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Neurophysiological impairments in multiple sclerosis – central and peripheral motor pathways

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ABSTRACT

A systematic review of literature was conducted comparing neurophysiological outcomes in persons with multiple sclerosis (PwMS) to healthy controls (HC), with studies of central nervous system (CNS) function comprising motor evoked potentials (MEP) elicited by transcranial magnetic stimulation (TMS), and studies of peripheral nervous system (PNS) function comprising electroneuronography (ENG) outcomes elicited by peripheral nerve stimulation. Studies comparing neuromuscular function, assessed during maximal voluntary contraction (MVC) of muscle, were included if they reported muscle strength along with muscle activation by use of electromyography (EMG) and/or interpolated twitch technique (ITT).

Studies of CNS function showed prolonged central motor conduction times, asymmetry of nerve conduction motor pathways and prolonged latencies in PwMS when compared to HC. Resting motor threshold, amplitude and cortical silent periods showed conflicting results. CNS findings generally correlated with disabilites. Studies of PNS function showed near significant prolongation in motor latency of the median nerve, reduced nerve conduction velocities in the tibial and peroneal nerves and decreased compound muscle action potential amplitudes of the tibial nerve in PwMS. ENG findings did not correlate with clinical severity of disabilities. Studies of neuromuscular function showed lower voluntary muscle activation and increased central fatigue in PwMS, whereas EMG showed divergent muscle activation (i.e. EMG amplitude) during MVC.

When comparing the existing literature on neurophysiological motor examinations in PwMS and HC consistent and substantial impairments of CNS function were seen in PwMS, whereas impairments of the PNS were less pronounced and inconsistent. In addition, impairments in muscle activation were observed in PwMS.

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune inflammatory and demyelinating disease in the central nervous system (CNS), being the most common non-traumatic cause of disability in young people.[1] The progressive disabilities accompanying MS-induced damages to the CNS are rather unpredictable as many pathways can be affected by demyelination.[2] Moreover, some studies have indicated that the peripheral nervous system (PNS) also becomes negatively affected by MS.[3]

However, changes related to the PNS remains to be elucidated.[4,5] Several studies have shown that degeneration of CNS ultimately leads to impairment in neuromuscular function such as muscle strength, which contributes to deterioration of physical function.[6] This appears to be particularly true for lower extremity neuromuscular function, as exemplified by the lower extremity muscle strength being substantially reduced in persons with MS (PwMS) compared to healthy controls (HC) (~25%).[7] Furthermore, lower extremity muscle strength is associated with walking capacity.[8] The mechanisms underlying the reduction in muscle strength are of both neural[9–11] and muscular origin, hence the term neuromuscular function.[11,12] As muscle strength is positively associated with walking capacity, walking impairments are frequent in MS.[13,14] Walking capacity is considered one of the most important bodily functions by PwMS.[13,15–17] This further highlights the importance of understanding the motor-related neurophysiological changes caused by MS. Nonetheless, no previous reviews have synthesised and linked the literature on CNS, PNS, and neuromuscular function in MS.

To cover neurophysiological changes of the CNS and PNS along with the changes in neuromuscular function in PwMS, investigations including motor evoked potentials (MEP) assessed by transcranial magnetic stimulation (TMS), electroneuronography (ENG) outcomes, electromyography (EMG) and interpolated twitch technique (ITT) outcomes, are of relevance (Figure 1). Outcome measures for each technique can be seen in Table 1.

FIGURE 1 INSERT APPROXIMATELY HERE

Consequently, this review will summarise existing MS-specific literature describing impairments related to the neural pathways, i.e. the transmission of nerve signals when travelling from the origin at the cerebral motor cortex through the CNS and subsequently PNS, to finally activate skeletal muscles. The aim of this systematic review is to provide an overview of the neurophysiological changes in CNS and PNS that contribute to the deterioration of neuromuscular and physical function in PwMS (Table 1), when compared to HC.

TABLE 1 INSERT APPROXIMATELY HERE

METHODS

This study is based on a librarian-assisted systematic search of the literature in the databases PubMed and EMBASE, which was initially performed in October 2018 then updated in April 2020.

