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Neuro-orthopaedic assessment and management in patients with prolonged disorders of consciousness

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Abstract:	Introduction: Following a severe acquired brain injury, neuro-orthopaedic disorders are commonplace. While these disorders can impact patients' functional recovery and quality of life, little is known regarding the assessment, management and treatment of neuro-orthopaedic disorders in patients with disorders of consciousness (DoC). Objectives: Describe neuro-orthopaedic disorders in the context of DoC and provide insights on their management and treatment. Methods: A review of the literature was conducted focusing on neuro-orthopaedic disorders in patients with prolonged DoC. When no articles could be found, literature in non-DoC population was reported. Results: Few studies have investigated the prevalence of spastic paresis in patients with prolonged DoC as well as its correlation with pain. Pilot studies exploring the effects of pharmacological treatments and physical therapy on spastic paresis show encouraging results yet have limited efficacy. Other neuro-orthopaedic disorders, such as heterotopic ossification, are still poorly investigated. Conclusion: The literature of neuro-orthopaedic disorders in patients with prolonged DoC remains scarce. We recommend treating neuro-orthopaedic disorders in their early phase to prevent complications such as pain and improve patients' recovery. Additionally, this approach could enhance their ability to behaviourally demonstrate signs of consciousness, especially in the context of covert awareness.

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Abstract

Introduction: Following a severe acquired brain injury, neuro-orthopaedic disorders are commonplace. While these disorders can impact patients' functional recovery and quality of life, little is known regarding the assessment, management and treatment of neuro-orthopaedic disorders in patients with disorders of consciousness (DoC).

Objectives: Describe neuro-orthopaedic disorders in the context of DoC and provide insights on their management and treatment.

Methods: A review of the literature was conducted focusing on neuro-orthopaedic disorders in patients with prolonged DoC. When no articles could be found, literature in non-DoC population was reported.

Results: Few studies have investigated the prevalence of spastic paresis in patients with prolonged DoC as well as its correlation with pain. Pilot studies exploring the effects of pharmacological treatments and physical therapy on spastic paresis show encouraging results yet have limited efficacy. Other neuro-orthopaedic disorders, such as heterotopic ossification, are still poorly investigated.

Conclusion: The literature of neuro-orthopaedic disorders in patients with prolonged DoC remains scarce. We recommend treating neuro-orthopaedic disorders in their early phase to prevent complications such as pain and improve patients' recovery. Additionally, this approach could enhance their ability to behaviourally demonstrate signs of consciousness, especially in the context of covert awareness.

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Article type: Review article

1. Introduction

Prolonged Disorders of Consciousness (DoC) include coma (no arousal and no awareness), the Vegetative State (VS)/Unresponsive Wakefulness Syndrome (UWS) meaning that the patient can display reflexive movements and eye opening without awareness of oneself or their surroundings (Laureys et al., 2010), and the Minimally Conscious State (MCS), a state in which patients show fluctuating purposeful behaviours without being able to functionally communicate (J T Giacino et al., 2002). Importantly, the severe disabilities present in patients with DoC integrally influence patients' functional outcomes.

The recent European and American Guidelines (Giacino et al., 2018; Kondziella et al., 2020) focused on behavioural tools and advanced diagnostic techniques, which are recommended in patients with DoC. However, neuro-orthopaedic complications and motor disabilities were largely overlooked. These complex motor disorders can influence the diagnosis, prognosis, and therapeutic management of patients with DoC (Formisano, 2021). Indeed, the presence of severe motor disabilities may interfere with the motor output of those with DoC, who despite some intact partially preserved cognitive abilities, may feel imprisoned in their body without the possibility to interact with their environment through overt motor behaviours. This condition has been defined as cognitive-motor dissociation (Schiff, 2015), covert awareness (Owen et al., 2007), non-behavioural MCS (Stender et al., 2014) or MCS* (Gosseries, Zasler, & Laureys, 2014; Thibaut et al., 2021) and functional Locked-in Syndrome (fLIS) (Bruno, Vanhaudenhuyse, Thibaut, Moonen, & Laureys, 2011; Formisano, Pistoia, & Sarà, 2011; Formisano, D'Ippolito, & Catani, 2013). However, recent reviews on covert awareness have highlighted the heterogeneity of the terms used in the literature and encouraged the unification on a of a common taxonomy (Schnakers et al., 2022; Zasler, Aloisi, Contrada, & Formisano, 2019). A better characterization of this state, including its motor component, is also warranted.

The main causes of severe motor disabilities in patients with DoC consist of diffuse spastic paresis (Thibaut et al., 2014; Winters et al., 2022; Zhang et al., 2021), commonly associated with pathological postures, such as decortication and decerebration (Dolce et al., 2002). Spastic paresis is often linked to pain perception and hyperpathia, which may impact patients' quality of life (Bargellesi et al., 2018; Thibaut et al., 2014; Zasler, Formisano, & Aloisi, 2022). In this context, a thorough assessment of pain using standardised scales (such as the Nociception Coma Scale-Revised – NCS-R (Chatelle et al., 2012) – should be systematically considered as will be discussed in the following sections. This also leads to the conceptualisation of vicious circle involving spasticity and diffuse pain perception.

Neuro-orthopaedic disorders can gravely impact DoC patients' functional recovery, quality of life and possible diagnosis. Here, we review of the most frequent neuro-orthopeadic disorders in DoC (i.e., spastic paresis), before detailing additional symptoms and motor complications that may occur. Finally, assessments and treatment options, in the context of DoC, will also be discussed.

2. Spastic paresis

2.1 Definitions

About a third of patients who suffer from a stroke or a traumatic brain injury will develop upper motor neuron syndrome potentially leading to spastic paresis (Urban et al., 2010; Wissel et al., 2010). This syndrome can occur following any central nervous system lesion involving the corticospinal tract and parapyramidal tracts along the cortex, brainstem and spinal cord. Spastic paresis includes a neurological and a muscular disorder (Gracies, 2015). The muscular disorder, called spastic myopathy, arises due to a lack of mobilisation of muscular groups placed in the short position. This will induce a cascade of molecular, biomechanical and physiological changes leading to spastic myopathy, which manifests clinically as muscular stiffness. It is important to stress that, as this disorder is due to a lack of mobilisation, it is (partially) avoidable if appropriate care is provided (Thibaut et al., 2018a). The spastic myopathy causes an increase in muscle tone without

electromyographic muscle activity which (in contrast to spasticity) does not depend on the speed of mobilisation.

The second disorder is comprised of two distinct components: (1) spastic overactivity, which includes spasticity, spastic dystonia and spastic co-contraction, and (2) stretch-sensitive paresis (Gracies, 2015). Regarding *spastic overactivity*, the most known disorder is spasticity, which is often erroneously employed to name all mechanisms and related clinical symptoms linked to spastic paresis. A commonly accepted definition of the so-called *spasticity* is the clinical observation of an increase in velocity-dependent stretch reflexes in response to passive movement (Gracies, 2005b), which can be captured using scales such as the Modified Ashworth Scale (MAS) (Bohannon & Smith, 1987) or the Modified Tardieu Scale (MTS) (Boyd & Graham, 1999). Besides, spastic dystonia is described as an inappropriate muscle activation at rest, which is also sensitive to passive stretch. Another aspect is spastic co-contraction, which is the involuntary antagonist activation during agonist active mobilisation. *The second component* of the neurological disorder, stretch-sensitive paresis is characterised by a decrease in the central commands to the agonist muscle, leading to a reduction of the voluntary recruitment of agonist motor units (Gracies, 2015). Associated reactions can also arise, such as spastic muscle overflow, which corresponds to an inappropriate muscular activation distant from the initial muscle contraction (e.g., flexion of the elbow when standing up), or the irradiation reflex or stretch reflex (myotatic reflex (Bhattacharyya, 2017)), when a muscle is (over)extended. All these neurological phenomena will negatively impact the patient's ability to move, thus increasing the lack of voluntary movement and risk of prolonged immobilisation. It is also important to note that the muscle disorder superimposes on the neurological disorder, exacerbating the symptoms of each. Despite the dramatic consequences of spastic paresis, the prevalence of these components in different aetiologies is still poorly investigated, and not studied at all in patients with DoC. However, a better characterisation of these different clinical manifestations in different aetiologies is fundamental to provide appropriate treatments (Thierry Deltombe et al., 2018).

