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## **Relationship between intensive care unit-acquired weakness, fatigability and fatigue: what role for the central nervous system?**

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**Running title:** Physiological causes of fatigue

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Abbreviations:

**CIM**: critical illness myopathy; **CIP**: critical illness polyneuropathy; **CNS**: central nervous system; **FACIT-F**: functional Assessment of Chronic Illness Therapy for Fatigue; **HRQoL**: health-related quality of life; **ICU**: intensive care unit; **ICUAW**: intensive care unit-acquired weakness; **MFI-20**: multidimensional Fatigue Inventory; **SF-36**: 36-item Short Form Health Survey; **TMS**: transcranial magnetic stimulation; **VT**: vitality item of the SF-36

## **Abstract**

*Purpose:* To provide a comprehensive review of studies that have investigated fatigue in intensive care unit (ICU) survivors and questions the potential link between intensive care unit-acquired weakness (ICUAW), fatigability and fatigue. We also question whether the central nervous system (CNS) may be the link between these entities.

*Material and methods:* A narrative review of the literature that investigated fatigue in ICU survivors and review of clinical trials enabling understanding of CNS alterations in response to ICU stays.

*Results:* Fatigue is a pervasive and debilitating symptom in ICU survivors that can interfere with rehabilitation. Due to the complex pathophysiology of fatigue, more work is required to understand the roles of ICUAW and/or fatigability in fatigue to provide a more holistic understanding of this symptom. While muscle alterations have been well documented in ICU survivors, we believe that CNS alterations developing early during the ICU stay may play a role in fatigue.

*Conclusions:* Fatigue should be considered and treated in ICU survivors. The causes of fatigue are likely to be specific to the individual. Understanding the role that ICUAW and fatigability may have in fatigue would allow to tailor individual treatment to prevent this persistent symptom and improve quality of life.

## **Keywords**

Central nervous system; fatigue; fatigability; intensive care unit-acquired weakness.

## 1. Introduction

Survivors of critical illness experience long-term physical disability [1], associated with increased use of health care services [2] and deteriorated health-related quality of life (HRQoL) [3]. Around 30% of all critically ill patients will develop generalized muscle weakness, i.e. intensive care unit-acquired weakness (ICUAW), that is defined as “*a syndrome of generalized limb weakness that develops while the patient is critically ill and for which there is no alternative explanation other than the critical illness itself*” [4]. ICUAW is characterized by skeletal muscle wasting and weakness and associated decrements in functional capacities [5].

Chronic and severe sensations of fatigue are major contributors to poor HRQoL [6] and higher usage of health care services, as already reported in cancer patients for instance [7]. Fatigue has been defined as a “*subjective lack of physical and/or mental energy, perceived by the individual or caregiver to interfere with usual and desired activities*” [8], that is unrelated to previous activity and is not alleviated by rest or sleep. Fatigue is recognized as one of the most prevalent and debilitating symptoms in many clinical conditions [9], including ICU stays [6, 10]. Fatigue likely interferes with the rehabilitation process after ICU discharge by limiting exercise capacities [11] and may have an important contribution to the decreased HRQoL reported in ICU survivors, although the direct nature of the relationship between fatigue and HRQoL in ICU survivors has yet to be demonstrated [12]. Fatigue is highly complex in ICU patients/survivors, mainly due to the wide range of pathologies and conditions associated with ICU stays, and because of the multitude of situational and environmental factors that the ICU patients/survivors can experience during their stay.

Recently, a new taxonomy has been proposed to better apprehend the complex and multifactorial concept of fatigue and acknowledge its two attributes, i.e. performance and perceived fatigability, two concepts that are closely interrelated [13]. Performance fatigability is defined as a decline in an objective measure of physical performance (e.g. muscle force) during and/or after a given exercise, while perceived fatigability refers to any changes detectable at rest or during exercise that regulate the integrity of the performer, e.g. motivation, pain, core temperature. Note that the term fatigability will be used throughout this review to refer to the performance facet of this entity.

While the link between ICUAW and fatigability is conceivable but not clearly established, these two entities could potentially contribute to fatigue in ICU survivors. Following

identification of all studies referring to fatigue in ICU patients/survivors, the primary aim of this review is to document the link between these three entities. Despite a paucity of data in the existing literature, we also question the role that the central nervous system (CNS) could potentially have on ICUAW, fatigability and fatigue, this role being rarely considered thus far. With the aim to alleviate fatigue and improve HRQoL, potential treatments are also discussed.

## **2. Prevalence of fatigue in ICU patients and survivors**

This section provides a description of studies quantifying fatigue in ICU patients/survivors, with a summary provided in Table 1. While preliminary evidence displayed that around 50% of ICU survivors suffer from persistent fatigue from three months [14] to one year after ICU discharge [15], only 3 recent papers focused on ICU-related fatigue as a primary outcome measure either in ICU adults [6, 10] or children [16].

