 6 and 7 of this thesis.

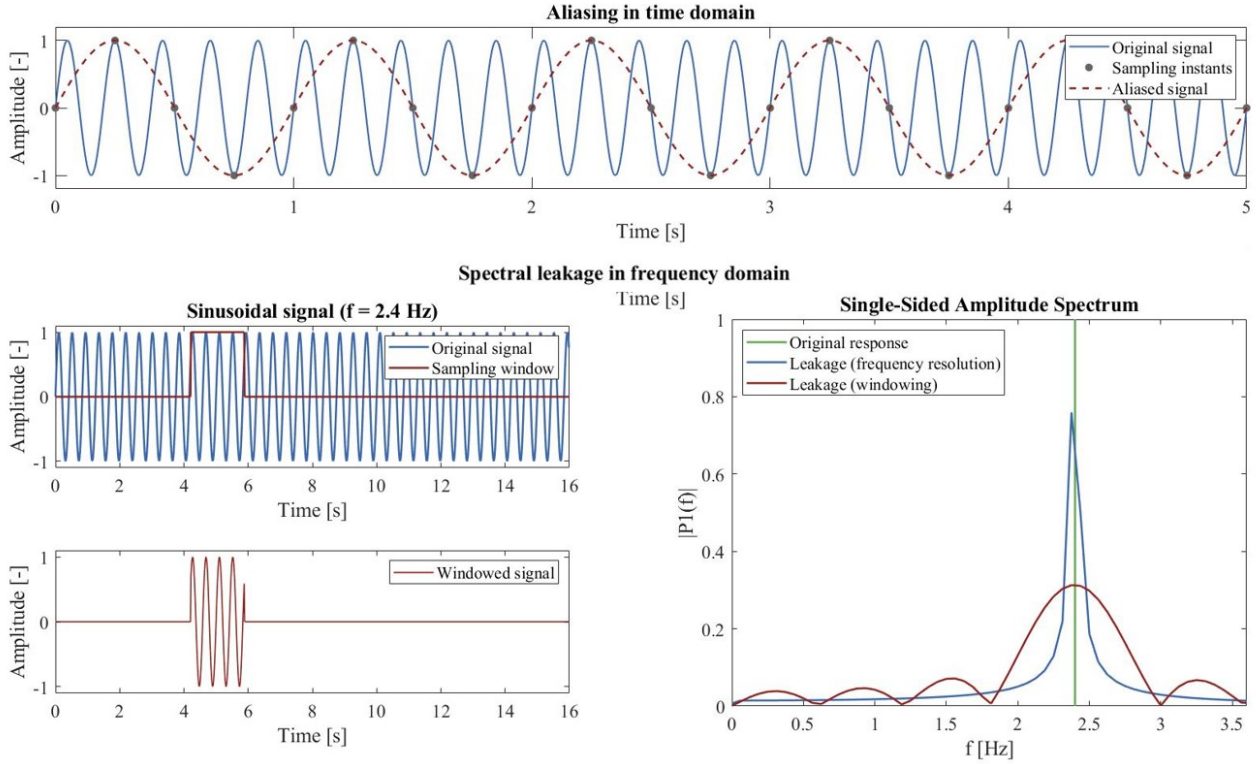

Fig. 19 *Examples of aliasing and leakage:* On the top, an example of a reconstructed aliased signal (red dashed) due to low sampling frequency *vs* the original signal (solid blue line). On the bottom *is an example of spectral leakage in the frequency domain.* The spectrum (bottom-right) shows the theoretical frequency response of the signal (solid green line*). T*he leakage due to the frequency resolution *(*blue line) *leads to a* frequency spread. *T*he leakage due to *the* windowing (green line) *leads to a higher* frequency spread *due to discontinuities in the time domain*. Choosing a proper frequency resolution and window function to collect the signal reduce*s* the leakage, resulting in a narrower frequency interval. *Created with MATLAB_R2021b*

4.3 Gait Analysis

Walking is one of the most complex human sensorimotor integration functions. Thus, assessing walking parameters is a recognized valuable clinical and research tool to unveil peripheral motor and CNS impairments. The systematic instrumented measurement and evaluation of walking ability is referred to as gait analysis [153]. Walking is formally defined as a method of locomotion involving the use of the legs to provide support and propulsion [154]. To allow the body to move forward, alternatively, one limb acts as the source of support while the other advances itself. This cyclic pattern of movements is defined as the gait cycle [154]. The human gait cycle can be divided into two main

periods, namely, the stance period and the swing period. The stance period denotes the time of foot contact with the ground, lasting about 60% of the gait cycle. On the contrary, the swing period represents the time of limb advancement when the foot is not in contact with the ground (40% of the gait cycle) [155]. Two fundamental gait events identify these periods: the initial heel contact (or heel strike) prompting the beginning of the stance phase and the toe-off of the same foot initiating the swing phase (see **Fig. 20**).

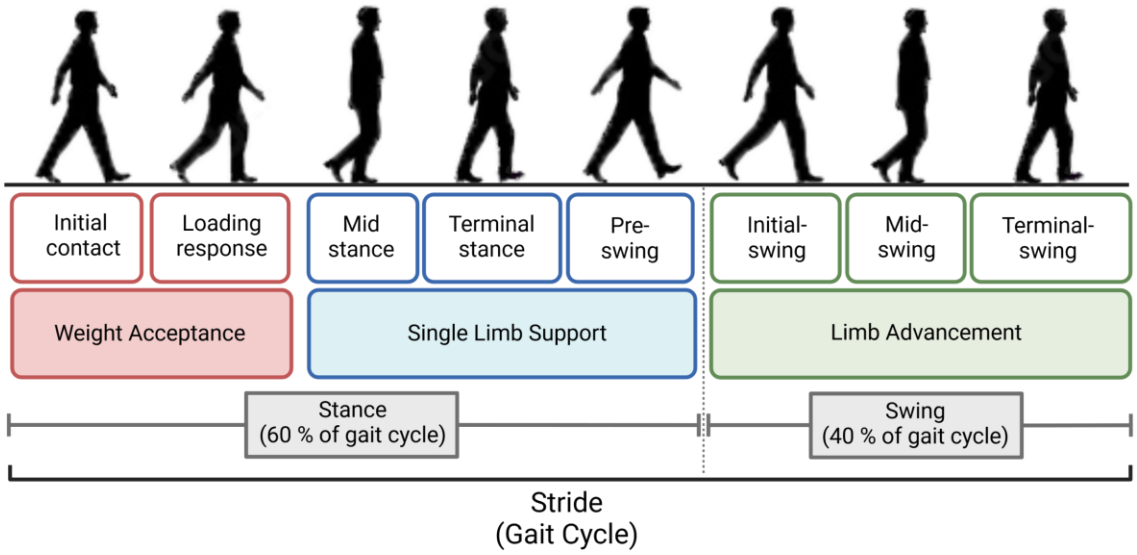

Fig. 20 *Gait cycle and gait-related tasks. Created with Biorender.com*

Each period can be further divided into specific events, each one associated with specific gait-related tasks: *(1) The weight acceptance task* aims to stabilize limbs after the swing phase, absorb the shock after contact with the ground, and preserve body progression. The initial contact event determines the beginning of the weight acceptance task. The rotation of the limb over the heel (first rocker of the gait cycle, **Fig. 21**), allows weight to transfer onto the forward limb. During this transfer, the knee is flexed to provide shock absorption. *(2) The single limb support task* begins after the midstance phase, characterized by the shank rotation over the supporting foot (second rocker of the gait cycle, **Fig. 21**). Follow the terminal stance phase in which the centre of mass advances forward in front of the supporting foot while the heel raises off the ground (third rocker of gait cycle, **Fig. 21**). *(3) The limb advancement task* begins immediately after the toe-off event, with the initial-swing phase. During the

swing phase, the foot is lifted from the floor: in the initial swing phase, the hip, knee, and ankle are flexed to create foot clearance over the ground. In the mid-swing, the thigh reaches its peak advancement till the terminal swing phase, characterized by the final advancement of the shank and foot positioning for the new contact with the ground.

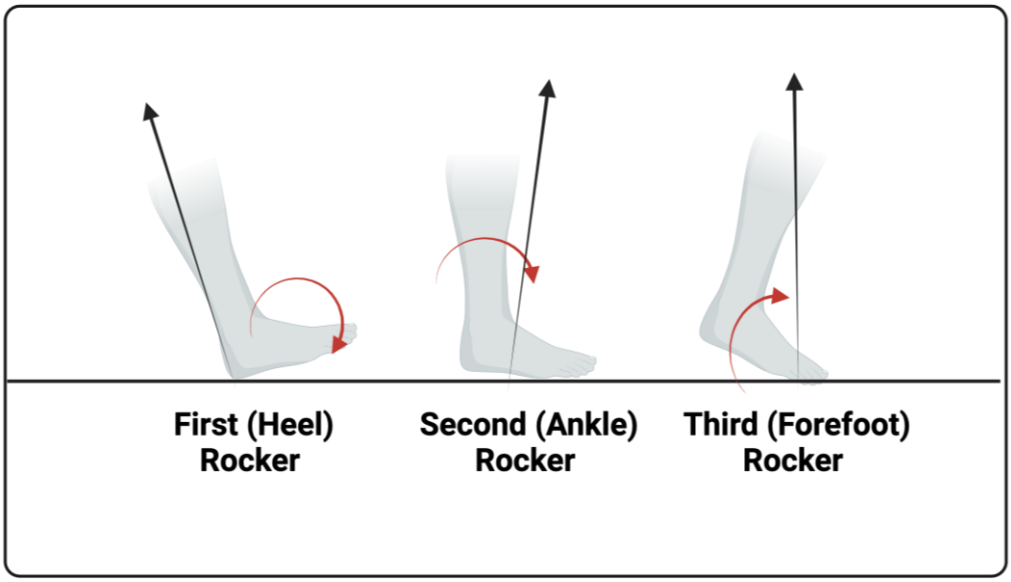

Fig. 21 *Gait rockers. Created with Biorender.com*

4.3.1 Gait Analysis Parameters

When speaking about gait analysis, many parameters can be collected, describing different aspects of gait. Spatiotemporal parameters concern spatial (distance) and temporal (time) characteristics of walking (see Table 1). At the same time, kinematics describes the time course changes in position and orientation of body segments in terms of displacements, velocities, and accelerations (i.e., joint angles, angular velocities, angular accelerations).

Table.1 Spatiotemporal gait parameters

	Gait Parameter	Operational Definition	Measurement Unit
Spatial	Step length	Distance between two successive heel strikes of two different feet	cm
	Stride length	Distance between heels of two consecutive foot-strikes of the same foot	cm

	Step width	The lateral distance between the heel centres of two consecutive foot contacts	cm
Temporal	Cadence	Number of steps per minute	steps/min
	Step Time	Time from the initial contact of one foot to initial contact of the opposite foot	seconds
	Stride Time	Time between the initial contacts of two consecutive foot contacts of the same foot	seconds
	Stance time	Time from heel strike to toe-off of the same foot	seconds
	Swing time	Time from toe-off to heel strike of the same foot	seconds
	Single Support Time	Time between the last contact of the opposite footfall to the initial contact of the next footfall of the same foot	seconds
	Double Support Time	Double support time is the sum of the time of two periods of double support in the gait cycle	seconds
Spatiotemporal	Gait speed	Distance walked over the time walked	m/s
	Stride speed	Stride length over the stride time	cm/s

4.3.2 Gait Analysis Systems

Many different instruments and methods are currently adopted to study human gait. Optoelectronic systems (e.g., Vicon) are the gold standard in motion capture. They are employed to obtain kinematics data using infrared cameras, which record the 3D positions of infrared-reflecting passive markers over the body. The system's accuracy depends on several factors, such as the proper positioning of the cameras relative to each other, the position of the markers on the body, the chosen calibration procedure, and the motion of the markers within the capture volume [156]. The spatial position of the markers is defined from multiple 2D images using the principle of stereoscopy. The coordinates of a marker are defined from at least two images from two video cameras in different positions. Optoelectronic systems are often adopted together with force platforms (see **Fig. 22**) used to measure

ground reaction forces (GRF) exerted by the ground on the body in contact with it. Force platforms are usually formed by rectangular metal plates, providing 3D GRF components, the centre of pressure (Cop) components defining the location of the force vector, and the orthogonal moment component. These data have been frequently used to provide information on postural control in both healthy and pathological populations.

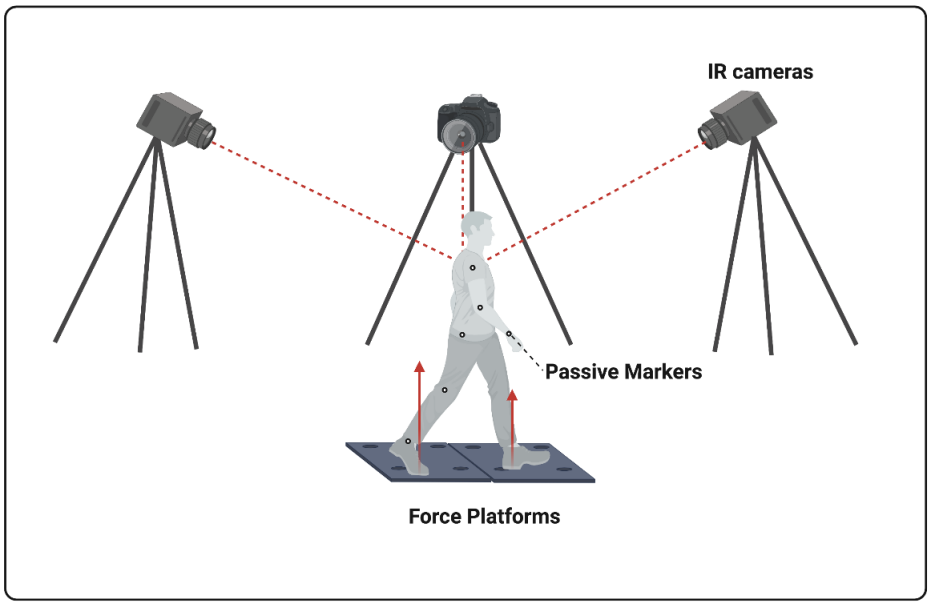

Fig. 22 *Schematic gait analysis experimental setup. Created with Biorender.com*

However, optoelectronic systems present several disadvantages, among whom they are bound to be used in a laboratory. Additionally, the lengthy procedure of subjects' preparation makes it often difficult to be used with special clinical populations (e.g., Dravet syndrome). Thus, non-optical capture systems are increasingly adopted to develop more ecological experimental protocols, as they can be used outside a laboratory. Particularly, Inertial Measurement Units (IMUs) offer several advantages: portable, user-friendly, low-cost, suitable for outdoor use, and easier to calibrate. IMUs include a triaxial accelerometer, gyroscope, and magnetometer whose signals are utilized to estimate the orientation of the sensor coordinate system (SCS) with respect to a global coordinate system (GCS). The GCS refers to Earth's fixed reference system depending on the gravity and Magnetic Nord direction. Sensors are applied over the body in different possible configurations [157]. The SCS needs

to be referred to the body segment coordinate system (BSC) on which IMU is fixed to measure limb orientation over time.

4.3.3 IMU data analysis

In the study reported in chapter 5, IMUs were used to quantify gait spatiotemporal and kinematic parameters. To extract these parameters, a custom gait analysis algorithm based on Tuca et al., [158] was developed in MATLAB R2020b. More in detail the method implies the following steps:

1. Data pre-processing: raw accelerations and gyroscope data were digitally filtered during data gathering. The sensor fusion algorithm used an optimized Kalman filter combining different sensory elements to return the most reliable solution for 3D orientation. Also, the gravitational force was eliminated from acceleration. The recorded files were exported from MVN software into an XML file format. They were then converted into more suitable .mat files ready to be post-processed in MATLAB.

2. Data processing: the identification of gait events was based on Perry's definition of heel strike (HS) and toe-off (TO) events [155]. HS events were detected on the function describing the knee angle variation on the sagittal plane, as the points of the function corresponding to the maximum knee extension (see **Fig. 23**). TO events were defined based on the function describing the ankle angle variation on the sagittal plane, as the points of the function corresponding to the maximum ankle plantarflexion (see **Fig. 23**). To test algorithm reliability, walking events were additionally identified by visually inspecting the walking trials on MVN software and then compared with those automatically identified by the MATLAB algorithm. Due to between-subjects gait variability, the model was then tuned to avoid false event detections.

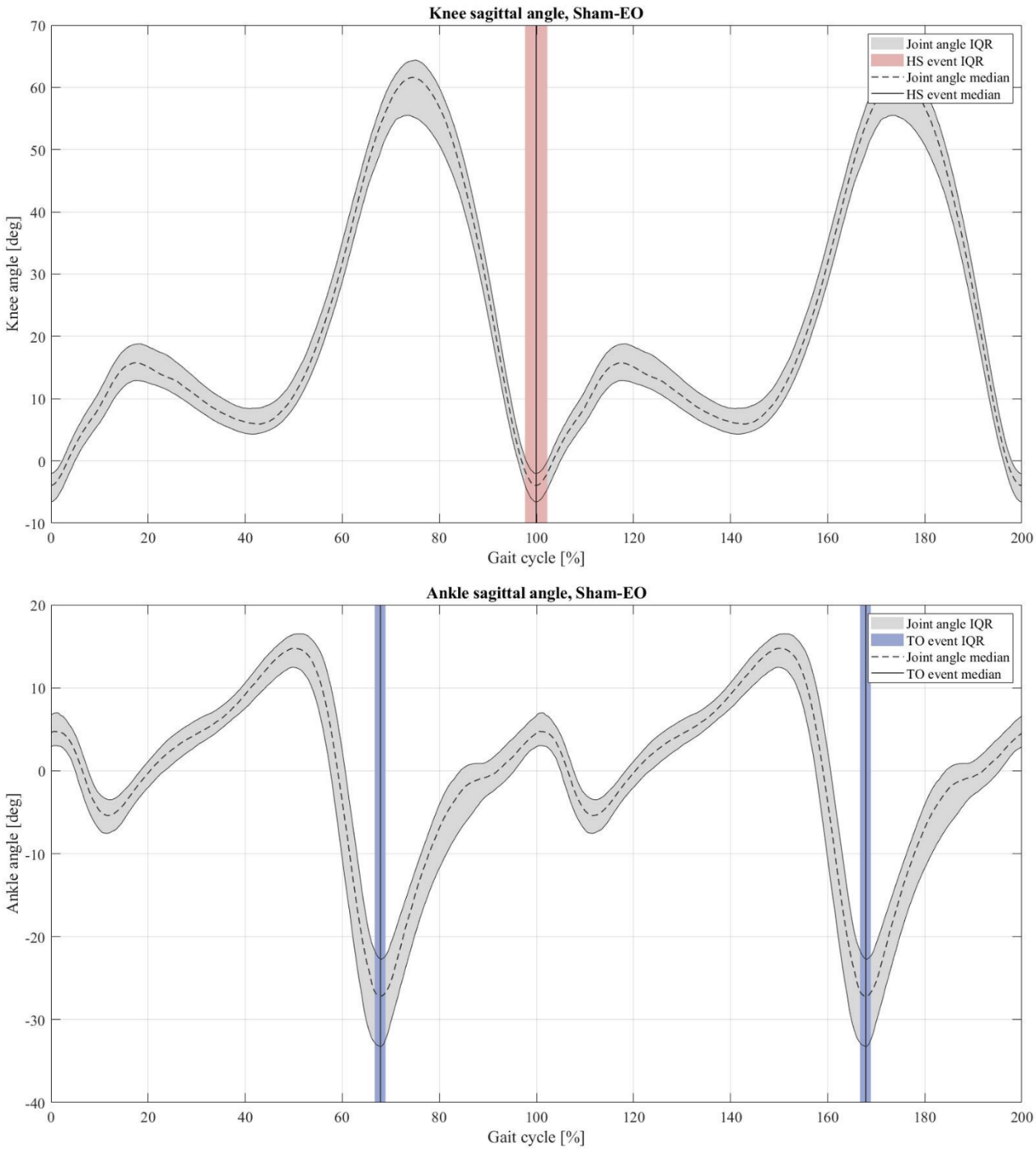

Fig. 23 *Gait events and joint angles on the sagittal plane:* on the top the variation of the knee angle on the sagittal plane within two gait cycles. Dashed lines represent the median knee angle values at each point of 30 healthy subjects. The corresponding grey bands are the interquartile ranges. The heel strike event corresponds to the minimum value of the knee angle function (i.e., maximum knee extension). The solid line and the pink band indicate, respectively, the median and the interquartile range of the heel strike event occurring for the 30 subjects (normalized with respect to gait cycle). On the bottom is represented the function corresponding to the ankle angle on the sagittal plane within two gait cycles. Dashed lines represent the median ankle angle values at each point of 30 healthy subjects. The corresponding grey bands are the interquartile ranges. The toe off event corresponds to the minimum value of the ankle angle function (i.e., ankle maximum plantarflexion). The solid line and the blue band indicate, respectively, the median and the interquartile range of the toe off event occurring for the 30 subjects (normalized with respect to gait cycle). *Created with MATLAB_R2021b*

Chapter 5.

Doctoral Research Projects

5.1 Disentangling cerebellar and parietal contributions to gait and body schema: an rTMS study

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Abstract

Background: The clinical overlap between motor and cognitive signs and symptoms of posterior parietal cortex (PPC) or cerebellar lesions can mask their relative contribution to the sensorimotor integration process. **Objective:** This study aimed to identify distinguish motor and cognitive features to disentangle PPC and cerebellar involvement in two sensorimotor-related functions: gait and body schema representation. **Method**: Thirty healthy subjects (21 females; mean age: 23.4 ± 2.9) were enrolled and randomly assigned to PPC or cerebellar stimulation group. Sham stimulation and 1Hz repetitive-Transcranial-Magnetic-Stimulation were delivered for 20 minutes over P3 or right cerebellum before a balance, walking and distance estimation task. Trials were repeated with eyes open (EO) and closed (EC) and kinematic measures recorded with eight inertial measurement units. **Results:** Increased instability emerged in both groups in real *vs* sham stimulation. PPC increased ellipse area and range of movement in anterior-posterior (RMSap) and mediolateral directions with EC, while cerebellar increased instability was observed both with the EC (RMSap) and EO (length of the centre of mass trajectory). PPC spatiotemporal variability increased in EC *vs* EO after real_stimulation (cadence, speed, stance, step time). The same was observed in the cerebellar group (speed, step length). In both groups, step width increased after real_stimulation_EC. Increased kinematic variability of ankle and knee angles was observed in both groups in

real_stimulation_EC *vs.* EO. Distance estimation in real_stimulation_EC was altered in PPC, leading to distance overestimation. **Conclusions:** Stability, gait variability and distance estimation parameters can be used to disentangle cerebellar and PPC sensorimotor integration deficits. Differential diagnosis efficiency can benefit from this methodological approach.

Keywords:

rTMS; Body schema; Gait; Inertial Measurement Unit; Sensorimotor integration

Introduction

Sensorimotor integration is the process whereby different sources of sensory inputs are integrated by the central nervous system (CNS) to guide motor program execution [1]. Proprioceptive and visual signal integration is critical for efficient locomotion: vision is primarily used to explore the environment and identify obstacles and their locations relative to the body, while proprioception provides constantly updated information on body segment positions [2]. Two key brain areas are mainly responsible for integrating multisensory information pertaining to gait: the posterior parietal cortex (PPC) and the cerebellum [3]. PPC receives inputs from visual cortices shaping the dorsal stream ("vision-for-action" pathway), which is involved in the real-time control of actions [4]. PPC integration of visual signals with proprioceptive ones allows transforming spatial location, orientation, and motion of objects into the coordinate frames of the motor effectors [5]. This process is critical in efficient goal-directed motor planning and anticipatory adjustments for online movement corrections (e.g., obstacle avoidance), in which visual perception plays a substantial role, and in compensatory postural adjustments. Studies on cats proved that many cells in PPC show changes in discharge before and during gait modifications, both when visual information is provided and not, underlying the role of this area in the estimation of limb position relative to the position of an obstacle [6]. This evidence forms the basis for the PPC body schema: an internal unconscious and constantly updated representation of body positions in space and the configurations of its parts in relation to each other and the world [7], [8].

Similarly, the cerebellum is supposed to play a role in integrating multisensory cortical and subcortical inputs and in online detection and correction of motor errors [9]. Sensory signals from different peripheral receptors reach the cerebellum, which also receives inputs from motor cortices [10]. The integration of these signals is thought to be part of the cerebellar feedback and feedforward error detection processes involved in online motor adjustments [11]. Involvement of the cerebellum in the encoding of limb spatial position has also been proposed [11].

Besides motor involvement, lesions in both these brain structures have been associated with similar cognitive deficits, namely visuomotor integration, spatial cognition, working memory, and expressive language [12]–[14].

Current knowledge on PPC and cerebellar contributions to sensorimotor integration focuses mainly on reach-to-grasp movements [15] and often relies on studies conducted separately on people with parietal or cerebellar lesions. The overlap between many motor and cognitive deficits resulting from PPC or cerebellar lesions can mask their relative contribution to sensorimotor integration processes. This often prevents straightforward localizing diagnosis [16]. Thus, disentangling their relative contribution has both a clinical and a theoretical rationale.

Aims

This study aims to define motor and distinguishing cognitive features to disentangle PPC and cerebellar involvement in two sensorimotor-related functions: gait and body schema. Specific aims were: (1) identify specific stability, spatiotemporal, and kinematic parameters associated with either parietal or cerebellar functional inhibition; (2) assess the potential of the walking distance estimation task to discriminate PPC and cerebellar contributions to sensorimotor integration.

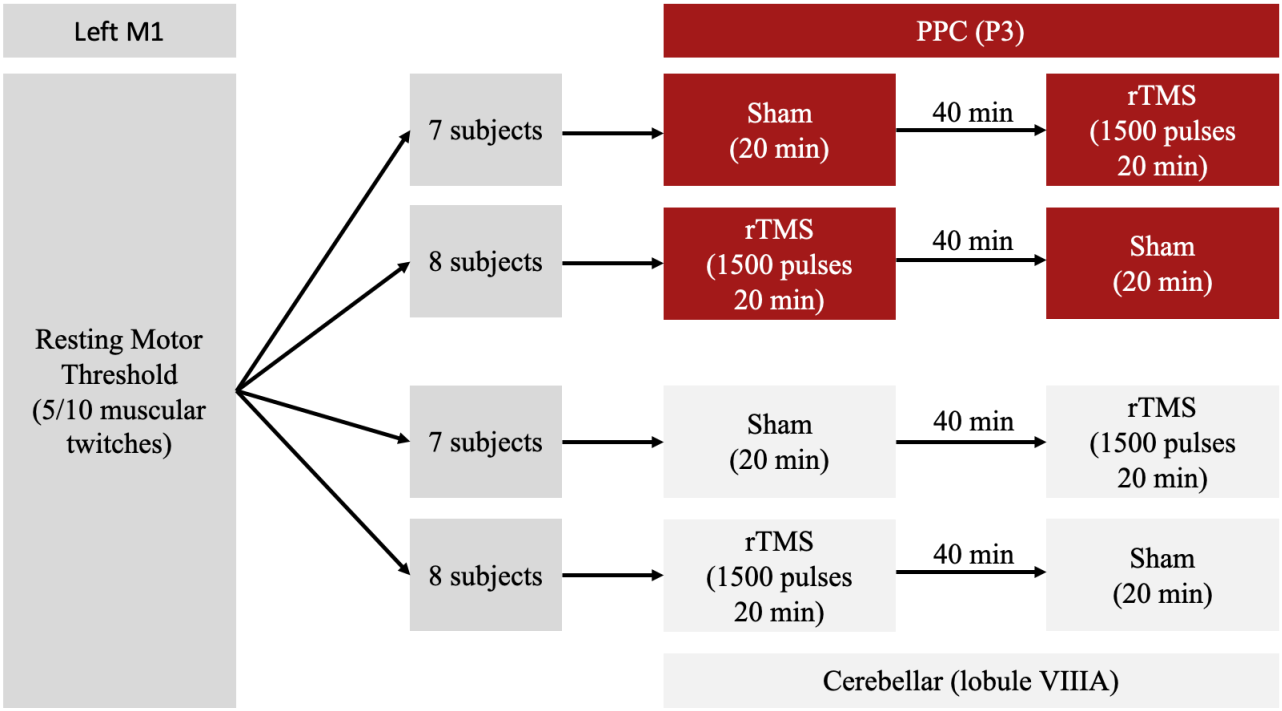
Material and methods

This study was carried out in accordance with the guidelines of the Declaration of Helsinki and was approved by the ethical committee of the Department of General Psychology, University of Padua (protocol N.4562).