The location of brain lesions, thus the aetiology, is likely crucial for the development of spastic paresis. In patients with cerebrovascular aetiology, the distribution of spasticity may involve one or both sides of the body, with the pathological flexor pattern at the upper limb, and extensor at the lower limb (Figure 1). Patients who have suffered from an anoxic brain injury or a brainstem lesion may present mixed features of rigido-spasticity due to the dysfunction of the extrapyramidal pathways. These pathways extend from the brainstem to the basal ganglia, pre-frontal and frontal brain regions and can result in pathological posture, such as decortication or decerebration (Figure 2). Patients with traumatic aetiology may also present focal lacero-contusions and/or diffuse axonal injury, which generally consist of micro-haemorrhagic lesions, commonly affecting the white matter, the periventricular areas, corpus callosum, brainstem and cerebellum (Adams et al., 1989a). This distribution of cerebral micro-lesions may resemble the multifocal ischaemic encephalopathy and the consequent vascular parkinsonism. Other secondary parkinsonisms (Formisano et al., 2009) due to some neurosurgical complications like hydrocephalus, or meningo-encephalitis may also be associated to spastic paresis, as in post-traumatic or in post-encephalitic parkinsonism (Formisano & Zasler, 2014; Jellinger, 2004).

2.2 Spastic paresis in DoC

In patients with DoC the proportion of patients suffering from spastic paresis (as measured with the MAS – see section 2.3, thus not allowing to discriminate one symptom from another) is extremely high, ranging from 57 to 95% (for a review see : Geraldine Martens, Laureys, & Thibaut, 2017) and for a more recent prevalence study see : Zhang et al., 2021). Indeed, it has been shown to be the most frequent complication (e.g., dysautonomia, seizure, shunt placement or heterotopic ossification – HO) observed in two cross-sectional studies in prolonged DoC (Ganesh et al., 2013; Nakase-Richardson et al., 2013).

In addition to the extensive brain damage, the high prevalence of spastic paresis might be linked to the extensive periods of immobilization these patients endure with very limited voluntary movements.

Indeed, as mentioned, spastic paresis can be exacerbated due to disuse and immobilisation (Baude et al., 2019; Gracies, 2005a). Spastic paresis, immobilisation and muscle disuse will favour atrophy, loss of sarcomeres and accumulation of connective tissue and fat, thus enabling a positive feedback loop o which limits the patient's ability to voluntarily move. Patients with DoC often face all these situations together, which could lead to the exacerbation of spastic symptoms and further hinder the ability to express signs of consciousness, due the impairment of motor output. This hypothesis is in line with previous a finding showing that spasticity is not the only component explaining the increased MAS scores, muscle retraction and joint fixation observed in patients with DoC since no correlation between MAS scores and the Hmax/Mmax ratio (i.e., indicator of the severity of spasticity in stroke (Thierry Deltombe et al., 2018) – see section 5) was found in a cohort of patients in prolonged DoC (Martens, Foidart-Dessalle, Laureys, & Thibaut, 2017).

Regarding the evolution of spastic paresis, a recent longitudinal study in patients with prolonged DoC (> 12 month post injury), showed that both the aetiology and the diagnosis seem to influence the development of spasticity over time. Indeed, the authors found that in TBI patients, spasticity (upper limb) tended to increase in a delayed manner compared to non-TBI aetiologies (Winters et al., 2022). In addition, patients in UWS/VS demonstrated an increase in spasticity (lower limb) over a two-year period while it remained stable for patients in MCS. These preliminary findings, resulting from the first longitudinal study, highlight that the worsening of clinical signs of spasticity varies according to the type of brain lesion and the level of consciousness. However, the possible factors explaining such differences still need to be determined.

2.3 Assessment of spastic paresis

Spasticity is commonly assessed using the MAS and/or the MTS. The MAS specifically evaluates the level of resistance to passive movement but does not allow the quantification of the impact of velocity on passive movement (key component of spasticity), neither the angle of contraction outbreak nor possible tendon retraction (by means of range of motion amplitude – ROM). Indeed, this scale measures the resistance to passive movement adequately, but mainly evaluates a

combination of contractures, spastic dystonia, in addition to spasticity itself (Gracies et al., 2010). On the other hand, the MTS takes into account these characteristics, thus could be considered more accurate to characterise the different components of spastic paresis (Yelnik et al., 2010). However, for patients with prolonged DoC, as most of them suffer from joint fixation to some extent (Thibaut et al., 2014), the use of the MTS is often limited as it is often not feasible to perform the assessments with the three different velocities nor the two ROM (i.e., angle of muscle reaction and full ROM). Ideally, a combination of the two scales could provide a more accurate characterisation of spastic paresis in patients with DoC. It should be noted that other scales to evaluate spastic paresis and its impact on patients' functional outcome exist for other population of patients, such as the Patient's Disability Scale (Brashear et al., 2002); however, they require the patient's active participation, therefore cannot be used in patients with DoC.

Besides these two scales, electrophysiological assessments, such as electromyography (EMG), can be used to quantify spastic paresis in a more objective, sensitive and reliable manner. Several responses to electrical or mechanical stimuli exist, such as: (i) the M response (i.e. the direct motor response caused by stimulation of the alpha fibres), the Hoffmann reflex (H-reflex; allows assessment of the excitability of the alpha motor neuron), the F-wave (low amplitude wave that follows the M response) or the tendon reflex (T-reflex) (Voerman, Gregoric and Hermens, 2005; Bhattacharyya et al., 2017). The ratio of the maximal H-reflex amplitude and of the maximal M response amplitude is called Hmax/Mmax ratio, which reflects the percentage of excited motoneurons via the H-reflex in comparison to the direct activation of the motoneurons – M response (Katz et al., 1992). The Hmax/Mmax ratio can sometimes be an indicator of the severity of spasticity due partly to the hyperexcitability of the alpha motoneuron through sensitive inputs. This ratio has been shown to be correlated with the severity of spasticity in other neurological populations such as stroke (e.g. Deltombe, Jamart, Hanson, & Gustin, 2008)). Recently, Martens and collaborators have investigated the correlation between the H/M ratio and the MAS scores in a cohort of 21 patients with prolonged DoC (Martens, Deltombe, Foidart-Dessalle, Laureys, & Thibaut, 2019). Interestingly, some patients

with scores of 4 on the MAS (i.e., severe spasticity) did not present an increased H/M ratio (i.e., ratio < 0.5), while two patients with an exaggerated ratio (i.e., ratio > 0.5) in the lower limbs, did not demonstrate any signs of spasticity (i.e., MAS = 0). These findings highlight that the Hmax/Mmax ratio does not seem to accurately reflect MAS scores in patients with prolonged DoC, supporting the fact that these patients suffer from a combination of motor disorders, which may include spasticity, muscle overactivity, spastic dystonia, spastic cocontraction, among others (Baude et al., 2019). That withstanding, there is a crucial need to better characterise the different component of spastic paresis in patients with DoC, in order to provide accurate treatment options.