As a subjective symptom, fatigue is generally assessed using self-report questionnaires or visual analogue scales (Table 2). It has been reported in cooperative ICU patients, using both an adapted version of the Edmonton Symptom Assessment Scale [17] and visual analogue scales [18, 19], that fatigue can develop early during ICU stays. Concerningly, various studies report that fatigue may persist from months to years after ICU discharge. Fatigue was recently investigated in ICU survivors using the Functional Assessment of Chronic Illness Therapy for Fatigue (FACIT-F) [10]. The mean score was ~39 in ICU survivors [10] while it was reported to be ~44 in the general USA population [20]. While a score < 34 has been defined as ‘clinically relevant fatigue’ in cancer patients [21], it is important to note that this was assessed one year after discharge, and the severity of fatigue would plausibly have been reduced throughout this period. Although moderate to strong correlations ( $r = 0.66\text{--}0.84$ ) have been reported between FACIT-F score and the score obtained with the vitality domain (VT) of the 36-item Short Form Health Survey (SF-36) [10, 22], it has been suggested that this latter score should be interpreted carefully to discriminate fatigue [10]. Nevertheless, many studies used VT to indirectly investigate fatigue as one component of HRQoL and are reviewed in [23]. Further studies have since been published [10, 24], and Table 1 provides an updated summary. The majority of these studies have reported lower scores in ICU survivors (higher fatigue), i.e. scores between 30–58 out of a total score of 100, compared with scores of ~60-70 in large samples of healthy adults, e.g. [24]. One should note, however, that some studies on ICU survivors reported similar scores when compared to healthy patients, e.g. 64

[24] and 66 [10]. Although the low scores generally reported in ICU survivors may suggest that fatigue is prevalent after ICU discharge, such interpretation should be made with caution since i) there is no cut-off value for VT and ii) the validity of this score to accurately assess fatigue has been questioned as mentioned above [10]. Despite the reliability and validity of the Multidimensional Fatigue Inventory (MFI-20) to measure fatigue in ICU survivors being questioned [25], the same group reported that ~55% and 40% of ICU survivors presented clinically relevant symptoms of fatigue 3 and 6 months after ICU discharge [6]. The Modified Given Symptom Assessment Tool was used in another recent study reporting that fatigue was a prevalent symptom in ICU survivors, with ~85, 75 and ~81% of patients reported fatigue 2 weeks, 2 and 4 months after ICU discharge [26]. Finally, Langerud et al. [27] recently used the Lee fatigue scale to report that ~15% and 14% of ICU survivors experienced fatigue at 3 and 12 months post-ICU discharge.

These findings suggest that fatigue is a major issue amongst ICU survivors that may persist up to several months following ICU discharge. One should note, however, that large variability is reported either in i) the score obtained for the same questionnaire (e.g. SF-36) or ii) the proportion of ICU survivors reporting fatigue. Differences in population (e.g. sex, age, level of physical activity), ICU conditions (e.g. reasons for admission, duration of mechanical ventilation) and experimental characteristics (e.g. time between ICU discharge and questionnaire survey) may explain this variability. Since fatigue scores were considerably higher after  $23 \pm 14$  days of hospitalization [26] than 9 days [27], it may be tempting to suggest that longer stay leads to higher fatigue. However, considerable differences in sample size (i.e. 31 vs 118, respectively) as well as differences in the methods used to assess fatigue compromise the robustness of this statement. At present, it seems difficult to ascertain that any specific ICU-related parameter has a particular influence on fatigue. For instance, the groups of Steenbergen et al. [12] and Wintermann et al. [6] reported a similar proportion of fatigued ICU survivors (~40%) despite large differences in ICU related variables, e.g. total ICU stay of 6 and 66 days and total mechanical ventilation duration of ~2.5 and 45 days, respectively. Note that both groups used different measurement tool, i.e. VT and MFI-20, respectively, limiting the robustness of the comparison in fatigue prevalence between the two studies. Recent data suggested, however, that fatigue could be associated with specific factors, such as sex, illness severity, medical comorbidities, a diagnosis of coronary heart disease, major depression or fear of dying [6]. Nevertheless, these data are isolated and further studies are warranted to shed light on the factors that could be associated with fatigue.

Surprisingly, while many studies have investigated fatigue in ICU survivors as one component of HRQoL, the few studies dedicated to fatigue have only been published in the last decade [6, 10, 16]. Although some of these data reported a correlation between the fatigue score and HRQoL [6], a causal relationship between fatigue and HRQoL seems currently difficult to ascertain. However, with fatigue being a limiting factor for physical exercise [11], it is plausible that a relationship exists between fatigue and HRQoL, as already reported in patients with chronic obstructive pulmonary disease [28]. Overall, despite the variability in the questionnaire-related outcomes, there is evidence that fatigue is prevalent in ICU survivors. Further studies are needed to shed light on its clinical consequences and its impact on functional outcomes.

### **3. Intensive care unit-acquired weakness and fatigability**

#### *3.1. Etiology of intensive care unit-acquired weakness*

Functional and structural alterations occur early in muscles (critical illness myopathy, CIM), or nerves (critical illness polyneuropathy, CIP), or both (critical illness polyneuromyopathy), during critical illnesses requiring ICU stay [29]. CIP and CIM have been suggested to be the principal causes of ICUAW [5]. These alterations may persist up to several years following discharge [30] and may decrease exercise tolerance and HRQoL [31]. Briefly, CIM refers to deteriorated muscle function influenced by various factors, with the primary contributor being muscle atrophy occurring in response to increased breakdown and altered muscle repair [31], with other factors, e.g. muscle membrane inexcitability [32] or mitochondrial [33] and satellite cells [34] dysfunction, being also involved. Electrophysiological-related outcomes defined CIP as axonal degenerations of both peripheral nerve motor and sensory fibers [30], but the exact mechanisms remain to be fully understood. Limb weakness is the main clinical sign for all CIM- and/or CIP-related alterations, and is generally assessed using the Medical Research Council Scale [35], where the strength of six upper- and lower-limb muscle groups are tested bilaterally. Further, ICUAW may be diagnosed by electrophysiological signs of neuromuscular dysfunction [36]. Thus, besides its peripheral origins, ICUAW may be explained, at least in part, by alterations at the CNS level [13]. While CNS injuries are largely described in the literature with biologic, electroencephalography [37] and magnetic resonance imaging-related evidence [38], the role of the CNS in ICUAW has been under-investigated. This is surprising given that CNS alterations (especially an increased inhibitory activity) may be incurred by the use of some medications in ICU [39]. Delirium, defined as “*a reduced*