The literature search on neurophysiological motor changes in PwMS were performed in 3 subcategories (CNS, PNS and muscle), that all adopted the following inclusion criteria. Studies had to:

1. Enrol patients with a definite diagnosis of MS according to the McDonald criteria (including previous versions of the diagnostic criteria from before the latest version in 2017).[18–22]
2. Compare findings from PwMS to HC.
3. Evaluate motor neural pathways utilizing TMS, ENG, and EMG or the interpolated twitch technique (ITT).
4. Report separately on PwMS in studies evaluating mixed clinical populations.
5. Enrol more than 10 PwMS.
6. Include matched HC and use these as comparator.
7. Evaluate the upper and/or lower extremity.
8. Be available as full text peer reviewed articles.
9. Be written in English, Danish, German or Persian.

For the CNS subcategory the applied free-text search terms were: "*Multiple sclerosis AND evoked potentials AND motor*" in PubMed and "*multiple sclerosis AND evoked potentials AND evoked response*" in EMBASE.

For the PNS subcategory the applied free-text search terms were: "*Multiple sclerosis AND peripheral nervous system AND conduction*" in PubMed and "*multiple sclerosis AND peripheral nervous system AND nerve conduction*" in EMBASE.

For the muscle subcategory the applied free-text search terms were: "*Multiple sclerosis AND electromyography AND muscle*" in PubMed and "*multiple sclerosis AND electromyography AND muscle*" in EMBASE. Furthermore, following free-text search terms were applied: "*Multiple sclerosis AND interpolation AND twitch*" in PubMed and "*multiple sclerosis AND interpolation*

AND twitch" in EMBASE. Figure 2 shows the flowchart of the literature search and the subsequent results.

FIGURE 2 INSERT APPROXIMATELY HERE

RESULTS

FIGURE 3 INSERT APPROXIMATELY HERE

Central nervous system assessed by TMS-evoked muscle contractions

TABLE 2 INSERT APPROXIMATELY HERE

Resting Motor Threshold (RMT): Several studies have evaluated RMT (Table 2), which is thought to reflect corticospinal excitability and the integrity of the corticospinal tract.[23] RMT is defined as the lowest intensity of stimulation necessary to elicit a motor evoked potential of at least 50 μV in at least 50% of trials at rest.[24] Several manuscripts reported that RMT was significantly higher in PwMS compared to HC.[25–29] However, no intergroup difference in RMT was found by in the majority of the studies.[30–36]

MEP Latency: MEP latency is a measure reflecting the signal transmission time from the cerebrum to the recording electrode on the muscles in the extremities from the initial stimulation of the motor cortex. Delayed *MEP* latency in PwMS compared to HC has been demonstrated in several studies examining both the upper and lower extremities (Table 2).[26,33,35,37–39] No intergroup difference was found in Thickbroom et al..[40] Nantes et al. further divided the group of PwMS with a *relapsing remitting MS* (RRMS) into a group with *preserved* and a group with *impaired motor function*, respectively. Prolonged MEP latency was found in the impaired group when compared to both HC and the MS group with preserved motor function ($p < 0.001$).[35] Firmin et al. assessed the individual latency distribution in order to assess slower parts of central motor pathways.[41] The triple stimulation technique (TST) with stepwise extension of TST delay was applied, allowing

determination of the MEP latency distribution for each patient. The study found significantly wider MEP latency distributions in PwMS than in HC.[41]