Participants

Thirty participants recruited among the undergraduate students of the psychology department of Padova University took voluntarily part in the study and provided written informed consent. All were right-handed and had a normal or correct to-normal vision. Inclusion criteria comprised no neurological, psychiatric, or medical condition contraindicating transcranial magnetic stimulation (TMS) [17]. Exclusion criteria consisted of diagnosed gait alterations or movement abnormalities and orthopaedic pathologies. After TMS eligibility assessment, 15 participants were randomly allocated to the PPC and 15 to the cerebellar stimulation group. Randomization was ensured by assigning each subject a number reflecting the enrollment order: odd numbers were allocated to the PPC group, and even numbers to the cerebellar one. Each subject received the sham and the real stimulations within a single-day session in a counterbalanced order (see **Fig. 1**).

Fig.1 TMS subjects random allocation and condition balancing.



Repetitive Transcranial Magnetic Stimulation (rTMS)

rTMS was delivered using a Magstim-Rapid² stimulator with a D70² B.I. air-cooled figure-of-eight coil allowing long stimulation sessions. Left PPC and right cerebellum were chosen as targets of the stimulation: left PPC seems to play a general role in walking in the real-world and visuomotor adaptations [18], [19] while right cerebellum (i.e., VIII-A lobule of the posterior cerebellum) is reachable by TMS and is associated with motor functions [20]. Each subject underwent two sessions of stimulation within the same day:

1. The rTMS [1500 pulses, 1Hz frequency at 90% intensity of the individual resting motor threshold (rMT)] was delivered over either the left PPC or cerebellum. Low-frequency rTMS (≤1Hz) has been proven to have inhibitory effects, with an after-effect duration proportional to the length of the stimulation period [21]–[24].

2. A sham coil delivered a control stimulation over the same areas and for the same time.

The order of stimulation sessions was counterbalanced across participants. To control for possible carry-over effects, we waited 40 minutes between the two sessions (i.e., 20 minutes longer than the estimated after-effects of the stimulation [21]–[23].

The rMTs were assessed via motor-evoked potentials (MEPs) by delivering single-pulse TMS over the primary motor cortex (M1). The coil was placed tangentially to the scalp with the handle pointing backwards and laterally at 45° away from the sagittal axis [25]. The muscular elicited activity was recorded over the right hand's first dorsal interosseus muscle (FDI). The minimum output intensity leading to 5 MEPs in 10 consecutive trials was selected as individual rMT. The rTMS stimulation intensity was eventually set at 90% of the rMT. The coil was positioned tangentially to the scalp over

P3 to localize the left PPC, according to the international 10-20 EEG coordinate system [26]. To target the cerebellum, we positioned the coil 1 cm inferior and 3 cm lateral to the inion, following most studies [27], [28]. In this case, the coil was positioned tangentially to the scalp with the handle directed upwards: this was shown to be the optimal coil orientation to reach the cerebellum [20]. We did not opt for a double-cone coil to stimulate the cerebellum, as suggested in other works [27], as this was proved to induce invasive stimulation, often leading to pain and discomfort in neck muscles [29].

Inertial Measurement Units (IMUs)

Participants were equipped with eight synchronized Xsens MTw IMUs (Xsens technologies, Enschede, Netherlands) secured with straps respectively on the sternum (xiphoid process), pelvis (vertebra L5), tights (left and right trochanters), shanks (left and right proximal medial frontal aspect), and feet. The sensors provide filtered and strapped-down samples of acceleration, angular velocity, and magnetic rate vectors, as well as the estimated quaternion of orientation [30]. The data are transferred at a rate of 100 Hz and transformed into an inertial coordinate system [30]. Anthropometric parameters were gathered for every subject, including weight, sole shoe height, and foot length. IMUs sensors were calibrated following the recommended stand still and walking procedure allowing the software model to establish a relation between sensors and segment orientation [30]. The subjects stand still with arms straight alongside the body and palms facing the legs for 2.5 seconds (i.e., N-pose). Then, they were asked to walk forward for an additional 5 seconds, make a U-turn and walk back to the starting N-pose [31].

Postural stability was assessed through the following parameters: (i) centre of mass (COM) path length trajectory (PL); (ii) ellipse area containing 95% of the COM points (EA); (iii) COM range of movement (ROM) in anterior-posterior (ROMap) and mediolateral directions (ROMml); (iv) root mean square (RMS) of the COM positions in anterior-posterior (RMSap) and mediolateral directions (RMSml). Spatiotemporal parameters of interest were the following: cadence (step/min), speed (m/sec), stance and swing times (sec), single and double support time (sec), stride and step time (sec), stride and step length (m), and step width (cm). To evaluate lower body kinematics, we considered hip, knee, and ankle joint angular displacement in the sagittal plane. For each parameter mentioned above, we quantify within-subject variability. A widely used measure of variability is the coefficient of variation (CV), defined as the ratio of the standard deviation to the mean. Thus, the CV value is highly sensitive to the presence of outliers and assumes a normal population sample distribution [32].

On the contrary, the interquartile range (IQR), defined as the difference between the 75th and 25th percentiles of the data, does not require a normality assumption, and it is, therefore, more robust to the presence of outliers [32]. Considering this, we opted for IQR as a measure of data variability. All the parameters were normalized by individual height, weight, and feet length via a detrending normalization technique [33].

Task

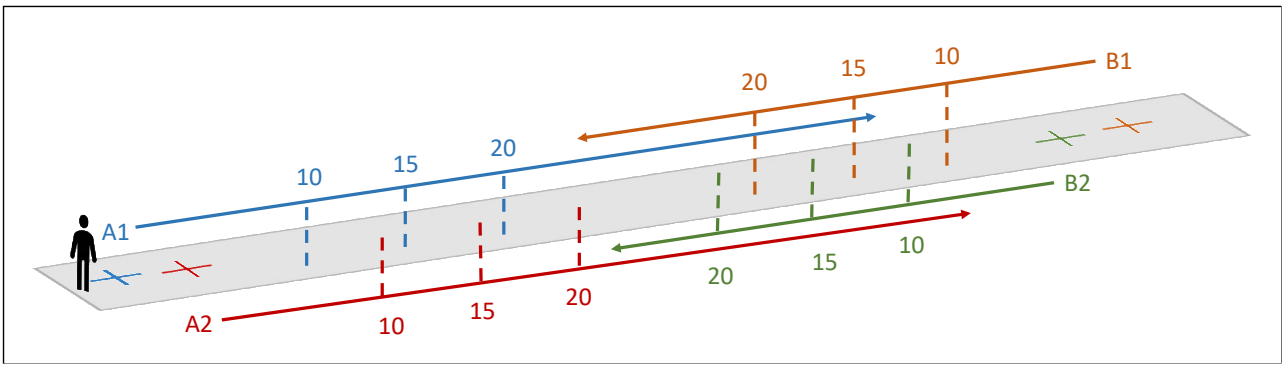
Each of the following tasks was executed donning the IMUs after the sham and the real stimulations in following presentation order:

1. Balance assessment: Romberg's Test is a clinical neurological assessment to evaluate postural instability (ataxia) [34]. Ataxia may have a cerebellar or sensory aetiology. People with sensory ataxia can compensate for balance instability via visual feedback but display upright instability when visual information is precluded. On the contrary, people with cerebellar ataxia display balance instability both with the eyes open (EO) and closed (EC) [35]. A re-adaptation of Romberg's test was used to assess balance before and after the stimulation. Specifically, subjects were asked to stand, keeping their feet hip-width apart, with their arms straight alongside the body. Firstly, they had to stand still for 10 seconds keeping their eyes open; secondly, the task was repeated with the eyes closed.

2. Walking assessment: participants were asked to walk at a self-selected speed on a 20 meters walkway four times.

3. Body schema assessment: a distance estimation task was used to assess possible body schema alterations while wearing IMUs. At the beginning of each trial, participants were asked to settle in one of four possible starting positions (i.e., A1; B1; A2; B2), keeping their eyes closed till the start of each trial. Once the experimenter instructed them to open their eyes, a target was presented for 3 seconds at three possible distances from the starting position (i.e., 10, 15, and 20 meters). Varying target distances and starting positions prevented possible learning effects. Immediately after the target was removed, the participant was instructed to walk till the estimated target position was reached (see **Fig. 2**).

Fig.2 Distance estimation task



Schematic representation of the distance estimation task conditions. A1, A2, B1 and B2 represent the position from which the subject started to walk to reach the target at 10, 15 or 20 meter distances.

Participants were advised to avoid using any strategy to estimate the target position (e.g., counting steps, looking at landmarks) and to rely just on their body position in space with regard to the target. Half of the trials were executed with the eyes open (12 trials) and half with the eyes closed (12 trials) after sham and real stimulations. Once the participant

reached the estimated target position, one experimenter measured the distance travelled from the starting position through a laser distance meter. Eyes conditions, distances, and starting conditions were randomized in RStudio software. No feedback was provided about the performance at the end of each trial. Tasks execution lasted about 15 minutes.

Data Analysis

1. Stabilometry and gait: a custom post-processing algorithm was developed in MATLAB-R2020b. Xsens output files were processed to identify gait events [i.e., heel strike (HS) and toe-off (TO), [36]] for each trial. The HS and TO events detection were based on knee and ankle sagittal angle functions. The events were used to identify gait cycles for the right and left sides. The first and last two meters of each trial were removed from the analysis to avoid confounding effects from starting and stopping at the edges of the walkway [37].

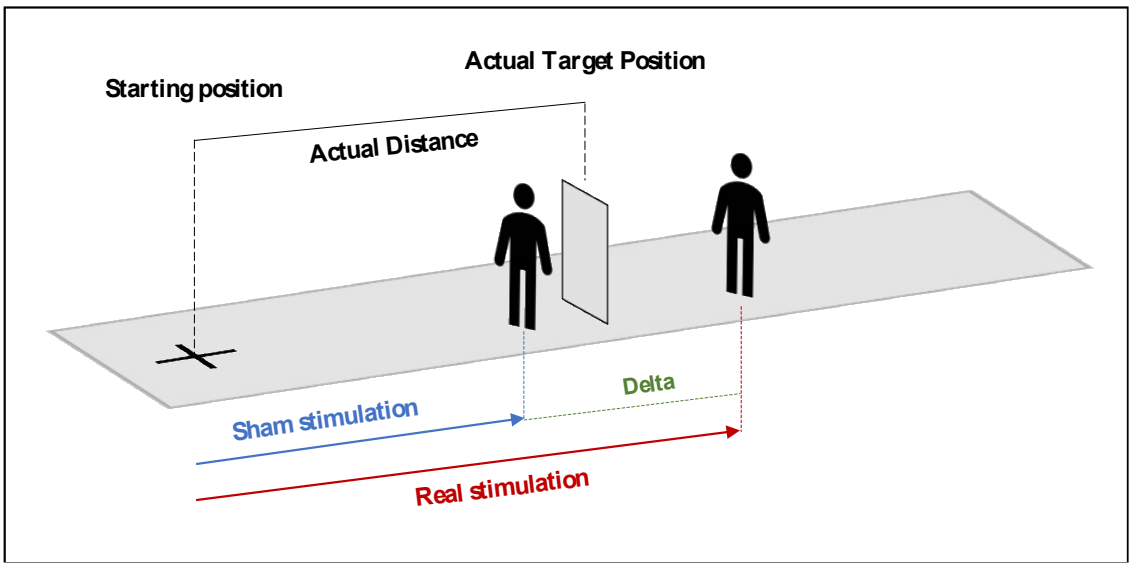
2. Distance estimation task: to control for inter-individual variability in the ability to estimate distances, we considered the performances in the sham trials as measures of the actual individual ability to estimate distances. Then, we computed the difference between the distance travelled after the real stimulation and the distance travelled after the sham stimulation separately for each distance and eye condition (i.e., EO: 10, 15, 20 m; EC:10, 15, 20 m). See **Fig. 3** for a schematic representation. Delta values were used as indices of the stimulation effect on the ability to estimate distances, with:

Delta = 0 index of no effect of stimulation

Delta > 0 index of overestimation of distance

Delta < 0 index of underestimation of distance

Fig.3 Schematic representation of delta values computation



Delta values were calculated as the difference between the path travelled after real stimulation in meters (red line) and sham stimulation (blue line). Trials were clustered and analysed separately by distance (10m, 15m, 20m) and eyes condition (open, closed).

Statistics

The statistical analysis was performed using the RStudio software (RStudio Team, 2015, Version 1.2.5001). Statistical significance was set at p-value < 0.05. Data distribution was tested with a Shapiro-Wilks normality test. A two-sided Wilcoxon rank sum test or a two-sample t-test was performed according to data distribution to compare PPC and cerebellar groups. Within-group differences to test for possible stimulation effects (sham *vs* real) and eyes effects (EO *vs* EC) were tested with a paired sample t-test or a paired two-sided Wilcoxon rank sum test.

Results

Participants

Of the 30 participants initially recruited (21 females and 9 males; mean ± SD age: 23.4 ± 2.9; range: [19-31]), one subject of the PPC group was excluded from the analysis as the TMS coil moved from the target region during the real stimulation. See **Table 1** for demographics related to the final analysed sample.

Table 1. Demographic characteristics of the sample

Parameter	Units	PPC	Cerebellar
Age	*years*	24 ± 2,95	22 ± 2,79
Females	*%*	64%	73%
Body Mass	*kg*	64,14 ± 12,30	66,89 ± 12,30
Height	*m*	1,71 ± 0,10	1,71 ± 0,10
BMI	kg/m^2	21,80 ± 2,24	22,59 ± 2,76
RMT	*%*	58%	59%
Nasion-Inion	*cm*	35,10 ± 2,36	35,28 ± 2,14
A1-A2	*cm*	34,92 ± 1,90	35,92 ± 1,77

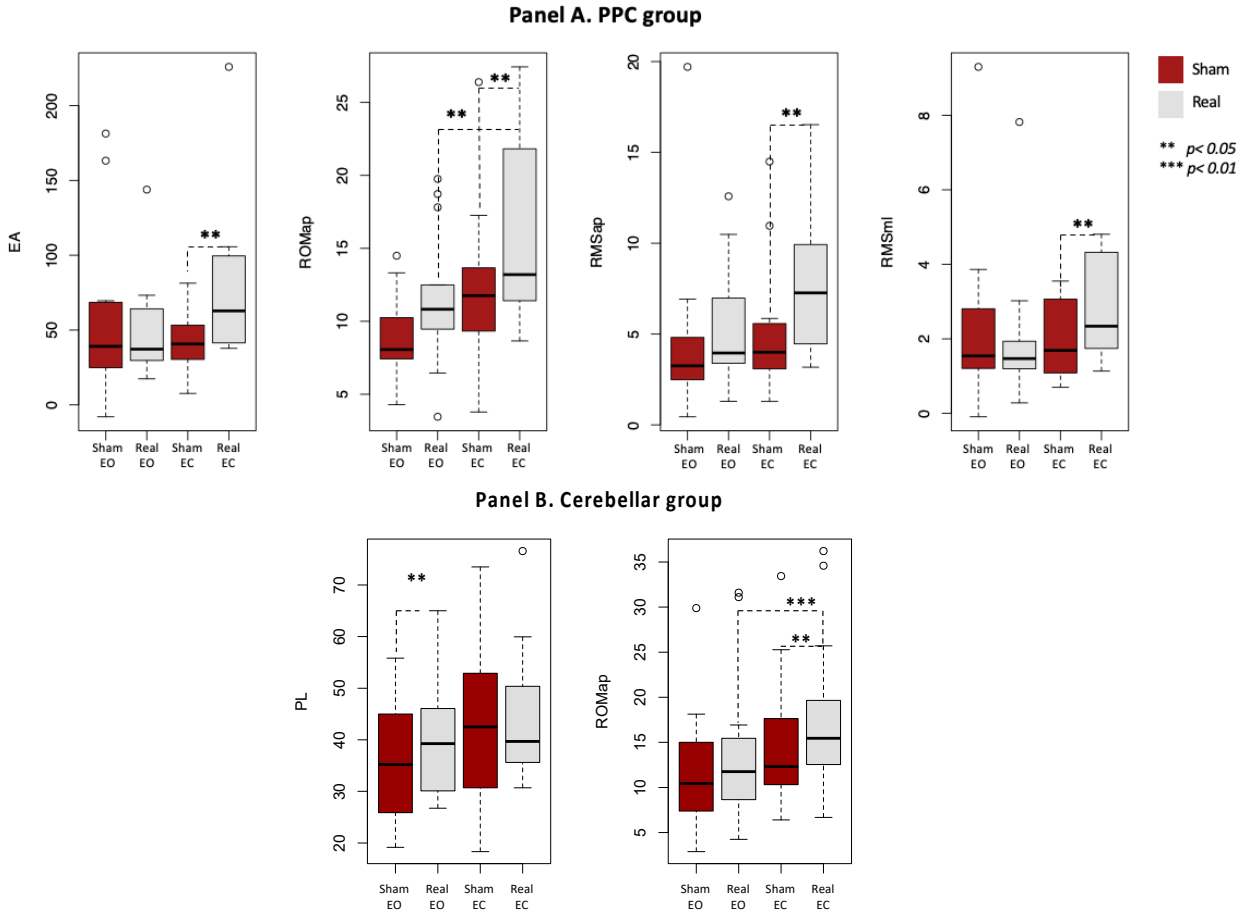
PPC: Posterior Parietal Cortex; BMI: Body Mass Index; RMT: Resting Motor Threshold; A1-A2: distance between earlobe electrodes.

Balance assessment: Roberg's Test

The Shapiro normality test revealed no normal distribution for all the variables. **Fig.4** shows significant results of balance performances. Real stimulation EC *vs.* sham stimulation EC within the PPC group showed higher EA (p-value = 0.04),

ROMap (p-value = 0.02), RMSap (p-value = 0.04) and RMSml (p-value = 0.03) after the real stimulation. Additionally, PPC in real stimulation EO *vs.* EC conditions showed higher ROMap in the EC condition (p-value = 0.04). Similarly, the cerebellar group displayed higher ROMap after the real stimulation in the EC condition compared to the sham EC one (p-value = 0.03), and in the real stimulation EC condition compared to the real stimulation EO one (p-value = 0.01). The PL of the cerebellar group resulted longer after the real stimulation compared to the sham in the EO condition (p-value = 0.04). A between group difference emerged in the real stimulation EC condition, with PPC group having higher RMSml compared to cerebellar group (PPC mean ± SD: 2.72 ± 1.29 mm; cerebellar: 1.47 ± 0.45 mm; p-value = 0.01). All variables mean ± SD are reported in Supplementary material, Table S1.

Fig.4 Romberg's Test results



Significant Romberg's Test data of PPC group (Panel A), and cerebellar group (Panel B) are represented. Data on eyes open (red fill colour) and eyes closed (grey fill colour) conditions for both sham and real stimulation are reported. Panel A: PPC group show higher EA, ROMap, RMSap and RMSml in the real stimulation EC condition compared to the sham one (mean ± SD real EA: 78.22 ± 52.77 vs. sham: 42.42 ± 22.97; real ROMap: 16.11± 6.66 vs. sham: 12 ± 5.22; real RMSap: 8 ± 3.99 vs. sham 5 ± 3.49; real RMSml: 3 ± 1. 29 vs. sham: 2 ± 1,01). ROMap after real stimulation resulted higher in EC vs EO real stimulation (real ROMap EC: 16.11± 6.66 vs. real EO: 11.51 ± 4.58) Panel B: Cerebellar PL resulted higher after real stimulation in the EO condition compared to the sham one (mean ± SD real PL: 40.46 ± 12.65 vs. sham: 36.21 ± 12.32). Cerebellar ROMap increased after the real stimulation compared to sham in the EC condition (mean ± SD real ROMap: 18 ± 8.64, vs sham: 14 ± 7.65) and compared to the real EO condition (mean ± SD real EO: 13.41 ± 8.1).

Gait: spatiotemporal

The Shapiro normality test revealed no normal distribution for all the variables. Spatiotemporal parameters (mean ± SD) of PPC and cerebellar group are reported respectively in **Table 2** and **Table 3**. PPC group significantly increased the variability from sham EC condition to real EC condition in cadence (sham_mean ± SD: 2.69 ± 2.05 step/min, real: 4.39 ± 2.08 step/min, p-value = 0.01) and stride time (sham_mean ± SD: 0.05 ± 0.03 s, real: 0.07 ± 0.04 s, p-value = 0.01). Significant differences were observed between EO and EC conditions after real stimulation in the variability of cadence (EO_mean ± SD: 2.36 ± 1.11 step/min, EC: 4.39 ± 2.08 step/min, p-value = 0.01), speed (EO_mean ± SD: 0.05 ± 0.02 step/min; EC: 0.11 ± 0.07 step/min, p-value = 0.02), stance time (EO_mean ± SD: 0.04 ± 0.04 s, EC: 0.06 ± 0.03 s, p-value = 0.02), and step time (EO_mean ± SD: 0.02 ± 0.01 s, EC: 0.04 ± 0.02 s, V = 10, p-value < 0.01). No differences were observed between the EO and EC conditions after sham stimulation in the same variables. Swing time significantly increase after real stimulation in the EC condition (mean ± SD: 0.35 ± 0.02 s) compared to the EO one (mean ± SD: 0.04 ± 0.04 s, p-value < 0.01), while no differences were observed between EO and EC conditions after sham stimulation. The same pattern was observed for the step width, which increased after real stimulation in EC condition (mean ± SD: 12,29 ± 3,80 cm) compared to EO one (mean ± SD: 11,65 ± 4,20 cm, p-value =0.03).

Cerebellar group significantly increased the variability of the stride length after real stimulation in the EC condition compared to sham (sham_mean ± SD: 0.15 ± 0.06 m, real: 0.17 ± 0.06 m, p-value = 0.04). Cerebellar group' speed variability increased after real stimulation in the EC condition compared to the EO one (EO_mean ± SD: 0.07 ± 0.03 m/s, EC: 0.12 ± 0.08 m/s, p-value = 0.05) while no differences were observed between the EO and EC condition following the sham. In addition, step width increased after real stimulation in the EC condition (mean ± SD: 12,13 ± 3,89 cm), compared to the EO one (mean ± SD: 10,86 ± 3,43cm, p-value < 0.01) while no differences were observed between the equivalent sham conditions. No significant between group differences were observed.