2.4 Management of spastic paresis

2.4.1 Physical therapy and rehabilitation approaches

Physical therapy (PT) is the first line treatment for patients with spastic paresis. Stretching is the most common approach used in patients with DoC, aiming to work on the viscoelastic properties of the muscle-tendon units and increase its extensibility, thus limiting the consequences of spastic myopathy. Despite its common use, to date, there is still no consensus on the optimal dosage of stretching to limit spastic paresis, especially in patients with DoC. A recent meta-analyses did not find enough evidence on its effectiveness in stroke (spasticity and range of motion (Gomez-Cuaresma et al., 2021)). A cross-sectional study in 109 patients in prolonged DoC evaluated the link between spasticity (as measured with the MAS), muscle contractures and the amount of weekly PT sessions patients received (Thibaut et al., 2018b), taking into account additional covariates, such as time since injury and medication. A negative correlation was found between the frequency of PT and both MAS scores and the presence of muscle contracture. In addition, time since injury and antispastic medication seemed to negatively and positively, influence the development of muscle contractures respectively (Thibaut et al., 2018b). Based on these findings, PT appears to be beneficial to reduce (or avoid dramatic increase of) spastic paresis in patients with DoC. This is especially important since

the severity of spasticity has been shown to correlate with pain levels in patients with DoC, which might affect their quality of life (Bonin et al., 2022; Thibaut et al., 2014).

Beside PT and stretching, casting represents a valuable alternative to immobilise the limb in a stretch position for several hours per day. This technique is usually used to improve muscle length, increase joint range of motion and reduce contracture pain and spasticity. However, scientific evidences of efficiency is yet to support this method to reduce spasticity in various neurological disorders (Lannin et al., 2007). In addition, this technique can induce pain if not properly applied, therefore it should be used carefully in non-communicative patients such as those with DoC.

Complementary to PT, orthoses, or splints are a valuable alternative to casting to ensure proper limb positioning. Since there are limited risks of skin lesions or other mechanical types of pain being induced, orthoses are considered as very safe and can be placed for several hours per day, without any supervision from the medical staff. Despite the lack of practical guidelines, orthoses have shown some promising effects in a pilot study in patients with prolonged DoC. In a first RCT, the effects of a soft splint positioned in patients' hands were tested to promote finger and wrist extension, and ensure hand opening, which is crucial for cares (Thibaut et al., 2015). Seventeen patients in prolonged DoC received either 30 minutes of soft splints or 30 minutes of manual stretching of the fingers and wrist's extensors. Both interventions improved spasticity of the finger flexors, while hand opening increased only for the splint group. Even if the long-term effects of soft splints positioned along patient's hands still need to be confirmed, this tool represents a safe, easy to use, and promising approach to manage spasticity of the upper limbs' extremities. It is important to consider that casting may also provoke a rebound effect once removed or sometimes induce contact ulcers (when hard material is used), often resulting in increased spasticity and secondary pain sources.

Tilt tables are also often used by physiotherapists to promote physiological standing position. This approach, applied 1 hour per day for 3 weeks, has been tested alone or in combination with a stepping device in 50 patients with prolonged DoC. The authors found an improvement in signs of consciousness in patients in prolonged DoC for the group receiving tilt table alone and no effect on

spastic paresis in both groups (Krewer et al., 2015). In addition, a RCT conducted in the acute setting, tested the effect of a robotic stepping verticalisation protocol compared to conventional therapy performed in the intensive care unit. They demonstrated that this verticalisation protocol could enhance short-term and long-term functional and neurological outcomes of patients with DoC (Frazzitta et al., 2016). Specifically, improving responsiveness as measured with the CRS-R and reducing the orthostatic hypotension, caused by standing, thanks to the muscular activation of the stepping device.

Another RCT on 47 patients tested the effects of 16 sessions over a 4-week period of robotic verticalisation with functional electrical stimulation, without functional electrical stimulation, and a control group (conventional PT) (Rosenfelder et al., 2023). All three groups improved, and no difference could be identified between the three interventions.

In conclusion, PT is essential to avoid retraction and joint fixation in DoC but, to date, there are no scientific guidelines for the application of the different therapies in patients suffering from spastic paresis. Importantly, PT might be painful for patients with DoC and appropriate courses of pain management should be investigated (see section 5).

2.4.2 Positioning and bed-rest syndrome

During the acute phase, the main concern is around the prevention of secondary damage. This can take the form of one of the following: prolonged bed-rest syndrome (Scarponi & Zampolini, 2018), which include bed sores, muscle atrophy and contractures, Intensive Care Unit-Acquired Weakness (ICU-AW), osteoporosis, joint ankyloses and peri-articular ossification (Ippolito, Formisano, Caterini, et al., 1999b, 1999a; Ippolito, Formisano, Farsetti, et al., 1999), also named neurogenic heterotopic ossification (NHO) (Bargellesi et al., 2018; Mazzoli et al., 2019) (see section 4).

Recurrent sepsis may cause diffuse muscular atrophy by Critical Illness Polyneuropathy (CIP)/Critical Myoneuropathy (CRIMYNE)/ICU-AW or compression neuropathies, due to pathological postures, such as decortication, decerebration or triple flexion at the lower limbs (Figure

2). In this context, an adequate bed positioning with specific cushion placement is essential. Other devices are also useful such as a bow to lift the weight of the bed sheets and blankets in order to prevent dropping of the foot (R. et al Formisano, 2021).

2.4.3 Pharmacological treatment of spasticity

As for the treatment of severe spasticity and pathological postures, anti-spastic drugs may be useful, such as baclofen, dantrolene, tizanidine and diazepam. In this section we will distinguish drugs having a general or a local action and classify them based on their mechanisms of action. Importantly, therapists should remain cognisant of the idea that spasticity induces pain and is aggravated by it. Thus, management of spastic paresis should always stat with effective analgesia.

Centrally acting medications

GABA-agonists: Baclofen works pre- and post-synaptically as a gamma aminobutyric acid (GABA-B) agonist at the spinal level. It restores the presynaptic inhibition interrupted by the spinal cord or brain injury, and decreases the overstimulation of the alpha motor neuron responsible for spasticity. As its diffusion across the blood-brain barrier is low, a sufficient concentration at the spinal level is necessary which can lead to supra-spinal side effects such as confusion, drowsiness. At high doses, or during withdrawal, this treatment is also suspected to increase the risk of epilepsy (Romito et al., 2021). Therefore, special attention should be given when prescribing Baclofen to patients with epilepsy, however it should also be noted that the epileptogenic effect of baclofen remains controversial (Buonaguro et al., 2005).

Benzodiazepines, such as diazepam, act on post-synaptic GABA-A receptors. However, their sedating effect prevents its long-term use. Alpha2 agonists such as tizanidine are better documented than those of clonidine and show less hypotension side effects. Nevertheless, both drugs share side effects such as sedation, hypotension, hallucinations and increased QT interval.

Dantrolene is the only drug that has a purely muscular action, uncoupling excitation and contraction by inhibiting calcium release at the sarcoplasmic reticulum. The reported side-effects are drowsiness,

dizziness, weakness, fatigue, and diarrhea which are usually transient (Krause et al., 2004). Dantrolene is however, contraindicated in active hepatic disease. Its mild hepatotoxic side effects are relatively uncommon (1%), but liver injury is estimated to occur in 0.1-0.2 % ("Dantrolene," 2017). *Tizanidine* may be useful also for painful spasms, although arterial hypotension has been reported as a possible side effect (Rita Formisano, 2021). Importantly, tizanidine is also contra-indicated in patients with arterial hypotension and diazepam should be avoided for it has detrimental effects on neural plasticity and cognitive impairment (Bhatnagar et al., 2016; Feeney et al., 1993; R. et al Formisano, 2021).

Interestingly, a retrospective review on spasticity management in a cohort of 146 patients admitted to a DoC rehabilitation program (Zhang et al., 2021) reported that baclofen was the most commonly used oral treatment for spasticity in patients with DoC (32%). Benzodiazepines were used for medical problems other than spasticity (seizure, sympathetic storm, catatonia or myoclonus). Tizanidine and Dantrolene were only occasionally used. These treatments were discontinued in a large proportion of patients, which was correlated with an improvement of their state of consciousness.

