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Review article

The role of clinical neurophysiology in the definition and assessment of fatigue and fatigability

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ABSTRACT

Though a common symptom, fatigue is difficult to define and investigate, occurs in a wide variety of neurological and systemic disorders, with differing pathological causes. It is also often accompanied by a psychological component. As a symptom of long-term COVID-19 it has gained more attention.

In this review, we begin by differentiating fatigue, a perception, from fatigability, quantifiable through biomarkers. Central and peripheral nervous system and muscle disorders associated with these are summarised. We provide a comprehensive and objective framework to help identify potential causes of fatigue and fatigability in a given disease condition. It also considers the effectiveness of neurophysiological tests as objective biomarkers for its assessment. Among these, twitch interpolation, motor cortex stimulation, electroencephalography and magnetencephalography, and readiness potentials will be described for the assessment of central fatigability, and surface and needle electromyography (EMG), single fibre EMG and nerve conduction studies for the assessment of peripheral fatigability.

The purpose of this review is to guide clinicians in how to approach fatigue, and fatigability, and to suggest that neurophysiological tests may allow an understanding of their origin and interactions. In this way, their differing types and origins, and hence their possible differing treatments, may also be defined more clearly.

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1. Introduction

Chronic, disruptive fatigue is a significant symptom in several chronic diseases, with a myriad of definitions. Since the turn of the century, there has been several attempts to delineate and differentiate different types of fatigue in pathophysiological terms (Chaudhuri and Behan, 2004; Kluger et al., 2013; Kuppuswamy, 2017). Some have focussed on symptoms reported by patients, which may be defined as 'the state of weariness following a period of exertion, mental or physical, characterized by a decreased capacity for work and reduced efficiency to respond to stimuli,' (Dittner et al., 2004), 'a reversible decrease or loss of abilities associated with a heightened sensation of physical or mental strain even without conspicuous effort, due to an overwhelming feeling of exhaustion, which leads to an inability to sustain or difficulty in sustaining even routine activities,' (Staub and Bogousslavsky, 2001). Others have tried to capture the mechanisms of fatigue such as 'difficulty in initiation of or sustaining voluntary activities,' (Chaudhuri and Behan, 2004) and 'a percept arising primarily from alterations within the activational systems that inform voluntary action,' (Kuppuswamy, 2017).

These approaches have, at times, been confused by conflation of two distinct phenomena both described as fatigue; the 'feeling' or 'perception' which can only be described using self-reported measures such as questionnaires, and a reduction in performance over time, measurable by behavioural and neurological indices. This confusion has led to some proposing the use of the term 'fatigue' to refer only to the 'feeling' and not to performance changes, which are then referred to as 'fatigability' (Kluger et al., 2013). We will adopt this nomenclature. A further source of confusion arises from attributing fatigue and fatigability to different underlying neural systems. The terms 'mental' and 'physical' fatigue have been commonly interpreted as mental fatigue; perception involving higher order cognitive networks (fatigue in accordance with the new proposal); and physical fatigue; performance change related to reduced motor output (fatigability in accordance with the new proposal). However, it is important to note that both 'fatigue' and 'fatigability' may apply in both motor output and cognitive function.

The possible sites and mechanisms of fatigue are illustrated in Fig. 1.

Both fatigue and fatigability may also have 'central' and 'peripheral' origins within different systems. Within sensorimotor networks, changes seen in the neuromuscular junction and the muscular end organ are labelled as peripheral fatigability, while changes in neural networks proximal to the neuromuscular junction are labelled central fatigability. (Note: The dichotomisation into central and peripheral does not directly map on to fatigue and fatigability). Both central and peripheral changes are seen within the sensorimotor networks with repetition of activity, and therefore both central and peripheral factors contribute to performance fatigability (Gandevia et al., 1996; Gandevia et al., 1995b). Though the origins of fatigue are still debated, the general consensus is that it must be generated within the brain, and is possibly a result of poor integration between anticipated and real sensory input (Greenhouse-Tucknott et al., 2022; Kuppuswamy, 2022). Evidence from those with various diseases supports the idea that altered attention to a wide range of sensory inputs including proprioceptive, visual and auditory, (De Doncker et al., 2020), in the absence of explicit autonomic dysfunction, may lead to fatigue due to impaired sensory processing in this population.

The application of the concept of central and peripheral fatigue in cognitive systems is somewhat trickier, as the output of the cognitive system converges on the sensorimotor system, such as speech or movement. Metrics such as reaction time, movement speed and accuracy of movement capture the decline in cognitive function. Such motor metrics need to be relied upon as cognitive function does not have any independent effector organs. For purposes of this review, we will focus on fatigue and fatigability within the sensorimotor system.

1.1. Fatigue in sensorimotor systems

Measurements of fatigue, by self-report, have repeatedly been shown to be distinct from metrics of fatigability by force, speed of movement, etc), with little relation between fatigue and fatigability (Dobkin, 2008; Enoka and Duchateau, 2016; Kluger et al., 2013) 'Effort' is also used alongside other self-reported measures of fatigue, though its definition also remains unclear. It has also been used in relation to force output, while others tag it to brain's estimated 'cost' of a forthcoming or a completed task. To avoid confusion, and despite being imprecise, there is some agreement that the term 'perceived effort' can be used, instead of effort, to describe the brain's estimated action cost. Perceived effort has long been thought to arise from a combination of both central (de Morree et al., 2012; Marcora, 2009; Miall et al., 2000; Slobounov et al., 2004; Staiano et al., 2018; Zenon et al., 2015) and peripheral inputs (Allen et al., 2007; Brooks et al., 2013; Lafargue et al., 2003; Monjo et al., 2018; Taylor and Gandevia, 2008), with several experiments manipulating one or the other resulting in changes in perceived effort (a detailed review of perceived effort is beyond the scope of this review). More recently, there has been a shift in thinking to suggest that perceived effort is more closely linked to central motor commands than to muscle afferent inputs. A recent *meta*-analysis of studies performing nerve block experiments to attenuate muscle afferent activity and then measure perceived effort, showed no difference in perceived effort associated with a muscle contraction either with or without the nerve block indicating that