Table 2. PPC group spatiotemporal parameters

PPC Group									
Parameter	Units	Sham		Real		Sham EO *vs* EC	Real EO *vs* EC	Sham *vs* Real EO	Sham *vs* Real EC
		EO	EC	EO	EC				
Cadence	*[step/ min]*	115,95 ± 7,25	106,64 ± 6,91	115,93 ± 6,38	106,72 ± 5,77	ns	ns	ns	ns
Cadence IQR		2,62 ± 1,45	2,69 ± 2,05	2,36 ± 1,11	4,39 ± 2,08	ns	**0.01**	ns	**0.017**
Speed	*[m/s]*	1,41 ± 0,16	1,12 ± 0,16	1,43 ± 0,12	1,14 ± 0,11	< 0.01	< 0.01	ns	ns
Speed IQR		0,07 ± 0,03	0,09 ± 0,08	0,05 ± 0,02	0,11 ± 0,07	ns	**0.02**	ns	ns
Stance Time	*[s]*	0,701 ± 0,053	0,779 ± 0,065	0,699 ± 0,043	0,776 ± 0,053	< 0.01	< 0.01	ns	ns
Stance Time IQR		0,051 ± 0,068	0,055 ± 0,031	0,040 ± 0,040	0,064 ± 0,031	ns	**0.02**	ns	ns
Swing Time	*[s]*	0,337 ± 0,018	0,349 ± 0,021	0,337 ± 0,020	0,353 ± 0,023	ns	**< 0.01**	ns	ns
Swing Time IQR		0,039 ± 0,069	0,027 ± 0,009	0,048 ± 0,079	0,027 ± 0,014	ns	ns	ns	ns
Single Support	*[s]*	0,337 ± 0,018	0,349 ± 0,021	0,337 ± 0,020	0,353 ± 0,023	< 0.01	< 0.01	ns	ns

Single Support IQR		0,039 ± 0,069	0,027 ± 0,009	0,048 ± 0,079	0,027 ± 0,014	ns	ns	ns	ns
Double Support	*[s]*	0,182 ± 0,020	0,219 ± 0,030	0,183 ± 0,015	0,215 ± 0,022	< 0.01	< 0.01	ns	ns
Double Support IQR		0,038 ± 0,068	0,041 ± 0,038	0,038 ± 0,068	0,041 ± 0,043	0.02	ns	ns	ns
Stride Time	*[s]*	1,037 ± 0,064	1,129 ± 0,078	1,036 ± 0,060	1,130 ± 0,071	< 0.01	< 0.01	ns	ns
Stride Time IQR		0,030 ± 0,013	0,053 ± 0,028	0,033 ± 0,006	0,073 ± 0,041	< 0.01	< 0.01	ns	**0.01**
Step Time	*[s]*	0,520 ± 0,033	0,564 ± 0,038	0,519 ± 0,030	0,563 ± 0,034	< 0.01	< 0.01	ns	ns
Step Time IQR		0,023 ± 0,008	0,036 ± 0,022	0,021 ± 0,007	0,043 ± 0,023	ns	**< 0.01**	ns	ns
Stride Length	*[m]*	146,55 ± 8,65	126,07 ± 12,60	148,46 ± 7,12	128,93 ± 9,88	< 0.01	< 0.01	ns	ns
Stride Length IQR		0,07 ± 0,02	0,11 ± 0,05	0,06 ± 0,02	0,13 ± 0,05	0.01	< 0.01	ns	ns
Step Length	*[m]*	73,33 ± 4,33	62,63 ± 6,57	74,12 ± 3,56	64,03 ± 5,10	< 0.01	< 0.01	ns	ns
Step Length IQR		0,08 ± 0,08	0,10 ± 0,09	0,06 ± 0,03	0,09 ± 0,06	< 0.01	< 0.01	ns	ns
Step Width	*[cm]*	11,05 ± 4,49	11,84 ± 4,61	11,65 ± 4,20	12,29 ± 3,80	ns	**0.03**	ns	ns
Step Width IQR		3,03 ± 1,06	5,15 ± 1,35	2,77 ± 0,63	4,96 ± 0,89	< 0.01	< 0.01	ns	ns

Mean values ± standard deviations of spatiotemporal parameters and mean interquartile range ± standard deviations, as measure of spatiotemporal parameters variability. P-values in bold are the meaningful ones. NS = not significant (p>0.05)

Table 3. Cerebellar group spatiotemporal parameters

Cerebellar Group									
Parameter	Units	Sham		Real		Sham EO *vs* EC	Real EO *vs* EC	Sham *vs* Real EO	Sham *vs* Real EC
		EO	EC	EO	EC				
Cadence	*[step/ min]*	113,83 ± 6,54	99,90 ± 11,26	113,18 ± 7,00	99,32 ± 14,20	< 0.01	< 0.01	ns	ns
Cadence IQR		3,16 ± 1,67	5,40 ± 3,10	2,72 ± 1,11	4,38 ± 2,83	ns	ns	ns	ns
Speed	*[m/s]*	1,42 ± 0,15	1,08 ± 0,23	1,43 ± 0,16	1,07 ± 0,26	< 0.01	< 0.01	ns	ns
Speed IQR		0,08 ± 0,02	0,12 ± 0,06	0,07 ± 0,03	0,12 ± 0,08	ns	**0.05**	ns	ns
Stance Time	*[s]*	0,713 ± 0,048	0,833 ± 0,100	0,716 ± 0,052	0,844 ± 0,145	< 0.01	< 0.01	ns	ns
Stance Time IQR		0,033 ± 0,015	0,094 ± 0,055	0,031 ± 0,023	0,101 ± 0,091	< 0.01	< 0.01	ns	ns
Swing Time	*[s]*	0,343 ± 0,013	0,372 ± 0,028	0,344 ± 0,012	0,371 ± 0,029	< 0.01	< 0.01	ns	ns
Swing Time IQR		0,015 ± 0,011	0,033 ± 0,014	0,016 ± 0,019	0,031 ± 0,014	< 0.01	< 0.01	ns	ns
Single Support	*[s]*	0,343 ± 0,013	0,372 ± 0,028	0,344 ± 0,012	0,371 ± 0,029	< 0.01	< 0.01	ns	ns
Single Support IQR		0,015 ± 0,011	0,033 ± 0,014	0,016 ± 0,019	0,034 ± 0,018	< 0.01	< 0.01	ns	ns
Double Support	*[s]*	0,187 ± 0,021	0,233 ± 0,042	0,188 ± 0,022	0,241 ± 0,063	< 0.01	< 0.01	ns	ns
Double Support IQR		0,019 ± 0,015	0,042 ± 0,020	0,022 ± 0,014	0,050 ± 0,039	< 0.01	0.03	ns	ns
Stride Time	*[s]*	1,055 ± 0,058	1,204 ± 0,122	1,061 ± 0,062	1,215 ± 0,174	< 0.01	< 0.01	ns	ns
Stride Time IQR		0,040 ± 0,013	0,115 ± 0,063	0,033 ± 0,008	0,129 ± 0,108	< 0.01	< 0.01	ns	ns
Step Time	*[s]*	0,529 ± 0,030	0,601 ± 0,058	0,533 ± 0,032	0,607 ± 0,084	< 0.01	< 0.01	ns	ns
Step Time IQR		0,025 ± 0,006	0,063 ± 0,035	0,023 ± 0,009	0,073 ± 0,061	< 0.01	< 0.01	ns	ns
Stride Length	*[m]*	151,68 ± 8,76	128,05 ± 16,29	152,09 ± 9,25	129,06 ± 13,87	< 0.01	< 0.01	ns	ns
Stride Length IQR		0,76 ± 0,04	0,15 ± 0,06	0,07 ± 0,02	0,17 ± 0,06	< 0.01	< 0.01	ns	**0.04**
Step Length	*[m]*	75,54 ± 4,21	63,90 ± 7,78	75,63 ± 4,36	64,58 ± 6,63	< 0.01	< 0.01	ns	ns
Step Length IQR		0,06 ± 0,02	0,09 ± 0,03	0,06 ± 0,02	0,10 ± 0,04	< 0.01	0.01	ns	ns
Step Width	*[cm]*	11,09 ± 3,39	11,67 ± 4,04	10,86 ± 3,43	12,13 ± 3,89	ns	**< 0.01**	ns	ns
Step Width IQR		3,39 ± 1,05	5,54 ± 1,80	3,02 ± 0,54	5, 66 ± 1,66	< 0.01	0.01	ns	ns

Mean values ± standard deviations of spatiotemporal parameters and mean interquartile range ± standard deviations, as measure of variability.

P-values in bold are the meaningful ones. NS = not significant (p>0.05)

Gait: Kinematic

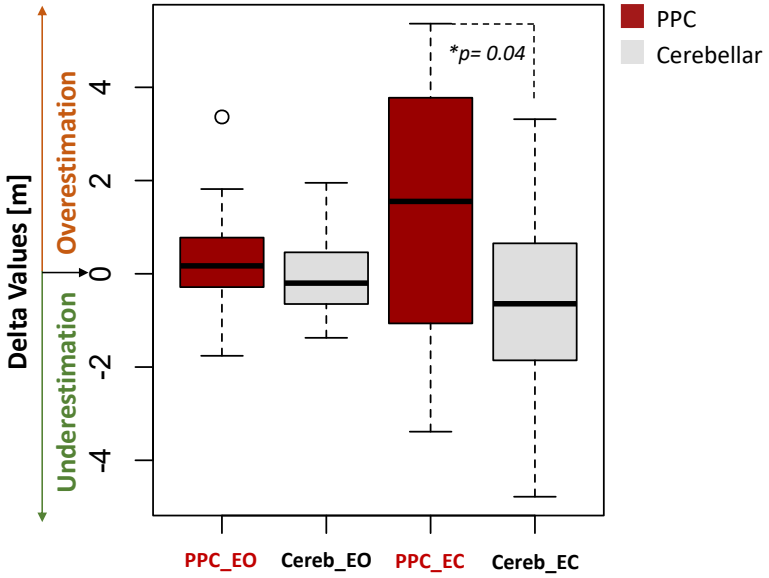
The Shapiro normality test revealed no normal distribution for all the variables. All kinematic parameters (mean ± SD) of PPC and cerebellar group are reported in Supplementary material **Table S2**. PPC group after real stimulation increased the variability of the following kinematic parameters in the EC condition compared to the EO one: average knee angle (EO_mean ± SD: 1.98 ± 1.05 deg; EC: 2.21 ± 0.97 deg, p-value = 0.05), knee angle at foot elevation (EO_mean ± SD: 3.43 ± 1.31 deg; EC: 3.96 ± 1.22 deg, p-value < 0.01), ankle minimum angle (EO_mean ± SD: 4.07 ± 1.94 deg; EC: 4.97 ± 1.12 deg, p-value = 0.02), ankle angle at toe off event (EO_mean ± SD: 4.07 ± 1.94 deg; EC: 4.97 ± 1.12 deg, p-value = 0.02). No significant variations between sham EO *vs*. EC condition were observed for the same parameters. Knee ROM increased after real stimulation between EO and EC (EO_mean ± SD: 65.52 ± 5.79 deg; EC: 66.08 ± 5.88 deg, p-value = 0.02). Additionally, the hip ROM increased after real stimulation in the EC condition compared with sham (sham_EO mean ± SD: 37.37.42 ± 4.14 deg; real_EO: 38.39 ± 4.37 deg, p=0.02).

Cerebellar group show increased variability of the maximum ankle angle and of the knee angle at foot elevation after the real stimulation in the EC condition compared to the EO one, respectively: maximum ankle angle (EO_mean ± SD: 2.05 ± 0.58 deg; EC: 2.57 ± 0.84, p<0.01); knee angle at foot elevation (EO_mean ± SD: 3.77 ± 1.85 deg; EC: 5.24 ± 2.16, p=0.02). The variation of the average ankle angle increased as well from sham EC condition to real EC condition (sham_EC mean ± SD: 1.76 ± 0.97 deg; real_EC: 2.61± 1.72 1, p=0.02). No significant between group differences were observed.

Distance Estimation Task

The Shapiro normality test revealed normal distribution for delta values in the 10 m (p-value = 0.07) and 20 m (p-value = 0.56) conditions. No normal distribution emerged for deltas of the 15 m condition (p-value = 0.04). Significant difference emerged between PPC and cerebellar groups in the EC condition for the 20 m distance, with PPC group overestimating distances compared to cerebellar group (median error [range] of PPC EC: 1.55 m [-0.84; 3.48]; Cerebellar EC: -0.64 m [-1.86; 0.65], p-value = 0.04). Results are summarized in **Fig.5**. For all conditions mean and median values see Supplementary material, **Table S3**.

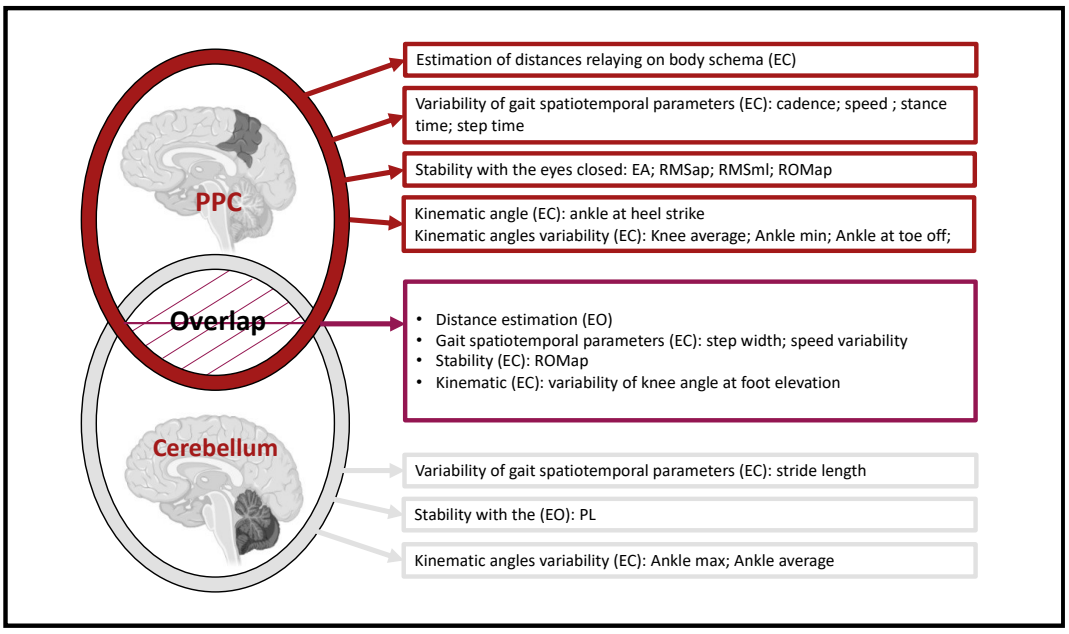
Fig.5 Distance estimation results



Boxplots represent the delta values computed as (real – sham) travelled paths, in the trials of the target appearing 20 m from the starting point. Delta values around 0 are indices of no changes in the ability to estimate distances after stimulation. Positive value indicates overestimation whereas negative values underestimation. PPC group in the eyes closed trials (EC), tended to overestimate the target position [median error (1st-2nd quartile): 1.55 m (-0.84, 3.48)] significantly more than cerebellar group [median error (1st-2nd quartile): -0.64 m (-1.86, 0.65)]. No significant differences were observed between groups in the trials performed with the eyes open [median error (1st-2nd quartile) PPC_EO: 0.047m (-0.33, 0.62); median error cereb_EO: 0.20m [-0.65, 0.46]).

Results on balance, spatiotemporal, kinematic and distance estimation parameters are summarized in **Fig.6**.

Fig.6 Summary of the results



Discussion

This study aimed to address the functional contribution of PPC and cerebellum to gait and body schema. Specifically, we were interested in elucidating their roles employing an rTMS paradigm. Our data have proved the potential of specific gait and stability parameters as well as the walking distance estimation task to differentiate PPC and cerebellar contribution to sensorimotor integration. More in detail: increased instability emerged in both groups after the real stimulation compared with the sham condition. Notably, the PPC group resulted unstable in the EC condition, while cerebellar group instability was observed both with the EC and EO conditions. Spatiotemporal gait variability increased after real stimulation, mainly between EO and EC conditions in both groups but affecting different parameters: mainly temporal parameters in the PPC group and spatial parameters in the cerebellar group. Gait kinematics of the ankle and knee was affected by the stimulation in both groups between the EO and EC conditions, possibly disclosing two patterns of gait alterations. Finally, the altered walking distance estimation task affecting just the PPC group may highlight the role of this area in body schema representation.

PPC functional inhibition effects

PPC functional inhibition effects emerged when visual feedback was lacking. PPC group instability increased after real stimulation as measured by higher EA and increased ROM on the anterior-posterior and mediolateral axis in the EC condition. No differences between sham and real stimulations were observed with eyes open. These results align with previous studies showing the effects of sensory ataxia (SA) on Romberg's test [35]. In SA, peripheral impairments of the somatosensory afferents lead to interruption of sensory feedback used to track our limb positions in space. This, in turn, leads to gait abnormalities (e.g., increased stepping width) and instability when patients cannot visually compensate for the lack of peripheral sensory feedback. The PPC has a crucial role in integrating multisensory signals to provide a coherent representation of our body in space (i.e., body schema) and to set proper motor outputs [38]. By functionally inhibiting the PPC, we interfered with the central process of sensory integration, mimicking sensory ataxia. This explains why the PPC group balance was altered just in the absence of visual feedback. Secondly, cadence, speed, stance, and step time variabilities increased after the real stimulation, as well as the step width in the EC condition compared to the EO one. These gait features can be interpreted as signs of unsteady gait, typically observed in people with SA when visual information is lacking: general disturbances of sensory feedback and/or integration during walking (regardless of the sensory modality) have been proved to be tightly linked to increased spatiotemporal gait variability [9]. Altering PPC sensory integration processes leads to an altered perception of steps' timing and placing, resulting in higher temporal variability and a wider support base. Kinematic alterations in the PPC group affected mainly the ankle joint: we observed a larger ankle angle at heel strike, compatible with the so-called "heavy step" walking and higher variability of the knee angle at foot elevation, compatible with the "high stepping" pattern [39], both typical of SA. The increased variability in

other ankle angles (i.e., minimum ankle angle, the angle at toe-off) and knee angles (i.e., average knee angle) may be the result of a general alteration in the body schema leading to the inefficient ankle and knee placements while walking [40].

Cerebellar functional inhibition effects

The cerebellar role in gait and balance emerged after the real stimulation and was less dependent on visual feedback. Instability was observed after the real stimulation in the EO (i.e., longer PL) and EC condition (i.e., increased ROM in the anterior-posterior axis). Literature on cerebellar ataxia is in line with these findings, showing that people with cerebellar lesions have instability regardless of the visual feedback compensation [35].

The observed wider base of support may be the expression of a compensatory strategy of the cerebellar group for keeping their balance while walking, which is a predominant characteristic of gait cerebellar ataxia (CA) [41]. Similarly, the observed increased variability in stride length and velocity matches the variable timing and spatial irregularity of foot placement in CA [41]. Increased gait variability seems to be the predominant emerging feature of the cerebellar inhibited group, as also observed in the kinematic of the knee (i.e., knee angle at foot elevation) and ankle angles (i.e., maximum and average angles). Contrary to expectations, these features emerged just in the EC trials. This may be the result of a not optimal stimulation of the cerebellum, which is a deeper brain structure compared to the PPC, thus more challenging to be reached with TMS [27]. Thus, the effects of stimulation may have become evident due to the summative effects of stimulation and task difficulty (i.e., tasks with the eyes closed).

PPC and Cerebellum: differences and overlap

After real stimulation, PPC and cerebellar group performances differed in several ways. First, the performance in the distance estimation task. After the real stimulation, the PPC group showed a significant overestimation of distances in longer trials (i.e., 20 m distances) in the EC condition compared to the cerebellar group. In the cerebellar group, the error rate between the EC and EO conditions was steady and near zero. This finding highlights the predominant role of PPC in using sensation to relate the body to target positions when walking. To explain the ability to estimate distances walked when visual info is not provided, the existence of a locomotor body schema has been previously hypothesized [42]. According to this theory, internalized knowledge of body segment lengths and position in space, along with the perceived flexo-extensions of lower limb joints while walking, allow humans to estimate travelled path distances [43]. As the internalized model of the body originates from PPC multisensory integration [44], the TMS inhibitory effect may have altered this capacity. Second, visual feedback plays a role in stability maintenance. PPC integrates visual feedback among the other sensory signals to keep balance. Thus, removing the compensatory role of vision in a balance task may disclose a PPC deficit.

On the contrary, cerebellar balance deficits do not improve with visual feedback. Third, even if spatiotemporal and kinematic analogies emerged after cerebellar and PPC functional inhibition (see **Fig.6**), two different tendencies can be

observed: PPC group was mainly affected in the temporal features of the eyes closed walking (i.e., cadence; speed; stance time; step time) while the cerebellar group in spatial ones with no impact of visual feedback (i.e., stride length and step width). While in PPC, increased time variability may result from disturbances of sensory feedback integrations [45], cerebellar wide-based walking and variable step length may be indices of the need for stability during locomotion.

Limitations

This study has a few limitations to point out. First, we couldn't use a system of neuro-navigation to target the sites of stimulation. These data should be replicated using neuro-navigation to spot with higher consistency the sites of stimulation. Second, the coil we adopted (i.e., figure-of-eight coil) is not the recommended one to reach the cerebellum: a double cone coil would be better to reach this and other deeper brain structures. However, some authors reported that double cone coil stimulation often led to pain and discomfort in neck muscles [27]. Additionally, many studies succeeded in stimulating the cerebellum by adopting a figure of eight coil [46]. Lastly, future studies should address the problem of tasks' order presentation, to ensure the absence of related biases, by randomizing the order of tasks between subjects.

Conclusions

This study provides contrasting motor and motor-related cognitive functions following PPC and cerebellar functional inhibition. Visual feedback role in balance control, eyes closed distance estimation tasks, and the prevalence of gait variability in spatial vs temporal parameters may be valuable indices to disentangle between a cerebellar or parietal sensorimotor integration deficit. Clinical practice can benefit from these results: i) new assessment procedures could be developed considering the disclosing diagnostic potential of gait and stability parameters; ii) the compensatory role of visual feedback can mask eventual PPC-related motor deficits; thus, differences between EO and EC performances should be tested; iii) tasks such as the distance estimation by walking are easy to administer, reliable and can be engaging for children. This type of paradigm looking for distinguishing similar clinical conditions can be used to improve differential diagnosis and consequent tailored rehabilitation.

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5.2 Brain oscillatory activity in adolescent idiopathic scoliosis

OPEN

Brain oscillatory activity in adolescent idiopathic scoliosis

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Pathophysiology of Adolescent Idiopathic Scoliosis (AIS) is not yet completely understood. This exploratory study aims to investigate two aspects neglected in clinical practice: a defective postural central nervous system control in AIS, and alterations of body schema due to scoliosis spinal deformities. We recorded EEG data and balance data in four different standing positions in 14 adolescents with AIS and in 14 controls. A re-adaptation of the Image Marking Procedure (IMP) assessed body schema alterations on the horizontal (Body Perception Indices (*BPIs*)) and vertical direction (interacromial and bisiliac axes inclinations). Our results revealed no differences in balance control between groups; higher EEG alpha relative power over sensorimotor areas ipsilateral to the side of the curve and a significant increase of theta relative power localized over the central areas in adolescents with AIS. The difference in *BPI* shoulder and *BPI* waist significantly differed between the two groups. The inclinations of the perceived interacromial axes in adolescents with AIS was opposite to the real inclination. Increased theta activity and alpha lateralization observed may be a compensatory strategy to overcome sensorimotor dysfunction mirrored by altered body schema. Scoliosis onset might be preceded by sensorimotor control impairments that last during curve progression.

Abbreviations

AIS	Adolescent idiopathic scoliosis
CNS	Central nervous system
PPC	Posterior parietal cortex
MRI	Magnetic resonance imaging
fMRI	Functional magnetic resonance imaging
EEG	Electroencephalography
TMS	Transcranial magnetic resonance imaging
LI	Laterality Index
BTD	Big toe distance
IMD	Inter-malleolar distance
EFL	Effective foot length
MFW	Maximum foot width
COP	Center of preassure
PL	Sway path length
EA	Ellipse area
AP	Antero-posterior
ML	Medio-lateral
RMS	Root mean square
SI	Simmetry index
QoL	Quality of life
SRS	Scoliosis Research Society
PS	Perceived size
AS	Actual size
BPI	Body Perception Index
BPIg	General Body Perception Index

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Adolescent Idiopathic Scoliosis (AIS) is a three-dimensional morphological spinal deformity, characterized by the deviation of the spine in the frontal plane (> 10 Cobb degrees) and the concurrent rotation of the affected vertebral bodies[1,2]. Epidemiological studies report an estimated prevalence of 1–3% among adolescents (10–16 years), with girls being more severely affected[3].

Although being a widespread disease, studied for decades, the cause and the pathophysiology of AIS is not yet completely understood, but multi-factorial hypotheses have been proposed: genetic predisposition, hormonal dysfunctions[4], defective postural control by the central nervous system (CNS)[5], and alterations of body schema[6–8]. There is growing evidence of cortical involvement in AIS suggesting that AIS could be the expression of a sub-clinical nervous system disorder. Indeed, visuo-spatial perceptual impairments, body spatial orientation alterations, and sensory integration disorders have been described[9]. According to the neurodevelopmental theories of AIS, a temporal imbalance between the musculoskeletal maturation and the central re-adaptation of body schema would in turn result in improper trunk muscles response to compensate for scoliosis initiating process[9]. Body schema is defined as the internal, unconscious representation of our body boundaries and shape, constantly updated by sensory information (e.g., visual, proprioceptive, tactile, kinesthetic) and responsible for setting proper motor output[10]. Just a few studies tried to assess body schema in AIS clinical population, providing indirect indices of altered postural perception, and global lower awareness of the body[11]. However, a validated assessment instrument is still lacking. The postulated maturation delay of the CNS body schema[9], could result from a peripheral impairment in sensory processing, a CNS multi-sensory integration impairment, and/or a motor output impairment.

Observations of impaired motor control were reported on brain imaging studies suggesting that an anomalous sensorimotor integration contributes to the cause of AIS, but there is uncertainty about the level of the central nervous system accounting for this dysfunction. Studies using structural magnetic resonance imaging (MRI), functional MRI (fMRI) and electroencephalography (EEG) revealed anomalies in the CNS: asymmetries in brainstem corticospinal bundles[12], volumetric differences between adolescents with AIS and controls in brain regions functionally related to motor control and coordination[13], and abnormal patterns in the motor network of adolescents during movement execution[14].

Early studies investigating brain activity in scoliosis reported, for the first time, EEG paroxysmal activity at rest[15]—i.e., bilaterally synchronous activity spread over large areas of both hemispheres. An increase of the amplitude of the peak in alpha rhythm ([7.5–12.5] Hz) was found at central, frontal, parietal and occipital regions during standing posture indicating the need for increased cortical processing to maintain balance control in normal upright standing in adolescents with AIS compared to controls[16]. The increase in theta frequency power and suppression of alpha, beta and gamma powers were observed when proprioception was altered, during vibration applied over the tendons of the soleus/gastrocnemius and tibialis anterior of both ankles[17]. In this case the alpha desynchronization, reflecting the excitability of the sensorimotor cortex, provided indications that adolescents with AIS needed more cortical resources to process sensory information to control their body sway. A Transcranial Magnetic Stimulation (TMS) study reported lower intracortical inhibition, higher motor cortex excitability, and preserved spinal inhibitory circuits[18], demonstrating evidence of central nervous system involvement in AIS.

The aims of this exploratory study are threefold: (1) to compare the EEG activity in adolescents with AIS and controls, to examine the brain oscillatory changes related to balance control; (2) to unveil possible alterations in the postural control mechanisms and (3) to investigate body schema alterations. Based on the literature background, we hypothesized that compared to controls, adolescents with AIS might show: (1) altered brain activation of the sensorimotor network; (2) larger sway on the frontal plane, as a result of a less efficient control of their balance on the plane with the larger scoliotic deformity; (3) altered body schema reflecting the altered activation of the sensorimotor network. Results may represent a valuable biomarker of AIS progression and offer novel therapeutic targets according to the identified pathophysiological patterns.

Methods

Participants. Fourteen adolescent girls with a confirmed diagnosis of AIS[1] (age range 13–17 years; Cobb angle: 20°–55°; Risser sign: 0–4; no spine surgery) were recruited at the Adolescence Spine Diseases Diagnostic and Therapeutic Centre of the Padova University Hospital. Fourteen adolescent girls without AIS (age range 11–16 years; no spinal pathology or any known neurological or musculoskeletal disorders; no clinically relevant back hump), i.e., controls, were recruited at the Sports Medicine and at Physical Activities Unit–"ai Colli" Social Health Department of the Padova Hospital (Tables 1, 2). Controls (CTRL) were enrolled from a population of sporty females (involved in sport activities for less than 10 h per week) who visited the hospital for a certificate of good health, mandatory for any physical activity. A team of physicians with expertise in adolescent spine diseases collected the anamnestic information and the clinical data (Table 3). Parents gave their written informed consent to participate in the study. All methods were performed in accordance with relevant guidelines and regulations and in accordance with the Declaration of Helsinki.

All the participants underwent a physical examination: trunk asymmetries, shoulders and hips inclination sides were registered. Bunnel's scoliometer was used to measure the paravertebral humps in the forward bent position[19,20]. For adolescents with AIS only, we collected the last standing full-spine posterior-anterior radiological image recorded within the last three months prior participating in the study. Cobb angle method was used to measure curves entity[21], while the apical vertebral rotation was recorded by means of the Perdriolle method[22] either or Nash and Moe method[23]. The side and the anatomical site of the scoliosis convexity was collected (Table 3). All adolescents with AIS were treated using a full-time brace.

Prior to data collection, height and body mass were collected and handedness was assessed with the Oldfield Questionnaire[24], with all participants being right-handed.

Subject ID	Age (years)	Menarche (months)	Body Mass (kg)	Height (m)	BMI (kg/m²)	Sport (type)	Sport (h/week)
1	17.1	25	53.5	1.69	18.73	Dance	3
2	13.7	12	52.0	1.62	19.94	–	–
3	13.9	19	44.0	1.61	17.08	Dance	1
4	14.1	20	62.0	1.75	20.24	–	–
5	15.7	42	66.0	1.64	24.69	Gymnastic	6
6	14.0	25	57.0	1.65	20.94	Swim	3
7	15.0	No	45,5	1.71	15.65	Volleyball	4
8	16.3	17	38.0	1.48	17.35	–	–
9	13.6	13	54.0	1.63	20.32	Dance	7
10	14.0	33	54.0	1.48	24.65	–	–
11	15.1	34	54.0	1.64	20.20	Dance	5
12	15.7	43	44.0	1.62	16.77	Atlethics	5
13	14.2	40	54.0	1.64	20.08	–	–
14	15.9	46	44.0	1.58	17.63	–	–

Table 1. Adolescents with AIS' descriptive characteristics.