Although oral treatments are usually cheaper and easier to administer, given their side effects, they should only be administered in case of widespread spasticity and after failure of the loco-regional therapeutic approach.

Locally acting medications

Botulinum toxin injection: this toxin produced by the bacterium *Clostridium Botulinum* acts by inhibiting the release of acetylcholine vesicles from peripheral nerve terminals in the neuromuscular junction (Chang et al., 2013a). Unlike other treatments, its effect is reversible. It appears one to two weeks after the injection and lasts between two and six months. The frequency of injections and the dose should be adapted according to the clinical response, but it is necessary to space the injections at least three months apart because of the risk of immunisation (Chang et al., 2013b; Yelnik et al., 2009). This treatment is recommended for localised spastic muscle groups, in the absence of tendon

retractions or muscle stiffening. The injection is guided using electromyography or ultrasound tracking techniques, which makes it safe with limited side effects.

Even if focal spasticity could be treated with botulinum toxin injections, it is crucial to use this approach in conjunction with soft splints or functional compression bandages to reduce pain and prevent tendon retraction and joint ankyloses (Clemenzi et al., 2012).

Alcohol and phenol injections reduce spasticity by chemical neurolysis (irreversible destruction of the nerve. Mixed motor/sensory peripheral nerve blocks is not recommended due to the risk of sensory disorders (Yelnik et al., 2009). Nerves with low sensory activity and high motor predominance can be treated using this approach. The advantage of injecting motor points or motor branches is that the risk of dysesthesia is greatly reduced compared to mixed sensory motor nerve blocks. This treatment has the advantage of being less expensive than botulinum toxin but since nerve destruction is irreversible, it is not recommended as a first-line treatment. The benefits of alcohol or phenol treatment should be weighed up relative to those of surgery. Moreover, alcohol treatment induces fibrosis, making subsequent surgery more difficult. In the cohort of Zangh et al., local injections (botulinum toxin or phenol neurolysis) were administered to the majority of patients. 56.9% received botulinum toxin and 51.4% received phenol, while some patients had both types of injection. The most frequent targets were the upper limb and neck muscles (Zhang et al., 2021).

Intrathecal Baclofen (ITB) provides effective intramedullary concentrations that would be impossible to reach with oral baclofen without central side effects. It is recommended for diffuse spasticity. Side effects of ITB are relatively rare, especially sedative effects. However, attention should be paid to cachectic patients that are used to bed sores as it could lead to dramatic infections of the pump system (i.e., meningitis). The main complication is the risk of severe withdrawal in the case of pump dysfunction. The pump must be monitored by a specialised team in order to avoid infection, overdosing or withdrawal of treatment due to pump failure (Yelnik et al., 2009).

The majority of clinical case reports of patients with DoC who had ITB show a significant decrease in their MAS scores after a few months of treatment (Martens et al., 2017). In the Zangh et al cohort, a third of patients (52/146) had an ITB trial with a 92,3% positive rate, and 70.8% of them were finally implanted.

It is worth noting that ITB has been shown to be linked to consciousness improvement in some open-label studies (Formisano et al., 2019; Sara, Pistoia, Mura, Onorati, & Govoni, 2009).

2.4.4 Surgical treatments

Usually, in rehabilitation, the aim of any treatment modality is to improve function by restoring the balance between agonist and antagonist muscles. However, patients with DoC have limited or no voluntary movements. Therefore, the objectives of surgical interventions are either to prepare the patient for further rehabilitation in the case of clinical evolution or palliative (e.g., comfort, hygiene) (Ajisebutu & Hawryluk, 2022). For instance, surgical intervention can be required to facilitate some care practises given by nursing staff (perineal care by easier hip abduction, dressing by improved elbow extension, easier finger extension for palm hygiene, positioning, etc.). It may also be necessary to carry out surgical intervention in the case that spasticity leads to irreversible deformities of the skeletal system or constant pain.

The timing of treatment is important. Performing surgery too early after the injury should be avoided as the patient's functional recovery is still unknown. Waiting longer can have the advantage of resulting in a more stable condition, however, the patient might have already developed some level of permanent muscle contracture. Therefore, depending on the timing since the initial incident and the clinical picture, treatment options can significantly vary (Mikalef & Power, 2018b).

Before any surgical intervention, it is important to perform presurgical assessments. In these cases, the use of motor blocks (i.e., local injections of anaesthetics) are warranted to differentiate spastic hypertonia from musculo-tendinous retraction, particularly when the this is not determined in

previous any clinical examinations. The detection of legitimate muscular retractions can lead to neuro-orthopaedic surgical procedures.. They also allow a transient clinical evaluation of the effects of a neurolysis or an injection of botulinum toxin, prior to the treatment which will result in a more durable action (for extensive review, see : Hashemi, Sturbois-Nachef, Keenan, & Winston, 2021). The surgical treatment for upper limb spasticity and its sequelae are usually considered only after conservative treatment has failed, and when no further neurological recovery is expected (Kritiotis et al., 2019). Shoulder adduction and internal rotation contractures commonly develop in patients after upper motor neuron injury. They are often painful and impair axillary hygiene. Thus, tenotomy of the pectoralis major, latissimus dorsi, teres major, and subscapularis can be used to improve the position of the arm, in patients with non-functional upper limbs (Namdari et al., 2011). Selective peripheral neurectomy can be considered for focal or segmental spasticity which usually result in improvement of the MAS and passive range of motion. Regarding the elbow, the most common posture is elbow flexion which can be painful and lead to skin breakdown. Positive results were obtained with elbow flexor releases (brachialis, brachioradialis, biceps brachii) in patients without active control to improve passive motion and pain. Additionally, clenched fists with a thumb-in-palm deformity is often seen in upper motor neuron syndromes. In the absence of volitional movement, tenotomy and muscle release can be considered. Some articles suggest to employ tendon transfer (Mikalef & Power, 2018a). One of the most common techniques is a transfer of the flexor digitalis superficialis tendon to flexor digitalis profundus, to reduce pain, nailbed infections and skin maceration in the palm (Pappas et al., n.d.). As an last resort, wrist fusion by arthrodesis can be performed in patients with severe wrist joint contracture (Mikalef & Power, 2018a).

Regarding lower limbs, the majority of procedures improves movement and gait function and, importantly, require active rehabilitation. Therefore, they are rarely indicated in patients with DoC unless they are clinically evolving towards an active rehabilitation program and emerging from their DoC. Besides, palliative procedures, treatments of spastic hip deformities have the most repercussions in terms of comfort. These include hip flexion deformity with skin complications due

to hyper-pressure, hip adduction with repercussions on the sitting position and on hygiene of the perineum, medial or lateral rotation with repercussions on the sitting position and the risk of pressure points, and hip extension with the inability sit stably (Denormandie et al., 2003b; Hosalkar et al., 2022). At the knee level, patients with DoC will also have difficulties in sitting in case of spasticity of the quadriceps femoris with deformation in extension (Denormandie et al., 2003a).
It should be noted that there is little specific literature on surgical management of spasticity in patients with DoC. Surgical treatment options include many different approaches and result in a combination of the aforementioned procedures. A multidisciplinary assessment, a careful identification of the daily issues that the patients encounter, and setting goals for the surgery are important prerequisites for any of these invasive interventions, which can be often painful and irreversible (Genêt et al., 2019).