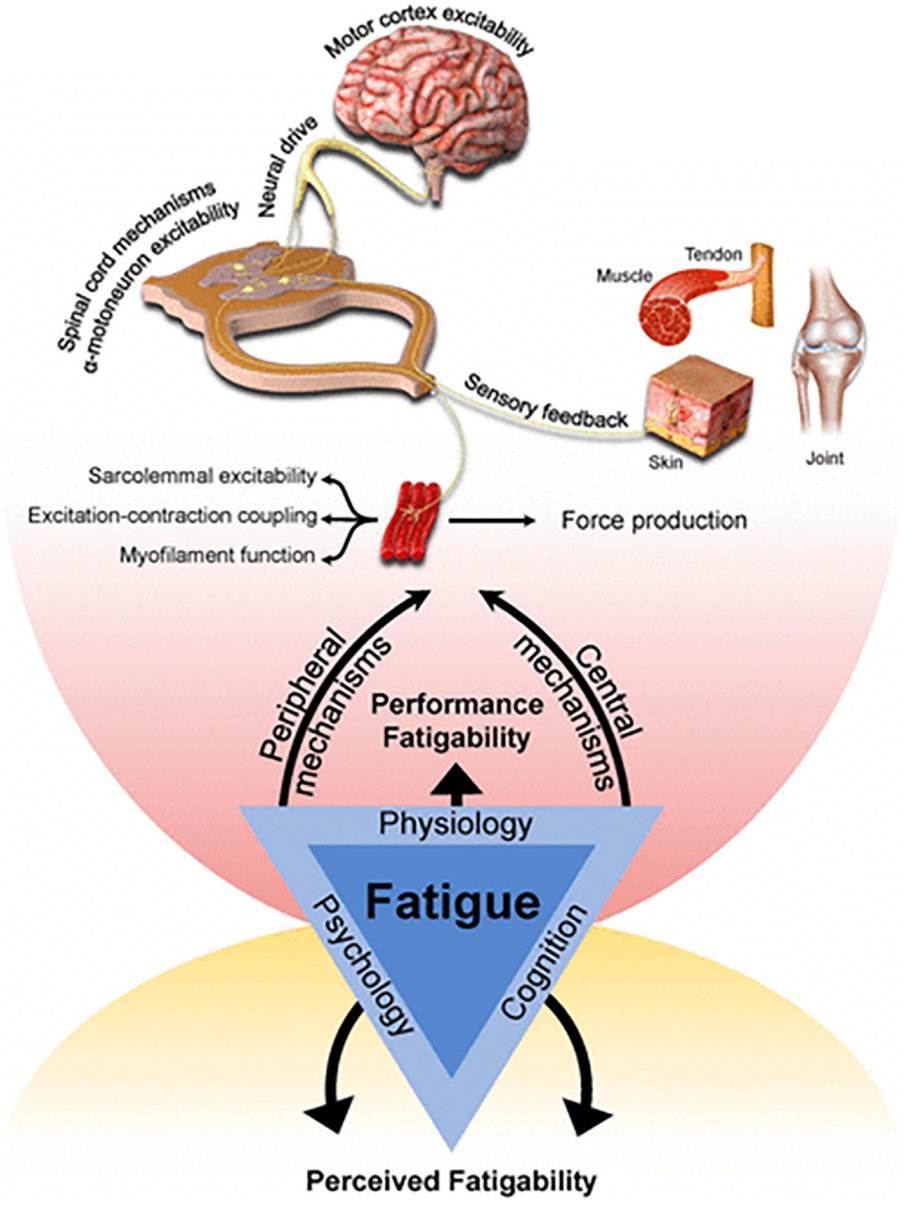

Fig. 1. Schematic diagram of the sites and possible mechanisms of fatigue. From Patikas et al. (2018).

the metric of perceived effort is entirely central in origin (Bergevin et al., 2023). While further studies are needed to confirm this finding, evidence from disease conditions also indicate perceived effort may be a measure of altered central processing rather than a readout of peripheral disturbance.

Perceived effort is altered in a range of neurological disorders including, stroke, multiple sclerosis, schizophrenia and Parkinson's disease. In all, there is increased perception of effort despite similar muscle output/energy expenditure. In minor stroke (without identifiable lesions on MRI scans either in the primary or secondary motor areas), despite similar motor output, perceived effort associated with the force is variable, with the variability explained by self-reported levels of fatigue (De Doncker et al., 2020). In multiple sclerosis, despite similar VO2max, walking feels more effortful in patients than unaffected controls (Morrison et al., 2008). In Parkinson's movement related effort perception is altered in a way unrelated to the severity of motor symptoms (Martino et al., 2016). In all these diseases fatigue is a significant symptom, and recent proposals have suggested that this might be the cognitive perception related to high perceived effort, with the primary pathology involving central processing of sensory input, rather than altered sensory input per se (Kuppuswamy, 2017, 2023). Whilst definitive evidence for this sensory attenuation model of fatigue is still lacking, this theoretical framework can explain findings related to fatigue in several of the neurological diseases mentioned, and so provides reasonable grounds to include perceived effort as a viable measure of fatigue in neurological disorders. Perceived effort or perceived exertion is normally quantified using the Borg Scale or bespoke task-specific statements rated using a Visual Analog Scale.

At this juncture it is important to note that perceived effort, and fatigue, can be informed by variables other than sensorimotor factors, such as altered interoception driven by homeostatic imbal-