Subject ID	Age (years)	Menarche (months)	Body mass (kg)	Height (m)	BMI (kg/m²)	Sport (type)	Sport (h/week)
1	14.7	43	84.5	1.6	33.64	Gymnastic	9
2	14.0	13	48.5	1.6	19.80	Gymnastic	10
3	14.0	24	48.5	1.6	18.83	–	–
4	11.6	1	50.0	1.5	20.95	Boxe	3
5	13.4	8	52.0	1.6	21.37	Volleyball	7
6	15.5	46	52.0	1.6	20.44	Atlethics	3
7	14.8	21	67.0	1.6	25.22	Gymnastic	8
8	15.5	36	45.0	1.6	17.47	Gymnastic	5
9	14.2	13	52.0	1.8	16.98	Handball	4,5
10	14.6	24	56.5	1.6	21.14	Gymnastic	9
11	13.7	4	50.0	1.7	17.30	Swim	10
12	13.6	26	49.0	1.6	20.26	Dance	5
13	16.6	65	70.5	1.7	24.39	Volleyball	7
14	14.9	36	50.0	1.6	20.16	Dance	5

Table 2. Controls' descriptive characteristics.

Subject ID	Brace (months)	Cobb (°)	Curve site	Curve lateralization	Risser Sign (%)
1	48	20	Thoracic	Right	100
2	20	21	Thoracic	Right	80
3	30	38	Thoracic	Right	100
4	1	43	Thoracic	Right	75
5	19	21	Lumbar	Right	100
6	4	24	Thoracic	Right	40
7	19	25	Thoracolumbar	Right	90
8	7	55	Thoracic	Right	85
9	1	25	Lumbar	Right	10
10	65	22	Thoracic	Right	100
11	27	27	Lumbar	Left	60
12	1	24	Lumbar	Left	100
13	30	28	Lumbar	Left	85
14	41	28	Lumbar	Left	100

Table3. Anthropometric characteristic of adolescents with AIS.

Experimental paradigm. To answer our research questions and test the hypotheses we made, participants underwent a data collection session, which consisted of EEG, balance and motion recordings complemented with a procedure to assess the participants' body schema. The instrumental data were acquired at once for each task and postural condition. Data synchronization was ensured, as balance and motion data were collected by the same motion capture system, which also served as a master to trigger the EEG acquisition. Participants were asked to stand upright on a force platform in two conditions:

- with their eyes: (1) open (*OE standing*), and (2) closed (*CE standing*) for 3 min;
- with their arms raised laterally to 90° and with: (3) eyes open (*OE arms up*), and (4) closed (*CE arms up*) for 1 min. This task has the twofold purpose of: (1) inducing a larger postural unbalance on the frontal plane, to further challenge the participants on that direction (i.e. where the larger scoliotic deformity displays); and (2) eliciting an asymmetrical activation of the spine muscles, which we expect to be unbalanced on adolescent with AIS, and to be reflected on an unbalanced activation of sensorimotor brain areas to counteract the effect of the scoliotic curve.

For each standing position, participants were instructed to keep their feet at their shoulder width, looking at a fixation cross (∼ 3 m in front of the participant) during the eyes open conditions (see Supplementary Materials).

Subsequently, participants underwent a re-adaptation of the Image Marking Procedure (IMP)[25].

Adolescents with AIS performed the experiment without the brace removed two hours before the acquisition.

EEG data. EEG signals (32-channels system; BrainAmp 32MRplus, BrainProducts GmbH, Munich, Germany) were acquired using an analogic anti-aliasing band pass-filter at 0.1–1000 Hz and converted from analog to digital using a sampling rate of 500 Hz. The reference was between Fz/Cz and ground anterior to Fz. The data were processed in Matlab R2018b (MathWorks, Natick, MA, Usa) using personalized scripts based on EEGLAB toolbox (http://www.sccn.ucsd.edu/eeglab)[26]. The EEG recordings were band-pass filtered from 1 to 30 Hz (the optimal Chebyshev finite impulse response filters were designed using Parks–McClellan algorithm, the order was customized to minimize the error in the pass and stop bands). Noisy channels were identified by visual inspection and interpolated using the nearest-neighbour spline method (average percentage of channels interpolated: 6.5%). Eyes movements and cardiac activity were removed using independent component analysis (FastICA algorithm implemented in EEGLAB) based on the waveform, topography and time course of the component (average percentage of components removed: 9.9%), and data were re-referenced to the average reference. Individual epochs containing non-stereotyped artifacts were also identified by visual inspection and removed from further analysis (average percentage of epochs removed: 7.4%, resulting in, on average, 43.1 EEG epochs of 2 s exploited for the following analysis).

The fast Fourier transform was applied to non–overlapping epochs of 2 s and then averaged across epochs. The recordings were Hanning windowed to control for spectral leakage. Power spectra were estimated for all frequencies between 1 and 30 Hz, then the relative power (%) was calculated by dividing the power of each frequency bands (delta [1–4] Hz, theta [4.5–7.5] Hz, alpha [8–12] Hz, and beta [13–30] Hz) with the total power of [1–30] Hz. The relative power was computed to reduce the inter-individual deviation associated with absolute power due to the inter-individual difference in skull and scalp conduction[27]. The frequency range was limited to [1–30] Hz considering that power spectral density shows a decrease in power with increasing frequency (1/f) and the presence of the power supply noise at 50 Hz.

A laterality index (LI), describing the contrast in amount of activation (i.e., relative power in alpha band) between the right and left hemisphere, was calculated during all the tasks according to:

$$LI = \frac{P_I - P_C}{P_I + P_C} \tag{1}$$

where P_I is the average of power of central electrodes ipsilateral to the curve (C4, Cp2 and P4 for adolescents with AIS with right main curve; C3, Cp1 and P3 for adolescents with AIS with left main curve) and P_C is the average of power of central electrodes contralateral to the curve (C3, Cp1 and P3 for right main curve; C4, Cp2 and P4 for left main curve). LI can thus range from + 1 (exclusively ipsilateral) to −1 (exclusively contralateral).

Considering that the curve may cause an asymmetric EEG topography, we a priori divided adolescents with AIS with right ($N = 10$ participants) and left ($N = 4$) main curve in performing the statistical comparisons with controls. Because relative power values were not all normally distributed (data distribution was tested by using Lilliefors test[28]), non-parametric tests were applied. We performed two-sided Wilcoxon rank sum tests to compare relative power in each frequency bands among controls and adolescents with AIS with right main curve ($p < 0.05$). Considering the sample size and the exploratory nature of the study, no corrections for multiple comparisons were performed in hypothesis testing.

Balance and motion data. To test whether adolescents with AIS have an impaired balance control, we asked all the participants to perform the postural trials on a force platform, which returns the ground reactions and the Center of Pressure (COP) trajectory. COP is considered as a proxy of the Center of Mass movement and, thus, meaningful for balance performance[29]. Participants were instructed to find a comfortable position for their feet while standing on the force platform (9 components; BERTEC 4060-10, Bertec Corporation, Ohio, US; 2000 Hz). Feet position was marked on the floor with adhesive tape to ensure consistent positioning among trials. The relative foot placement was measured to estimate the base of support, which is approximated to the area of a trapezium having the following dimensions: the big toe distance (BTD) as the largest parallel side, the

inter-malleolar distance (IMD) as the smallest parallel side, and the distance of big toes from the line joining the heel extremities (effective foot length, EFL) as the height[29]. Additionally, the maximum foot width (MFW) was collected, defined as the widest aspect of the foot, perpendicular to line joining the distal end of the great toe to midpoint of the heel[29]. Participants were asked to stand as still as possible to record the Center of Pressure (COP) trajectory and assess their balance control performances. Before calculating balance parameters, COP time series were low-pass filtered with a recursive 2nd-order Butterworth filter, cut-off equal to 10 Hz. Balance parameters might be affected by the duration of the acquisition. Thus, a single epoch of 40 s was retained for the analysis and the computation of the balance parameters from each of the recordings (lasting 3 min for the upright *standing* and 1 min for the *up arms* condition)[30].

The following parameters were calculated from the COP trajectory to assess balance control performances of the participants: (1) length of COP trajectory (PL); (2) area of the ellipse containing the 95% of the COP points (EA); (3) range of motion (ROM) and root mean square (RMS) of the COP displacement along the anterior–posterior (ROM-AP and RMS-AP, respectively) and medial-lateral (ROM-ML and RMS-ML, respectively) directions[31]. Parameters were then normalized by the participants' height, body mass, base of support and maximum foot width through a detrending normalization technique[29,32]. The detrending normalization consists in estimating the correlation between each parameter and subjects' anthropometry, and then iteratively correcting each parameter with the linear model that best fits the data. This method keeps values with their original range and measurement unit, but it removes any dependencies from confounding variables[32].

The postural task performed in the *OE arms up* and *CE arms up* conditions was expected to further challenge the balance of the adolescents with AIS, inducing a larger postural unbalance on the frontal plane, which is the plane most affected by the scoliotic deformity. Such a challenging position could affect the ability of adolescents with AIS to hold the arms' position during the trial. To estimate the elbow angle $\varepsilon(t)$ in the *OE arms up* and *CE arms up* conditions, participants were equipped with nine retroreflective markers placed on the tubercle of the seventh cervical vertebra (C7), on the posterior aspect of the acromion (bilaterally and on the most prominent point), on the lateral epicondyle of humerus (bilaterally), and on both styloid process of ulna and radius (bilaterally). 3D marker trajectories were collected with a 10 IR-camera stereophotogrammetric system (Vero v2.2, Vicon Motion Systems Ltd, UK; 100 Hz). Labelling, gap filling and smoothing through a Woltring routine[33] of marker trajectories were conducted within Vicon Nexus (v2.11, Vicon Motion Systems Ltd, UK).

In brief: the average of the wrist markers approximates the wrist joint centre, and the forearm segment is defined by the line joining the elbow marker to this point; the arm segment is defined by the line joining the shoulder marker to the elbow marker; the elbow angle time series $\varepsilon(t)$ is estimated as the angle between the forearm and the arm segments. The following parameters have been defined to quantify the variation over time of the elbow angle and its symmetry between left and right sides:

- directional root mean square (dRMS, °):

$$dRMS = \begin{cases} RMS\{\varepsilon(t)\}, & \text{if } \bar{\varepsilon}(t)|_{t=38,\ldots,40} - \bar{\varepsilon}(t)|_{t=1,\ldots,3} \geq 0 \\ -RMS\{\varepsilon(t)\}, & \text{if } \bar{\varepsilon}(t)|_{t=38,\ldots,40} - \bar{\varepsilon}(t)|_{t=1,\ldots,3} < 0 \end{cases} \quad (2)$$

  with ε, being the time average of the elbow angle over the selected time window;
- coefficient of variation of the angle (CV, %), i.e., the $\frac{RMS}{\bar{\varepsilon}(t)} \cdot 100$;
- Symmetry index (SI, %):

$$SI = \frac{\bar{\varepsilon}_L(t) - \bar{\varepsilon}_R(t)}{\bar{\varepsilon}_L(t) + \bar{\varepsilon}_R(t)} \cdot 100. \quad (3)$$

Balance and motion data were tested for possible differences between-groups (AIS vs. CTRL) through an unpaired two-sided Wilcoxon rank sum tests ($p < 0.05$). Differences in balance performances due to the eye condition (*OE* vs *CE* comparison) were tested through a paired two-sided Wilcoxon rank sum test ($p < 0.05$), to account for repeated measures design within the same group (AIS and CTRL).

Body schema assessment. A re-adaptation of the Image Marking Procedure (IMP) was used to assess the body schema[25]. The IMP was previously used to assess body schema, especially body size perception (horizontal direction) and general body awareness[34]. This projection test assesses subjects' ability to implicitly represent their body (specifically those parts more affected by scoliosis: shoulder, back, waist) based on a tactile stimulation. As it was never used before on adolescents with AIS, we re-adapted it to evaluate both the horizontal and vertical body representation. Participants were asked to stand blindfolded in front of a roll of wrapping paper, pretending looking themselves in a mirror. The experimenter stood behind the subject firmly touching with his fingertip seven chosen body segments, namely: the top of the head, the acromioclavicular joints (right and left), waist width (right and left), and the trochanters of the femoral bones (right and left). Each participant was provided with a pencil and asked to make a cross on the paper where the touched body segment was imagined to be projected (see Supplementary Materials). At the end of the marking, participants approached the paper to allow the experimenter to mark the actual position of the touched points with the use of an L-shape ruler placed at 90° angle relative to the longitudinal axis of the body. Distances in cm between the corresponding right and left points of shoulders, waist and hips marked by the subjects (perceived size: PS) and by the experimenter (actual size: AS) were measured with a ruler. For each subject, body perception indices (*BPIs*) related to each body segment (shoulders, waist, and hips) were calculated using the following formula:

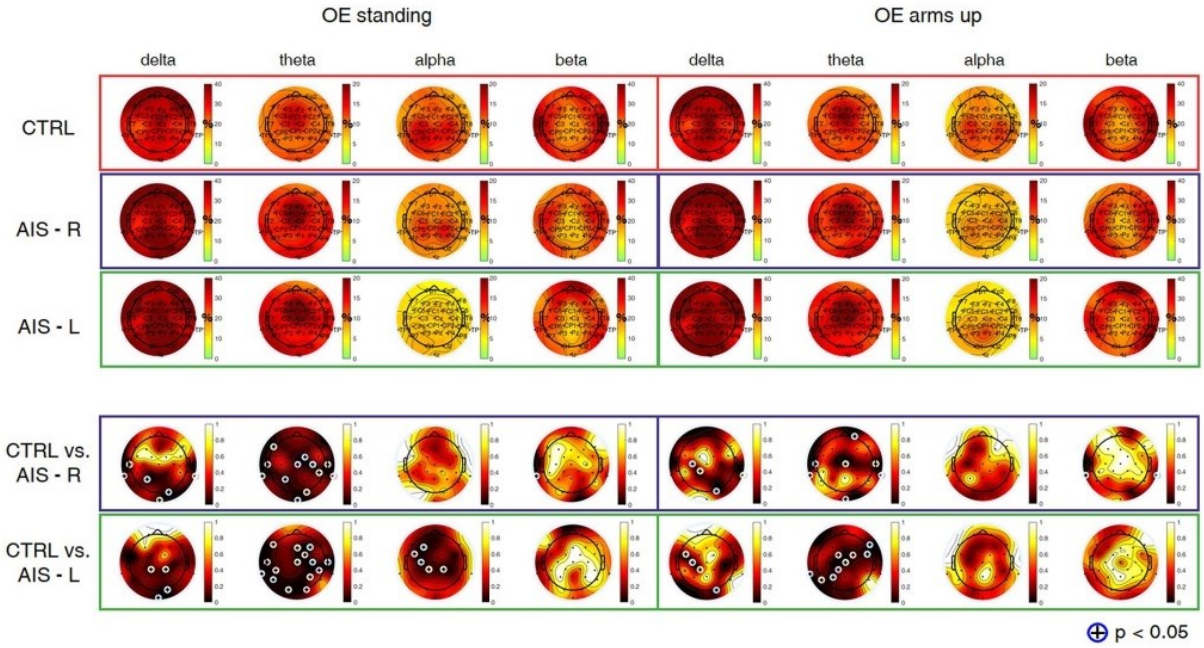

Figure 1. Topographic maps of relative power (%) in delta [1–4] Hz, theta [4.5–7.5] Hz, alpha [8–12] Hz, and beta [13–30] Hz bands, during *OE standing* and *OE arms up*, averaged from 14 controls (CTRL) (first row), 10 adolescents with AIS with right main curve (second row) and 4 adolescents with AIS with left main curve (third row). The fourth and the fifth rows represent *p*-maps derived from the Wilcoxon rank sum test (adolescents with AIS with right main curve: AIS-R vs. CTRL; adolescents with AIS with left main curve: AIS-L vs. CTRL). Statistical results were highlighted with (+) for $p < 0.05$.

$$BPI = \frac{PS}{AS} * 100 \tag{4}$$

A general *BPI* (*BPIg*), determined as the *BPIs* average was calculated as well. The classification of *BPIs* was performed through normative values[35]: hypo-schematic (underestimation of actual body size, $BPIg < 99.4\%$; adequate body size estimators ($BPIg > 99.4\%$); hyper-schematic (over-estimation of actual body size, $BPI > 112.3\%$).

To assess possible body schema distortions on the vertical axis, we compared the actual deviation from verticality (degrees) and its lateralization (right or left) with the perceived ones. Toward this aim, we defined for each subject an angle formed by the prolongation of the segments connecting right and left perceived points of shoulders, waist or hips, (depending on the principal curve location), and by the segment connecting the corresponding right and left actual points. To characterize curve laterality, we assumed positive values if the perceived curve convexity was right-oriented, and negative values if it was left-oriented (see Supplementary Materials).

As *BPIs* scores were normally distributed (Shapiro–Wilk normality test) we performed unpaired two-sampled t-test to compare AIS and controls *BPIs* scores related to each body segment and *BPIs* average scores ($p < 0.05$). To evaluate eventual body schema distortions related to the whole trunk perception, we additionally calculated *BPIs* shoulder/waist ratio, as the delta between these two measures and we performed unpaired two-sample t-test between groups ($p < 0.05$).

All methods were performed in accordance with the relevant guidelines and regulations.

Ethics approval and consent to participate. Informed consent was given from all subjects and/or their legal guardian(s) for participation and publication of identifying information/images in this study. All methods were performed in accordance with relevant guidelines and regulations and in accordance with the Declaration of Helsinki. This study was carried out in accordance with the recommendations of the Ethics Committee of the Teaching Hospital of Padova.

Results

EEG data. Average results from power spectral density analysis are summarized in Figs. 1 and 2 for controls and adolescents with AIS. In the *OE condition* (Fig. 1), significant differences were observed during *OE standing* and *OE arms up* between controls and adolescents with AIS with right and left main curves in slow rhythms (i.e., delta and theta) over central and parietal electrodes ($p = 0.0417$). Comparison between controls and adolescents with AIS with left main curve indicated significant differences in alpha range also over left sensorimotor and parietal areas during *OE standing* ($p = 0.0415$).

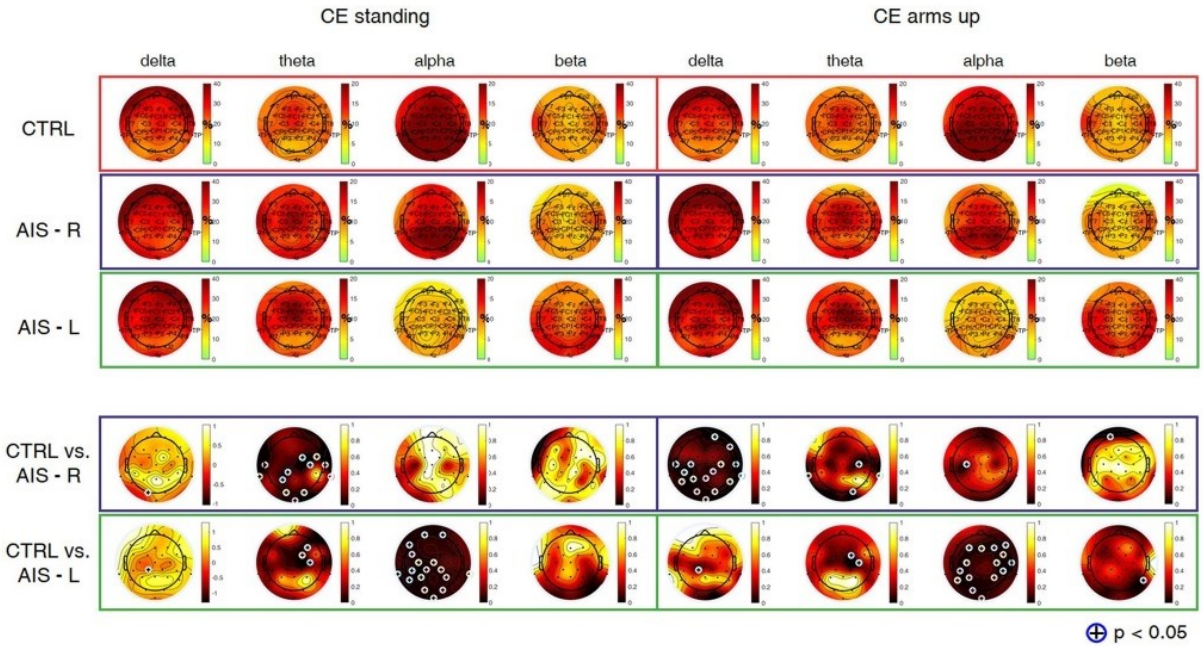

Figure 2. Topographic maps of relative power (%) in delta [1–4] Hz, theta [4.5–7.5] Hz, alpha [8–12] Hz, and beta [13–30] Hz bands, during *CE standing* and *CE arms up*, averaged from 14 controls (CTRL) (first row), 10 adolescents with AIS with right main curve (second row) and 4 adolescents with AIS with left main curve (third row). The fourth and the fifth rows represent *p*-maps derived from the Wilcoxon rank sum test (adolescents with AIS with right main curve: AIS-R vs. CTRL; adolescents with AIS with left main curve: AIS-L vs. CTRL). Statistical results were highlighted with (+) for $p < 0.05$.

In the *CE condition* (Fig. 2), significant differences were observed during *CE standing* between controls and adolescents with AIS with right main curve in theta rhythm over central and parietal electrodes ($p = 0.0218$). *CE arms up* produced significant differences in delta band over central and parietal electrodes ($p = 0.0225$) and in alpha band over C3 ($p = 0.0326$). Comparison between controls and adolescents with AIS with left main curve indicated significant differences over central regions in delta and theta bands during both tasks ($p = 0.0384$) and over left sensorimotor and parietal areas during *CE standing* ($p = 0.0354$) and over both sensorimotor areas in alpha band during *CE arms up* ($p = 0.0340$). Relative powers were comparable between the two postures within each condition (*OE* and *CE*).

EEG data demonstrated alpha power increase of the sensorimotor area ipsilateral to the main scoliotic curve, as evidenced by the significant changes of LI ($p = 0.0434$) mainly in adolescents with AIS with right main curve during *CE arms up* (Fig. 3).

Balance and motion data. Figure 4 shows results of balance performances as assessed through EA, PL, RMS-AP and RMS-ML in *standing* (panel A) and *arms up* (panel B) conditions with both eyes open and closed (white and gray fill color, respectively) in both adolescents with AIS and controls. No differences were obtained between groups, whereas a strong significance (AIS: $p = 0.00085$; CTRL: $p = 0.00049$) was obtained when testing differences between *OE arms up* and *CE arms up* conditions for PL (Fig. 4B). A weak significant difference ($p = 0.035$) was obtained for RMS-AP in adolescents with AIS between *OE* and *CE standing* (Fig. 4A).

From results on motion data, the only significant difference was found for the SI in the controls ($p < 0.013$) (See Supplementary Materials).

Body schema data. *BPIg* scores did not differ between controls and adolescents with AIS (AIS: mean ± SD = 88.47 ± 19.75; CTRL: 86.31 ± 16.64; $p = 0.75$) as well as *BPIs* related to each body segment: *BPI* of shoulders (AIS: 81.88 ± 21.24; CTRL: 85.55 ± 18.00; $p = 0.62$), *BPI* of waist (AIS: 97.94 ± 31.13; CTRL: 91.37 ± 16.03; $p = 0.48$), *BPI* of hips (AIS: 85.59 ± 21.39; CTRL: 82.00 ± 22.75; $p = 0.67$). The *BPIg* scores in both controls and adolescents with AIS, resulted mainly hypo-schematic with 8 of 14 adolescents with AIS and 12 of 14 controls having *BPIg* scores lower than 99.4%.

The *BPI* delta (*BPI* shoulder minus *BPI* waist) resulted significantly different between the two groups (mean ± SD *BPI* delta of AIS group: 29.52 ± 18.72 vs. controls: 12.35 ± 9.3; $p = 0.004$) (Fig. 5A).

Qualitative analysis of the test showed that in 12 out of 14 adolescents with AIS the inclinations of the perceived interacromial axes in girls having thoracic principal curve and bisiliac axes in girls with lumbar principal curve was opposite to the real inclination (Fig. 5B). Conversely, controls' perception of their inclination resulted opposite to the real inclination in 3 out of 14 cases (Fig. 5C). The real angle (i.e., degrees describing the inclination

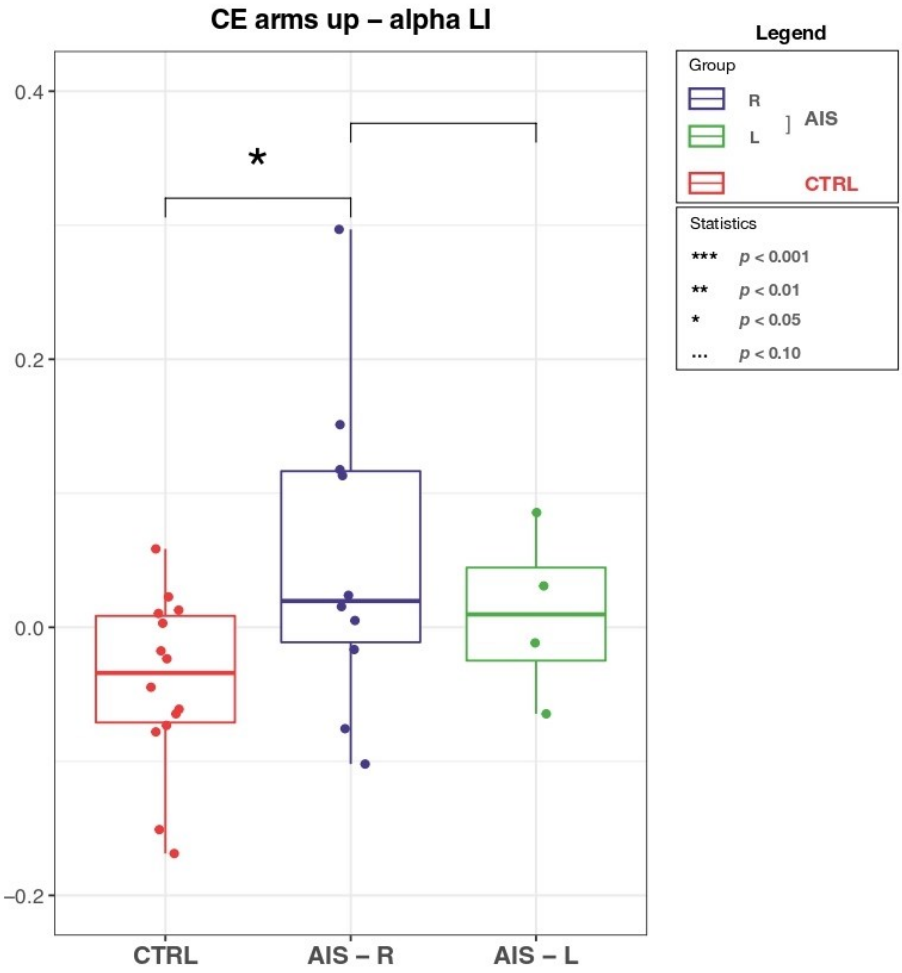

Figure 3. Grand-average LI in alpha band during *CE arms up* for controls (CTRL), adolescents with AIS with right main curve (AIS-R) and adolescents with AIS with left main curve (AIS-L). On each box, the central red line indicates the median, and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. The whiskers extend to the most extreme data points not considered outliers, and the outliers are plotted individually using the '+' symbol. Significant difference ($p < 0.05$) was observed between CTRL and AIS-R.

of the interacromial or bisiliac axes resulting from the actual projection of body segments, as measured by the experimenter) and the perceived angle (i.e., degrees describing the inclination of the interacromial or bisiliac axes resulting from the participants' perceived projection of body segments) should coincide in a healthy subject and be represented by the points lying over the bisector of the first and third quadrant in Fig. 5B,C.