Central motor conduction time (CMCT): Morgante et al. examined CMCT, which is the time it takes the nerve signal to travel through the CNS to the spinal motoneuron.[30] This study examined the CMCT to the first dorsal interosseus and abductor pollicis brevis muscles. It was concluded that CMCT was significantly prolonged in PwMS with fatigue ($p = 0.006$) and without fatigue ($p = 0.001$), when compared to HC. However, there were no differences between fatigued and non-fatigued PwMS ($p = 0.5$).[30] Similarly, a majority of reviewed studies applying TMS reported significantly prolonged CMCT in PwMS compared to HC (Table 2).[25,29,30,32–34,36,39,42–44] In addition to finding prolonged CMCT, Von Meyenburg et al. also compared asymmetry of CMCT in the left and right motor pathways and observed an increased asymmetry index in PwMS (also when divided into RRMS, *secondary progressive MS* (SPMS) and *primary progressive MS* (PPMS)) when compared to HC.[42] Firmin et al. found that CMCT distributions for RRMS, *progressive MS* (PMS) and HC differed significantly between PMS and HC, while distributions between RRMS and HC did not differ.[41]

MEP amplitude: MEP *amplitude* is a measure of corticospinal excitability.[45] A majority of studies (Table 2) showed that MEP amplitude was significantly reduced in PwMS when compared to HC.[25,28–30,32,35,36,39,46] However, Sheean et al., Thickbroom et al., and Liepert et al. did not find MEP amplitudes to differ from HC in PwMS.[33,38,47] Conte et al. examined PwMS with SPMS and RRMS and compared them to HC; MEP amplitude was lower in SPMS than in RRMS and HC.[39] In line with this, Firmin et al. demonstrated survival functions demonstrating decay of MEP amplitudes using the triple stimulation technique (TST) and showed a slower decrease of amplitudes with increasing TST delays in PwMS compared to HC.[41] Furthermore, the same study showed that the survival functions of PwMS with RRMS resembled those of HC but differed from progressive MS. Morgante et al. examined MEP amplitude in PwMS with and without fatigue and found, that compared to HC the MEP amplitude increased when transcranial magnetic stimulation was delivered 150 ms, 100 ms and 50 ms before onset of EMG when doing a voluntary movement.[30] As the only study, Neva et al. reported that EDSS correlated with the linear slope of the MEP amplitude input-output (IO) curve, which assessed corticospinal excitability using a varying range of stimulation intensities. The linear slope of the IO curves was determined using a

plot of MEP duration and peak to peak amplitudes versus stimulator intensity.[26]

Cortical silent period (CSP): CSP is thought to reflect intracortical inhibition and manifests as an interruption of electromyography (EMG) activity following a suprathreshold TMS pulse.[35] Neva et al. also demonstrated a significant delay of the onset of CSP in PwMS compared to HC, which can be a reflection of prolonged MEP duration in PwMS or an abnormal regulatory mechanisms of local corticospinal inhibitory mechanisms.[26] The same study and Thickbroom et al. found no intergroup differences in CSP duration.[26,36] Nantes et al. demonstrated that CSP duration was significantly prolonged among PwMS with impairments compared to HC.[35] Nantes et al. found CSP prolongation even in RRMS with impairments compared to RRMS without impairments,[35] while Thickbroom et al. found prolongation of CSP during sustained contractions.[36]

Several studies have measured ipsilateral silent periods (iSP), which is a putative electrophysiological marker of callosal demyelination.[48] Findings suggest that iSP durations were positively associated with disability in terms of the *Expanded Disability Status Scale* (EDSS),[49] which is in line with another study by Schmierer et al.[50] Furthermore, Cabib et al. have demonstrated significant differences in iSP latency, but not in iSP duration, which is longer in PwMS compared to age- and gender-matched HC.[37]

Disruptions in the short intracortical inhibition (SICI) may represent a disinhibition in the motor cortex in PwMS.[47] Conte et al., Liepert et al., and Stampanoni et al. all found reduced SICI in PwMS compared to HC,[28,39,47] while Morgante et al. and Nantes et al. did not find any intergroup difference.[30,35]

Peripheral nervous system assessed by ENG-evoked muscle contractions

TABLE 3 INSERT APPROXIMATELY HERE

Latency: Emad et al.[51] found no differences in *latency* of the action potentials in median and tibial nerves between PwMS and HC (Table 3). Similarly, Gartzen et al. did not find differences between the two groups in regards to latencies of the tibial and peroneal nerves,[4] whereas Görgülü et al. found prolonged latencies in right peroneal and left median nerves in PwMS compared to HC.[52] In a longitudinal study with 13 PwMS and 13 HC, Hidasi et al.[5] examined the median nerves twice in PwMS and HC three years apart. At both examinations a trend towards a

difference in latency between PwMS and HC was observed but did not yield statistically significant differences.[5] There were no changes in latencies in HC and PwMS at baseline and after three years.[5]