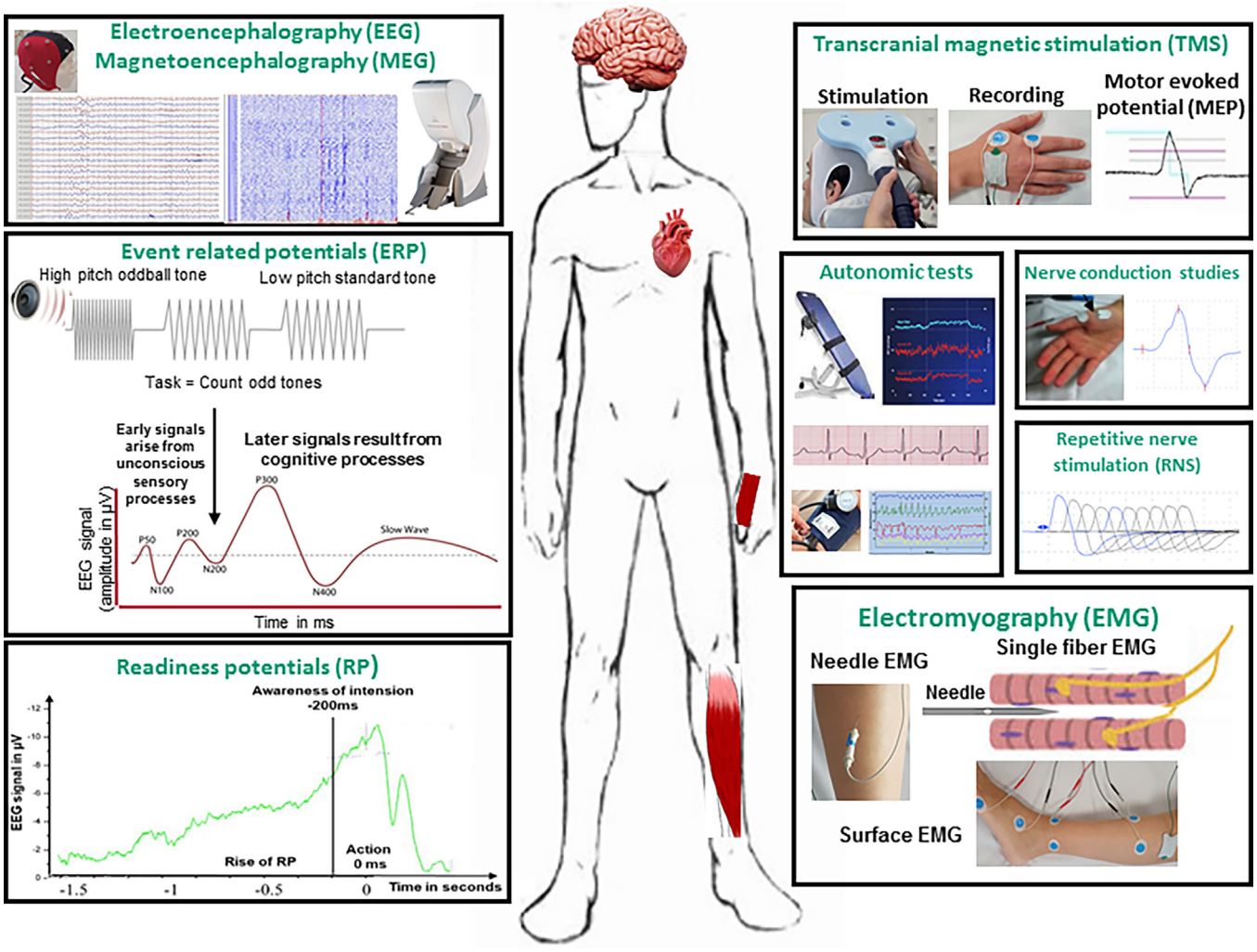

Fig. 2. Schematic diagram of the neurophysiological methods used in measuring fatigue and fatigability.

ances in diseases like multiple sclerosis (Manjaly et al., 2019). While a summary of all factors contributing to fatigue is beyond the scope of this review, the intention is to highlight how measures related to sensorimotor function can be useful biomarkers of fatigue.

In Fig. 2, the neurophysiological methods to measure fatigue and fatigability are illustrated.

2. Measuring fatigue and fatigability

2.1. Central activation failure (CAF) and twitch interpolation techniques

"Central fatigue" is the progressive decline of voluntary drive during sustained exercise caused by the decline of firing rate of cortical or spinal motoneurons. This mechanism is also known as central activation failure (CAF) (Kent-Braun and Le Blanc, 1996). Supraspinal fatigability is characterized by reduced excitability of the primary motor cortex (M1) and reduced corticospinal output (Gandevia, 2001), which is in part due to inadequate neural drive from structures upstream the M1, e.g., premotor area and basal ganglia (Chaudhuri and Behan, 2000; Taylor et al., 1996). At a spinal level central fatigability occurs with submaximal recruiting of motor units or submaximal discharge rate from those motor units that are recruited.

Twitch interpolation is usually used to differentiate between central and peripheral fatigue. Maintained twitch as weakness develops refers to central fatigue while declining twitch as weakness develops occurs distally at the neuromuscular junction or muscle, and anything more proximal is considered "central" even if it occurs in the motor axon, proximal to the stimulation site (Taylor et al., 2016). Activity-dependent hyperpolarization/conduction block in motor axons may also lead to muscle fatigue (Tsuneyama et al., 2022).

The "exhaustion" of cortical motor neurons during contractions leading to fatigability, i.e. the decrease in excitability and firing rate, depends on intrinsic changes of motoneuron properties, and changes in descending drive and afferent feedback. Repetitive activation (repeated firing) of motoneurons leads to a decrease in their excitability to excitatory synaptic inputs and in the excitatory drive to spinal motor neurons (Post et al., 2009; Taylor et al., 2016).

Small-diameter muscle afferents (groups III/IV), which are chemically and/or mechanically sensitive and activated by metabolite accumulation within the muscle (e.g., hydrogen ions, inorganic phosphates, and lactate), are activated and this leads to sensations of muscle overload and pain (Amann et al., 2015; Haouzi et al., 1999; Hayes et al., 2009) and to reduced voluntary drive to the muscle (Laurin et al., 2015) (Gandevia, 2001;

Kaufman et al., 1984). This is thought to occur through inhibitory influences either at the level of spinal motor neurons (Martin et al., 2006) or at cortical levels (Gandevia et al., 1996). Indeed, their temporary blockade can increase motoneuronal output (Hureau et al., 2019).

Submaximal voluntary drive is not only related progressive decline of cortical motor neurons' firing rate during fatiguing exercises; it is also an active inhibitory mechanism suppressing the corticomotor output with a presumed protective purpose, to prevent muscle overload and damage The cortical silent period (SP), an interruption of voluntary muscle contraction by transcranial magnetic stimulation (TMS) of the contralateral motor cortex, derives from inhibitory $GABA_B$ interneurones which limit the discharge of corticospinal neurones. SP is prolonged after sustained maximal voluntary contraction (MVC) for about 30 min (see Paragraph 2.2) thus indicating an activation of intracortical inhibitory networks (Brasil-Neto et al., 1994; Brasil-Neto et al., 1993; McKay et al., 1996; Samii et al., 1996b; Taylor et al., 1996). CAF is partially counterbalanced by excitatory inputs from the so-called motivational system (a fronto-striatal loop) and from cognitive control (Chaudhuri and Behan, 2000). It is classically assessed by means of the so-called twitch interpolation technique (Gandevia, 1998; Hales and Gandevia, 1988).

2.1.1. Twitch interpolation by electrical nerve stimulation

Twitch interpolation by electrical nerve stimulation involves the measurement of the size of the twitch produced by a supramaximal interpolated nerve or cortical stimulus during MVC. The presence of an evoked twitch suggests that the stimulated axons are not all recruited voluntarily or that they are discharging at sub-tetanic rates.