Discussion

The three aims of this exploratory study were: (1) to compare the EEG activity in adolescents with AIS and controls during posture; (2) to unveil possible alterations in the postural control mechanisms and (3) to investigate body schema alterations. We hypothesized that adolescents with AIS compared to controls might exhibit: (1) altered brain activation of the sensorimotor network; (2) larger sway on the frontal plane, i.e., the plane with the larger scoliotic deformity; (3) altered body schema reflecting the altered activation of the sensorimotor network. Our results revealed: (1) significant increase of delta and theta relative powers, compared to controls, localized over the central areas; a significant LI increase in alpha range observed in adolescents with AIS with main right curve compared to controls during *arms up* with eyes closed, demonstrating an imbalance between the two sensorimotor areas; (2) no differences in balance performances between groups; (3) no differences between controls and adolescents with AIS for the single body segment, but the test of body schema underlined a possible alteration in the overall trunk representation, namely in the perception of the shoulders-waist proportion, and in its inclination.

The main result of the study is the significant increase of delta and theta relative powers, compared to controls, localized over the central areas. Theta frequency band is recognized to be involved in balance control[36].

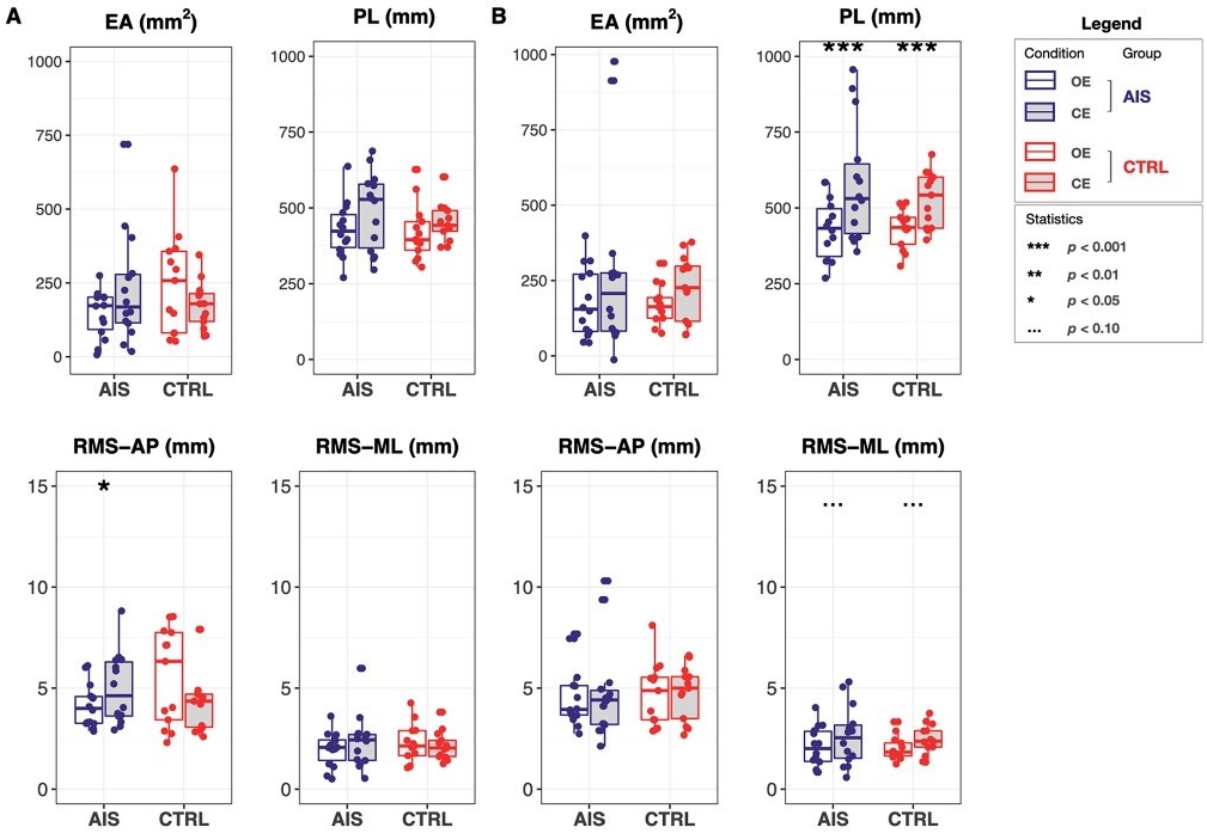

Figure 4. Balance performances as assessed through confidence ellipse area (EA), sway path length (PL) and the root mean square of center of pressure trajectory in the anterior–posterior and medial-lateral directions (RMS-AP and RMS-ML, respectively) in: (**A**) *standing*, and (**B**) *arms up* conditions. Boxplots are filled with white for eyes open (*OE*) and gray for eyes closed (*CE*). Statistical results were highlighted with: '***' for $p < 0.001$, '**' for $p < 0.01$, '*' for $p < 0.05$, and '...' for $p < 0.10$.

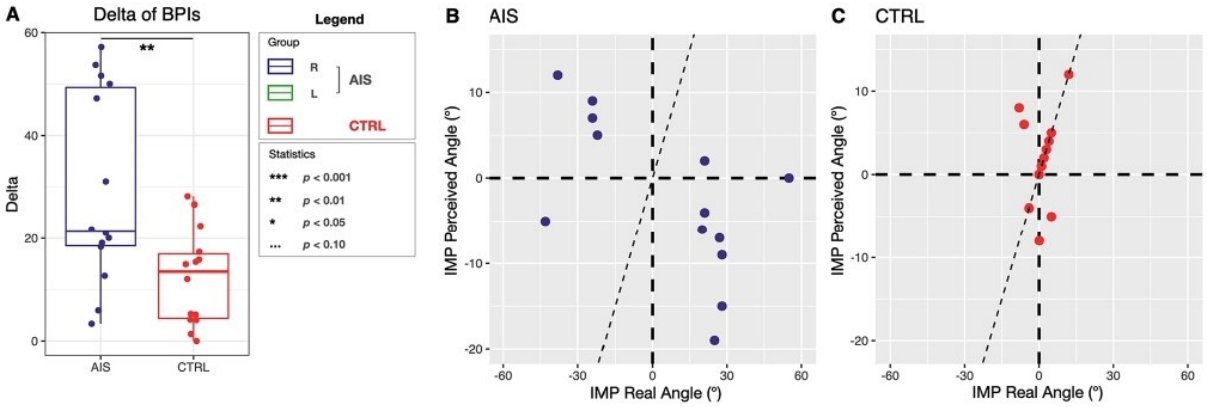

Figure 5. (**A**) *BPI* delta values defined as the difference between shoulder *BPI* and waist *BPI*. A significant difference emerged between mean delta *BPIs* of adolescents with AIS and controls ($p < 0.01$). (**B,C**)) On the x axis are plotted the real angles as measured with IMP while on the y axis the perceived angles as measured with IMP. To characterize curve laterality, we assigned positive values when curves' convexity was right-oriented, and negative values when left-oriented. (**B**) In the adolescents with AIS 12 out of the 14 girls perceive their curve orientation as opposite to the real one. (**C**) For the control group, just 3 out of 14 girls perceive their curve orientation as opposite to the real one.

Theta band activity intensifies when control demands are increased[37]; it is reported to rise with increasing

balance demand in parietal areas[38], as well as in frontal areas[39–41]; it has also been suggested to represent error detection and processing during postural maintenance[38]. Theta power increase with task complexity has been demonstrated in multiple contexts, including dual tasks[36] where an increase of cortical recruitment was found to keep up performance in the elderly.

Gebel et al.[42] found significant increases of theta frequency band power in frontal and central areas with increasing balance task difficulty in adolescents. Moreover, previous studies on healthy adults reported that the increase in theta power may originate from the anterior cingulate cortex and sensorimotor areas, which are highly involved in sensory information processing[38,43].

In adolescents with AIS, the theta power increase during all the tasks within central clusters may reflect a higher information processing load due to increased postural demands caused by the scoliosis. The no balance difference and the increased brain activity in this frequency range could reflect greater postural control during balance tasks (with eyes open and closed, with and without arms up). These results (i.e., the overall theta increase over central areas) suggest that adolescents with AIS adapted their brain activity to prevent large body sway due to the scoliosis.

The lateralization of alpha relative power is in line with fMRI data showing Blood Oxygen Level Dependent (BOLD) activation increase of motor areas and a greater interhemispheric asymmetry index[14]. The overactivation of contralateral supplementary motor area, observed when performing motor task with either hand, emphasizes the asymmetry of motor activation and demonstrates an abnormal pattern of brain activation supporting the hypothesis of sensorimotor dysfunction. The increase of alpha power lateralization could indicate an increase of communication relayed to the sensorimotor area ipsilateral to the scoliotic curve due to the balance task. The alpha lateralization observed in our results may be a compensatory strategy to overcome sensorimotor dysfunction. A possible explanation of these changes could be attributed to impaired sensorimotor integration predominantly at the cortical level, results found also in other studies[14,16]. Brain oscillations, thanks to neural plasticity, can reorganize in a system attempting to compensate for a dysfunction; the asymmetry observed in adolescents with AIS may be related to either a sensorimotor impairment or a brain compensatory mechanism. Maybe scoliosis onset is preceded by sensorimotor control impairments that last during curve progression. This in turn could lead to develop an altered body schema of the trunk and its inclination. We infered that the "unbalance" in alpha power spectra between the two hemispheres in the sensorimotor areas might be linked with the "unbalance" in body perception in AIS. Indeed, we evidenced: (1) an alpha lateralization ipsilateral to the scoliotic curve; (2) the opposite inclination of the perceived interacromial axes compared to the real inclination; and (3) an abnormally widest perceived waist compared to shoulders only in adolescents with AIS. Further investigations are worth performing to investigate this relationship. However, we cannot exclude the possibility that our finding on the abnormally widest perceived waist compared to shoulders could be the result of brace treatment. Body schema is plastic by definition, and capable of incorporating objects in short times[44].

Before identifying the therapeutic target, other neurophysiological investigations must be carried out: high-density EEG to localize cortical sources; connectivity analysis to understand whether the alterations detected in the rhythms are also reflected in terms of connections between the brain areas of the motor sensory network. A methodological limitation of this study is the approach of sensor space localization by means of only 30 EEG channels. Source localization analysis requires at least an EEG system with 64 channels for data acquisition. Therefore, future studies may use high-density EEG systems to specify and localize the functional areas during increasing postural demands. Moreover, it could be interesting to explore the influence of brace on body perception. In this pilot study, indeed, we only considered participants which already underwent brace treatment. Another limitation is the limited number of participants. We faced some issues in recruitment since recordings were performed during the second lock-down in Italy due to COVID-19 pandemic (i.e., Veneto region barred residents from leaving their homes except for work, health or basic needs, and among commercial activities, only supermarkets and pharmacies stayed open).

The obtained results lead to refuting the initial hypothesis of adolescents with AIS having worse balance performance than controls, even when considering the postural task with the arms up that we expected to unveil and magnify such differences between the two groups. However, when looking at the symmetry index (SI) calculated on the elbow angle in the up arms condition, controls did act differently in the eyes open and eyes closed condition ($p = 0.013$), whereas no differences were obtained within the adolescents with AIS. This different behavior is probably to be ascribed to the larger variability that characterizes the SI values calculated for adolescents with AIS, compared to controls, which may again suggest different postural control of the adolescents with AIS. Building on this consideration, we would expect to observe different brain cortical activity on the sensorimotor areas between adolescents with AIS and controls, which we indeed observed on EEG rhythms associated with postural control. Although further investigations are worth performing, we may conclude that adolescents with AIS have no functional balance disorder, but they show different and asymmetrical activation of the sensorimotor areas of the brain (i.e., theta increase and alpha lateralization). Theta increase might represent a higher level of attention[36] in performing symmetric tasks in adolescents with AIS and alpha lateralization might stand for the brain reorganization in a system attempting to compensate for a dysfunction. This dysfunction is testified by the altered body schema (i.e., opposite to the real one) in adolescents with AIS.

A longitudinal study with a larger cohort is still needed to verify if these abnormal EEG findings may represent a valuable biomarker of scoliosis progression. The results can offer novel therapeutic targets as for example training based on biofeedback, evaluating the performance by monitoring EEG changes. The marked lateralisation observed and body schema alterations could also be useful for setting up personalized and targeted corrective postural exercises. Nowadays, treatment options for scoliosis consider exclusively biomechanics perspectives, except for some innovative approaches and hypotheses, still needing scientific evidence. One future development is the investigation of the EEG as a tool to assess the probable development of scoliosis in the individual case. Thanks also to the development of mobile EEG systems, it will be possible to study the sensorimotor components

even during movement tasks used to increase postural instability (e.g. by using a balance board). It still remains unclear whether the reported cortical functional state changes are either the cause or consequence of AIS. A longitudinal study is needed to find evidence to try to clarify this aspect.

Conclusions

Our results provide evidence of an increased theta activity and a lateralized alpha activity in adolescents with AIS. Whether these processes are a cause or a consequence of AIS needs to be further investigated. The identification of an abnormal EEG pattern may describe a much more complex physiopathology of AIS and promote new multi-domain treatment approaches to improve patients' care quality.

Data availability

The datasets generated and/or analysed during the current study are not publicly available due to participants' privacy. Anonymous Data and Code will be made available upon reasonable request to the Corresponding Author. None of the experiments was preregistered.

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Author contributions
Conceptualization and data collection: M.B., M.R., R.D.M., E.F. Patient recruitment: F.C., F.G., M.D.G., S.M. Data analysis: M.B., M.R., R.D.M., E.F. Supervision: S.M. Original draft preparation: M.B., M.R., R.D.M., E.F. All authors critically discussed the results. All the authors read, reviewed and approved the final manuscript.

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Competing interests
The authors declare no competing interests.

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5.3 Beyond physiotherapy and pharmacological treatment for FMS: tailored tACS as new therapeutic tool

Beyond physiotherapy and pharmacological treatment for fibromyalgia syndrome: tailored tACS as a new therapeutic tool

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Abstract
Fibromyalgia syndrome (FMS) is a complex pain disorder, characterized by diffuse pain and cognitive disturbances. Abnormal cortical oscillatory activity may be a promising biomarker, encouraging non-invasive neurostimulation techniques as a treatment. We aimed to modulate abnormal slow cortical oscillations by delivering transcranial alternating current stimulation (tACS) and physiotherapy to reduce pain and cognitive symptoms. This was a double-blinded, randomized, crossover trial conducted between February and September 2018 at the Rehabilitation Unit of a teaching Hospital (NCT03221413). Participants were randomly assigned to tACS or random noise stimulation (RNS), 5 days/week for 2 weeks followed by ad hoc physiotherapy. Clinical and cognitive assessments were performed at T_0 (baseline), T_1 (after stimulation), T_2 (1 month after stimulation). Electroencephalogram (EEG) spectral topographies recorded from 15 participants confirmed slow-rhythm prevalence and provided tACS tailored stimulation parameters and electrode sites. Following tACS, EEG alpha1 ([8–10] Hz) activity increased at T_1 ($p=0.024$) compared to RNS, pain symptoms assessed by Visual Analog Scale decreased at T_1 (T_1 vs T_0 $p=0.010$), self-reported cognitive skills and neuropsychological scores improved both at T_1 and T_2 (Patient-Reported Outcomes in Cognitive Impairment, T_0–T_2, $p=0.024$; Everyday memory questionnaire, T_1 compared to RNS, $p=0.012$; Montréal Cognitive Assessment, T_0 vs T_1, $p=0.048$ and T_0 vs T_2, $p=0.009$; Trail Making Test B T_0–T_2, $p=0.034$). Psychopathological scales and other neuropsychological scores (Trail Making Test-A; Total Phonemic Fluency; Hopkins Verbal Learning Test-Revised; Rey–Osterrieth Complex Figure) improved both after tACS and RNS but earlier improvements (T_1) were registered only after tACS. These results support tACS coupled with physiotherapy in treating FMS cognitive symptoms, pain and subclinical psychopathology.

Keywords Pain · Fibrofog · Non-invasive transcranial stimulation · Rehabilitation · Random noise stimulation (RNS)

Introduction

Fibromyalgia syndrome (FMS) is a complex chronic pain disorder, defined as widespread musculoskeletal pain in the absence of demonstrated tissue damage, and associated with symptoms ranging from affective disturbances, fatigue, and sleep alterations, to cognitive dysfunctions [1]. Cognitive difficulties are referred by 50–80% of people with FMS [2] and are ranked as the fifth most severe symptom [3]. "Fibrofog" was coined to describe the typical subjective experience

Laura Bernardi and Margherita Bertuccelli authors contributed equally to this work.

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of cognitive dysfunction in FMS, characterized among other, by concentration difficulties, forgetfulness, mental confusion and inability to multitask [4]. One of the most frequently reported cognitive dysfunctions in FMS is attention deficit [5]: people with FMS show poor performances in cognitive tests requiring to deal with distractors or any source of stimulus competition, such as divided attention, inhibition, set-shifting [6], working memory [7], semantic memory and speed of processing [8]. It is still unclear if these cognitive symptoms are primarily disease manifestation or a consequence of it. Many co-occurring symptoms in FMS such as depression, anxiety, sleep disturbances and pain perception may contribute and account for cognitive problems, even if no study found an unequivocal relation between these factors and the cognitive performance [4]. However, a relationship between pain intensity, affective and cognitive dysfunction has been postulated based on the overlap of brain areas involved in pain processing and cognition [9, 10]. This observation leads to the hypothesis that cognitive alterations in FMS arise because of resource competition with pain processing [6].

Physiotherapy is nowadays the most widely recognized and beneficial treatment for fibromyalgic pain symptoms. Literature reports effective pain and depression reduction associated with aerobic and strengthening exercises [11]. However, physiotherapy alone is not able to provide long-lasting effects involving other symptoms than pain.

Current research is focusing on biomarkers which may account for both pain processing alterations and cognitive fibrofog. Single-photon Emission Computed Tomography (SPECT) and Functional Magnetic Resonance Imaging (FMRI) revealed abnormal activation of thalamic nuclei, sensory cortex, anterior cingulate, insula and prefrontal cortices during pain processing in FMS [12, 13]. Electroencephalographic (EEG) studies show increased theta rhythm primarily localized in frontal brain regions and anterior cingulate cortex [14, 15], which are part of the thalamo-cortical circuit. On this ground, chronic pain referred by people with FMS has been interpreted as the result of a "thalamo-cortical dysrhythmia" [14] characterized by a shift of oscillatory frequencies in the thalamo-cortical circuits.

Neuromodulation techniques [non-invasive brain stimulation (NIBS): transcranial magnetic (TMS) and transcranial direct current stimulations (tDCS)] may modulate EEG frequency rhythms [16, 17] and shift cortical EEG generators [18, 19]. Up to now, NIBS has been mainly applied in FMS with the hypothesis of reducing the increased activity described over prefrontal and sensory cortices. TDCS was previously administered with this aim. By generating low-intensity sub-threshold electrical fields, tDCS is able to modify neuronal transmembrane potentials and in turn modulate cortical excitability by bringing the underlying neurons closer to their firing threshold [20, 21]. Repetitive TMS (rTMS) delivered over M1 was administered as well to reduce FMS pain symptomatology [22]. However, studies on the effect of rTMS and tDCS report a variable efficacy on amelioration of symptoms and quality of life in FMS [23, 24].

Focusing instead on abnormal oscillatory activity in FMS, EEG activity normalization may be considered a therapeutic target. No study has explored the effect of transcranial alternating current stimulation (tACS) for the treatment of this clinical population [25].

TACS is a non-invasive, handy technique which may modulate endogenous brain oscillations [18, 25] when administrated as an alternate, sinusoid current. It has been demonstrated that tACS is able to shift EEG rhythms in other thalamo-cortical dysrhythmias [26]. Unlike tDCS, tACS does not induce any polarization effect but can modulate the ongoing brain activity by forcing the membrane potential to oscillate away from its resting state towards hyper-polarized or depolarized state. This results in the so-called entrainment effect: increasing of neuronal firing time-locked to the frequency of stimulation [27].

We hypothesize that tACS delivered over the cortical area showing the greatest EEG alteration (i.e., higher slow rhythms power) may have beneficial effects on both pain and cognition by shifting EEG activity towards physiological frequencies. To test this hypothesis, we applied tACS as a primer for a specific rehabilitation program.

Materials and methods

The randomized, double-blind, crossover design was approved by the ethics Committee of the teaching Hospital of Padova University, Italy, (protocol no. 3507/AO/15). Each participant, before taking part in the experiment, was informed about the study and provided written informed consent. The study was registered on ClinicalTrials.Gov (NCT03221413).

The present study reports preliminary data from participants with chronic pain. The original protocol planned inclusion of individuals with neuropathy; due to the principal investigator change of affiliation, access to this clinical population was no more possible and FMS was included, given that both FMS and neuropathic pain are characterized by increased slow thalamo-cortical oscillations in theta frequency band [14, 16]. This allowed the application of the same stimulation protocol. Clinical and neuropsychological tests were adjusted and tailored to FMS. To enhance research transparency, we used the recently updated CONSORT guidelines for cross-over trials [28] and the CONSORT checklist for crossover designs (see Supplementary material 1).

Primary outcome was reduction of the main FMS symptom, pain, measured with a visual analog scale (VAS) on a Likert scale from 0 to 10.

Participants

Participants ($N = 15$, 2 males; age: mean ± standard deviation: 53.07 ± 4.18 years) were recruited as volunteers by the Italian Association of FMS (AISF) and enrolled by a blinded researcher in charge of the study conduction (LB), who also assigned them to sequence of intervention. Inclusion criteria were: diagnosis according to the diagnostic criteria for fibromyalgic syndrome [29]; score higher than 3 at the Visual Analog Scale for pain (VAS); pain non-responsive to at least two analgesic drugs administered in adequate dose for at least 3 months; stable pharmacological treatment during the study. Exclusion criteria were: contraindications to neurostimulation (pregnancy, metal fragments/implants, epilepsy, previous skull fractures, pacemaker); comorbid psychiatric illnesses or substance abuse disorders; minor age. Scalp EEG control data from twenty-one healthy volunteers (9 males; age: 45.14 ± 14 years) were obtained [30] using the same EEG setting.

EEG data acquisition and analysis

Five minutes of open-eyes resting-state EEG signal (32-channel system; BrainAmp 32MRplus, BrainProducts GmbH, Munich, Germany) were acquired at a sampling rate of 5 kHz with the reference between Fz/Cz and ground anterior to Fz positioned according to a 10/10 system, band-pass filtered at 0.1–1000 Hz and digitized.

The data were processed in Matlab (MathWorks, Natick, MA) using personalized scripts based on EEGLAB toolbox [31]. The EEG recordings were band-pass filtered from 1 to 30 Hz and down-sampled at 500 Hz. Visible artifacts (eyes movements, cardiac activity, and scalp muscle contraction) were removed using independent component analysis, and data were processed with a common average reference. Two-seconds EEG epochs (i.e., non-overlapping segments of 1000 samples) were extracted for each participant and a fast Fourier transform (FFT) was applied. The recordings were Hamming windowed to control for spectral leakage. Power spectral density ($\mu V^2/Hz$) was estimated for all frequencies and the relative power (%) was computed by dividing the power of each frequency band (delta [1–4 Hz], theta [4.5–7.5 Hz], alpha1 [8–10 Hz], alpha2 [10.5–12.5 Hz], beta [13–30 Hz]) with the total power in the range 1–30 Hz.

A z test ($p < 0.05$) was used to compare each participant versus controls and a statistical map, defining the electrodes in which relative power value differs from those of the control group, was provided [32].

Trial design, stimulation parameters and tACS treatment

Participants were randomly assigned with a computer-generated list (allocation ratio 1:1) to tACS or random noise stimulation (RNS as active sham). Each participant underwent 10 stimulation sessions lasting 30 min, 5 times a week, for two consecutive weeks, followed by 60 min of physical rehabilitative exercise. After a wash-out interval of 4 weeks from the conclusion of the first cycle, participants were crossed to the other group (Fig. 1). Participants were tested before program start (T_0), at conclusion of each cycle [stimulation and physical rehabilitation (T_1; T_1')], and after the 4-week wash-out interval (T_2; T_2'), with resting EEG, VAS, SF36, neuropsychological tests

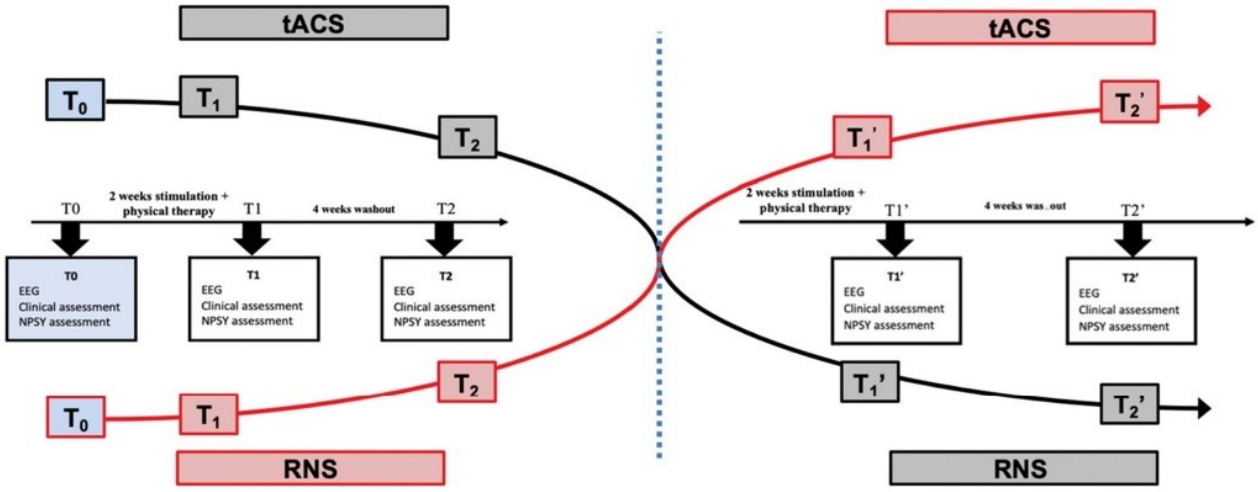

Fig. 1 Schematic representation of the experimental design

and questionnaires. T_0 values were recorded only before the start of the whole experiment.

Baseline (before the whole protocol started) resting-state cerebral activity provided stimulation parameters (frequency and anode position on the scalp). EEG from participants was compared with those of a healthy control group to identify scalp areas in which a significant difference in frequency band spectral power was detected. We supported the hypothesis that a non-invasive stimulation though potentially different from the natural oscillations of the target brain region could modulate neuronal networks and shift oscillations into a physiological range. For this reason, we compared the power spectra of the participants with the one of the controls. Each participant was stimulated in the EEG frequency band that presented lower amplitudes compared to controls. Those showing higher slow frequencies (theta, delta, alpha1) spectral power were stimulated with beta-tACS at 30 Hz, while the ones showing higher fast frequencies (beta, alpha2) were stimulated with theta-tACS at 4 Hz. Figure 2 displays statistical maps derived from one participant showing higher theta activity over left motor area, compared to controls, and thus stimulated with beta-tACS over that cortical area. In case a subgroup should display a prevalence of faster frequencies (alpha2, beta), they were to be stimulated with slow tACS at 4 Hz.