*ability to direct, focus, sustain and shift attention*" [40], could potentially interact with ICUAW [36]. Indeed, it has been indirectly suggested that early rehabilitation in the ICU improves physical function (i.e. reduces ICUAW) and may reduce the duration of delirium [41]. ICU-induced delirium has been related to alterations within the CNS (e.g. neuroinflammation, brain injury, see figure 1 in [42]), strengthening the hypothesis that CNS alterations may play a role in ICUAW. Further, inflammation has been reported as one of the main causes of ICUAW. Inflammation-related sequelae are generalized to the entire body, including CNS structures [43], especially known as septic encephalopathy. An association between septic encephalopathy (and its underlying CNS dysfunction) and ICUAW has been suggested [44]. Finally, reduced motoneuron excitability (under the influence of centrally-mediated persistent inward currents) has been suggested to greatly contribute to ICUAW [45]. Although these arguments suggest that CNS alterations likely play a role in ICUAW, further studies are warranted to shed light on these potential interactions. In addition, we may speculate that prolonged periods of immobilization, as is common in ICU [30], along with additional factors (e.g. the use of specific medication, systemic inflammation, delirium), could induce CNS alterations during ICU stay that may persist after discharge. Out of the ICU context, prolonged periods of immobilization in bed (20–30 days) have been reported to alter CNS functioning (e.g. [46]). The main mechanisms are i) alterations in proprioceptive information and ii) adaptive changes at both spinal (e.g. pre- and/or post-synaptic inhibition-related mechanisms [46]), and supraspinal (e.g. decrease in corticospinal tract excitability due to reduced sensory input to the motor cortex [47]) levels.

The lack of data on CNS alterations in ICU survivors is striking and the use of reliable investigation tools should be considered in future studies to address this question. Figure 1 displays physiological alterations in ICU survivors and Table 3 describes the techniques that could be used to examine CNS dysfunction. CNS alterations can be assessed using electrophysiological techniques. The voluntary activation level, where the patient must maximally contract his muscle while a transcranial magnetic (TMS) or peripheral nerve stimulation is delivered, gives an indication on the efficiency of the nervous command to be delivered to the muscle. Low intensity and painless stimulation could be easily used to investigate spinal alterations in ICU survivors, i.e. spinal loop efficacy between *Ia* afferent and alpha motoneuron with pre- and post-synaptic-associated mechanisms. In contrast, the direct evaluation of intrinsic motoneuron properties requires strong and uncomfortable stimulations at the cervicomedullary or thoracic level and appears more difficult to be used with ICU survivors. Supraspinal alterations may be investigated with single- and paired-pulse

TMS, which allow to assess corticospinal and intracortical excitability and inhibition. Overall, TMS and electrical nerve stimulation offer promising tools to further understanding on the role of the CNS in muscle induced alterations in ICU survivors (Figure 1) due to being inexpensive, non-invasive and easy to implement. Note that all the aforementioned techniques (with the exception of few parameters such as the motor evoked potentials that can be recorded on relaxed muscles) have to be used in cooperative ICU survivors able to voluntarily contract their muscles. Specific ergometer now allows to record volitional and non-volitional muscle force produced by bedridden ICU patients [48], and such techniques could be used in cooperative ICU patients during their stay to early detect CNS alterations. In addition, the use of functional magnetic resonance imaging could be useful to give complementary information on ICU-induced CNS alterations, especially on the neuronal mechanisms of CNS functioning and to define abnormal patterns of brain activations resulting from disease [49]. Yet, one should note that this method requires considerable expertise and expensive materials.

### *3.2. Potential association between intensive care unit-acquired weakness and fatigability*

While performance fatigability refers to a change in objective performance measures over time [13], it should be distinguished from weakness that is a diminished ability of a rested muscle to exert maximal force, independently of any previous physical activity [50]. Although the link between ICUAW and fatigability is not clear, one may suggest that ICUAW may increase the level of fatigability, that induces a reduced capacity to maintain activities [51]. Indeed, patients with muscle weakness will perform any kind of physical activity (e.g. stairs climbing) at a higher percentage of their maximal capacity than their healthy counterpart, potentially contributing to impaired fatigability in weakened patients. Recently, we suggested that a greater level of fatigability could lead to a greater reduction in functional capacity, particularly for activities of daily living [9]. To date, only two studies had performed measures of fatigability in ICU patients/survivors. It has been reported that patients with recent-onset sepsis and multi-organ failure are weaker than healthy matched controls, yet the decrease in force after a 20-min fatiguing protocol (i.e. reflecting performance fatigability) was the same between ICU patients and healthy subjects when expressed in percentage of pre-values [52]. It has been recently confirmed that ICU survivors are weaker (i.e. lower maximal force during an isometric knee extension) than healthy controls [53]. Nevertheless, the latter study found that endurance capacities (i.e. the time the subjects were able to sustain a contraction until exhaustion) were lower in ICU survivors (one year after discharge)

compared to their healthy counterpart [53]. The possible physiological causes of fatigability, however, were not investigated in these two studies.