Merton was one of the first to test for failure of central activation. He used an electrically elicited twitch superimposed on a maximum voluntary muscle contraction to assess the subjects' full activation of their adductor pollicis muscles (Merton, 1954). The twitch is assessed by measuring surface electromyography (EMG) activity and muscle torque by force transducers. The electrical nerve stimulation consists in single shocks or train of pulses at tetanic frequency; the intensity must be supramaximal, otherwise it will activate fewer motor axons because of activity-dependent reductions in axonal excitability (Gandevia et al., 2013). The smaller the interpolated twitch the smaller the extra force available from the muscle, and hence the greater the level of 'voluntary' activation of the muscle. In fatiguing exercise the superimposed twitch increases and thus voluntary activation appears to decline (Gandevia et al., 1995a).

A difficulty with this technique is that the twitches superimposed on near-maximal voluntary effort are relatively small compared with the background force and may go undetected unless stringent attempts are made to measure them accurately. Moreover, twitch interpolation by stimulation of peripheral axons does not determine the level of the nervous system involved in the activation reduction.

2.1.2. Twitch interpolation by transcranial magnetic stimulation (TMS) of the motor cortex

Non-invasive methods to stimulate the motor cortex, such as transcranial magnetic stimulation (TMS), can provide further elucidation of the site of central activation failure. The paradigm consists in evoking a motor evoked potential (MEP) in a muscle already maximally activated by sustained effort by means of a supramaximal TMS pulse (about 130–150 % resting motor threshold) on the contralateral cortical hot spot (Todd et al., 2003b).

Corticomotor output declines progressively during prolonged contraction, i.e., central fatigability develops and accounts for a small but significant loss of maximal central activation. In parallel, the TMS-evoked superimposed muscle twitch in the target muscle increases (Gandevia et al., 1996). The twitch-like increment in force during MVC and the elicitation of a superimposed MEP by TMS of the motor cortex provides supplementary evidence not only that some motor units are firing at rates that are sub-tetanic for their muscle fibres but also that the motor cortical output is submaximal (Gandevia et al., 1990).

The cortically evoked superimposed twitch usually is expressed as a percentage of voluntary background EMG activity; it also involves extrapolation of the linear relationship between the amplitude of the cortically evoked superimposed twitch and voluntary torque for contractions of 50–100 % MVC (Todd et al., 2003b). This method has revealed submaximal activation of somatic muscles during maximal voluntary efforts towards respiratory muscles, assessed in diaphragm (Gandevia et al., 1990) and then thenar (Herbert and Gandevia, 1996) and elbow flexor muscles (Todd et al., 2003b). These TMS-based interpolation techniques are useful in investigating the increase of superimposed MEP, i.e. the progressive decline in voluntary activation, during maximal efforts (Gandevia et al., 1996; Loscher and Nordlund, 2002; Taylor et al., 2000; Todd et al., 2003a). They have most commonly been applied to elbow flexors but also to knee extensors and other muscle groups (e.g. back muscles) in applied physiology and sport science studies (Lagan et al., 2008; Lee et al., 2008; Todd et al., 2016).

TMS-based interpolation techniques, however, have some technical challenges including the possibility of co-stimulating antagonist muscles; poor linearity of the voluntary torque and superimposed twitch relation; and intra- and inter-individual variability in the TMS-evoked EMG and force responses (Todd et al., 2016). Ultimately, all twitch interpolation techniques depend on the ability of control subjects to drive their motor system so that the muscle produces its maximum force.

2.2. Post-exercise depression (PED) of motor cortex excitability

Excitability in the motor cortex appears to be modulated differently during and after exercise depending on whether the exercise is fatiguing or non-fatiguing. The amplitude of TMS-evoked MEPs increases in relaxed muscles after low-intense exercise that does not induce muscle exhaustion (post-exercise facilitation, PEF) (McKay et al., 1996; Samii et al., 1996b). However, a long-lasting decrease in MEP amplitude may occur with high-intensity prolonged exercises that induce muscle fatigability (i.e. reduction of MVC) or a subjective feeling of exhaustion (post-exercise depression, PED), (Brasil-Neto et al., 1994; Brasil-Neto et al., 1993; McKay et al., 1996; Samii et al., 1996b; Taylor et al., 1996). PED is also characterized by a prolongation of the cortical SP (Brasil-Neto et al., 1994; Brasil-Neto et al., 1993; McKay et al., 1996; Samii et al., 1996b; Taylor et al., 1996), and by a reduction of the cortical representation maps of the fatigued muscles obtained with TMS (Zanette et al., 1995).

PED is thought to decrease the voluntary corticomotor output and consequently limit the production of muscle power during the recovery period (Brasil-Neto et al., 1993; Petersen et al., 2003). MEP amplitude in the fatigued muscles recovers completely after a mean period of 35 min (Zanette et al., 1995).

The intracortical localization of PEF and PED has been demonstrated in control subjects (Brasil-Neto et al., 1993; Petersen et al., 2003; Zanette et al., 1995). Exercise-related facilitation and inhibition of MEPs' amplitude were demonstrated for TMS-evoked MEPs whereas transcranial electrical stimulation (TES)-induced MEPs remained unchanged (Brasil-Neto et al., 1994; Brasil-Neto et al., 1993; Samii et al., 1996b; Zanette et al., 1995). Since TES activates the axon hillock of pyramidal neurons, whereas TMS acts at presynaptic level (Amassian et al., 1987), presynaptic

intracortical structures are more likely involved in the excitability modulation involved in fatigability. M-wave and H-reflex amplitudes were not affected by fatiguing exercise, ruling out a contribution of spinal motor neurons or of peripheral nervous system in the genesis of PED (Brasil-Neto et al., 1993; Samii et al., 1996b; Zanette et al., 1995).

Di Lazzaro and colleagues (2003) recorded TMS-evoked corticospinal volleys in three subjects with an electrode implanted at cervical epidural level. After a 2 min MVC, the total amplitude of descending waves evoked by TMS was reduced by about 45 %; this effect was evident both for descending volleys originating from *trans*-synaptic activation of corticospinal cells (I waves) and for descending volleys originating from direct activation of corticospinal axons (D waves), thus directly demonstrating suppression of the corticospinal output, that parallels the post-exercise MEP suppression (Di Lazzaro et al., 2003).

PED may be considered a sort of "activity-dependent" cortical plasticity: the ability of the motor cortex to adapt its outflow in relation to motor performance and muscle state. The modulation of the corticospinal output may be triggered by a feed-forward control arising from the motor program or by feedback sensory information of muscle overload.

Recent evidence has shown that the perception of fatigue induced by repetitive fast finger tapping may have physiological mechanisms different from those accounting for fatigue during an isometric contraction, even in cases of matched effort durations. Fatigue induced by short-lasting repetitive movements produced measurable changes only within intracortical inhibitory circuits (Madrid et al., 2016) while fatiguing isometric contraction has a clear effect on spinal inhibitory mechanisms following motoneuronal excitation, such as after-hyperpolarization and recurrent inhibition (Arias et al., 2015). These studies suggest that isometric or repetitive fatiguing tasks produce two different kinds of fatigue, one involving lower-level effects and the other more intracortical. This must be taken into account when applying these techniques to the study of fatigue and fatigability, as the variability of the type, duration and intensity of the exercise may lead to differing results of uncertain or ambiguous mechanism.