Stimulation was applied by a battery driven external stimulator (BrainStim, E.M.S., Bologna, Italy) via two sponge electrodes (5 × 7 cm), with an intensity ranging from 1 to 2 mA. Anode was positioned for each subject over the scalp area showing highest power spectral difference; cathode over the ipsilateral mastoid. The RNS was an alternate current with random amplitude and frequency, respectively, in the intervals (1–2) mA and (0–100) Hz, with electrodes applied over the same sites as for real stimulation". [17].

Clinical assessment

The following clinical scales were administered to test pain and the self-reported health state:

(1) Visual Analog Scale (VAS) [33]: a 10-point Likert scale, ranging from none to extreme amount of pain.
(2) Short Form 36-item Health Survey (SF-36) [34]: the short form of a questionnaire inquiring participants' health state. The 36 items are clustered into 8 domains: physical activity/functionality (10 items), limitations due to physical health (4 items), limitations due to emotional status (3 items), physic pain (2 items), general healthy sate perception (5 items), energy/fatigue (4 items), social activities (2 items), mental health (5 items) and one single question on the perceived changes in the health state.

Neuropsychological and psychopathological assessment

To test cognitive, affective and psychopathological domains, we designed a battery which comprises the following standardized neuropsychological tests and questionnaires for:

(1) Psychopathological self-assessment: Beck Depression Inventory-II (BDI-II) [35]; Brief Symptom Inventory (BSI) [36]; the State–Trait Anxiety Inventory [37].
(2) Self-reported cognitive assessment: Patient-Reported Outcomes in Cognitive Impairment (PROCOG-P) [38]; Everyday Memory Questionnaire Revised (EMQ-R) [39].
(3) Neuropsychological assessment: the Montréal Cognitive Assessment (MoCA) [40]; the Rey–Osterrieth Complex Figure Test [41]; the Digit Symbol-Coding (from the Wechsler Adult Intelligence Scale 4th edition [42]; the Hopkins Verbal Learning Test-Revised [43];

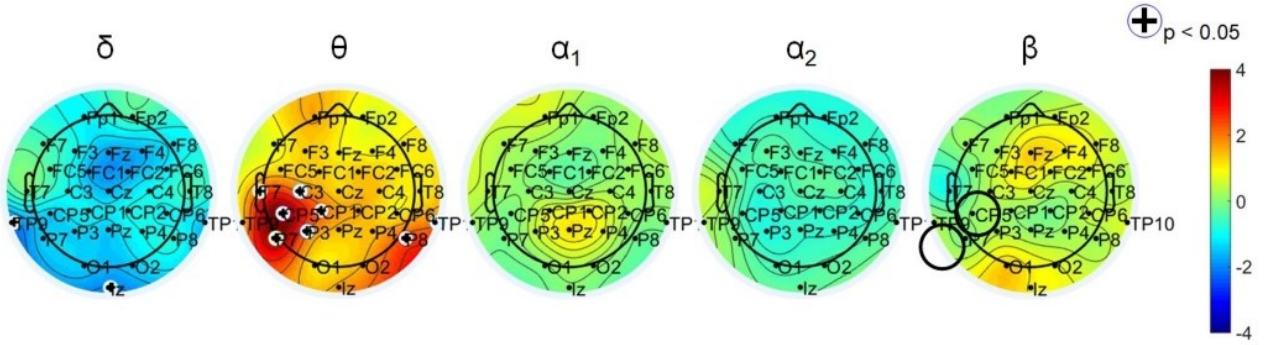

Fig. 2 Statistical maps (*z* values) derived from one subject with FMS vs. control group. Participant n. 6 shows higher theta activity, compared to controls, over left motor area. She was stimulated with beta tACS over CP5 (black circles: anode over area of highest theta power, cathode over ipsilateral mastoid)

the Trail Making Tests A and B [44]; the Phonemic Verbal Fluency task [45]. For detailed description of each test, see Appendix A.

Physiotherapy program

The European League Against Rheumatism (EULAR) guidelines have been used to design the physiotherapy program [46]. Physiotherapy program included 30 min of aerobic exercise followed by 15 min of muscular stretching and 15 min of breathing and guided relaxation techniques. Participants received 60-min physical rehabilitation at the end of each stimulation session, 5 times a week, for two consecutive weeks, both in the first and second experimental arms. See the online resources (Table T1) for the complete physiotherapy program.

Statistical analysis

Region of interests (ROIs) were identified based on electrodes location: right frontal ROI: Fp2, F8, F4; right motor ROI: FC2, FC6, C4, Cp2; right parietal ROI: CP6, P8, P4. Contralateral ROIs were identified on the left hemisphere. EEG frequency power was calculated for each of these ROIs and used for subsequent analysis. Statistical analyses aimed at detecting differences in EEG frequencies, neuropsychological, psychopathological or clinical variables with respect to baseline and intervention. Each comparison was based on complete case analysis, so all available subjects were considered when their observations could be collected. Non-parametric methods were employed due to sample size. Spectral power of all EEG bands over different ROIs were compared to detect differences between the conclusion of the cycle (T_1) and the end of the wash-out interval (T_2) and between the condition of the subjects in each of those times (T_1 and T_2) and their baseline (T_0) by means of the Wilcoxon signed-rank test for paired samples. EEG frequencies were compared also between tACS and RNS with a paired samples Wilcoxon signed-rank test. All changes in variables related to the neuropsychological and psychopathological assessments and to the clinical assessment collected at different time point were tested with the same scheme with a Wilcoxon signed-rank test, assuming the usual critical level 0.05. All statistical analyses were performed with the R statistical software [47].

Test power calculation

Sample size was computed on the basis of a functional outcome which is not available for subjects who actually entered the study. For this reason, an analysis of the power of the test employed was performed. The primary outcome is the change in the VAS scale between the beginning of the study and the end of intervention. Since the Wilcoxon rank-sum test is a non-parametric test, the assumption of a standard parametric distribution for the data under the alternative hypothesis is avoided. A discrete distribution is assumed for the difference in VAS which ranges between − 1 and 6, with probabilities equal to those empirically observed, thus the median difference equals 1.5. Under such assumptions, a simulation study was performed in order to detect the power of the Wilcoxon signed-rank test. Based on 10,000 simulations, with the observed sample size, the power of the test is 85%.

Results

Twenty-four participants were recruited. Enrolment flow diagram is reported in the online resources (Fig. F1). For demographic characteristics see Table 1. Seven participants did not meet inclusion criteria (2 had contraindication to tACS, 3 had a psychiatric disease, 2 had recently changed drug regimen). Of the remaining 17, 15 completed the first arm of the study (1 drop out, 1 change of drugs during trials), and 11 both study arms (1 change of drugs, 1 due to stroke, 2 dropouts for personal reasons).

EEG

The open-eyes resting-state EEG confirmed low rhythm prevalence over fronto-central cortical regions (11/15 participants) [13, 15]. Alpha1 power increased at T_1 ($p = 0.024$, CI (− 1.89, − 0.13)) after beta-tACS compared to RNS over bilateral M1 (Fig. 3). Alpha 2 showed a non-significant increase between T_1 and T_2 both after tACS and RNS over bilateral M1.

Clinical assessment scales

VAS scores significantly decreased in 9 cases out of 14 from T_0 to T_1 (p 0.010, CI(0.5, 4.0)) after tACS. This effect was no longer seen at T_2, where just 4 subjects out of 14 reported a reduced pain perception compared to T_1.

After RNS, no significant improvement was seen between T_0 and T_1 as just in 7 cases out of 14 we observed a reduction in VAS scores ($p = 0.062$) as well as between T_1 and T_2 where just 4 subjects reported pain symptoms reduction ($p = 0.757$).

Several items of the Short Form 36-item Health Survey (SF-36) improved after both tACS and RNS. See the online resources (Tables T2, T4) for significant p-values and median scores related to each subitem.

Table 1 Demographic and clinical characteristics of included participants

Subject	Age (years)	Sex	Education (years)	Prevailing rhythm	Stimulation site	Stimulation frequency	Pharmakon
1	51	F	16	Theta	F3	30 Hz	Duloxetine (60 mg)
2	49	F	12	Theta	C3	30 Hz	Amitriptyline (10 mg ttx2)
3	51	F	13	Theta	Cp5	30 Hz	Hydroxychloroquine (200 mg)
4	56	F	13	Alpha 1	C4/Cp2	30 Hz	Tizanidine (4 mg)
5	55	F	16	Theta	C3/Cp5	30 Hz	Venlafaxine (75 mg)
6	49	F	9	Theta	Cz-Fz	30 Hz	Gabapentin (300×3), venlafaxine (75 mg)
7	55	F	8	Theta	Cp5	30 Hz	Alprazolam (0,25 mgx2), pregabalin (150mgx3), Trzodone (100 mg)
8	50	M	11	Alpha 2	Cz-Pz	4 Hz	Alprazolam (25mgx2), Amitriptyline (10 mg), Tizanidine (2mgx2)
9	50	F	13	Alpha 2	Pz	4 Hz	Gabapentin (300×2), Duloxetine (60 mg), Lormetazepam (2 mg), Zolpidem (50 mg), Sirdalud (2 mg), Tapendatol (50 mgx2)
10	50	F	16	Theta	F4	30 Hz	Pregabalin (100 mg), Duloxetine 60 mg
11	65	F	9	Delta	C3	30 Hz	–
12	53	F	11	Theta	Cp5	30 Hz	–
13	57	F	13	Theta	Cp5	30 Hz	Duloxetine (60 mg); Pregabalin (75 mg)
14	52	F	8	Beta	C3	4 Hz	–
15	53	M	17	Beta	Pz	4 Hz	–

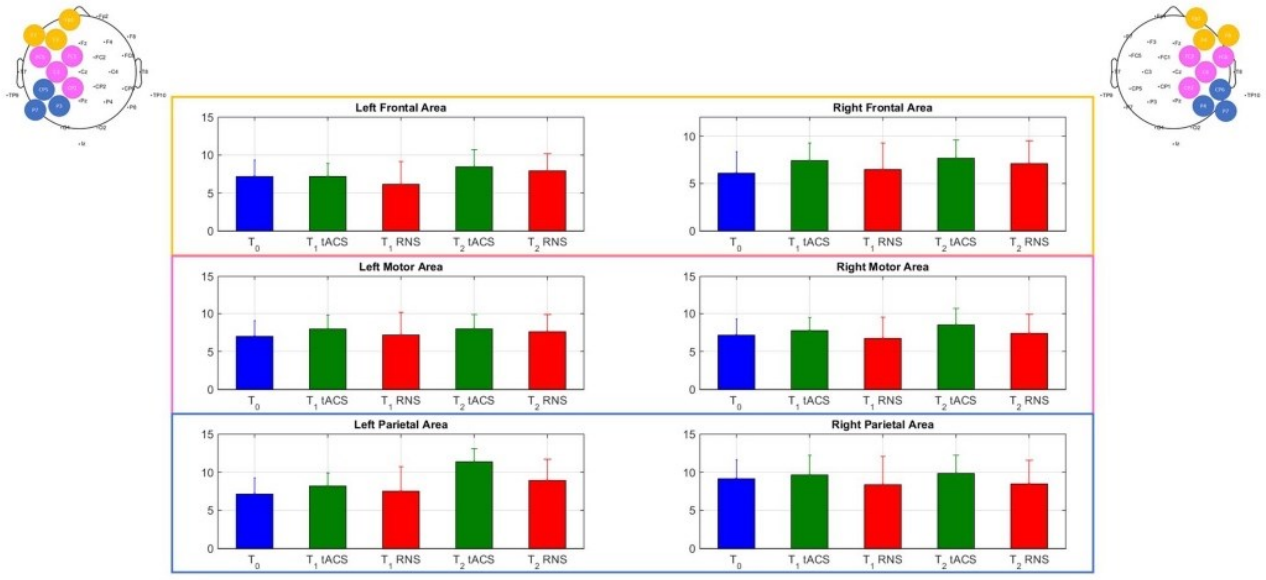

Fig. 3 Group results. Median relative power and standard error in alpha1 range at each evaluation time point (T_0, T_1 tACS, T_1 RNS, T_2 tACS, T_2 RNS). Region of interests are identified based on electrodes location (mean of relative power): left frontal area —i.e., Fp1, F7, F3; right frontal area—i.e., Fp2, F8, F4; Left motor area—i.e., FC1, FC5, C3, Cp1; right Motor Area—i.e., FC2, FC6, C4, Cp2; left Parietal Area—i.e., CP5, P7, P3; Right parietal area—i.e., CP6, P8, P4

Neuropsychological and psychopathological assessment

(1) Psychopathological self-assessment: the State–Trait Anxiety Inventory, assessing baseline state and trait anxiety levels, shows low trait anxiety in our sample at baseline (mean ± standard deviation = 37.26 ± 7.63; median = 38). Depressive symptoms, assessed with the BDI-II, decreased in the tACS group between T_0 and T_1 ($p < 0.001$, CI (4.0, 12.0)), and T_0 and T_2 ($p = 0.006$, CI (5.0, 13.0)), as well as in the RNS group between T_0 and T_1 ($p = 0.008$, CI (1.0, 10.5)). The BSI global severity index score, a measure of the current level of perceived symptomatology, significantly decreased after both tACS and RNS between T_0 and T_1 (respectively, $p = 0.042$, CI (0.01, 0.11), and $p = 0.027$, CI (0.02, 0.23)). Several subitems of the BSI improved after both tACS and RNS. Tables T3 and T5 in the online resources, respectively, report the p-values and the median scores for each subitem.

(2) Self-reported cognitive assessment: the skill loss subitem of the Patient-Reported Outcomes in Cognitive Impairment (PROCOG-P) improved after tACS at T_0–T_2 ($p = 0.024$, CI (0.05, 0.59)). The performance in the Everyday memory questionnaire (EMR.Q) resulted significantly improved in the group receiving the tACS compared to the RNS at T_1 ($p = 0.012$, CI (1.5, 16.5)).

(3) Neuropsychological assessment: among neuropsychological tests, a significant improvement is observed in the MoCa scores after tACS at T_0–T_1 ($p = 0.048$, CI (− 4.5, 0.0)) and at T_0–T_2 ($p = 0.009$, CI (− 4.5, − 0.5)). In the Trail Making Test A (TMT-A), we observed a significant increased speed in the RNS group between T_0 and T_2 ($p = 0.035$, CI (0.0, 15.0)). The TMT-B time significantly decreased in the tACS group between T_0 and T_2 ($p = 0.034$, CI (0.0, 37.5)). Total Phonemic Fluency scores increased in the group receiving tACS between T_0 and T_2 ($p = 0.013$, CI (− 10.0, − 1.0)) and errors decreased ($p = 0.025$, CI (0.0, 2.0)). In the RNS group, an increase was observed between T_1 and T_2 ($p = 0.006$, CI (− 9.0, − 1.5)). In the HVLT-R, the tACS group improved significantly both at T_0–T_2 and T_1–T_2 (respectively, $p = 0.008$, CI (− 9.0, − 1.0), and $p = 0.009$, CI (− 5.5, − 1.0)); the RNS group improved between T_0 and T_2 ($p = 0.012$, CI (− 14.5, − 2.0)). The Rey–Osterrieth Complex Figure time score improved in the tACS group between T_0 and T_1 ($p = 0.025$, CI (7.0, 49.0)), and T_0 and T_2 ($p = 0.049$, CI (0.0, 42.0)), and between T_0 and T_2 after RNS ($p = 0.037$, CI (3.5, 69.0)).

In the online resources (Table T6) are reported the median scores of each administered test.

Discussion

Our data confirm cognitive and EEG activity abnormalities in a sample of people with FMS. This neurophysiological finding informed the choice of the neurostimulation paradigm: tACS combined with an ad hoc physical program was effective in shifting EEG frequencies, reducing pain, and improving neuropsychological and psychopathological tests.

Slow rhythm prevalence in fronto-central cortices are a hallmark of FMS [16]: fast tACS aimed to interact with these abnormal brain oscillations and shift them towards more physiological frequencies [18, 25]. Eleven out of fifteen participants of the initial sample showed theta rhythm prevalence in frontal regions and/or sensorimotor areas. As hypothesized, tailored tACS normalized EEG activity [48]. Although beta-tACS decreases the prevalent theta power in our sample, the induced shift was towards slightly faster (alpha1 or alpha2) bands and not towards beta band. This observation may be explained with the complexity of the targeted pain circuit, the pain matrix [49]. Neuroimaging and neurophysiological studies demonstrated that nociceptive stimulations activate large brain network comprising somatosensory, insular, cingulate areas, and with a temporal delay frontal and parietal areas [50]. FMS pain-related symptomatology is believed to be associated with neuroplastic changes in this network [51]. Taking this into account, we argue that focal tACS stimulation is less likely to radically impact on a large cortical/subcortical network, like the one represented by the pain matrix. Indeed, tACS efficacy in EEG activity normalization was observed in the treatment of other thalamo-cortical dysrhythmias such as in Parkinson's disease, in which the closely circumscribed thalamo-cortico-basal circuit was targeted [18].

We found the primary motor cortex (M1) and sensorimotor areas to emerge as the main targets for the neurostimulation based on the topography of EEG abnormalities. Although M1 is not directly part of the pain matrix, previous studies proved its modulatory role in other chronic pain syndromes [51]. M1 stimulation appears to activate phasic and rapid activity of lateral thalamic nuclei, which in turn activate a cascade of events in the medial thalamus, anterior cingulate/orbitofrontal cortex and periaqueductal gray matter.

Thus, we argue that tACS delivered over M1/sensorimotor cortices may have a modulatory effect on the pain matrix and consequently reduce pain, as proved by reduced VAS score. The absence of significant improvements at T_2 confirms previous reports [52, 53] on the lack of long-lasting effects of NIBS: our experimental paradigm was able to modulate pain during the experiment itself and immediately after, but the pain reduction faded after 4 weeks. This observation calls for the development of portable NIBS devices which may be used for home therapy. In addition, the lack

of effects after RNS can be considered a proof as well of the benefit induced by the real stimulation and physiotherapy treatment.

Physiotherapy may be a co-factor in pain reduction; however, as only the tACS group reported a significant decrease of VAS, an effect of stimulation per se accounting for this outcome is highly likely. TACS may have acted as a primer for the motor cortex, increasing the potential excitability of the underlying cortex and amplifying the ensuing physiological activation obtained through motion.

While the results of tACS on pain suggest a determinant role of neurostimulation, the overall positive effect of physical activity on health perception is well known and observed also in our cohort.

A general health increased is observed in both groups (tACS and RNS), as assessed by SF-36 scores of functionality, energy, social activity and pain subitems.

Similraly, physical activity may have affected also BSI and BDI-II. BSI assesses somatization, obsessive compulsive tendencies and anxiety; scores improved in both groups between T_0 and T_1. BDI-II assesses depressive symptoms; it decreased significantly in short and medium term (T_0–T_1 and T_1–T_2) in the tACS group. It is unclear if this improvement results from a primary effect of the stimulation and the physiotherapy, both previously demonstrated to be effective in depressive symptoms amelioration [54, 55] or if it is a consequence of pain reduction per se. Pain and depression are strictly linked; thus, a reduction of one can lead to beneficial effects on the other. However, depressive symptoms seem to ameliorate also in the RNS group in the short term (T_1), which did not show a significant reduction in VAS scores. In this case, the positive effect of physiotherapy may have played a determinant role.

The PROCOG-P skill loss subitem as well as the EMR.Q improvement in the tACS group can be interpreted as a consequence of the stimulation, which by increasing alpha1 band prevalence, may have boost cognitive performances and the relative perception of self-cognitive abilities. However, pain and depression reduction may have played a role by influencing subjects' general attitude on their capacities. This underlies the need to test cognitive abilities also with neuropsychological standardized test, to disentangle subjective and objective measures of cognitive functioning.

A positive correlation between theta power increase and cognitive deficit in healthy adults is reported [56]; whereas, high power of alpha rhythm is positively correlated with memory and attention performances [57]. TACS stimulation, increasing alpha1 band prevalence, may explain the observed improvements in the MoCA scores, which comprises attention, short-term memory and working memory tasks.

The same can be assumed for TMT-B performance assessing divided attention and set-shifting, whose improvement is observed only in tACS condition. On the contrary, TMT-A performance speeds up only in the RNS group. We argue that this task, assessing mainly visual searching abilities, could have been less influenced by the protocol as less involved in FMS symptomatology compared to the other domains tested.

The other cognitive tasks comprising the phonemic fluency test, the HVLT-R and the time copy component of the Rey Complex Figure test, improved both after tACS and RNS stimulation. Faster improvement in performances were observed at T_1 after tACS, compared to the RNS later improvement (T_2). We argue that tACS combined with physical activity is likely to speed up the process of cognitive performance improvement in FMS, which can anyway be triggered by physical rehabilitation. Indeed, many studies highlight the modulation effect of physical activity on cognitive functioning and general wellbeing [58].

By delivering tailored tACS associated with ad hoc rehabilitative intervention, we succeeded in reducing the main concerns reported by people suffering FMS [59]: pain symptoms and cognitive dysfunctions, including both self-reported measures of perceived impairment and neuropsychological tests performance.

The improvements observed in the group receiving RNS combined with physiotherapy can be explained in light of the multiple-level beneficial impact of physical activity on clinical and cognitive symptoms. However, tACS group showed more pervasive and faster symptoms reduction, pointing out stimulation efficacy.

Limitations

The main limitation is the small sample size. Nevertheless, the sample homogeneity concerning age, sex and education level, adds value to results reliability.

It is pointed out that, considering the dimension of the sample size and the exploratory nature of the study, no corrections for multiple comparisons were performed in hypothesis testing. Future studies should replicate the validity of this treatment approach on a larger sample.

A potential bias could be concomitant drug therapy. Evidence to date suggests interaction effects between drugs with psychotropic effects and neurostimulation techniques [60] Even if not such interaction is clearly reported for tACS, we controlled for possible confounding effects by keeping participants' pharmacological therapy unchanged during the whole protocol.

Conclusion

These data provide evidence of the efficacy of combining personalized tACS and physiotherapy in the treatment of pain, cognitive symptoms and subclinical psychopathology of FMS. Even if the involved mechanisms are still not completely understood, tACS over the sensorimotor cortex coupled with physiotherapy seem to be a promising approach in treating this complex syndrome.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the ethics committee of the teaching Hospital of Padova University, Italy, (Protocol No. 3507/AO/157.

Informed consent A written informed consent was obtained from all participants.

Appendix A. Neuropsychological testing

Clinical and Psychopathological assessment

The beck depression inventory-II (BDI-II) [35] was used to assess depression. It consists of a 21-item questionnaire yielding a composite score of self-reported symptom severity. Standard cut-off scores are: 0–9 = minimal depression, 10–18 = mild depression, 19–29 = moderate depression, and 30–63 = severe depression.

Brief symptom inventory (BSI) [36] is a self-reported questionnaire designed to identify relevant psychopathological symptoms experienced during the last week. The questionnaire is composed by 53 items concerning nine symptom dimensions: Somatization, Obsession–Compulsion, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid ideation, and Psychoticism. The questionnaire provides also three global indices of distress: Global Severity Index (a measure of current level of symptomatology), Positive Symptom Distress Index (a measure of the intensities of symptoms), and Positive Symptom Total (a measure of total number of experienced symptoms). GSI T scores > / = 63 are considered clinically significant, also all cases in which two of the subscales scores are 63 or greater.

The state–trait anxiety inventory [37] is a 40-item self-report questionnaire assessing state and trait anxiety levels. Scores range from 20 to 80, with higher scores indicating higher levels of anxiety severity.

Cognitive self-assessment

Patient-reported outcomes in cognitive impairment (PROCOG-P) [38] is a 55-item self-administered questionnaire designed to measure a range of patient-reported symptoms and their impact in patient's daily life during the last two weeks. The instrument is designed to detect the patient's perspective on his/her cognitive impairment and impact. Items are rated on a five-point Likert scale and the questionnaire includes seven subscales whose scoring is calculated as the mean value of items belonging to each specific subscale (range 0–4).

The PROCOG-P subscales are: affect, skill loss, semantic memory, short-term memory, cognitive functioning, long-term memory and social impact. The subscales give extensive description of the patient experience of his/her cognitive impairment and allow us to assess separately different memory-related symptoms and the emotional impact of symptoms and repetitive behaviors. A total score is the sum of all items (range 0–220). Higher scores indicate both greater impact and severity of cognitive impairment.

Everyday memory questionnaire revised (EMQ-R) [39] is a subjective measure of memory deficiency in everyday life during last month. Total score is the sum of all 13 items, ranged from 0 to 41, with a mean total of 9.75 (SD 8.6), and it is considered as a good measure of change. Higher the score, worse subjective memory functioning.

Neuropsychological assessment

The montréal cognitive assessment (MoCA) [61] is a 30-point brief cognitive screening scale with short time of administration. MoCA is one of the most commonly used tools in clinics assessing general cognitive functioning. It measures a broad spectrum of cognitive abilities that are relevant to several disorders involving CNS [61]. In particular, MoCA was developed to explore frontal cognitive domains (i.e., attention, executive functions, and conceptual

thinking), all domains usually already affected in the early stages of these disorders. Authors identified scores less than 26 as a good cut-off for detecting cognitive impairment.

The Rey–Osterrieth complex figure test [41] is a measure of visuo-spatial constructional abilities and visuo-graphic memory, but also cognitive planning, organizational strategies and executive functions. The task is composed of two parts, direct copying (assessing perception and visuo-spatial construction) and delayed reproduction (assessing implicit visuo-spatial memory). We used the three minutes (short) delay to assess visual memory. Given that repeated administrations of the ROCF resulted in significant improvements of performance, we used alternative forms: The Modified Taylor Complex Figure, and two out of the four complex figures devised for repeated assessments by the Medical College of Georgia Neurology group [62].

The digit symbol-coding (from the Wechsler Adult Intelligence Scale 4th edition [42]), is a measure of graphomotor working memory and speed of processing. It consists of digit–symbol pairs followed by a list of digits. Participants must write the corresponding symbol under each digit (ranged from one to nine) as fast as possible in a limited time interval (120″). Digit Symbol appears to be relatively unaffected by intelligence, memory, or learning. Motor persistence, sustained attention, response speed, visuomotor coordination, all have some role in digit symbol performance, which is also affected by education, gender and age. No practice effects appeared after repeated administering [62].

The hopkins verbal learning test-revised [43] is a test that assesses verbal learning and memory. The test consists of three trials of free recall of a 12-item composed of four words belonging to three different semantic categories. The authors provide six parallel forms leading to equivalent results in the normal population. We used three lists (N 1, 5, and 6) and considered only the free recall as outcome measure.

The trail making tests A and B [44] measure attentional speed, sequencing, visual search and mental flexibility. Part A (TMT-A) assesses motor speed, part B (TMT-B) assesses complex divided attention and set-shifting, difference between B and A (i.e., B/A ratio) gives a measure of cognitive shifting cost and allows us to control for motor impairment. Practice effect is under discussion, especially in the case of short time interval, and we used three parallel forms [63].

The phonemic verbal fluency task [45] requires patients to freely generate as many words as possible that begin with a specific letter (phonemes) in 60 s. The task requires patients to retrieve words of their language and to access their verbal lexicon, focus on the task, select only words following specific rules and avoid repetitions and words that start with phonemes close to the target one. It is therefore considered dependent on executive control, beyond the involvement of verbal abilities. The outcome consists in the total correct words produced through three letters. In the literature different letter combinations are available to longitudinal studies.

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Chapter 6.

General Discussion

The experimental protocols developed and presented in this thesis aimed to better understand the dysfunctional sensorimotor integration mechanisms of DS, AIS and FMS to enrich the literature on this topic and provide new insights into their treatment and rehabilitation. Along these lines are discussed the resulting main points.