Amplitude: Emad et al., Hidasi et al., and Görgülü et al. found no differences in amplitudes of action potentials in the median and tibial nerves when comparing PwMS and HC,[5,51,52] while Gartzen et al. noted a reduction in motor amplitude of the peroneal and tibial nerve in PwMS of 18.5 % and 3.7 %, respectively.[4]

Nerve Conduction velocity (NCV): In a cross-sectional study Emad et al.[51] found reduced median and tibial motor NCV in PwMS compared to HC. Using the same study design Gartzen et al. concluded that the conduction velocity of peroneal and tibial nerves was reduced in 7.4 % and 5.5 % of all PwMS, respectively.[4] Görgülü et al. found reduced conduction velocities in the left peroneal nerve in PwMS compared to HC,[52] while Hidasi et al did not demonstrate intergroup differences.[5]

Refractory periods: Boërio et al. studied motor nerve excitability of the ulnar nerve in PwMS with normal nerve conduction parameters and compared absolute and relative refractory periods and percentages of refractoriness and supernormality.[53] For supernormality it was found that the nerve threshold falls below the resting value, during interstimuli intervals of 2.6 and 7 milliseconds when compared to HC. The study also found that both absolute and relative refractory periods were prolonged in PwMS compared to HC. Furthermore, percentage of refractoriness was increased, while supernormality was markedly reduced in PwMS when compared to HC.[53]

Central nervous system assessed by voluntary muscle contractions (EMG and interpolated twitch technique)

TABLE 4 INSERT APPROXIMATELY HERE

Amplitude: EMG amplitude provides an overall estimation of muscle activation since it is related

to the number of motor units recruited and the rates at which they discharge action potentials (rate coding).[54] Scott et al. calculated EMG amplitude using *root mean square* (RMS) during sub- and maximal voluntary contractions of the vastus lateralis muscle (Table 4).[55] It was found that the EMG amplitude was lower in PwMS compared to HC at voluntary muscle contractions ≥ 60% of MVC. Hameau et al. also reported lower EMG amplitudes of lower extremity muscles (e.g. vastus lateralis and rectus femoris) in PwMS compared to HC, that were consistently accompanied by lower maximal muscle strength in PwMS compared to HC.[11,53] The same study suggested a diminished voluntary muscle activation as the reason.[56] Interestingly, Kiselka et al. found that PwMS produced similar EMG activity of the triceps brachii muscle compared to age-matched HC across submaximal-to-maximal effort levels (% of EMG during MVC),[57] whereas Heller et al. found even higher relative triceps brachii muscle activation across submaximal-to-maximal effort levels.[58] Severijns et al. observed a decline in root mean square amplitude in PwMS when maximal contractions were repeated (i.e. inducing fatigue). However, this study did not observe any differences between PwMS and HC.[59]

Interpolated Twitch Technique (ITT): The technique is widely used to provide a quantitative measure reflecting the voluntary muscle activation (VA) that is obtained during maximal force production, i.e. a proxy of the neural output (in percentage) that reaches a given muscle.[60]
Wolkorte et al. found that persons with SPMS had reduced VA and weaker MVC compared to RRMS and HC (Table 4).[61] Also, Skurvydas et al. found that the MVC and VA were significantly reduced in the quadriceps muscles of PwMS compared to HC.[11] A reduced MVC of the quadriceps muscle and vastus lateralis was also found in Hameau et al and Scott et al. when comparing PwMS to HC.[55,56] Two studies by Steens et al. examined the first dorsal interosseus muscle and demonstrated a decrease in VA during sustained contractions in PwMS compared to HC but did not find intergroup differences in MVC in one study while MVC was reduced in PwMS in the other study.[31,43] Kiselka et al. also did not find intergroup differences in MVC.[57] Ng et al. found that ankle dorsiflexor MVC was 27% lower in PwMS compared to HC despite similar electrically evoked muscle force, thus indicating that the CNS-derived neural input was affected.[62] This corresponded well with the lower *central activation ratio*, as well as the lower number of foot-taps and slower rapid submaximal isometric contractions observed in PwMS compared to HC (see Table 1).[62] Wolkorte et al. calculated both muscle fatigue and peripheral fatigue, where the former was estimated using average voluntary force relative to MVC and the latter was estimated