This section highlights the necessity for future studies to investigate ICU-induced CNS alterations. The evaluation of both neural and muscle components of ICUAW should facilitate a better understanding of its causes. While fatigability has only been investigated in two studies with contradictory results and extremely small sample sizes [52, 53], its possible causes are unknown and warrant further investigation. Therefore, the link between ICUAW and fatigability remains merely speculative, although plausible. While these two entities could play a considerable role in fatigue in ICU patients/survivors, further work is required.

#### **4. Relationship between fatigue and fatigability/ICUAW**

In line with the definition given in the introduction, fatigue should not be confused with a deteriorated fatigue resistance to single acute exercise (i.e. fatigability), but these two entities may still interact. A deteriorated resistance to exercise, referring to greater reductions in functional capacities in response to physical tasks, may lead to fatigue accumulation [9]. Specifically, high levels of impaired physical function reached after daily tasks are likely to require longer periods of recovery before physical function is restored. If subsequent tasks are performed with incomplete recovery, fatigue can accumulate during these successive tasks. It is hypothesized that the interaction between fatigue and fatigability could contribute to fatigue in the long term (Figure 2A), particularly in patients with deteriorated physical function [9]. First, the increased fatigability (potentially due to ICUAW) may trigger nociceptive response from myelinated III and unmyelinated IV afferents fibers, due to an increase in metabolic perturbations for a given task. These afferent fibers have an inhibitory effect and a widespread influence on fatigability by reducing motoneuron firing rates [54]. Second, an increased muscle fatigability (i.e. perturbation in excitation-contraction coupling) may lead to higher motor unit recruitment to perform a given submaximal task. This higher central drive activates sensory brain areas through central corollary discharge, thereby increasing effort perception [55]. Thus, the increased contribution of these feedback/feedforward mechanisms in patients with high level of fatigability likely reduces the level of physical activity. This explains why patients “*probably titrate the level of their activity (i.e. minimize their energy expenditure during the day) to maintain perceived fatigue within a tolerable range*” [56]. Such self-pacing strategies may increase physiological deconditioning which will reinforce

feedback/feedforward mechanisms and, in turn, enhance the level of fatigue in a vicious circle (Figure 2B).

Thus, while a link between fatigability and fatigue may exist, as investigated in multiple sclerosis (e.g. [57]), evidence for such a relationship has never been considered in long-term fatigued ICU survivors so far. Besides an increased fatigability and other direct physiological and biological causes of fatigue, indirect causes such as psychological (e.g. depression), nutritional, social and behavioral factors (e.g. sleep disorders) may also contribute to fatigue. The multiplicity of factors makes fatigue unlikely to be due to a single cause, and only a comprehensive analysis of these causes may allow a better understanding of this symptom.

### **5. Which treatments to reduce fatigability as a strategy to potentially alleviate fatigue and improve HRQoL in ICU survivors?**

No studies have investigated the effectiveness of any treatments in preventing fatigue in ICU survivors. Assuming that an improvement in neuromuscular function can reduce fatigability and indirectly alleviate fatigue, this section aims to briefly present the strategies that may prevent the alterations in muscle function/mass (e.g. sarcopenia; [58]) and/or CNS functioning that arises after ICU stays. Nutrition-based therapy, exercise-based interventions and neuromuscular electrical stimulation are some of the most common therapies used in ICU patients/survivors to preserve muscle function [58]. The efficacy of such interventions in preventing impairments in muscle function and/or muscle mass is variable, with patients reacting favorably and others non-favorably to the therapy [58].

Treatment acting on the CNS should also be considered. We and others have shown that local muscle vibration can be efficient to strongly modulate the CNS after chronic uses in both healthy [59] and clinical populations, e.g. long-term immobilized patients [60]. Briefly, local vibration strongly activates the *Ia* afferents from muscle spindle receptors. The discharge of *Ia* afferents elicits an excitatory input onto alpha motoneuron at the spinal level but also have strong projections on some of the same cortical areas that are activated during voluntary contraction [59]. Functional electrical stimulation may also be useful to activate the sensory motor system, by stimulating cortical reorganization and subsequently causing changes in cortical excitability/inhibition [61]. This method has already been used in ICU patients to prevent functional alterations [62] but its effect on CNS remains to be better understood. These two methods would allow to strongly activate the neuromuscular system early during the hospital stay, when patients are unable to participate in active physiotherapy. Future studies should be conducted to investigate whether they could promote neuroplastic and

muscle changes that may improve functional capacities, then alleviating fatigue and increasing HRQoL.

Using various therapies that can stimulate the neuromuscular system, in combination with other treatments targeting other potential causes of fatigue, an effective strategy could be to tailor exercise intervention to these specific and individual causes. For instance, sleep disturbances have been reported in ICU survivors and linked with fatigue [63], and specific interventions [39] should be adopted in ICU survivors that report long-term sleep deprivation to alleviate fatigue. Other causes, such as inflammatory state, depression or nutritional status, should also be targeted to allow a complete understanding of the causes of fatigue, and specific therapies to these causes should be considered. We acknowledge that the aforementioned causes are hypothetical in the ICU context since, other than sleep quality, no studies have directly investigated the causal relationship between these factors and fatigue so far. Even so, the multifaceted nature of fatigue highlights the importance of treatment individualization. This is especially true in the ICU context because there is a broad array of reasons why people are in ICU, as well as different durations of hospital stay or different medications. All these factors mean that the causes of fatigue can vary considerably in ICU patients/survivors and need to be treated individually. Even if the data are still scarce, it has been suggested that intervention tailored to the individual's characteristics could enhance the effectiveness of the intervention in reducing fatigue (e.g. [64]). For instance, it has been suggested that cancer patients whose fatigue is primarily driven by inflammatory activity may be more responsive to anti-inflammatory therapies (either behavioral or pharmacological) while those whose fatigue is primarily driven by alterations in muscle contractile properties may be more responsive to exercise-based interventions or neuromuscular electrical stimulation [65]. We hypothesized that this is applicable to ICU patients/survivors and that therapy individualization should be part of the routine treatment of fatigue.