Previous studies have demonstrated a reduction of PEF, without changes in PED, in patients with chronic fatigue syndrome (Samii et al., 1996a), depression (Samii et al., 1996b; Shajahan et al., 1999), and cerebellar degeneration (Samii et al., 1997). An abnormal post-exercise increase of PEF (Nielsen and Norgaard, 2002) and an absence of PED has been observed in patients with multiple sclerosis who complain of fatigue (Mordillo-Mateos et al., 2019; Perretti et al., 2004).

The exact mechanisms underlying PEF and PED are not yet known. Exercise likely changes synaptic transmission within the motor cortex for several minutes, in a similar way as high frequency microstimulation of a synaptic pathway leads to enhanced or reduced transmission in animal models. Further studies, also using pharmacologic interventions able to influence long-term potentiation or depression mechanisms, could help clarify these processes and distinguish fatigue mechanisms in different categories of patients. PEF and/or PED alteration in patients with fatigue imply abnormal cortical activity in the postexercise period but could also reflect a more global derangement of sensorimotor or premotor cortices during or before movement.

2.3. Movement preparation

Supraspinal fatigability might be correlated to activity changes in cortical areas upstream the M1, such as pre-motor cortices, supplementary motor area (SMA), cingulate motor area and basal ganglia, all of which are involved in motor planning and preparation, with support for this from positron emission tomography and functional neuroimaging studies (Inglese et al., 2004; Roelcke et al., 1997).

2.3.1. Pre-movement facilitation

Several TMS studies have found an increase in corticospinal excitability during movement preparation in simple reaction time paradigms, about 80 msec before electromyographic (EMG) onset. The so-called "pre-movement facilitation" likely represents a period of gradual increase in neuronal activity in the M1 eventually rising above the threshold for discharging of spinal motor neurons (Chen et al., 1998; Pascual-Leone et al., 1992; Rossini et al., 1988; Starr et al., 1988).

In the classical paradigm, TMS is delivered after the 'go' signal to the motor hot spot of the target muscle preparing to move, at 50, 100 and 150 ms intervals before the expected EMG burst onset in a simple reaction time task. The amplitude of MEPs evoked in the movement preparation phase is compared to that of control MEPs (Morgante et al., 2011). Lack of pre-movement modulation of corticospinal excitability was demonstrated in some patients with multiple sclerosis and stroke who experienced fatigue (De Doncker et al., 2021; Morgante et al., 2011), suggesting that supraspinal fatigability in these conditions could be due to a dysfunction of cortical motor areas involved in movement preparation (Morgante et al., 2011).

2.3.2. Readiness potentials

The performance of a voluntary self-paced movement is preceded by a negative electroencephalography (EEG) potential termed readiness potential (RP) or *Bereitschaftspotential* which is considered to reflect movement preparation processes in SMA (Kornhuber and Deecke, 1965). RPs become apparent only by back-averaging EEG epochs in the 2 sec period before movement onset and are prominent in central electrode sites located above mesial motor cortical areas and peak contralateral to the moving limb.

The RP is commonly characterized as having an early and a late component. The early component (~1500–400 ms prior to movement onset) is a slow but gradual increase in negativity, symmetrical between the two hemispheres, that has been attributed to activity in the supplementary motor area and premotor cortex, whereas the late component (~400–0 ms) is generated by activity in the primary motor cortex (Shibasaki and Hallett, 2006).

Changes of RPs during fatiguing tasks have been investigated in self-initiated repetitive high-force contraction tasks, since it is not possible to record RPs in isometric contractions task (Freude and Ullsperger, 1987; Johnston et al., 2001; Schillings et al., 2006; Slobounov et al., 2004). These studies found a clear increase in the amplitude of the RPs in muscular-fatiguing contractions, suggesting increased M1 activation to compensate for peripheral fatigability. In contrast, the amplitude of RPs before self-initiated movements was found to be reduced in patients with chronic fatigue syndrome, which could suggest a relationship between altered SMA activity in preparation for movement and fatigue (Gordon et al., 1999).

2.4. Electroencephalography (EEG) and magnetoencephalography (MEG)

If supraspinal fatigability occurs 'upstream' of the motor cortex, then the areas involved become of interest. Their investigation has involved both EEG and MEG, to enable information on cortical network activity and reorganization, and functional connectivity.

At a population level and in controls, in a systematic review, various EEG indices were used to quantify human cognitive performance (Ismail and Karwowski, 2020). Based on the evaluation of 143 studies, the authors revealed considerable changes in EEG

indices during specific performance measurements, including subjective fatigue, mental workload, working memory, visual fatigue and error recognition. Most studies applied EEG power spectral density as linear methods to evaluate human cognitive performance. The authors concluded that future research should focus on applying computational methods and machine learning algorithms to facilitate the development of fatigue recognition and automatic adaptive systems. Such techniques may prove useful to understand self-reported fatigue in control groups. There is also increasing evidence that supraspinal fatigability occurs in neurological conditions including multiple sclerosis, Parkinsońs disease, stroke and traumatic brain injury (Kuppuswamy, 2023). It remains to be seen, however, if such methods will be useful in single subjects with various problems of supraspinal fatigability.

Fatigue is actually the most frequent symptom in those with multiple sclerosis, with a prevalence of between 52 % – 88 % depending on the variety of studies' population and the definition of fatigue (Adibi et al., 2022; Leocani et al., 2008). Fatigue also affects more than 50 % of those with Parkinsońs disease (Siciliano et al., 2018) and involves predominantly supraspinal fatigability, and is linked to the cognitive and attention deficits.

Leocani et al. examined the reactivity of EEG sensorimotor rhythms to voluntary movement, and found increased reactivity over frontal regions during motor preparation and execution in fatigable compared to non-fatigable patients, suggesting that overactivation of the brain areas associated with motor tasks could be one of the pathophysiological mechanisms of multiple sclerosis-related fatigue (Leocani et al., 2001). This has been found to be independent of disability level both in this study and in a more recent study where fatigue severity was linked to altered basal ganglia functional connectivity (Finke et al., 2015). However, Buyukturkoglu and co-workers found higher EEG-based functional connectivity at rest in multiple sclerosis patients with fatigue than controls in frontal areas in both beta and theta bands which was correlated with the severity of the fatigue (Buyukturkoglu et al., 2017). Why the increased perception of fatigue is associated with over-activity of EEG in frontal areas is unclear though it might reflect compensatory mechanisms.