2.4.4 Novel therapies

Non-invasive brain stimulation approaches, such as transcranial current stimulation (tCS) and repetitive magnetic stimulation (r-TMS) have been widely studied in the literature to promote motor function. Some studies, have also looked at its effects on hypertonia, especially in stroke (Alashram et al., 2023). In DoC, one RCT tested the effect of a single session of tCS (or sham) on spasticity (MAS), patients' responsiveness (CRS-R) and brain activity (EEG at rest) (Thibaut, Piarulli, Martens, Chatelle, & Laureys, 2019) in 14 post-coma patients. Using a multichannel device, the anodes (excitatory electrodes) were placed over the prefrontal cortex (F3 & F4), the cathodes (inhibitory electrodes) were positioned on the primary motor cortex (C3 & C4) bilaterally. While no effect was found on the CRS-R, a reduction of spasticity was identified for the finger flexors right after the stimulation in addition to an increased connectivity in the beta band in the active compared to the sham group. This first pilot study highlights the potential benefits of tCS to reduce spastic paresis in patients with DoC.

The spinal cord can also be targeted to reduce spastic paresis. A pilot open label study evaluated the effect of epidural spinal cord stimulation targeting the cervical spine in 21 patients in prolonged DoC (Vorobyev et al., 2023). In addition to an improvement of signs of consciousness in some patients, almost half of them presented a reduced spasticity.

Finally, radial shock waves have recently demonstrated an interesting efficacy on focal spasticity, generating a trophic effect on the treated tissues, due to phenomena of local angiogenesis, thus improving the elastic properties of the treated muscles (Mori et al., 2014).

3. Other central motor disorders

3.1 Secondary parkinsonism

Secondary parkinsonism may be present in patients with DoC, after severe TBI, but also after diffuse vascular or encephalitic brain damage or associated with hydrocephalus (Formisano & Zasler, 2014). This syndrome includes hypomimia, bradykinesia, sialorrhea and rigidity as in akinetic mutism; was first described as occurring secondary to diencephalic lesions, resulting in severe quadriparesis, mutism, akinesia, visual fixation and pursuit. It also includes the complete or near-complete loss of spontaneity and initiation, such that action, ideation, speech and emotion are uniformly reduced (Formisano, D'Ippolito, et al., 2011; Giacino, 1997).

Patients with DoC following severe TBI, especially when there is diffuse axonal injury, have been reported to present parkinsonian signs and symptoms (Bazarian et al., 2009; Di Russo et al., 2005; R. Formisano et al., 2009; Incoccia et al., 2004). Parkinsonian signs may also be due to focal lesions in the cerebral white matter involving the caudate nucleus and putamen (Davie et al., 1995), as well as the substantia nigra and the related dopaminergic pathway (de Morsier, 1960).

Animal studies have shown that even after moderate TBI, diffuse brain injury can result in substantia nigra neurovascular pathology that can be associated with neuroinflammation, as well as dopamine dysregulation (Van Bregt et al., 2012). In rat models, TBI has also been shown to induce a progressive

degeneration of nigrostriatal dopaminergic neurons (Hutson et al., 2011), which could explain signs of Parkinsonism. Research examining TBI as a risk factor for parkinsonism and Parkinson's disease is not a novel idea yet, the signs of Parkinsonism in DoC remain not fully understood and would benefit from further investigation.

In line with this hypothesis, drugs that improve Parkinsonism symptoms have shown some promising results in patients with DoC. Indeed, L-Dopa and other dopaminergic drugs, such as Amantadine, Apomorphine or Selegiline, in addition to preliminary findings in enhancing DoC patients' signs of consciousness (Thibaut, Schiff, Giacino, Laureys, & Gosseries, 2019), may also improve parkinsonian symptoms thus reducing motor impairments and in turn, enhancing patients' responsiveness (Giacino et al., 2012; Leone & Polsonetti, 2005). However, randomised and multicentre controlled studies on the efficacy of the most commonly used dopaminergic drugs for patients with DoC are still needed.

The seminal case report of dramatic behavioural improvement of a chronic MCS patient has been reported after central thalamic deep brain stimulation (Schiff et al., 2007), which may be interpreted as a specific effect at the mesocircuit level (Schiff, 2016) and could additionally be the consequence of a dopaminergic activation, as in Parkinson's disease.

3.2 Cerebellar Syndrome

Post-coma cerebellar syndrome may also be observed in brain injured patients, with clinical manifestations such as intention tremor, dysmetria, myoclonic jerks, and muscular hypotonia (Marks, 1993b), which are often present in patients with DoC. However, to date, very few studies are available on the incidence and prevalence of post-traumatic cerebellar syndrome in patients with severe acquired brain injury. For patients with DoC, a cerebello-pyramidal syndrome may be diagnosed after brainstem or cerebellar damage, as well as after diffuse axonal injury (Adams et al., 1989b), but some of their clinical manifestations (e.g., intention tremor) only arise when patients

emerge from MCS or can wilfully perform limb movements. Regarding myoclonic jerks, they have been reported in patients with DoC as a negative prognostic indication (Dolce et al., 2002). So far, only a few studies have investigated the efficacy of other treatments such as the beta-blocker propranolol (Formisano, 2021), or stereotactic surgery (Marks, 1993a), in non-DoC populations. Additionally, myoclonic jerks may be treated with Levetiracetam or with Clonazepam, although their sedative side effects may present a challenge for use in patients with DoC (Formisano, 2021).

4. Neuro-peripheral motor disorders and heterotopic ossification

Neuroperipheral disabilities like CRIMYNE (Latronico & Bolton, 2011), more recently named ICU-AW (Domenico Intiso, 2018) may cause severe motor disability and diffuse pain, however, little is known about these disabilities in the context of DoC. There is a significant association of neuromuscular weakness with age, duration of mechanical ventilation, and ICU mortality, among patients admitted in the ICU (ICU-AW). In fact, 7.8% of those who survived and 50% among non survivors experienced neuromuscular weakness (Baby et al., 2021). Common risk factors for ICU-AW include multiple organ failure, mobility restriction, hyperglycaemia, glucocorticoids and neuromuscular blocking agents (Al Hammouri et al., 2011; Wang et al., 2020). ICU-AW often results in a longer hospital stay and increased mortality (Tortuyaux et al., 2022). In addition, it increases the likelihood of prolonged care in rehabilitation centres and reduces physical function and quality of life in the long-term (Vanhorebeek et al., 2020). In patients with DoC, a recent study found that 61% had critical illness polyneuropathy and myopathy diagnosed with electroneurography-electromyography (Hakiki et al., 2022), which could worsen in parallel with the severity of the motor deficit, associated with diffuse muscle hypotrophy and neuropatic pain.

Finally, the prolonged bed-rest syndrome (Scarponi & Zampolini, 2018), together with central and peripheral extreme motor deficits may be associated with neuro-orthopaedic complications, such as peri-articular ossification, also defined as HO (Bargellesi et al., 2018; Ippolito, Formisano, Caterini, et al., 1999a; Ippolito, Formisano, Farsetti, et al., 1999), and more recently named NHO, often

associated with tendon retractions, deformity and ankyloses (Mazzoli et al., 2019). In a recent multicentre observational study 11.2% of a population of patients with DoC present NHO, which were independently associated with functional disability (DRS total score), bone fractures and spasticity (Estraneo et al., 2021). In this latter study NHO was also associated with VS/UWS diagnosis and traumatic aetiology. In another multicentre cross-sectional survey in post-acute rehabilitation setting, NHO involved one or more joints in 13.6% of the patients with severe acquired brain injury, with a significantly higher prevalence in young males, without any differences in relation to traumatic versus non-traumatic aetiology (Bargellesi et al., 2018). In the same study it was found that NHO prevalence was significantly higher in patients with diffuse rather than focal brain lesions, longer duration of coma and ventilation support, paroxysmal sympathetic hyperactivity, and spasticity. A longer interval between acute brain injury and admission to rehabilitation centre was also significantly associated with higher frequency of HO. Another study, also found that patients who are admitted later in rehabilitation often had suffered from more extensive brain damages and had more complications in the acute phase compared to those admitted earlier (Formisano et al., 2017).