## **6. Conclusions and perspectives**

Fatigue is highly prevalent in ICU survivors and may persist from some weeks to several months after ICU discharge. Although never investigated in the context of ICU so far, fatigue may play a considerable role in limiting exercise capacities, thereby interfering with the rehabilitation process. Furthermore, given that HRQoL is impaired in ICU survivors, and that there is an established link between fatigue and HRQoL in numerous health conditions, it is plausible that fatigue contributed to impaired HRQoL in this patient group. Further, fatigue

may also have social (e.g. reduced social interactions) and economic consequences (e.g. decreased productivity). The pathophysiology of fatigue is complex and multifactorial. More work is required to understand the roles of ICUAW and/or fatigability in fatigue. To date, muscle alterations have been well documented and related to ICUAW. Nevertheless, the link between ICUAW and i) fatigability and/or ii) fatigue remains to be established. Substantial work also remains to be done to investigate CNS alterations that develop early during the stay in ICU patients and that may persist after discharge in ICU survivors. One should keep in mind the likelihood that the causes of fatigue are specific to the individual. Thus, the individual characterization of such alterations would allow to tailor treatment to the causes of fatigue in each ICU patient to reduce/prevent this critical and persistent symptom and improve HRQoL.

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### *Authors contribution*

In the case of this review, RS, JM, LG, PI and GYM had the idea for the article. RS, CB and TL performed literature search and data analysis. RS drafted the work and all the authors critically revised the work and approved the final version of the manuscript.

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## Figure captions:

**Figure 1.** What we know and do not know about ICU-induced physiological alterations that may contribute to fatigue. *Italic writing highlights what we already know about physiological alterations induced by prolonged ICU stays. These are mainly muscle alterations. Red numbered boxes (and the corresponding black boxes) highlight what remains to be investigated.* The figure displays that knowledge on muscle alterations could be improved using MRI to investigate metabolic profiles (1). Further, this figure shows the lack of data about CNS alterations induced by the ICU stay and presents which methods could be used to improve this understanding (2–5). The red/green thunderbolt in the boxes represents the position where electrical or magnetic stimulations are delivered to assess PNS and TMS-related parameters (see Table 3 for a detailed description of these parameters).

$\alpha$  MN: alpha motoneuron; ATP: adenosine triphosphate; CMAP: compound muscle action potential; CMEP: cervicomedullary motor evoked potential; CST: corticospinal tract; ICF: intracortical facilitation; M1: primary motor cortex; LICI: long interval intracortical inhibition; MEP: motor evoked potential; MRI: magnetic resonance imaging; PCr: phosphocreatine; Pi: inorganic phosphate; PNS: peripheral nerve stimulation; ppTMS: paired-pulse TMS; PRM: posterior root-muscle reflex; SICI: short interval intracortical inhibition; SP: silent period; TMEP: thoracic motor evoked potential; TMS: transcranial magnetic stimulation.

**Figure 2.** Schematic representation of the effects of potential deteriorated fatigue resistance to acute physical activity (i.e. fatigability) on fatigue and on the tolerable amount of physical activity performed during the day (panel A, extracted and re-used from [9]). In this example, subject X is not limited in his daily activities while subject Y will reach his “limit of tolerance” because of fatigue accumulation, thus limiting his daily activities. Limiting daily activity will bring subject Y into the vicious cycle of fatigue (panel B).