While EEG has been used as an outcome measure for studies in stroke and brain-computer interfaces involving the control of computers and other assistive devices in neurorehabilitation (Sreedharan et al., 2013), it has not been used in studies to understand the pathophysiology of fatigue in these conditions.

Barwick et al. investigated the fatigue associated with mild traumatic brain injury in neurologically normal, athletically active people (Barwick et al., 2012). An increase in fatigue and a decrease in cognitive performance correlated with increased relative power of theta activity in EEG. The authors suggested that this finding should be considered by clinical practitioners while evaluating the symptoms of concussion and making a decision regarding the return-to-sport participation. In one study (Korinthenberg et al., 2004), predictive factors were investigated in children with minor head injury, including EEG in post-traumatic syndrome. Post-traumatic symptoms of headache, sleep disturbances and fatigue did not correlate with EEG findings either immediately after the injury or at follow-up investigation. The authors did not recommend routine EEG examination in very slight head injury.

There is no EEG study in patients with Parkinsońs disease and fatigue. One MEG study showed multiple sclerosis induced global network-level reductions in resting-state functional connectivity, and these changes correlated to disability and cognitive fatigue (Sjogard et al., 2021). There is no study on stroke, Parkinsońs disease and traumatic brain injury related fatigue and MEG.

In summary, existing studies provide some insights into the mechanisms of fatigue and fatigability but there is no evidence yet showing that EEG or MEG are clinically useful measures in this situation.

2.5. Event-related potentials (ERP)

ERPs are measured by EEG or MEG in response to specific sensory, cognitive or motor stimuli. Among different negative or positive waveforms, the P300 occurs at approx. 300 ms when using the oddball paradigm regardless of type of stimulus, i.e. tactile, auditory, olfactory, visual, and reflects cognitive function. Thus, P300 offers the opportunity to study neuroelectric activity related to cognitive processes including fatigue. In a recent study by Paolicelli and co-workers, MEG and high-density EEG were used to evaluate acoustic P300 features in a cohort of 16 people with early multiple sclerosis (Paolicelli et al., 2021). They found an inverse correlation between P300 amplitude and fatigue and proposed that decline in P300 amplitude might be a potential biomarker for fatigue in multiple sclerosis. Since the amplitude of P300 and other ERPs is a measure of attention devoted to the task, this has to be carefully controlled. This may not have been done in this study (Paolicelli et al., 2021), therefore, their finding may be of little significance. Data on ERPs in Parkinson's looking for neural correlates of fatigue are scarce. The auditory event related potential P300 may be the best indicator of mental function. In one study, lower amplitude and longer latency P300s were found in those with Parkinson's and fatigue compare with those without. They also suggested that fatigue may be associated with cognitive deficits in Parkinson's (Pauletti et al., 2019). A recent study by the same group, using loudness dependence of auditory evoked potentials, (a neurophysiological tool that has proved effective in measuring the serotonergic central function in vivo), suggested that an altered dopamine/serotonin balance, rather than a serotonin deficit alone, is involved in the genesis of fatigue in Parkinsońs disease (Pauletti et al., 2021).

2.6. Peripheral neurophysiological methods for the assessment of fatigability

Motor control and voluntary movements depend on the firing of spinal motoneurons through the corticospinal and other tracts, and then activation of the last portion of the neuromuscular system, motor units (the anterior horn cells, their axons and all the muscle fibres they innervate). This allows examination of the mechanisms and extents of both central and peripheral fatigue using muscle as a target organ.

2.6.1. Nerve conduction studies (NCS) and repetitive nerve stimulation (RNS)

Though NCS are important in the differential diagnosis of peripheral nervous system disorders related to fatigability, neither conduction velocities or amplitudes of the sensory and motor action potentials correlate with its degree.

RNS has a diagnostic value in peripheral fatigue attributed to neuromuscular junction disorders, in myasthenia gravis and in neuromuscular disorders with persistent de- and re-innervation. RNS is also useful in some muscle disorders associated with weakness and the development of muscle fatigue, such as muscle channelopathies and myotonic conditions. Since decrement may be seen in all these conditions, any correlation between decrement and fatigability would be of interest. In a recent study, however, no correlation was found between fatigability and RNS results in spinal muscular atrophy (Bartels et al., 2021) though in an earlier study, the 6-minute walk test was significantly correlated with decrement values in RNS (Pera et al., 2017). Abnormal decrement is also well-described phenomenon in amyotrophic lateral sclerosis/motor neurone disease, (ALS/MND), but no significant correlation has been found between decrement and handgrip fatigue

(Alanazy et al., 2017). This may indicate additional more central mechanisms in the fatigability in ALS/MND.

Activity-dependent conduction block has been proposed as a possible mechanism of fatigue both in PNS and CNS disorders. The excitability of axons changes when they are active, for instance, a voluntary contraction causes the active axons to hyperpolarise and cause conduction block in damaged axons. This has been shown to occur in chronic inflammatory demyelination polyneuropathy and multifocal motor neuropathy, both of which can be associated with fatigue. The same phenomenon in central axons has been proposed as a mechanism underlying fatigue in MS (Vucic et al., 2010).

The short-latency reflex (H reflex), which assesses monosynaptic reflex activity in the spinal cord and alpha motor neuron, and the long latency reflex, which assesses transmission of a stimulus to the supraspinal centres have been used for the assessment of peripheral and spinal mechanisms of fatigability before and after exercise (Duchateau and Hainaut, 1993) but not applied yet to conditions with fatigue.

2.6.2. Single fibre electromyography (sfEMG)

Fatigue is a frequent symptom, with or without fatigability, in several other neuromuscular disorders such as post-polio syndrome, immune mediated neuropathies such as Guillain–Barré syndrome, hereditary neuropathies, spinal muscular atrophy, ALS/MND and myopathies. sfEMG is an important clinical tool in the assessment of neuromuscular junction pathologies, and highly sensitive in the diagnosis of myasthenia gravis, though not specific to this condition. It may assist in the understanding of the contribution of neuromuscular junction failure to the degree of fatigue in all these disorders associated with fatigue. In all neurogenic conditions, even in radiculopathies (Kouyoumdjian et al., 2020), where there is axonal loss and collateral sprouting, increased jitter can be found due to immature neuromuscular junction function in reinnervated muscles. However, clinical fatigue scores have rarely been correlated with sfEMG results. Noto and co-workers found disabling muscle fatigability and high incidence of activity dependent block using stimulated sfEMG but there was no correlation between sfEMG results and clinical fatigue scores (Noto et al., 2013). However, in a recent study, long COVID fatigue scores were correlated to higher values of jitter (Agergaard et al., 2023) (see the long COVID section for details).