as postfatigue twitch relative to prefatigue twitch. It was concluded that people with SPMS had more voluntary muscle and central fatigue and less peripheral fatigue than HC. The change in VA and peripheral fatigue over time did not differ between SPMS and RRMS.[61] Severijns et al. examined force decline during high and low intensity contractions.[59] A significant decrease in MVC was seen over time in both groups, where PwMS did not show more decline than HC.[59] However, female PwMS showed lower VA compared to HC.[59]

DISCUSSION

The studies presented in this review examined neurophysiological changes in PwMS compared to HC. The main findings of the present review were that TMS-elicited MEPs showed prolonged CMCT, higher asymmetry index, prolonged latency, prolonged CSP and reduced amplitude in PwMS compared to HC, while results on RMT and amplitudes were conflicting (Table 2 and Figure 3). In a review by Yusuf et al. examining the neurophysiological aspects of PwMS found increased motor thresholds in 10 out of 20 studies.[63] In the only longitudinal study reporting ENG data for the PNS no statistically significant latency prolongation in the median nerve was reported in PwMS compared to HC.[5] Cross-sectional studies showed reduced motor NCV and amplitudes in the tibial and peroneal nerves (Table 3 and Figure 3). Studies reviewed regarding neuromuscular function using EMG and ITT showed lower VA and muscle strength in PwMS, while results on EMG amplitude and root mean squares obtained during MVC were conflicting (Table 4 and Figure 3).

Central nervous system assessed by TMS

Most of the existing studies show that MEP latencies and CMCT are prolonged in PwMS compared to HC. In addition asymmetry indexes in mixed groups of PwMS as well as in all MS-subtypes, were increased compared to HC.[42] Firmin et al. did not find differences in CMCT distributions between a mixed group of PwMS and HC. However, when data, comparing MS subtypes, was analysed, a significant difference between PMS and HC was observed, while distributions for RRMS and HC did not differ.[41] In line, CMCT was prolonged in PwMS when

compared to RRMS, despite having similar motor deficits, disease duration and spinal cord involvement.[64] Taken together, this suggests that CMCT shows larger decrements in PMS and/or in patients with higher disability levels. This interpretation is supported by Neva et al. who argues, that demyelination in corticospinal neurons are less pronounced at early stages of RRMS, which may explain the near-normal latency observed in this MS subtype, while the prolongation may become more pronounced as the disease progresses.[26]

The CSP is a complex inhibitory phenomenon caused by different spinal and supraspinal mechanisms and is generally considered a measure of intracortical GABAb transmission.[11,57,58] Studies showed that CSP was significantly correlated to performance and disability in PwMS and that CSP prolongation may indicate weakening corticospinal integrity in RRMS.[26,35] In accordance with the finding on CMCT, an increased disability level seems to change the CSP outcome as demonstrated by the findings of Nantes et al., where CSP duration was significantly prolonged among PwMS having physical impairments when compared to both PwMS without impairments and to HC.[35] This suggests CSP as a potential marker of disability in PwMS. However, when witnessing CSP prolongation in PwMS compared to HC it should be taken into account that PwMS are impaired in muscle rate of force development [7] as the re-onset of muscle activity signals the end of the CSP.[26] Thus CSP prolongation in PwMS may also be a reflection of changes in muscle properties and not only by GABAb-receptor mediated inhibitory circuits. It should be noted that measuring CSP in PwMS can be challenged by common symptoms presenting in PwMS such as cognitive difficulties, weakness etc., which can make it difficult for PwMS to perform the required task during measurements.