**Table 1.** Self-reported measures of fatigue in ICU patients and survivors

Study	Tested subjects	Mean $\pm$ SD age (years)	ICU parameters		Methods of investigation	Results
			Length of stay (in days)	Time of evaluation from ICU discharge		
Hall-Smith et a. [14]	26	NR	> 5	3 months	Unstructured and client-led interview	>50% of ICU patients (14 out of 26) reported fatigue
Higgins [19]	11 M / 9 F	53 $\pm$ 17	20 $\pm$ 12	During ICU stay	Visual analogue scale (rating from 0 'not tired, full of energy' to 10 'total exhaustion')	Mean score of 5.9 $\pm$ 2.6 20%, 35% and 45% of subjects were mildly (score between 0–3.9 cm), moderately (score between 4.0–6.0 cm) or severely fatigued (score between 6.1–10.0 cm), respectively
Eddleston et al. [66]	209 M / 161 F	51 $\pm$ 19	4 (1–11)	3 months	SF-36 (VT)	M: 48.9 $\pm$ 20.7 (< 65 yo) / 49.0 $\pm$ 27.3 (> 65 yo) F: 38.6 $\pm$ 22.5 (< 65 yo) / 40.3 $\pm$ 19.3 (> 65 yo)
Chaboyer and Grace [15]	139 M / 78 F	53 $\pm$ 19	14 $\pm$ 10	1 year	Telephone interviews	> 50% of patients reported fatigue
Graf et al. [67]	116 M / 37 F	65 $\pm$ 13	3 $\pm$ 2	1 and 9 months	SF-36 (VT)	44.8 $\pm$ 21.4 (1 month after discharge) 47.9 $\pm$ 21.9 (9 months after discharge)
Kvale and Flaatten [68]	60 M / 40 F	62	> 1	6 months and 2 years	SF-36 (VT)	48.5 $\pm$ 21.1 (6 months after discharge) 51.1 $\pm$ 20.5 (2 years after discharge)
Boyle et al. [69]	42 M / 24 F	59 $\pm$ 15	7 $\pm$ 5	1 and 6 months	SF-36 (VT)	36.7 $\pm$ 22.5 (1 month after discharge) 49.0 $\pm$ 25.5 (6 months after discharge)
Hofhuis et al. [70]	146 M / 106 F	67 $\pm$ 12	13 $\pm$ 15	0, 3 and 6 months	SF-36 (VT)	31.0 $\pm$ 16.8 (immediately after discharge) 56.4 $\pm$ 23.0 (3 months after discharge) 58.6 $\pm$ 22.8 (6 months after discharge)
Kelly and McKinley [71]	23 M / 16 F	60 $\pm$ 16	7 $\pm$ 7	14 weeks (4–28.5 weeks)	SF-36 (VT)	51.4 $\pm$ 2.3
Puntillo et al. [17]	171 (64% male)	58 $\pm$ 15	3–14	During ICU stay	Edmonton Symptom Assessment Scale (adapted)	74.7% of patients at high risk of dying reported to be fatigued

Intiso et al. [24]	23 M / 19 F	58 ± 14	22 ± 6	32 months	SF-36 (VT)	CIPNM: 45.8 ± 16.6 CIP: 45.8 ± 16.6 Without CNS: 47.7 ± 15.5 With CNS: 42.7 ± 18.8 CIM: 64.1 ± 5.8 CIP / CIM: 46.4 ± 21.3
Choi et al. [26]	26 M / 13 F (2 weeks) 21 M / 10 F (2 months) 19 M / 8 F (4 months)	55 ± 17 (2 weeks) 53 ± 17 (2 months) 52 ± 15 (4 months)	23 ± 14	2 weeks, 2 and 4 months	Modified Given Symptom Assessment Tool	85, 75 and 81% of patients reported fatigue 2 weeks, 2 and 4 months after discharge, respectively
Chlan and Savik [18]	40 M / 40 F	61 ± 15	Median: 14 (1–85)	During ICU stay (fatigue was measured each day of mechanical ventilation, up to 30 days)	Visual analogue scale (rating from 0 ‘not tired at all’ to 100 ‘the most tired I have ever been’)	60.7 ± 27.9 at day 0, with fatigue ratings increasing over the course of study enrollment
Steenbergen et al. [12]	273 M / 169 F (only 191 respondent)	68 (58–75)	6 (5–10)	1, 2 and 5 years	SF-36 (VT)	54.5 ± 21.2 (1 year after discharge) 54.1 ± 20.0 (2 years after discharge) 57.8 ± 21.3 (5 years after discharge) In addition to SF-36, 37% of patients complained about fatigue
Spadaro et al. [10]	38 M / 18 F	67 ± 10	6 ± 10	1 year	FACIT-F & SF-36 (VT)	39.1 ± 10.1 for the FACIT-F 65.6 ± 20.4 for the VT of SF-36
Colville et al. [16]	97	11 (7–17)	2 (1–38)	6 weeks	PedsQL MFS	83.4 ± 18.7
Wintermann et al. [6]	82 M / 31 F	61 (55–65)	66	3 and 6 months	Multidimensional Fatigue Inventory (MFI-20)	61 and 45 patients (out of 113) reported fatigue at 3 and 6 months after discharge, respectively



Langerud et al. [27]	118 (63.6% male)	55 ± 14	9	3 and 12 months	Lee Fatigue Scale	15.3% and 13.8% of ICU patients reported fatigue at 3 and 12 months after discharge
Ehooman et al. [72]	113 M / 165 F	58 (47–65)	5 (3–10)	3 and 12 months	SF-36 (VT)	41 (31–48) (3 months after discharge) Increase in the VT score at 12 months post-discharge when compared to 3 months (median variation: +2.7)

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CIM: critical illness myopathy; CIP: critical illness polyneuropathy; CIPNM: critical illness polyneuromyopathy; CNS: central nervous system involvement; F: female; FACIT-F: Functional Assessment of Chronic Illness Therapy for Fatigue (score between 0 and 52 with higher scores representing less fatigue; healthy control subjects presented a mean score of 44 out of 52); M: male; NR: data not reported; PedsQL MFS: Pediatric Quality of Live Inventory Multidimensional Fatigue Scale (score between 0 and 100 with higher scores indicating lower fatigue; healthy control subjects presented a mean score of 86.1 ± 13.6); SF-36: Short Form Health Survey (score between 0 and 100 with higher scores representing better health-related quality of life); VT: vitality domain of the SF-36 (healthy control subjects presented a mean score of 61-68 out of 100).