2.6.3. Surface EMG (sEMG)

Since sEMG is a practical and non-invasive procedure, it is used widely, particularly in sports medicine and rehabilitation research, to study fatigability (Sun et al., 2022). Muscle contractions produce surface recorded motor unit potentials, and these can be displayed on a computer using advanced signal processing algorithms. Artificial intelligence and machine learning have accelerated the use of sEMG in the assessment of fatigability particularly in its classification after exercise (Sun et al., 2022). During submaximal contractions, sEMG has shown that there is the recruitment of extra motor units and an increase in firing frequency whereas during high and maximal contractions the reverse occurs. (details of these are described below in Section 2.6.4).

sEMG can also be used, particularly with multichannel surface electrodes, to measure muscle-fibre conduction velocity (MFCV) (Zwarts et al., 2000). The frequency spectrum of MFCV reduces during exercise associated with fatigability. Although central changes in motor-unit firings may play a role (Keenan et al., 2007), these changes are attributed mainly to metabolic changes (Zwarts and Arendt-Nielsen, 1988). However, one study, (Naeije and Zorn, 1981) showed that EMG power spectral shifts during muscular fatigability may occur without a concomitant change in MFCV (see Section 2.6.4 for details of power spectral analysis).

sEMG is also part of the twitch-interpolarisation technique where, after percutaneous electrical or magnetic stimulation of motor nerve, the twitch superimposed on the peak force or power of an isometric contraction during a MVC is compared to the twitch evoked on the relaxed muscle. The detail of this technique is summarised in Section 2.1. Twitch-interpolarisation is used to explore both central and peripheral fatigability. The changes in the integrated EMG signal or CMAP during voluntary and evoked contractions are analysed to determine whether a decrease in MVC force can be attributed to the loss of muscle contractility, or whether central drive may contribute to this decrease (Vollestad, 1997). Peripheral fatigability may also be assessed by single twitch, high-, and low-frequency doublets and low-to-high frequency ratio after electrical nerve stimulation. Low-frequency fatigability is a long-lasting form of muscle fatigability where the decrease in force is higher at low stimulation frequencies than at high stimulation frequencies. To assess the low frequency fatigability, low-to-high frequency ratio is used as a response to trains of supramaximal electrical nerve stimulation (Allen et al., 2008). Since this procedure is quite unpleasant, responses to paired stimuli at 10 Hz and 100 Hz (high-, and low-frequency doublets) are usually preferred.

2.6.4. Motor unit recruitment and firing rate during exercise leading to fatigability

In healthy muscle, force decreases progressively during exercise leading to fatigability. The recruitment of motor units follows the motor unit size principle in a fixed manner where smaller and lower-threshold motor units are recruited before the large ones, although recruitment thresholds may change depending on the type of the exercise (Taylor et al., 2016).

The firing rate of motor units during exercise with fatigability has been extensively studied (Taylor et al., 2016). The firing rate is generally 5–8 Hz when motor units are first recruited in healthy muscles (Heckman and Enoka, 2012) but may increase up to 50–60 Hz during brief voluntary contractions without demonstrable fatigability (Enoka and Fuglevand, 2001). During maximal voluntary contractions with fatigability, firing rates decline up to 50 % compared to initial values. This reduction happens due to a number of factors, including a decline in neural drive, local intrinsic adaptations of the motoneuron (Taylor et al., 2016), or peripheral inhibitory feedback mechanisms. Unfortunately, the contribution of these factors to motor unit firing rates depends on the type of maximal voluntary contraction task, the muscle involved, and even muscle fibre type and motor unit numbers. These should be taken into account when comparing results from different studies. Using power spectral analysis of sEMG, (Komi and Tesch, 1979) studied fatigability during dynamic contraction in healthy young individuals and concluded that muscle contraction failure might be related to qualitative changes in the motor unit recruitment pattern and that these changes occur more rapidly in muscles composed of a high proportion of fast twitch muscle fibres than in muscles composed to a high proportion of slow twitch fibres.

The most often used parameter power spectral analysis is the power-spectral density, which is the general frequency composition of the data, i.e., density of the mean square value using Fast Fourier Transformation. There is normally a rise in EMG activity while doing stationary isometric contraction. During exercise leading to fatigability, the average amplitude, rise time and number of spikes of motor unit potentials increases while the power density function shifts to lower frequencies. Additionally, synchronization of motor units is seen as a result of fatigue.

One well-established and routinely used method that evaluates exercise with fatigability is the short and long exercise test in muscles testing CMAP amplitude (Fournier et al., 2004). Exercise tests,

NCS and EMG can guide clinicians toward subgroups of mutations in muscle channelopathies (Fournier et al., 2004).

3. Fatigability in ME/CFS and long Covid

Having considered the neurophysiological mechanisms of, and tests in fatigability, we now turn to one disease which is of great contemporary interest and in which these tests have been useful in elucidating one of its clinical problems. Fatigue is the most common symptom of long Covid (Soriano et al., 2022). This is one reason why recent literature has proposed a close overlap between long Covid and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Since in both conditions a central component often accompanies the symptoms, objective measures to correlate any fatigability with self-reported central and peripheral fatigue are urgently needed. A section is therefore devoted to objective measures of fatigability, both for understanding the pathophysiology and to inform clinical approaches in these conditions.

3.1. Myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS)

ME/CFS is a serious, long-term, multi-system disorder characterised by a wide range of symptoms including extreme fatigue, autonomic and cognitive dysfunction, sleep disturbances and pain. ME/CFS affects motor, sensory and cognitive processing networks, which may be assessed through differing neurophysiological methods.

Various measures of EEG have been used in ME/CFS, with varying results. A resting state quantitative EEG study showed lower beta 2 current density in a variety of cortical and subcortical regions including the somatomotor cortex, superior parietal lobe and precuneus and posterior cingulate in those with ME/CFS (Zinn et al., 2018). EEG Low-resolution electromagnetic tomography (LORETA) analysis in cohorts of those with ME/CFS found hypoconnectivity in delta, alpha and alpha-2 bands in patients compared with controls (Zinn et al., 2016). With brain EEG mapping (BEAM), significantly elevated levels of delta, theta and alpha 1 waves were found in the right frontal and occipital regions of those with ME/CFS (Wu et al., 2016). Sleep and awake EEG studies recording beyond the conventional EEG bands have shown lower ultra-slow delta waves (0.5–0.8 Hz) in ME/CFS groups than controls while the other frequency bands did not differ between the groups (Le Bon et al., 2012). Interesting though these studies are, they have not been compared with other chronic conditions, so whether they are specific to ME/CFS remains unclear. Similarly, their mechanisms and significance remain unclear. The hope of such research, to find neural correlates of fatigue states, remains distant. To explore such ideas, other studies have used EEG during cognitive tasks (word finding and dot localisation). Significant differences were found in left frontal-temporal- parietal regions in those with ME/CFS compared with controls (Flor-Henry et al., 2010), though of course causal correlation is difficult to show and its possible significance again can only be speculated upon.