There is some evidence that L-Acetyl Carnitine, a nootropic drug, may be useful for neuroperipheral motor disorders (CIP, CRYMINE, ICU-AW) (Intiso et al., 2011; Latronico, Shehu, & Seghelini, 2005). However, all nootropic drugs should be avoided in agitated patients. A specific treatment with GABAergic drugs, such as Gabapentin, Pregabalin or Clonazepam, can be co-administered, in case of diffuse pain (Formisano, 2021). For HO, the most common medical therapy includes indomethacin (Moed & Karges, 1994; Moore et al., 1998), which has been proposed not only to prevent HO, but also to improve splint tolerance, to reduce pain, and NHO recurrence after surgery (Formisano, 2021). Early removal of NHO and the use of a continuous passive motion machine after surgery has shown to be an efficacious treatment protocol positive functional recovery with low recurrence rate (Ippolito, Formisano, Caterini, et al., 1999a, 1999b; Ippolito, Formisano, Farsetti, et al., 1999).

5. Pain assessment and management

Spasticity or spastic paresis has been shown to be associated with pain both in patients with DoC (Thibaut et al., 2014) and other neurological disorders such as stroke or multiple sclerosis (Van Schayck & Weiller, 2002). Therefore, the assessment of and management of pain cannot be distinguished from the assessment and management of spastic paresis.

Pain assessment and management in patients with DoC is both challenging and require major attention (Zasler, Martelli, et al., 2022). Pain refers to an *"unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"* (Raja et al., 2020). As with any subjective experience, pain requires a report from the patient to be formally identified. However, patients with DoC do not have the ability to communicate, therefore are unable to report such experiences. These patients, unfortunately, face a high rate of potentially painful medical complications, among which neuro-orthopedics disorders are the most frequent (Ganesh et al., 2013).

As pain is subjective, it has been postulated that it requires access to consciousness to be experienced. In a seminal study using positron emission tomography (PET), it has been shown that patients in MCS show a preservation of activation pattern similar to healthy subjects following electrical stimulation (Boly et al., 2008). This finding stressed the need for behavioural tools being made available to specifically identify pain-related behaviours in this population. To this end, the NCS (Schnakers et al., 2010) and its subsequent revised version (NCS-R - Chatelle et al., 2012)) were developed and validated. More recently a personalised painful stimulation has been proposed in comparison with the standard painful stimulation consisting of the fingernail bed pressure (Formisano et al., 2020).

The NCS-R encompasses three subscales, including motor, verbal responses and facial expression. The scores at these subscales correlate with the local brain metabolism, such as in the ACC (Chatelle et al., 2014), but also, a total score of 5 or more at the NCS-R allows to identify a patient that has the neural basis for experiencing pain (i.e., preservation of local metabolism in the ACC and the left

insula (Bonin et al., 2019). This total score of 5 also means that by inference the patient is at least in MCS, even if clinically unresponsive (i.e., MCS*). The implications are huge, as in the last decade, numerous reports of patients displaying covert awareness have been published. These patients share diagnostic characteristics with UWS/VS using standardised behavioural assessments (such as the Coma Recovery Scale – Revised; Giacino, Kalmar, & Whyte, 2004), but have either a fluorodeoxyglucose-PET imaging compatible with the diagnosis of a MCS, namely MCS* (Thibaut et al., 2021), a cortical response to passive paradigms (higher-order cortex motor dissociation, HMD; (Edlow et al., 2017) or a response to an active paradigm such as in functional MRI (CMD; Schiff, 2015). This means that these patients, while behaviourally UWS/VS, are also potentially able to process pain. For this reason, we highlight the vital importance of treating any DoC patient equally with regard to their potential pain. This is especially pertinent in situations concerning nutrition and hydration withdrawal (Formisano & Zasler, 2020).

Spasticity has been consistently shown to be positively correlated with pain in patients with DoC (Martens et al., 2017), especially in cases of severe spasticity of the upper limb extremities (wrist and fingers' flexors) and the hip adductors (Bonin et al., 2022), which are usually mobilised and stretched during a PT session. Importantly, while we stated in a previous section that daily PT sessions might be efficient to manage spastic paresis in patients with DoC (Thibaut et al., 2018a), a recent clinical trial highlighted that patients with DoC present higher scores on the NCS-R during PT compared to baseline (i.e., tactile stimulation). More importantly, NCS-R scores during PT did not differ significantly compared to those observed during the nociceptive stimulation (i.e., pressure on the nailbed) (Bonin et al., 2022). Moreover, this study evaluated the efficacy of analgesic treatments to reduce pain (measured with the NCS-R), without any significant changes in pain level observed during both the controlled condition, PT and nociceptive stimulation. However, 66% of the patients included in this study did not receive any painkiller medication in their long-term care facility while 87% of them had severe spasticity with a MAS score ≥ 3. Based on these results, appropriate pain

management, especially before mobilisations and PT sessions should be provided to ensure patients' comfort.

Finally, while a lot of effort has been made to identify how patients with DoC experience pain, the fact that (repeated) nociceptive stimuli, even without inducing a painful experience, could have dramatic physiological effects on the autonomous nervous system and should considered as an independent factor (Bonin et al., 2023). Further studies investigating the consequences of such chronic nociceptive activity in patients with a DoC suffering from medical complications such as spastic paresis are required (Zasler, Formisano, et al., 2022).

8. Discussion and conclusion

While it is well known that spastic paresis can influence a patient's quality of life and interfere with their rehabilitation, the current literature shows an alarmingly high incidence of spastic paresis in patients with prolonged DoC (Martens et al., 2017; Zhang et al., 2021). Since these patients are already limited in their range of movement, spastic paresis constitutes one of the most important disabling factors to be treated. In addition, chronic inactivity may enhance the severity of spastic paresis and the various other side-effects (e.g. ankylose, tendon retraction or joint fixation). This is is in line with findings showing a positive correlation between severity of spasticity and time since brain injury (Thibaut et al., 2014). Moreover, disuse and paresis result in a decrease of cortical excitability of the motor cortical areas coupled with a decrease in motor representation of the immobilised body parts (Kaneko et al., 2003), which is especially important in the context of cognitive motor dissociation (Schiff, 2015). In conclusion, paresis and spasticity form a positive feedback loop which is exacerbated by prolonged immobilisation. It is, therefore, of upmost importance to break this cycle by managing these motor disorders from the first time the signs appear (a few days or weeks after the brain lesion) and by ensuring intensive mobilisation of the patient' limb, even if no active movement is yet possible. In other words, efforts should be made to

increase the intensity of passive treatments on the upper and lower limbs using, for example, a motorised movement trainer as soon as possible following brain injury.

Beside spastic paresis, additional neuro-orthopaedic disorders may arise, however, the literature is particularly scarce on this topic. Other motor disorders such as pathological and dystonic postures, secondary parkinsonism and cerebellar syndrome may occur and interfere with overt behavioural responsiveness and impact the recovery of functional communication of patients with DoC.

Finally, neuro-peripheral motor disorders and HO may be frequently associated with the central motor deficits and prolonged bedrest syndrome in patients with DoC, further interfering with the motor output and limit patients' purposeful interaction with their environment.

One could summarise the key message of this review article by stating that the car engine (consciousness) is crucial, but the chassis (motor output) is just as important to allow patients to express themselves, promote their functional recovery and enhance their quality of life. In this context, the preservation of mobility and limitation of neuro-orthopaedic disorders, should be a primary goal of rehabilitation as early as during the acute setting (eg, ICU). We encourage longitudinal studies investigating motor functions in DoC. Systematic reports of motor disorders severity as well as information on the patients' rehabilitation pathways, should be included in all studies on patients with DoC as these factors might influence patients' responsiveness and functional outcomes.