**Table 2.** Questionnaires used in ICU patients to evaluate fatigue.

Questionnaires	Description	Score interpretation
FACIT-F	The FACIT-F is a 13-item validated questionnaire assessing fatigue and its impact on daily activities and functioning over the past 7 days. It comprises item such as the level of fatigue (“I feel fatigued”), the level of tiredness (“I feel tired”), the level of weakness (“I feel weak all over”) and the impact of all these sensations on the ability to perform a usual level of activity (“I am able to do my usual activities”) or to keep eating habits (“I am too tired to eat) for instance. Five choices of responses are allowed for each item, ranging from “not at all” (score = 0) to “very much” (score = 4).	A final score between 0 and 52 is obtained, with lower score representing high fatigue and vice versa. A cutoff value of 34 has been proposed in cancer patients [21].
SF-36 (Vitality domain)	The SF-36 is a multidimensional questionnaire assessing HRQoL through 8 subscales. Specifically, the "vitality" subscale is strongly correlated with the FACIT-F score and may inform on perceived fatigue over the past 4 weeks. It comprises the following 4 items: "did you feel full of pep?"; “did you have a lot of energy?”; “did you feel worn out?”; did you feel tired?". Five choices of responses are allowed for each item, ranging from “all the time” (score = 1) to “none of the time" (score = 5).	A final score between 0 and 100 is obtained for the vitality domain, with low score to be interpreted as a patient that feels tired and worn out all the time.
ESAS	The ESAS is a 10-item patient-rated symptom visual analogue scale first developed to assess symptom in palliative care patients. It comprises the following items: pain, tired, short of breath, restless, anxious, sad, hungry, scared, thirsty, confused. The patient is asked to rate severity of each of these symptoms on a 10-cm line.	The sum of patient responses to these 10 symptoms (in millimeters) represents the ESAS distress score. Each symptom (e.g. tiredness) may be assessed separately (the higher the score the more prevalent the symptom).
MFI-20	The MFI-20 is a 20-item validated self-report measurement of fatigue severity, covering five principal dimensions (general fatigue, physical fatigue, mental fatigue, reduced motivation, reduced activity). Answers are rating from a score of 4 (absence of fatigue) to 20 (maximum level of fatigue).	A total fatigue score (range 20–100) is calculated by summing each item-related score. The higher the score the higher the fatigue. A cutoff value (score > 53) for high fatigue has been proposed [6].

MGSAT	This tool is used to measure patient self-reported physical symptoms that commonly occur in patients after ICU discharge, including fatigue. Patients are first asked about the presence or absence of these 10 symptoms. If the symptom is present, they are asked to rate its severity from 0 (not present) to 10 (as severe as it could be).	The sum of patient responses to these 10 symptoms gives a general symptom burden index (range 0–100). Each symptom (e.g. fatigue) may be assessed separately (the greater the score the more prevalent the symptom). There is currently no cut-off value to discriminate fatigue based on the 0–100 burden index. Then, the prevalence of fatigue is simply determined by the proportion of patients who simply answered “yes” or “no” when they are asked on the presence of each of the 10 physical symptoms, including fatigue.
LFS	The LFS is an 18-item questionnaire measuring fatigue and energy level. Each item is rated from 0 (no symptom) to 10 (very high symptom).	The mean of the 13 fatigue items and 5 energy items is calculated, with higher fatigue scores indicating severer fatigue and lower energy scores indicating lower levels of energy. Cutoff values (5.6 and 3.5 for fatigue and energy, respectively) have been proposed [73].

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These questionnaires are not specific to ICU patients and have been used in many other clinical conditions (e.g. cancer) to assess self-perceived fatigue. ESAS: Edmonton Symptom Assessment Scale; FACIT-F: Functional Assessment of Chronic Illness Therapy for Fatigue; HRQoL: health-related quality of life; LFS: Lee Fatigue Scale; MFI-20: Multidimensional Fatigue Inventory; MGSAT: Modified Given Symptom Assessment Tool; SF-36: 36-item Short Form Health Survey.