Autonomic nervous system dysfunction has been proposed as one of the primary mechanisms of ME/CFS (Wirth and Scheibenbogen, 2021). For instance, the prevalence of postural orthostatic tachycardia syndrome is increased in ME/CFS (between 13 % and 29 %) based on the heart rate dynamic responses during the head-up tilt test, though Valsalva tests could not distinguish ME/CFS patients from controls (Wirth and Scheibenbogen, 2021). Autonomic dysfunction in ME/CFS requires further research. Zinn and Jason explored the role of the cortical autonomic network (CAN) involved in higher-order control of autonomic nervous system functioning in those with ME/CFS, using resting-state qEEG, and source analysis (eLORETA) (Zinn and Jason, 2021). They found evidence of reduced higher-order homeostatic regulation and adaptability in ME/CFS which may suggest involvement of the cortical autonomic network, which may in turn be a potential therapeutic target for managing ME/CFS symptoms.

Surprisingly few studies have used needle EMG and/or sfEMG in ME/CFS and those that have do not show unanimity. Connolly et al. found increased fibre density in 11 of 35 participants with ME/CFS, with normal jitter (Connolly et al., 1993), while others have found increased jitter and blocking, (in all 10 participants (Jamal and Hansen, 1989), in 30 out of 40 participants (Jamal and Hansen, 1985), and in 16 out of 30 participants (Roberts and Byrne, 1994)). In all studies, participants had pronounced long term supraspinal and peripheral fatigability. One prominent feature of ME/CFS is pain which is often worse the day after the exertion. This feature may distinguish ME/CFS from myasthenia gravis. Studies are needed to correlate EMG and sfEMG findings with peripherally originating fatigability. This is not of course to exclude central involvement in these conditions as well; rather the balance between supraspinal and peripheral originating fatigability may be important both in its pathophysiology and its treatment.

3.2. Long Covid

Fatigue is also a common persistent symptom following SARS-CoV-2 infection and, together with chronic muscle or skeletal pain and cognitive impairment (́brain foǵ), constitutes the so-called long Covid syndrome. The cause or causes of these symptoms requires urgent delineation.

In 12 participants with persistent fatigue and ‘brain fog’ after severe Covid-19, Ortelli et al found a reduction in the cortical silent period, suggesting a disruption of the post-contraction depression mechanisms, after a fatiguing motor task, (Ortelli et al., 2021). The lack of PEDs in patients could reflect abnormal processing in the sensorimotor cortex after fatiguing muscle contraction, thus contributing to the exhaustion observed in this group after mild physical exertion. The changes in silent period duration which correlates with self-reported fatigue levels in patients supports this interpretation.

Furthermore, the patients exhibited altered intracortical GABAergic activity, shown by reduced short-interval intracortical inhibition (SICI) and long-interval intracortical inhibition (LICI) (Versace et al., 2021). Reduction in GABAergic activity within M1 may play a role in inadequate PED mechanisms.

Similar alterations in motor cortex excitability and output were demonstrated by TMS in a large cohort of patients with long Covid after mild symptomatic SARS-CoV-2 infections (Ortelli et al., 2022). Some authors have identified muscle dysfunction, from EMG and histopathological studies, as a consequence of long-Covid. Agergaard et al. showed myopathic changes with quantitative EMG (qEMG) in long Covid patients with myalgia and hyposthenia (Agergaard et al., 2021). The same authors have shown myopathic qEMG features and histopathological changes in skeletal muscle biopsies in those with fatigue, myalgia, and/or weakness persisting for up to 14 months after SARS-CoV-2 infection (Hejbol et al., 2022). More recently, mean jitter was found increased in up to 25 % of long Covid patients, using sfEMG. Importantly, these peripheral neuromuscular junction findings inversely correlated with quality-of-life scores (Agergaard et al., 2023). Collectively, these studies suggest that skeletal muscle dysfunction and neuromuscular junction instability may play an important role in post-Covid fatigability and fatigue even without overt clinical myopathy. Although EMG and histopathological changes in muscle biopsy were prominent, creatine kinase levels were normal or nearly normal.

These neurophysiological studies have shown that fatigue in long Covid can be associated with pathological processes both in

the muscle and in the motor cortex. Long-term dysfunction of neural and muscle cells may be sustained by inflammation or dysimmunity, triggered by SARS-COV-2 in predisposed individuals.

It remains to be determined whether these bottom- and top-end neurophysiological techniques can determine in individuals with long Covid, and other conditions with post viral fatigue, the origin of that fatigue, of importance since their treatment may differ. Recently, the clinical neurophysiology of acute and long Covid has been reviewed, although no specific electrodiagnostic signature for SARS-CoV-2 infection could be identified (Haykal and Menkes, 2023).

4. Conclusions

Clinical neurophysiology has methods and tools for the introduction of quantitative information into clinical medicine. However, such data must always be placed in relation to an individual's clinical symptoms. Clinical neurophysiology has good, well-validated methods of assessing neuromuscular junction and muscle nerve function; these need to be employed more carefully in the assessment of peripheral fatigability and correlated with symptoms of fatigue.

Central fatigue is inevitably more complex and more difficult to measure, especially as we move from the relatively simple sensorimotor system to other frontal and pre-frontal areas. This paper has suggested that some neurophysiological methods can begin to show the possible origins of central fatigue upstream of the motor areas, with MEP and post movement depression etc. Complex EEG has shown some promise in population studies but has not yet proved useful at the individual level.

As a consequence, in addition to quantitative methods, self-reported scales remain useful, together with careful clinical assessments. This is one reason why clinical neurophysiologists value each part of their specialty's name, both clinical and neurophysiology. This chapter has focussed on those techniques which have revealed some of the origins of fatigue and fatigability, but much work remains to be done on this pervasive and yet mysterious symptom complex. Our hope is that clinical neurophysiology may help define and measure fatigue and fatigability, and that if these, and their central and peripheral origins can be quantified and teased apart, then the understanding and treatment of a number of conditions involving fatigue and fatigability may become more logical and effective.

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