6.1 Clinical implications for rehabilitation in Dravet Syndrome

The research line on DS highlighted, first of all, the lack of a unified theoretical framework to explain DS motor and non-motor main symptoms. However, a careful revision of the literature proved that the separately proposed theories are not mutually exclusive but integral parts of a complex picture encompassing a pervasive sensorimotor-cerebellar dysfunction. Thus, the need emerged to separate the highly overlapping cerebellar and PPC sensorimotor clinical signs to possibly determine their relative contribution to DS final phenotype. This is mandatory to design effective rehabilitation programs targeting each subject's specific pool of symptoms. The TMS study aimed to accomplish this by disclosing specific postural, gait, and cognitive parameters associated with PPC or cerebellar functional inhibition. The hypothesis of a double dissociation between specific sensorimotor-related PPC and cerebellar parameters was confirmed, as well as the prevalent involvement of PPC in body schema formation. Several considerations on DS possible assessment and rehabilitation can be inferred from this study. First, wearable sensors such as the IMUs employed in the TMS study should be preferred when dealing with DS. IMUs are easy and fast to be donned, as well as to calibrate and can be used outside a laboratory setting. Most studies trying to characterize DS gait abnormalities adopted the traditional optoelectronic systems, which, even if highly reliable, require a more prolonged procedure of subjects' preparation, which is not optimal with these children. Indeed, several studies reported a loss of data related to poor compliance during the markers application

process [159]. Second, the necessity to assess body schema alterations in this clinical population. There are currently no studies focusing on this aspect of DS, although given the pattern of cognitive and motor abnormalities associated with DS, it is very likely impaired. There is a twofold reason why body schema alterations in DS should be assessed: (1) To improve the currently adopted gait rehabilitation programs. Gait management in DS involves mainly conservative treatment options such as physical therapy and orthotic supports (e.g., ankle foot orthoses) . Surgical interventions, on the other side, are seldom proposed due to DS cognitive disability and varying levels of cooperation which may prevent post-surgical rehabilitation. However, most motor rehabilitation programs do not consider the close relationship between cognitive and gait abnormalities. Given DS impairments in dorsal stream cognitive-related functions, they are likely to present body schema and body perceptual processing imperilments along with visuospatial alterations. Thus, rehabilitation interventions for gait and motor disorders in DS should also focus on empowering adequate body perception and representation to improve DS motor outcomes. This is particularly true for children with a predominant PPC pattern of impairment. Adopting integrated virtual reality-based training can be a fascinating, unexplored research field in this sense. Indeed, it has been proved that this type of intervention can improve the sensorimotor representation by augmenting the sensory feedback and, alongside, reducing the cognitive load and augmenting arousal and motivation [160]. However, there are a lot of challenges in accomplishing this. Indeed, the cognitive impairments of most DS children prevent a straightforward evaluation of the body schema deficits and the adoption of the most currently available cognitive rehabilitation protocols, which require patient compliance. Thus, innovative *ad hoc* evaluation and rehabilitation protocols need to be developed.

(2) Body schema metrics can be good markers to distinguish between cerebellar and PPC involvement. The TMS study provided evidence of an altered walking distance estimation ability in the group selectively inhibited in the PPC. No effect emerged in the cerebellar group. Cerebellar and PPC alterations are probably co-existent in DS. Thus, identifying if specific sets of symptoms (i.e., cerebellar or PPC) are more predominant in a child or a specific developmental period can be helpful

to direct rehabilitation toward a specific set of symptoms. The assessment of body schema alterations can be useful for this characterization.

A third general consideration can be made on the rTMS protocol application to help improve differential diagnoses. There is a broad literature on the use of TMS to induce virtual lesions on healthy subjects to study brain-behaviour interactions. However, its potential in identifying diagnostic parameters should be highlighted. If paired with a quantitative assessment such as the gait analysis, it can be utilized to disclose links between a specific brain impairment and a specific parameter which could be used to facilitate behavioural phenotypic characterization in several conditions.

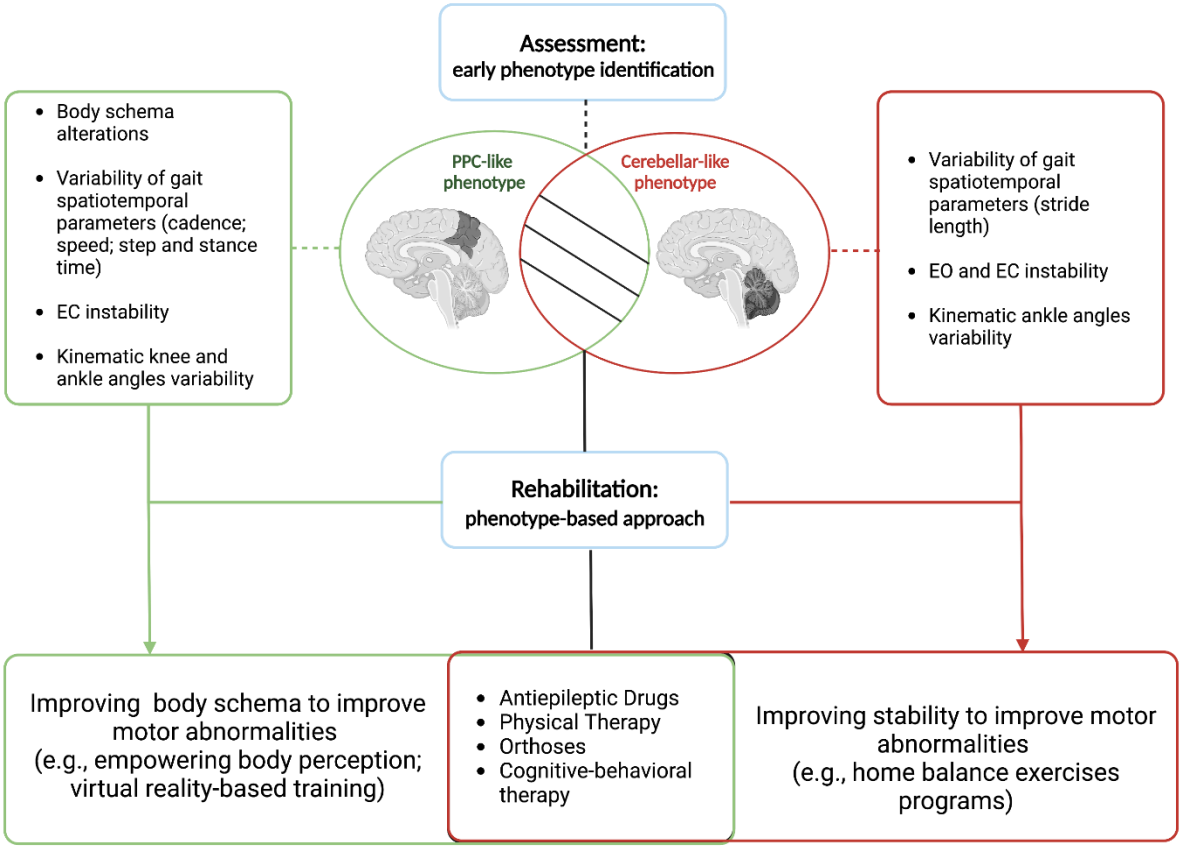

Fig. 24 *DS concluding remarks:* the schema summarizes the principal points emerging from the research line on Dravet syndrome. The early identification of a predominantly cerebellar or PPC phenotype through the evaluation of specific gait and cognitive parameters can help direct motor rehabilitation. *Created with Biorender.com*

6.2 Clinical implications for rehabilitation in Adolescent Idiopathic scoliosis

The second research line focusing on AIS disclosed several neglected aspects in assessing and treating this condition. Traditionally, AIS has been conceptualized and treated as a pure orthopaedic

condition, regardless of the vast amount of literature demonstrating the multiple factors playing a role in its onset and progression. Among them, the review on AIS focused on the contribution of body representational disorders. On one side, body image alterations emerged as a highly comorbid factor of this condition. On the other side, body schema was seldom assessed, even if multiple authors suggested a sensorimotor integration deficit as a possible dysfunctional mechanism of AIS development. Additionally, alterations were observed in the few works evaluating body schema, proving the importance of deepening this aspect. With this aim, a protocol to better characterize AIS sensorimotor integration deficits and body schema-related abnormalities was developed. The hypotheses of altered activation of the sensorimotor network and body schema were confirmed: central areas increased delta and theta relative powers and increased alpha power lateralization can be read as a compensatory strategy and/or the sign of a sensorimotor impairment. On the other hand, the test of body schema revealed a general alteration in the perceived shoulder-waist proportion and trunk inclination, possibly mirroring the sensorimotor integrations dysfunctions. Taken together, these findings lead to the need to rethink the current AIS treatment. Nowadays, treatment options for scoliosis target mainly biomechanics alterations, adopting brace and physiotherapy, which can impact just a part of the complex AIS spectrum of symptoms. AIS is a multifactorial syndrome and, as such, must be treated. Thus at least two other factors should be treated and evaluated to improve AIS taking care:

First of all, the psychological component should be routinely assessed. Body image disorders are a matter of fact in this condition, both because of the disfiguring appearance caused by the scoliosis curve, the adoption of noticeable braces, and the critical period of adolescence. Body image disorders are likely to result in the development of other psychopathologies, such as eating disorders, substance abuse, anxiety and depression [161], [162]. Indeed, several studies proved the comorbidity of these conditions in the AIS population. Thus, the assessment and longitudinal monitoring of the psychological states of these girls should be valuable tools to prevent the development of psychopathologies and improve their overall quality of life. This, in turn, could positively impact also

AIS treatment compliance (i.e., effective brace donning and physical exercise), which is a significant problem in AIS treatment [163]. Alongside the psychological component, the possibility of assessing the presence of any dysfunctional cognitive mechanism leading to body image alteration maintenance should be considered. For instance, attentional biases towards disliked body parts have been reported in several clinical populations with body image disorder (e.g., anorexia nervosa) and are part of problem maintenance and exacerbation.

Second, given the observed central sensorimotor integration dysfunctions, neurological examinations comprising the EEG employment should be considered an early assessment tool to understand AIS etiopathogenesis better and rethink its rehabilitation. In particular, EEG longitudinal monitoring during the brace plus physiotherapy treatment could give clinicians feedback on the ongoing treatment's efficacy and constitute a new neurophysiological biomarker of AIS progression. Tailored training based on EEG biofeedback could be consequently developed and associated with traditional physiotherapy exercises. Moreover, given these girls' specific pattern of body schema alteration, parallel rehabilitation of this aspect could speed up the process of spine realignment. For instance, paradigms of mental imagery associated with physiotherapy exercises could be beneficial.

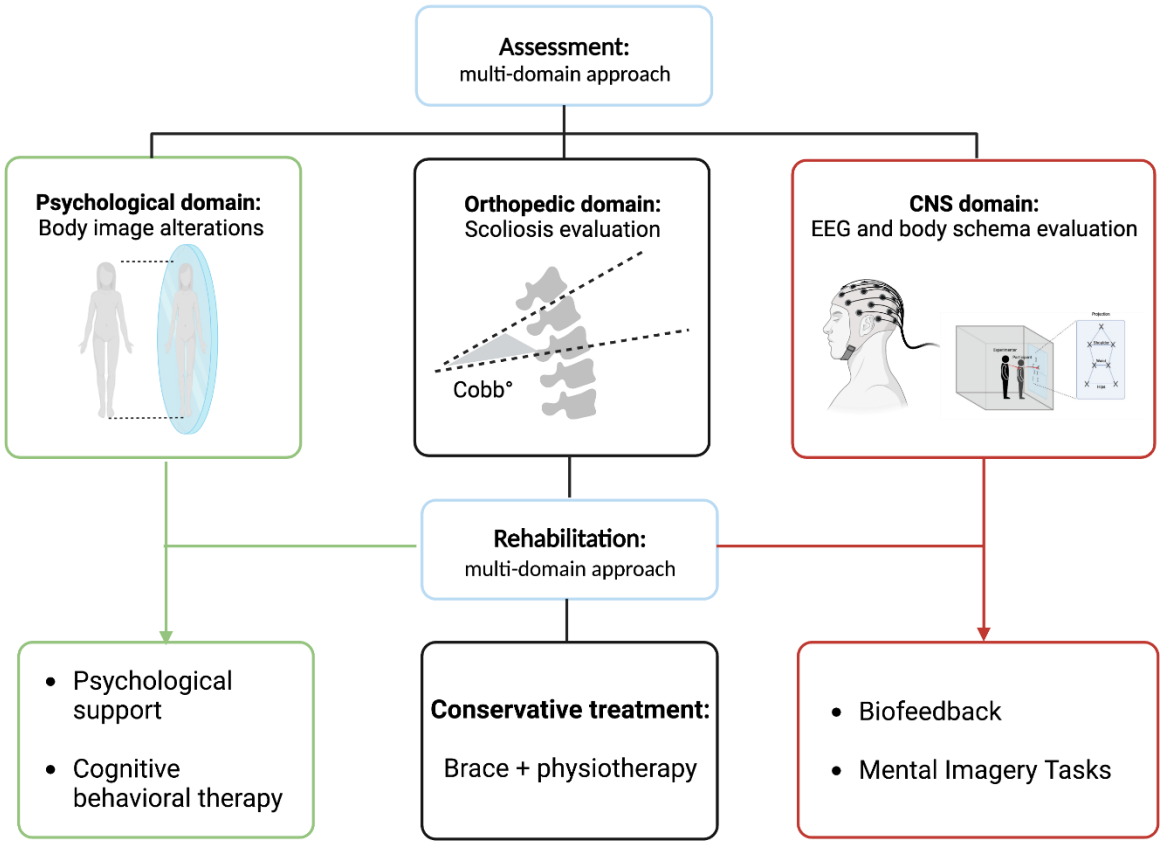

Fig. 25 *AIS concluding remarks: AIS should be considered a syndrome affecting multiple domains: physical, psychological and CNS. The assessment and treatment of each of them should be recommended for optimal taking care of patients. Created with Biorender.com*

6.3 Clinical implications for rehabilitation in Fibromyalgia Syndrome

The third research line was focused on FMS. There is general agreement on considering chronic pain disorders as the result of a complex brain network dysfunction rather than a pure nociceptive alteration. Indeed, many chronic pain conditions, including FMS, are characterized apart from pain by a pool of additional heterogeneous symptoms, such as fatigue and cognitive and affective alterations. These additional symptoms may disclose the overlapping between the altered brain circuits processing the pain and those regulating cognitive/affective processes. Starting from this idea I developed the third experimental protocol aiming to identify new possible biomarkers of FMS, which could account for both pain and non-pain symptoms. First, previous literature data on FMS abnormal EEG rhythms were confirmed: low rhythm prevalence over sensorimotor cortical regions was observed in most subjects. The implemented therapeutic strategy aimed to restore regular EEG

activity by delivering tailored tACS over the sites showing the most remarkable abnormalities. The tailored stimulation combined with ad hoc physical programs effectively brought the EEG activity closer to a physiological-like range and, in parallel, reduced pain and improved cognitive scores. Several considerations can be made to guide FMS treatment strategies from these results. First, the importance of individually tailored treatments: even if in most of the participants, the EEG activity was characterized by increased slow frequencies spectral power (i.e., theta, delta), a few of them show higher fast frequencies spectral power (i.e., beta, alpha). Additionally, even if mainly involving the frontoparietal network, the scalp areas showing maximum power spectral alterations differed between subjects. It is indeed recognized that different fibromyalgia subgroups exist with different clinical characteristics [164]. Identifying new biomarkers, such as the one proposed in this protocol, is thus desirable to try to catch these phenotypic differences better and accordingly direct treatments. Second, the EEG results are proof of FMS sensorimotor processes alteration, which need to be targeted to reduce pain. Physiotherapy alone can just momentarily relieve the pain without acting on its causes. Thus, combining physiotherapy with personalized non-invasive neurostimulation techniques such as the tACS can be a new promising approach to act on multiple aspects of the syndrome. However, as the observed beneficial effects on pain and cognitive symptoms were not long-lasting, longer experimental trials should be considered, as well as the possibility of developing portable NIBS devices to be used as home therapy. Moreover, the finding of altered FMS central sensorimotor network activity again points to the possibility of an altered body schema in this clinical population. This aspect has been poorly studied in the literature (see, for instance, [165]), but there is evidence of short-term pain reduction in FMS as a consequence of body schema modulation [166]. Thus, this neglected aspect has the potential to be included in a protocol for FMS pain reduction. Third, there is no doubt about the invalidating role of cognitive and affective symptoms in FMS. The cognitive "fibro-fog" characterized by attention, memory and executive function alterations should be treated and longitudinally evaluated to ameliorate these patients' general quality of life. Additionally, psychological support and cognitive behavioural therapies can be beneficial. Indeed, according to the

cognitive-emotional sensitization to pain theory [164], maladaptive coping styles when faced with adverse situations (e.g., avoiding, catastrophizing, hypervigilance) can be part of FMS dysfunctional modulation of pain and can increase the subjective pain intensity as well as stress level. Finally, the possible presence of depression and anxiety symptoms must be carefully evaluated, given their high comorbidity with FMS. The relationship between affective symptoms and pain is bidirectional; thus, it is difficult to determine if these symptoms are a consequence of prolonged exposition to pain or part of the disease *per se*. Indeed, alteration in HPA axis function, altered serotoninergic and noradrenergic function, and altered function of systems involving substance P, neurosteroids, and cytokines are shared abnormalities of depression and FMS. This led some authors to postulate the possibility of FMS and depression as disorders belonging to the same affective spectrum [167].

In conclusion, the assessment of fibromyalgia, and its treatment should be multidimensional and consider alleviating or aggravating factors and the effects of fibromyalgia on everyday life functional status and working ability.

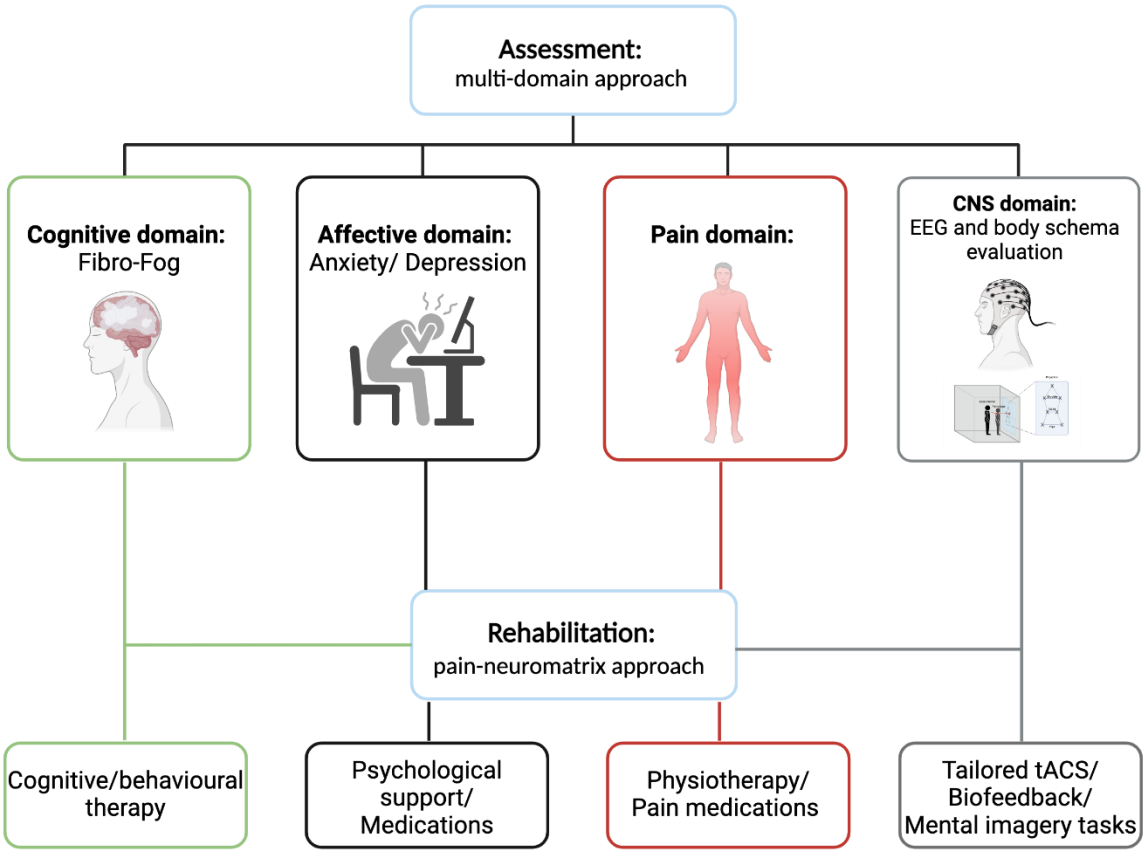

Fig. 26 *FMS concluding remarks: The pain neuromatrix theory can explain several FMS symptoms: pain, cognitive fibro-fog, and affective and CNS alterations. Evaluating all these components can provide a clearer picture of the nature of FMS disorders, which can vary from patient to patient. A tailored and comprehensive rehabilitation considering all the possible affected domains, and associating pain treatment with psychological, cognitive and affective support is thus recommended. Created with Biorender.com*

6.4 Future directions in sensorimotor assessment and rehabilitation

"Robotics is the intelligent connection of perception to action."

Michael Brady (1985)

This thesis discussed three different clinical conditions presenting some forms of sensorimotor integration deficits. However, the variety of conditions involving the sensorimotor integration system is countless, including brain trauma and injuries (e.g., stroke or spinal cord injuries), musculoskeletal and neuromuscular disorders, degenerative neurological diseases, as well as normal ageing. The deficits resulting from sensorimotor integration dysfunctions are highly disabling, limiting even simple everyday actions. Thus, research is primarily dedicated to finding new effective strategies for assessing and improving the rehabilitation of sensorimotor integration impairments. Proprioceptive and physical training are the most adopted rehabilitation approaches. Proprioceptive training can imply active movements/balance, in which patients are required to actively move a limb or the whole body with or without assistance and sensory feedback (e.g., visual feedback of the movement). Other types of proprioceptive training involve passive movements, requiring passive movement apparatus (e.g., therapeutic muscle vibration devices) [168]. Literature provides evidence of improvements in somatosensory and sensorimotor functions resulting from these types of proprioceptive trainings [168]. Together with these traditional approaches, the use of innovative technologies to improve sensorimotor deficits is increasingly taking hold. Among the different rehabilitation technological devices, the robots aiding sensorimotor stimulation are worth mentioning. The term "*robotic technology*" refers to any mechatronic device with a certain degree of intelligence that can physically intervene in patient behaviour to optimise and speed up his/her sensorimotor recovery [169]. Robotic devices have been used both for assessing human sensorimotor residual functions and re-training. Some examples of these approaches include [170]: (i) Strength enhancement, when greater resistance and load are required; (ii) Haptic function, resulting from the actuators' sensory information' feedback

on remote motion and/or tactile perception; (ii) Motor rehabilitation, in case of a disabled upper or lower limb, compensating for the lack of strength or movement precision in tasks compatible with the requirements of everyday life. For these purposes, upper/lower limb robotics systems, balance systems, and wearable sensors have been developed over the years.

Most of the rehabilitation devices implemented passive training modalities (i.e., robot-driven control, where the robot imposes the movement trajectories) or active training modalities (i.e., patient-driven, where the robot modulates actions performed by the patient) [169]. However, the so-called assistive modality seems to be the most effective for rehabilitation [169]. Assistive control helps the patient to reach a final goal reflecting the strategies adopted by conventional physical and occupational therapies. Notably, the assistance-as-needed approach is highly effective, as it implies active patient involvement, avoiding the risk of relying too much on the robot. This has been proven to boost neuroplastic changes [169]. The strategies adopted to achieve this aim imply, for instance, the introduction of challenges to make the task more difficult and engaging (e.g., the introduction of resistance to the participant's limb movements during the exercises).

Robotic rehabilitation presents several advantages compared to traditional therapies [169]: (i) it is suitable for performing long-lasting and repetitive motion tasks ensuring the intensity and precision required by rehabilitation training; (ii) It can reduce medical and nursing staff labour; (iii) It is suitable for personalised training; (iv) It usually integrates a variety of sensors which effectively monitor and record subjects' performance during the entire rehabilitation process; (v) The use of robots for rehabilitation introduces the possibility of developing at-home effective rehabilitation protocols.

Robotic technologies are often paired with bio-signal recordings (e.g., EEG, IMUs, EMG). Combining these two components can provide meaningful information on sensorimotor function impairment and level of recovery, as well as new insights into understanding recovery processes *per se*. However, many challenges are still open. First, the mechanical complexity: the exoskeleton should be lightweight, portable, efficient, and compliant but also able to provide enough support in case of severe impairments. Secondly, despite the numerous advantages described above, rehabilitation with

robotic technology is not successful *per se* but depends on several factors. Among them, the human-robot interaction should be considered: many studies proved the relationship between the embodiment of assistive devices and the efficacy of rehabilitation programs with those devices [171]. Embodiment can be defined as the process by which something external to the body can be integrated into it and perceived as part of the body schema due to multisensory integration [172]. The experience of wielding a tool is quite different from experiencing ownership over a limb: this should be considered when designing robotic devices that need to be physically attached to the body. The factors concurring to the embodiment of an external device are still a matter of research: for instance, it has been proved that the embodiment of a tool is not just driven by the tool functionality but also by the appearance/similarity with the effector is aiding [173]. With this in mind, further research on understanding the mechanisms that can determine the embodiment of external objects into the body is a pressing research goal for robotics rehabilitation.

Finally, rehabilitation with robotic devices is highly related to the patient's cognitive reserve and motivation. Cognitive reserve and motivation interact in determining subjects' experienced mental workload and robot usability, which are of primary importance in driving patients' likelihood to experience benefits from rehabilitation [174]. Thus, the parallel evaluations of patients' cognitive reserve, motivation, cognitive workload, and usability while using robotic devices can be valuable tools in predicting the final rehabilitation outcome and must be assessed. The following proposed schema (see **Fig. 27**) hypothesises the interactions of human and machine-related factors contributing to the efficacy of a rehabilitation program with robotic technologies.