Declaration of interest

All authors report no conflict of interest.

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Figure captions:

Figure 1. From left to right: Spastic and dystonic contractures, Klippel sign and spastic equinovarus foot.

Figure 2. The picture on the left represents a decortication posture, the one on the right, a decerebration posture.

Figure 3: The Nociception Coma Scale-Revised (Chatelle et al., 2012).

Figure 4: Variation in diagnosis of patients with pathological states of consciousness according to the level of recovery of cognitive and motor functions. UWS, unresponsive wakefulness syndrome; MCS, minimally conscious state; LIS, locked-in syndrome; in red, patients able to process nociceptive inputs and able to experience pain; in blue, patients processing nociceptive inputs but without evidence of pain experience; in purple, patients able to process nociceptive inputs and having the (probable) neural basis for pain experience (from (Estelle A.C. Bonin et al., 2023b)).

Figure 5: Changes in the NCS-R total score after tactile stimulation, noxious stimulation, and physiotherapy during the administration of a placebo (left panel) or an antalgic treatment (right panel). While analgesic treatment did not reduce pain levels, the scores on the NCS-R were significantly higher during physical therapy than the other two conditions.
NCS-R, Nociception Coma Scale-Revised; ns, no significance, **P < 0.01, ***P < 0 0.001). Taken from (Estelle A.C. Bonin et al., 2022).

Figures:

Figure 1

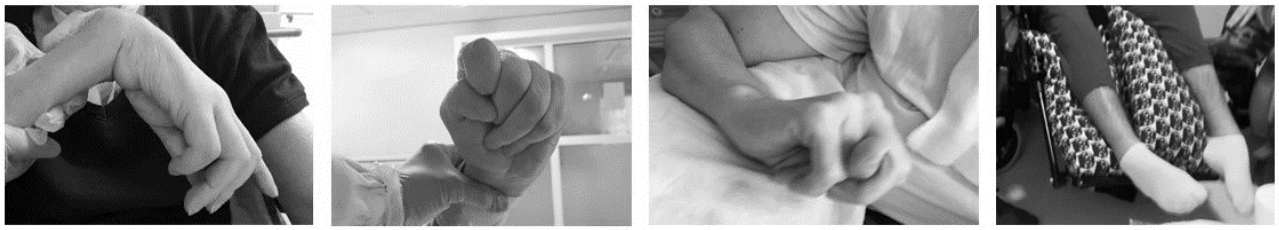


Figure 2

Figure 3

Motor response	
3	Localization to painful stimulation
2	Flexion withdrawal
1	Abnormal posturing
0	None/flaccid

Verbal response	
3	Verbalization (intelligible)
2	Vocalization
1	Groaning
0	None

Facial expression	
3	Cry
2	Grimace
1	Oral reflexive movement
0	None

Figure 4

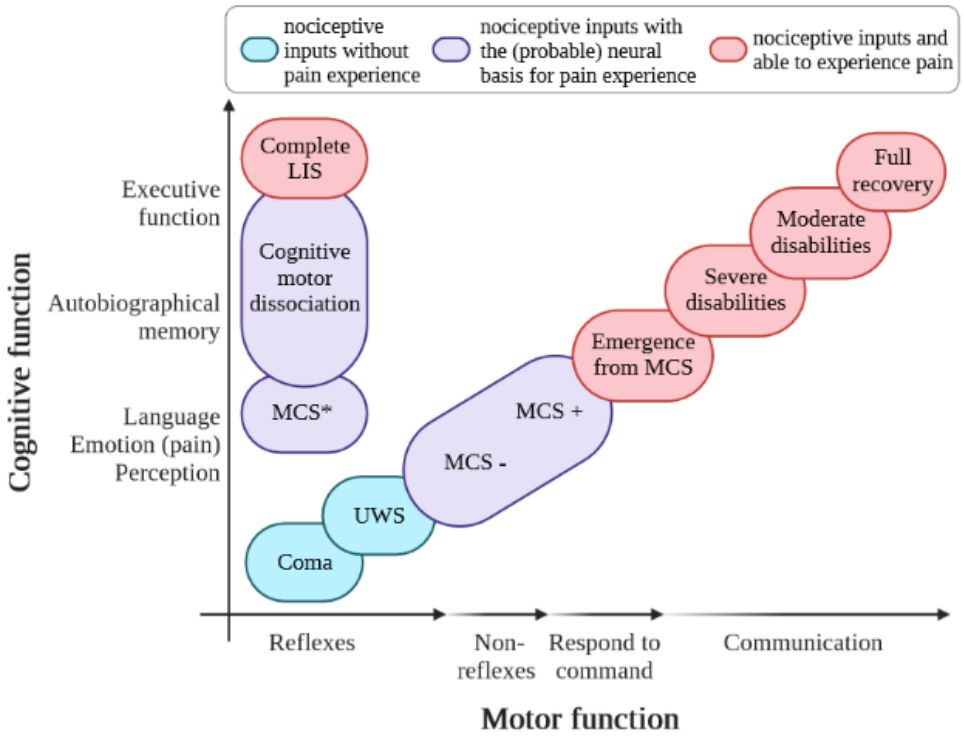
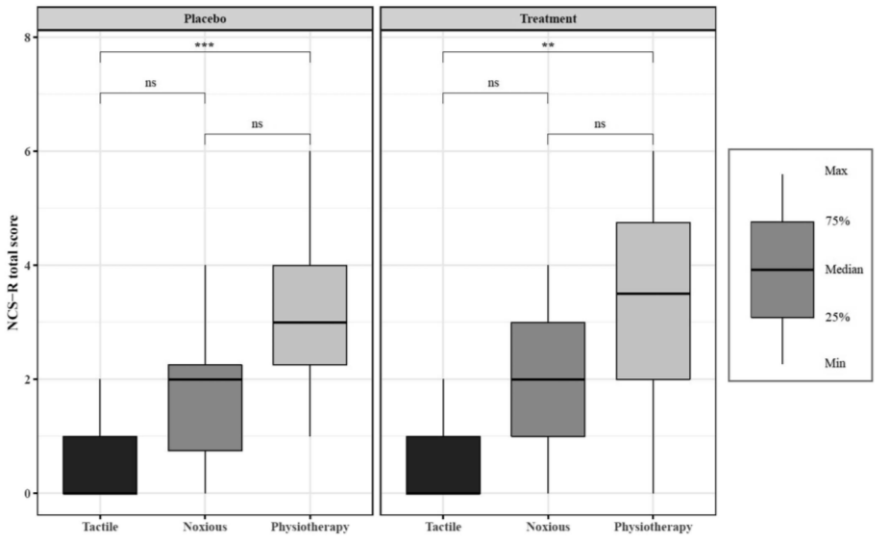


Figure 5


Placebo
Treatment
NCS–R total score
8
6
4
2
0
***
**
ns
ns
ns
ns
Tactile
Noxious
Physiotherapy
Tactile
Noxious
Physiotherapy
Max
75%
Median
25%
Min

Figure

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Figure

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Table 3.1. The Nociception Coma Scale – Revised

Motor response	
3	Localization to painful stimulation
2	Flexion withdrawal
1	Abnormal posturing
0	None/flaccid