**Table 3.** Summary of the investigation tools that could be used to assess CNS alterations in ICU patients

Method	Description of the method	Physiological signification	Advantages	Limitations
sEMG	EMG electrodes are positioned on the skin surface over the muscle(s) of interest and muscle activity is recorded during voluntary activities.	Any variations in the amplitude of the EMG signal during a maximal contraction could be interpreted as changes in neural drive.	<ul style="list-style-type: none"> <li>• Painless.</li> <li>• Simple to use.</li> </ul>	<ul style="list-style-type: none"> <li>• sEMG signal is influenced by many parameters (see Table 1 in [74]) limiting its reliability to inform on the intensity of the nervous command.</li> </ul>
Single- and paired-pulse TMS	A coil is applied over the motor cortex. A magnetic stimulation generates suprathreshold current in the brain to activate corticospinal neurons trans-synaptically, i.e. cortical interneurons are first activated. sEMG signal are recorded to record TMS-evoked parameters (MEP, SP, SICI, LICI, ICF).	TMS allows to investigate excitability (MEP)/inhibition (SP) mechanisms that occur in the corticospinal pathway, and intracortical facilitation/inhibition using paired-pulse stimulation methods, reflecting post-synaptic inhibition mediated by GABA <sub>A</sub> receptors (SICI and LICI) and excitatory glutamatergic circuit in the motor cortex (ICF),	<ul style="list-style-type: none"> <li>• Painless (even if some subject can be unsettled when using high stimulus intensities).</li> </ul>	<ul style="list-style-type: none"> <li>• Need to be associated with TMEP/CMEP to give reliable information about supraspinal alterations.</li> <li>• Various contraindications [75].</li> <li>• SP needs to be recorded in cooperative patient able to voluntary contract his muscle.</li> </ul>
VA <sub>PNS</sub>	An electrical/magnetic stimulation is superimposed at peak force during a maximal voluntary contraction. The amplitude of the force increment that occurs immediately after the stimulation is normalized by the amplitude of the evoked force recorded on the relaxed muscle to give a percentage of voluntary activation level (see Figure 1 in [76] for a graphical representation of this method).	Any increment in superimposed evoked force during contraction may reflect an incomplete recruitment of motor unit (i.e. spatially and/or temporarily).	<ul style="list-style-type: none"> <li>• Can be assessed with magnetic nerve stimulation to reduce pain.</li> </ul>	<ul style="list-style-type: none"> <li>• Requires a cooperative patient able to maximally contract his muscle</li> <li>• Does not allow to distinguish between spinal and/or supraspinal alterations.</li> <li>• Painful if electrical stimulation is used.</li> </ul>
VA <sub>TMS</sub>	A magnetic stimulation is applied over the motor cortex at peak force during maximal and submaximal voluntary contraction. A regression is used to estimate the amplitude of the force increment that would have been obtained on the relaxed muscle (see Figure 2 in [77] for a graphical representation of this method).	Any increment in superimposed evoked force during contraction may reflect an incomplete recruitment of motor unit.	<ul style="list-style-type: none"> <li>• May allow the concomitant recording of MEP and SP to give some information on supraspinal alterations.</li> </ul>	<ul style="list-style-type: none"> <li>• Requires a cooperative patient able to maximally contract his muscle</li> <li>• TMS-related contraindications [75].</li> <li>• May increase fatigue in already fatigued patient because of the consequent number of contractions required to evaluate VA<sub>TMS</sub>.</li> </ul>

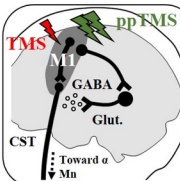
H-reflex/PRM	A low intensity electrical stimulation is applied on the motor nerve to preferentially activate large-diameter Ia muscle spindle afferent. The <i>Ia</i> afferent depolarization produces an action potential reaching the alpha motoneurons. It is observable on the EMG signal as the H-reflex. Stimulation at the lumbar level (i.e. posterior root-muscle reflexes, PRM) is also possible.	The H-reflex/PRM allow to assess the plasticity in spinal reflex pathways involving <i>Ia</i> afferents and alpha motoneurons.	<ul style="list-style-type: none"> <li>• Painless.</li> <li>• Possible to assess on the relaxed muscle.</li> </ul>	<ul style="list-style-type: none"> <li>• Influenced by many parameters particularly pre-synaptic inhibition exerted on <i>Ia</i> afferents preventing the interpretation of H-reflex as an index of Mn excitability.</li> <li>• Not easy to record in some muscles.</li> </ul>
CMEP/TMEP	A supramaximal electrical stimulation is applied at the level of the cervicomedullary junction near the pyramidal decussation (CMEP; for upper limb muscles) or at the thoracic level (TMEP; for lower limb muscles) to activate corticospinal neurons.	CMEP/TMEP allows to assess motoneuron excitability as the result of the motoneuron activation in response to the descending volley elicited by excitation of corticospinal axons.	<ul style="list-style-type: none"> <li>• Overcome the limitation presented by H-reflex recordings (i.e. not subject to pre-synaptic inhibition)</li> </ul>	<ul style="list-style-type: none"> <li>• Painful.</li> <li>• Difficult to record in some subjects.</li> <li>• Needs to be assessed during a voluntary contraction.</li> </ul>

CMEP: cervicomedullary motor evoked potential; H-reflex: Hoffmann reflex; ICF: intracortical facilitation; LICI: long-interval cortical inhibition; MEP: motor evoked potential; MRI: magnetic resonance imaging; PRM: posterior root-muscle reflex; sEMG: surface electromyography; SICI: short-interval cortical inhibition; SP: silent period; TMEP: thoracic motor evoked potential; TMS: transcranial magnetic stimulation; VA: voluntary activation.

### 5. Intracortical facilitation/inhibition

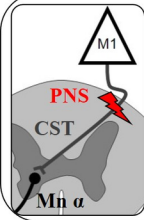
### 4. Corticospinal excitability/inhibition

- ❖ MEP
- ❖ SP
- ❖ SICI/LICI
- ❖ ICF



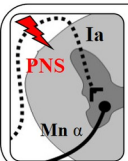
### 3. Motoneuron excitability

- ❖ CMEP
- ❖ TMEP



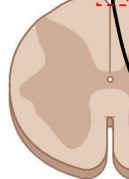
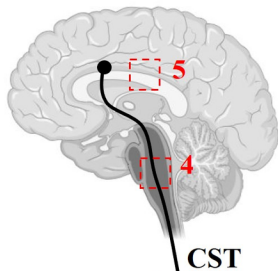
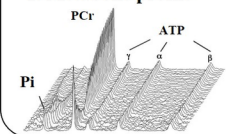
### 2. Spinal excitability

- ❖ H-reflex
- ❖ PRM



### 1. Metabolic profile

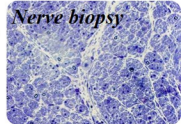
- ❖ MRI



### Critical illness polyneuropathy

- Axonal degeneration

Nerve biopsy



### Critical illness myopathy

- Muscle atrophy
- Muscle membrane inexcitability
- Muscle contractile dysfunction
- Mitochondrial dysfunction