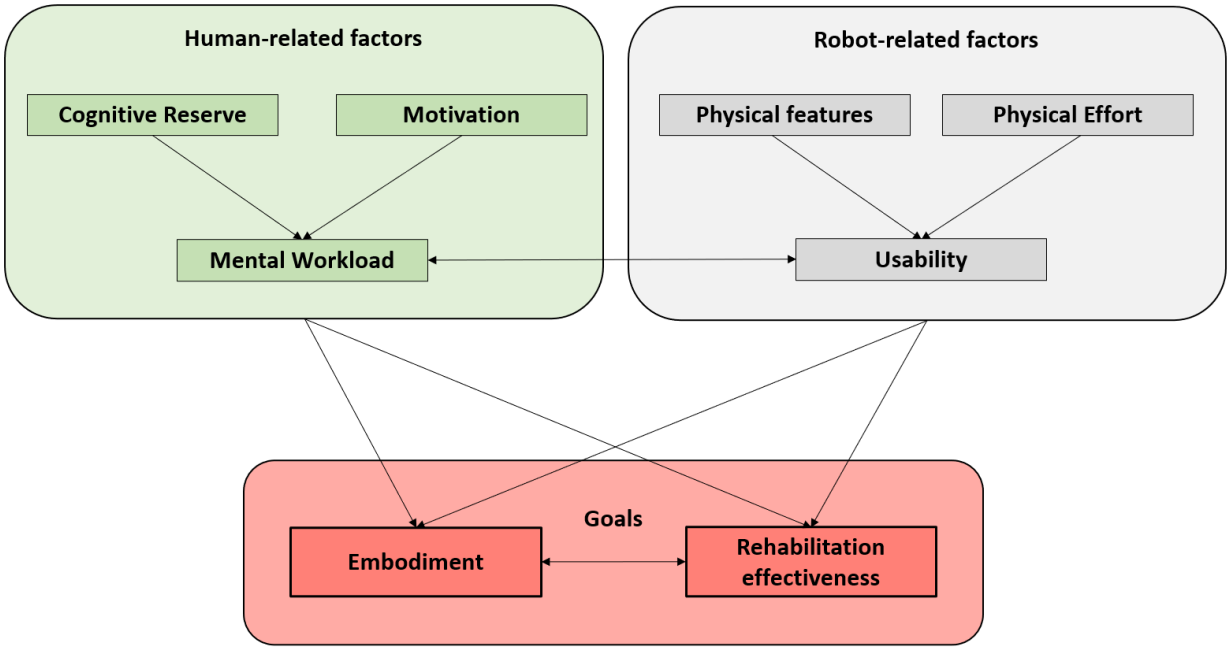

Fig. 27 *Rehabilitation with robotic technologies:* The schema summarizes the factors which are hypothesized to contribute to the efficacy of rehabilitation with robotic technologies. Human-related factors include the motivation and cognitive reserve of the patient, which together determine the experienced mental workload. Robot-related factors comprise the robot's physical characteristics (e.g., aesthetic) and physical effort required (e.g., weight, complexity), which determine the experienced usability. All these factors contribute to rehabilitation efficacy *per se* and robot embodiment which, in turn, affect rehabilitation effectiveness. *Created with Microsoft PowerPoint*

Considering the abovementioned factors, we are currently working in collaboration with the Spaulding Rehabilitation Hospital, Harvard University, on a paradigm with the final aim to propose a new lower limb exoskeleton relying on subjects' neurophysiological signal and designed considering the factors associated with a better embodiment (See Appendix 1). In summary, the protocol has a double long-term goal. First, to create a new software architecture to drive a lower limb exoskeleton (i.e., ExoRobo Walker) based on neurophysiological signals (i.e., EEG, EMG, accelerometers) to predict and prevent loss of balance. Secondly, identifying the psychological and neurophysiological factors that can facilitate human-robot interactions to boost their embodiment among different end-users (i.e., healthy young participants, healthy elderly, and neurological populations). To achieve these goals, the protocol implies: 1. the collection of EEG, EMG, and IMU data from young and older adults as they respond to repeated mechanical perturbations (i.e., pull tests) challenging their balance while wearing a lower limb exoskeleton; 2. The use of data features derived from EEG, EMG, and IMU recordings to control the same exoskeleton and augment study

participants' ability to regain their balance after repeated mechanical perturbations; 3. The determination of the neurophysiological and psychological factors associated with the embodiment of wearable devices.

These preliminary data will provide the basis for the ideation of a soft exoskeleton prototype to counteract the loss of balance and characterized by a better human-machine interaction capability.

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Appendix

Mass General Brigham

Institutional Review Board
Intervention/Interaction Detailed Protocol

Principal Investigator:	Paolo Bonato, PhD
Project Title:	Using an exoskeleton to augment the ability of older adults to respond to balance perturbations
Version Date:	December 2, 2022
Version Name/Number:	Initial Submission

1. Background and Significance

The World Health Organization (2021) reports falls as the second leading cause of injuries and deaths worldwide (https://www.who.int/news-room/fact-sheets/detail/falls). Falls are common in older adults and often result in moderate to severe injuries. Many factors contribute to an increase in fall risk in older adults, including older age (>75 years old), living alone, cognitive impairments, age-related central nervous system changes (i.e., visual, vestibular, proprioceptive, and postural impairments), age-related peripheral nervous system changes, and muscle weakness [1]. These factors negatively affect the ability of older adults to respond to balance perturbations.

Researchers have begun to explore the use of exoskeletons to detect biomechanical instabilities (i.e., following a balance perturbation) and augment the ability of older adults to restore their balance and hence avoid a fall [2-4]. Typically, exoskeletons rely on kinematic variables generated by inertial measurement units (IMU) to detect the initiation of a fall [5]. However, detecting a fall initiation solely based on kinematic variables may not be the best prevention approach. Neurophysiological data, such as electroencephalographic (EEG) and electromyographic (EMG) signals, could provide additional information to detect and possibly prevent falls. A recent study showed that EEG signals can enable the detection of anticipatory signs of a fall faster than muscular or kinematic responses [6]. Specifically, perturbation evoked potentials (PEP) can be detected as early as 75–134 ms after the onset of an external perturbation preceding both muscular (~180 ms) and kinematic (~350 ms) responses.

We will collect EEG, EMG, and IMU data from young and older adults as they undergo repeated pull tests. This data will capture the participant's response to the mechanical perturbation. We will

explore if EEG, EMG, and IMU data can be used to design exoskeleton control algorithms to respond to balance perturbations and hence allow study participants to avoid a fall.

2. Specific Aims and Objectives

The long-term goal of this project is to test the hypothesis that an exoskeleton controlled by EEG, EMG, and IMU data can prevent falls in older adults. As a first step toward testing this hypothesis, we propose to accomplish the following specific aims.

Aim 1. To collect EEG, EMG, and IMU data from young and older adults as they respond to repeated mechanical perturbations (i.e., pull tests) challenging their balance during quiet standing.

We hypothesize that the analysis of EEG, EMG, and IMU data will highlight distinct patterns of activity that are predictive of the Loss of Balance (LoB). Furthermore, we hypothesize that such patterns of activity are age dependent. In other words, we anticipate that EEG, EMG, and IMU data collected from young and older adults will highlight differences in the way the two groups respond to a mechanical perturbation. Finally, we hypothesize that the same EEG, EMG, and IMU data characteristics will be observed in response to the repeated mechanical perturbations when participants wear the exoskeleton and when they do not.

Aim 2. To explore exoskeleton control modalities via simulations that will use EEG, EMG, and IMU recordings as input to algorithms meant to augment the response to mechanical perturbations affecting participants' balance and hence avoid falls.

We hypothesize that the detection of EEG, EMG, and IMU patterns associated with a potential LoB will enable the deployment of exoskeleton control strategies to prevent falls in young and older adults.

3. General Description of Study Design

We will test study participants' response to a mechanical perturbation (i.e., the pull test) that is commonly utilized to assess balance impairments in patients with neurological conditions affecting postural stability. We will perform two sessions. Session A: without the exoskeleton and session B: with the exoskeleton. The exoskeleton will be programmed to be "transparent" to study participants. Meaning the exoskeleton will not generate any movement, resistance or assistance, to the individual wearing it.

We will recruit a group of older adults (65-85 years old) and a group of young adults (18-40 years old). Before enrollment, prospective participants will be contacted (typically by phone) by a member of the study team who will provide prospective participants with a detailed description of

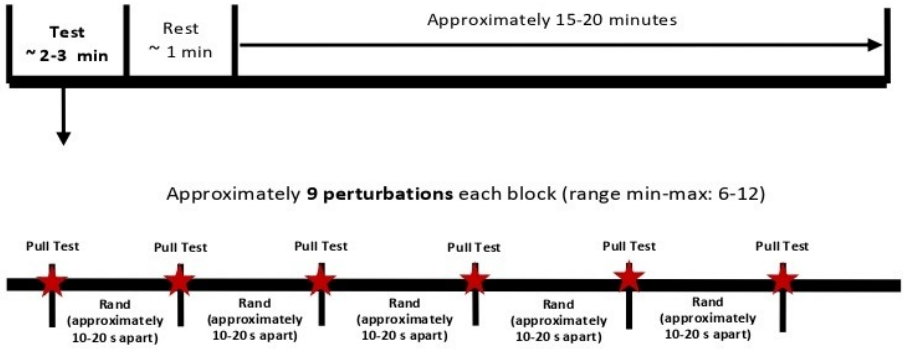
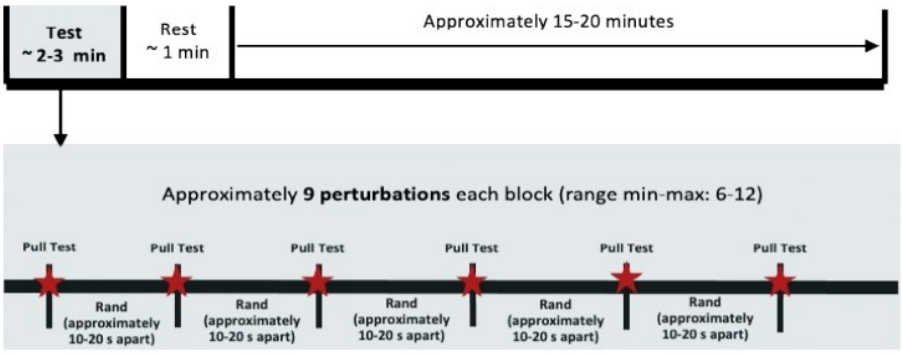
the study. If they express interest in participating, study staff will perform a preliminary assessment of their eligibility to participate in the study by asking a few questions concerning their medical history.

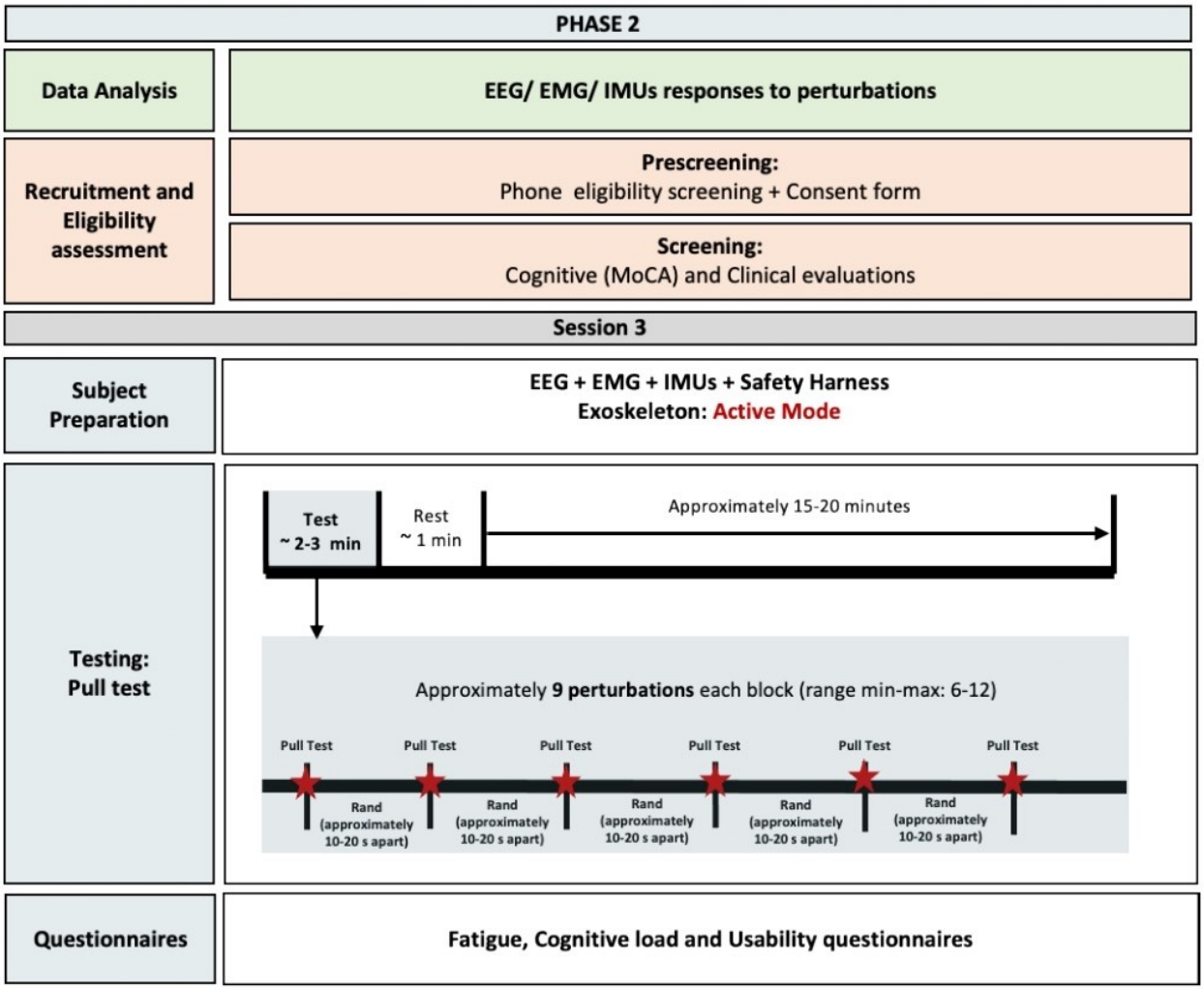
Individuals who appear to be eligible and are willing to participate in the study will be invited to undergo additional screening during an in-person visit in the Motion Analysis Laboratory (MAL) at Spaulding Rehabilitation Hospital (SRH). During this visit, we will first complete the initial screening process to see if the prospective participant meets the inclusion/exclusion criteria. If deemed eligible, study staff will prepare participants for the collection of biomechanical and neurophysiological data. Surface EMG electrodes, a 32-channel EEG cap, and IMUs will be positioned on several body segments to collect muscle activation patterns, perturbation evoked potentials, and kinematic variables. Force plates (AMTI, Watertown, MA) will be used to collect additional data on balance, such as their center of pressure (CoP) during perturbations. To ensure the accuracy of the biomechanical data, we will collect data using a camera-based motion capture system (VICON, Hauppauge, NY).

We will carry out two sessions (session A and session B). The order of the sessions will be randomized. During session A, participants will be instructed to perform a quiet standing task. At the beginning of each trial, we will collect approximately one minute of resting state data. This will serve as a baseline for the analysis of instability-related EEG and EMG patterns. Then a clinical researcher will administer a series of pull tests to perturb the participant's balance. In session B, we will ask the participant to wear the exoskeleton while undergoing the same procedure outlined for session A.

The two sessions are expected to last a total of approximately 3.5 hours. Data collected in the study will be used to create a model suitable to control the exoskeleton using a strategy designed to augment the participant's ability to respond to mechanical perturbations. This part of the study will rely on simulations to assess the feasibility of preventing falls by augmenting the ability of study participants to response to the mechanical perturbation and restore their balance despite displaying early signs of a fall initiation.

Mass General Brigham

Recruitment and Eligibility assessment	**Prescreening:** Phone eligibility screening + Consent form
	In Person Visit: Informed Consent Form Screening Questionnaires, Cognitive and Clinical Assessments
PHASE 1	
Session A	
Subject Preparation	**EEG + EMG + IMUs + Safety Harness**
Testing: Pull test	
Break	
Session B	
Subject Preparation	**EEG + EMG + IMUs + Safety Harness** **Exoskeleton: Transparent Mode**
Testing: Pull test	



4. Subject Selection

We will recruit a convenience sample of 30 individuals (15 young adults and 15 older adults). We will use the following inclusion/exclusion criteria.

Inclusion criteria:

- Male and female, 18 to 40 years old (young adult group) and 65 to 85 years old (older adult group)
- Self-reported ability to stand continuously for 30 minutes without an assistive device
- Anthropometric characteristics compatible with the exoskeleton:
  - Thigh length: approximately 13” to 18”
  - Shank length: approximately 13” to 18”
  - Hip girth: 30” to 45”

Exclusion criteria:

- Medical conditions (e.g., neurological, orthopedic) that could interfere with the ability of study participants to safely undergo the study procedures or affect their response to the pull test (e.g., peripheral neuropathy)
- Use of psychotropic medications or other medications that could interfere with the ability of the individual to undergo the study procedures or affect his/her response to the pull test
- Contraindications for the use of lower-limb exoskeletons (e.g., thromboembolic disease, progressive neurological disorders, cardiovascular or pulmonary contraindications, joint instabilities or compromised bone health, recent or non-consolidated fractures, osteoporosis).
- Skin lesions, infections, or rashes affecting the areas where the exoskeleton straps will be attached to the body.
- Anatomical characteristics that prevent a proper fitting of the exoskeleton (e.g., excessive thigh girth)
- Women who are pregnant (self-reported)
- Mild cognitive impairment assessed using the Montreal Cognitive Assessment (MoCA) normative data stratified by age and education [7].

Recruitment procedures:

Recruitment strategies will include the use of the following sources:

1. Physicians and therapists may refer interested patients to the study (we will provide physicians and therapists with study flyers and brochures to inform clinicians of the study details).
2. Flyers posted in outpatient clinics, therapy gyms, and public spaces both inside and outside the hospital campus.
3. Word of mouth
4. Individuals who previously agreed to be contacted about opportunities to participate in research studies at SRH will be contacted by phone by a study staff
5. Via the Partners Clinical Trials (Rally) website.

The study entails no cost to the participants. We will cover parking costs for all participants who park at the SRH garage while taking part in the study. Participants will be compensated for their time as specified below (see “Remuneration” subsection).

5. Subject Enrollment

During the first contact with the study team, a staff member will provide prospective participant with a detailed description of the study (typically over the phone). If interested and deemed likely to be eligible, a member of the study team will offer to send the informed consent form via email. Prospective participants will be encouraged to call study staff with any questions or concerns they might have prior to their first study visit. Upon arrival for the study visit, they will be given another copy of the informed consent form and study staff will review the procedures with them and answer any questions they might have. Consent will be obtained by the Principal Investigator, or a staff member designated by the Principal Investigator as adequately knowledgeable of the risks/benefits of the study and the vulnerability of the study population, and capable of critically assessing the subject's awareness of these factors. participants will be encouraged to continue to ask questions and express any concerns to study staff throughout their participation in the study. A participant's cognitive impairments and ability to follow instructions will be assessed using the MoCA test. If prospective participants fail this screening assessment, they will be excluded from the study. Enrollment will begin when the subject thoroughly understands and signs the informed consent form. Testing will only take place once the informed consent form is signed.

6. STUDY PROCEDURES

Below, we provide a detailed description of the study procedures.

Pre-screening

All study procedures will be carried out in the MAL at SRH. Prior to the first visit, we will administer a short screening questionnaire (typically by phone) to perform and preliminary assessment of eligibility to participate in the study. If a subject is willing and able to come to the MAL for the initial screening, the phone screening may be forgone in favor of an in-person interview to determine eligibility (using the same script). This pre-screening is not only undertaken to allow researchers to confirm the subjects' eligibility, but it is also an opportunity for the volunteer to ask any questions they might have regarding the study. The screening questionnaire will not contain identifiable information unless the subject is eligible and agrees to participate in the study.

Volunteers will be invited to participate in 1 visit consisting of two sessions (A and B) at the SRH MAL. The total visit should last approximately five hours.

Informed Consent and Screening

Initial evaluation informed consent will be obtained in person by trained study staff. Study staff will explain all the study procedures, the equipment being used, and the potential risks associated with the study procedures, as outlined in the informed consent form (ICF). Prospective study volunteers will be given sufficient time to consider their participation and to ask any questions they might have regarding the study. Once study staff has evaluated the participant's eligibility via a brief cognitive assessment (MoCA) and a health history review (i.e. previous diagnoses and medications), those found eligible will be allowed to continue with the study procedures. Epidemiologic and identifiable information (e.g. name, subject contact information, and their address) will be collected.

Clinical Assessment

The following tests will be carried out by trained study staff:

- Berg Balance test [8,9] assess static balance and fall risks in adults. 14 tasks are tested, each scored on a 5-point ordinal scale. Points are deducted based on timing of the task, and the need for supervision or assistance.
- Strength Assessment of the lower limbs: lower extremities will be tested to determine muscle strength using the Medical Research Council (MRC) Scale for Muscle Strength, a scale ranging from 0 (no identifiable muscle contraction) to 5 (the muscle moves actively against gravity with full resistance).
- Assessment of sensation: Light touch and pain sensation (monofilament test), vibratory sensation (mechanical diapason quantification), and proprioception.

Testing Session A

The following neurophysiological data will be collected:

1. EEG data: A 32-channel EEG cap will be put on the subject head (Enobio 32). We will use EEG electrodes with conductive gel. Electrode-skin impedance will be checked and considered acceptable if <5kΩ. Data will be sampled at 250 Hz and referenced to the Cz (i.e., midline central) electrode.

2. EMG data: Surface electromyographic data will be collected to study the characteristics of muscle activation patterns. We will follow the SENIAM (Surface Electromyography for the Non-Invasive Assessment of Muscles) guidelines to place up to 16 electrodes on several muscles, such as the following: Gastrocnemius, Tibialis Anterior, Rectus Femoris, Vastus Lateralis, Biceps Femoris, and Gluteus Maximus. Surface EMG electrodes will be secured to the skin using adhesive tape and Coban (self-adherent wrap) if needed. To ensure proper

contact, the skin will be cleaned with alcohol swabs and shaved (if necessary) prior to positioning the surface electrodes.

3. IMU data: Kinematic parameters will be obtained using up to 7 IMU units (Xsens, Enschede, The Netherlands) that will be secured with adhesive tape and/or straps to the lower body (e.g., sacrum, thighs, shanks, feet).

4. Force platform data: force platforms (AMTI) will be used to measure the ground reaction forces during the experiment.

5. Motion capture data: We will use the VICON system, which is a camera-based motion analysis system. Our system is equipped with hardware/software features enabling the synchronization of different neurophysiological signals. It includes standard video cameras to videorecord the session. When we record video data, we will ask participants for permission to use the recordings for scientific presentations.

Experimental Task

A trained clinician will administer a series of pull tests. The pull test is a measure of postural instability routinely administered in the clinic (e.g., during a neurological examination). During a pull test performed in the clinic, the clinician positions their hands on the patient's shoulders and suddenly pulls the patient backward. The participant's response to the pull test is assessed using an ordinal scale (between 0 and 4). We will use a set-up described in a previous study [10] to implement a modified pull test that relies on a harness attached to overhead ceiling lift without providing unloading to ensure safety and a load cell to measure the force exerted by study staff during the pull test. Study staff will manually generate a backward pull via a cable attached to the trunk harness and connected to a load cell, attached to the harness at shoulder height. As the pull force magnitude varies across trials, we will be able to elicit different motor response strategies to the mechanical perturbation. The pull force magnitude will be recorded for each trial and used to identify the segments of the EEG, EMG, and IMU recordings to be analyzed. The test will last about 25 minutes. During which we anticipate performing approximately 50 pull tests.

Testing session B

The experimental procedures summarized above for session A will be repeated during session B. However, during session B participants will wear an exoskeleton developed by engineers in the MAL and utilized in previous studies on children with cerebral palsy (IRB # 2019P002281) and healthy adults (IRB # 2020P000252). Study participants will be asked to wear appropriate clothing (athletic wear, which will be provided by the laboratory if needed). They will then be fitted

with the exoskeleton programmed in transparent mode. Transparent mode is defined as a control modality that does not modify the behavior of the user because it does not assist or resist the movement of the user. Study staff will measure the length of different body segments of the study participant and adjust the elements of the exoskeleton accordingly. Proper fitting will be checked by a trained study staff once the subject has donned the robotic device. If needed, further adjustments will be performed to ensure optimal fitting.

Remuneration:

Volunteers who participant in this study will receive up to $80. Participants will receive the following compensation for each session: $40 for session A; $40 for session B. Volunteers who fail the in-person screening will be compensated $20. In addition, we will cover parking fees at SRH for all study participants.

7. RISKS AND DISCOMFORT

All tests used in this study are standard and widely used instruments with minimal risks and will be administered by experienced clinical study staff.

Study participants might experience mild skin irritation due to the use of adhesive tape and sticky conductive gel for the EEG and EMG recordings. The procedures to prepare the skin prior to electrode placement could also cause mild skin irritation. Adhesive tape might be used to secure IMU units to the skin, with similar potential side effects. Wearing the electrodes exposes individuals to a risk that we deem equivalent to wearing an adhesive bandage for a few hours and peeling it off. The procedures to prepare the skin expose study participants to a risk equivalent to using an electric razor. To minimize these risks, we will use hypoallergic adhesive tape. Also, we will carefully inspect the skin prior to positioning sensors on the body and after completion of the data collections.

Mild skin irritation could be caused by the exoskeleton straps. The risk is equivalent to wearing an orthopedic joint pad for a few hours. Components of the exoskeleton are electrically insulated according to standards to avoid electrically related injuries. It is possible that the insulation material might break. To minimize risks to the subjects, we will periodically check the insulation of the wires that supply electrical power to the device. A safety switch, able to shut down the system instantly, is available to study staff to switch off the device in case of an emergency.

Study participants will likely experience fatigue and muscle soreness during the experiments. Excessive fatigue and muscle soreness will be minimized by allowing subjects to rest at any point during the experimental procedures.

There is a possibility that subjects could fall or trip during the experimental procedures. To minimize this risk, trained clinicians and study staff will closely monitor participants. Study participants could lose their balance and fall during the experiments. To minimize the likelihood of injuries, we will use a safety harness attached to an overhead lift.

Unintentional loss/disclosure of Protected Health Information may occur and is considered a minimal risk due to the security measures enforced at SRH. Confidential information will be kept in a locked filing cabinet, as well as in an MGB Dropbox folder and on password-protected computers in the MAL.

8. BENEFITS

Study volunteers are not expected to directly benefit from their participation in the study. Information gained during the study is expected to contribute to the development of robotic systems to prevent falls in older adults.

9. STATISTICAL ANALYSIS

Descriptive statistics will be derived for all the data features estimated from the EEG, EMG, and IMU data. Descriptive statistics will be derived as well as from the data collected using clinical assessments. Because of the exploratory focus of the study, we will limit the statistical analyses to measures of mean and variance of the variables of interest.

10. MONIOTRING AND QUALITY ASSURANCE

Because this study's procedures pose minimal risk to participants, bimonthly data and procedural reviews by the Principal Investigator (Dr. Bonato) in consultation with study staff will be sufficient to identify and ameliorate any potential safety issues. Any safety concerns about the equipment or testing protocol will be brought to the immediate attention of Dr. Bonato. Study staff will conduct bimonthly audits to ensure compliance with regulatory requirements for study documentation.

Approval of protocol, informed consent procedures, and recruitment will be obtained from the IRB during annual reviews.

Adverse event reporting will be done according to Partners Human Research Policy. Remedial action to prevent reoccurrence of the event will be instituted prior to the resumption of study procedures.

Study staff will conduct quarterly audits to ensure compliance with regulatory standards for study documentation.

11. PRIVACY AND CONFIDENTIALITY

The MAL will assign each participant an alphanumeric identifier, which will henceforth be the sole means of identification connected to the participants' data. All data will be collected under this identifier and will be kept isolated from any personal health information. All data will be stored locally in a secure system. Information shared with individuals outside of Partners will be labeled using an alphanumeric identifier and will be devoid of personal health information. Any video recordings and photos will be stored securely in the MAL. Only investigators listed on the study will have access to them. The video recordings will be destroyed after seven years from the date of study closure in compliance with Partners Record Retention Policy. Participants will be given the choice to have video/photo material used for academic articles and presentations.

- ☒ Study procedures will be conducted in a private setting
- ☒ Only data and/or specimens necessary for the conduct of the study will be collected
- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☒ Specimens collected will be maintained in a secure location with appropriate protections (e.g., locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g., encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communications with participants will comply with Mass General Brigham secure communication policies
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- ☐ Additional privacy and/or confidentiality protections

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