Verbal response	
3	Verbalization (intelligible)
2	Vocalization
1	Groaning
0	None

Facial expression	
3	Cry
2	Grimace
1	Oral reflexive movement
0	None

Figure

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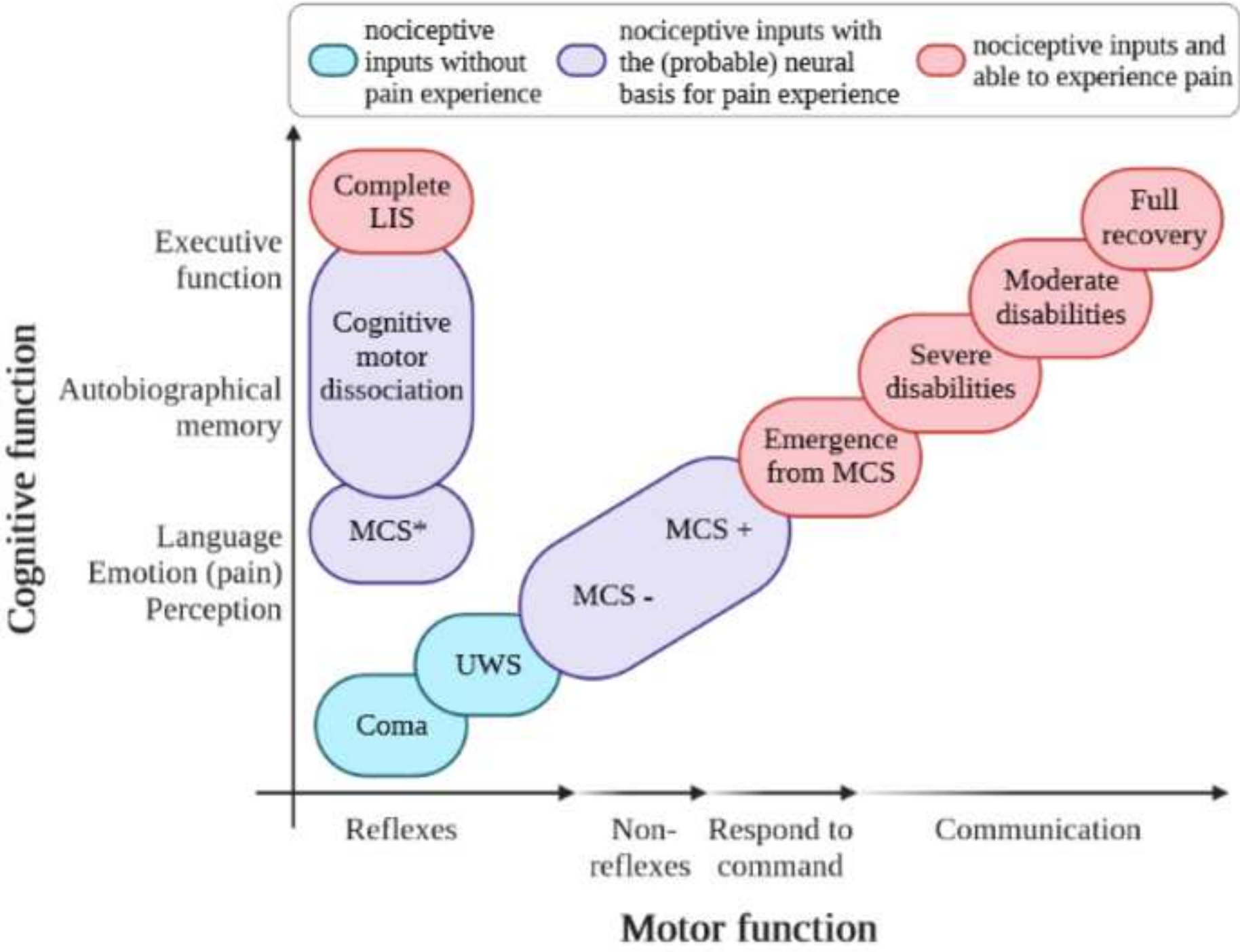

Figure

Click here to access/download;Figure;Figure5.png

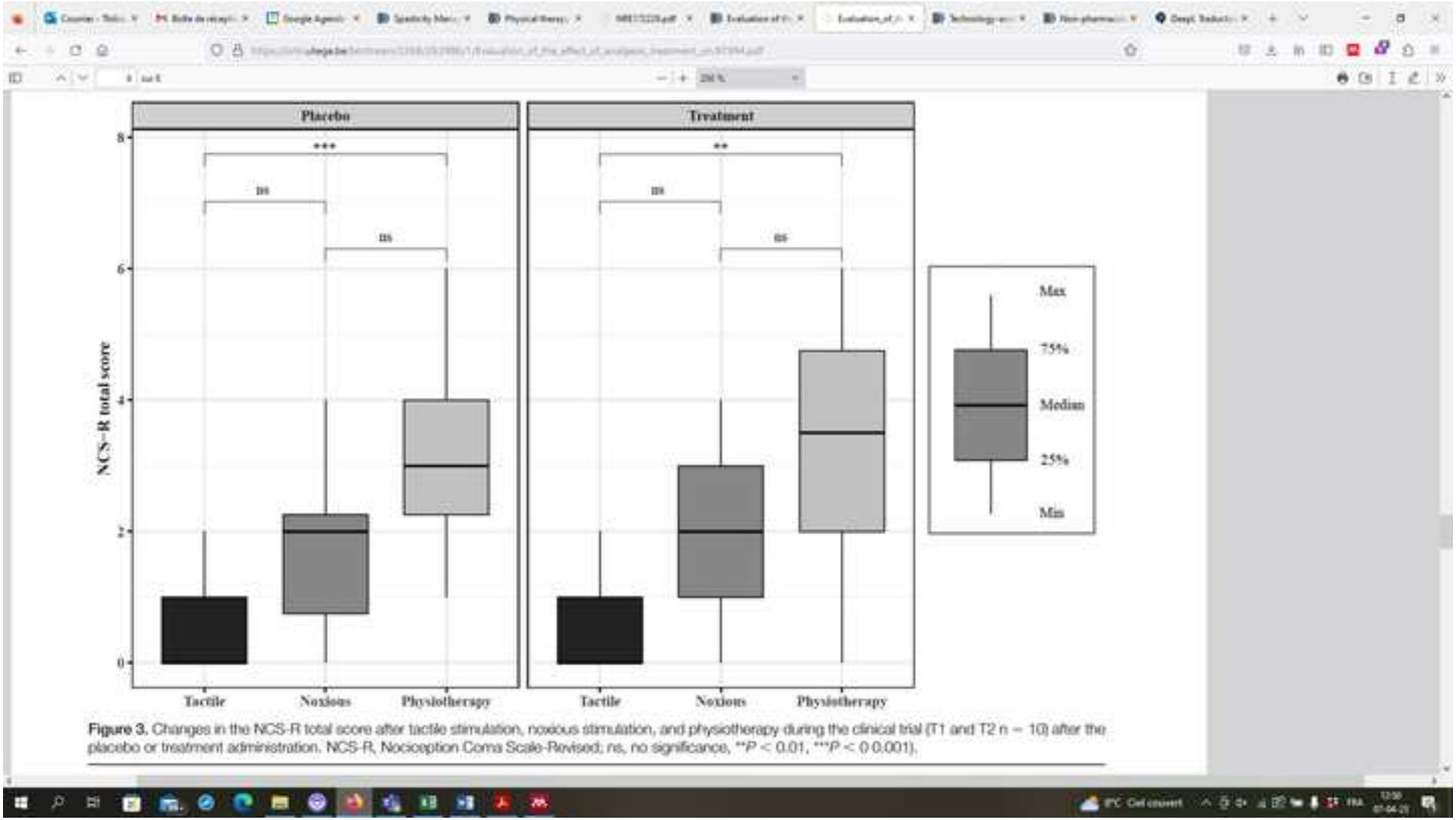

Figure 3. Changes in the NCS-R total score after tactile stimulation, noxious stimulation, and physiotherapy during the clinical trial (T1 and T2 n = 10) after the placebo or treatment administration. NCS-R, Nociception Coma Scale-Revised; ns, no significance, $^{**}P < 0.01$, $^{***}P < 0.0.001$).