Except for the study of Gagliardo et al.,[25] reviewed studies showed that MEP amplitude did not differ in RRMS when compared to HC. However, when MS subtypes were taken into account, it was shown that MEP amplitudes were lower in PMS than in both RRMS and HC. Morgante et al. measured MEP amplitudes before the onset of EMG of voluntary movement and found that the amplitude in PwMS increased before the voluntary movement.[30] This method is more likely to give an indication of movement preparation and planning and not necessarily the MEP amplitude as measured in other studies. A review by Yusuf et al. examining neurophysiology of fatigue in MS found reduced MEP amplitudes in 17 of 25 studies.[63] In addition, a correlation between MEP amplitude and EDSS was reported by Neva et al., and was suggested as predictor of disability in PwMS.[26] In the same study it is suggested that the decreased slope in the MEP amplitude curve may be due to neuronal dysfunction caused by cortical damage and demyelination in the

corticospinal tracts.

Impact of exercise and rehabilitation on neurophysiological changes

As mentioned above, Neva et al. reported that MEP amplitude was correlated with EDSS.[26] Furthermore, abnormal CMCT, latency and amplitude are all correlated with EDSS in PwMS.[65,66] In a study by Kale et al. examining 131 PwMS it was found that 83% had abnormal amplitudes, 52% had prolonged MEP latency and 49% had CMCT abnormalities.[65] Important questions relate to whether the observed impairments in MEP latency or amplitude can be positively impacted by targeted rehabilitation. A study by Nielsen et al., with 15 PwMS and 15 HC doing isometric non-fatiguing contractions found a significant post-exercise increase in MEP amplitude in PwMS compared to HC.[67]

A reduction in CSP could reflect task dependent adaptation of corticospinal inhibition and may explain the increase in strength by shortening of CSP induced by resistance training. This may suggest the possibility that specific exercise training may positively impact the CNS in PwMS. This effect can be seen in a study by Kidgell et al.,[68] where a group of healthy adults followed four weeks of resistance training of an intrinsic hand muscle, and another group of healthy adults did not undergo training. An increase in the MVC of 34% in the trained group compared to a 13% increase in the untrained group was demonstrated. However, there were no significant changes in the MEP latency or amplitude in the two groups, but CSP was reduced significantly in the trained group.[68]

Peripheral nervous system assessed by ENG-evoked muscle contractions

The reviewed cross-sectional studies showed no differences in motor latencies in tibial and peroneal nerves.[4,51] Hidasi et al.[5] conducted the only existing longitudinal study which prospectively examined the median nerve over three years, and found that PwMS showed a near significant prolongation of distal motor and sensory latencies compared to HC. Moreover, the study by Hidasi et al. revealed a mild and progressive deterioration of the PNS in MS, but it must be kept in mind that only one peripheral nerve was examined. Other studies have evaluated a

number of peripheral nerves to identify potential electrophysiological abnormalities. However, they all concluded that electrophysiological abnormalities were not associated with the severity of neurological disabilities.[69,70]

The number of ENG studies on the PNS is limited making definite conclusions difficult. The majority of ENG studies comparing PwMS to HC are cross-sectional and show some degree of latency impairment. In line, impaired motor NCVs in the tibial and peroneal nerves were found in a small percentage of PwMS. However, the ENG results did not correlate with severity of disabilities. This is underlined in Jende et al., where normal ENG results were obtained in PwMS who underwent magnetic resonance neurography (MRN) of the tibial and peroneal fascicles.[3] Here, the MRN visualised a significant amount of lesions in the PNS in PwMS (151.5 ± 5.7) compared to HC (19.1 ± 2.1).[3] This cross-sectional study therefore suggests that PNS changes are very subtle and may escape detection during ENG examinations.[3] Taken together, the few existing ENG studies do indicate minor motor and sensory PNS impairments in PwMS, that seem to depend on disease severity, and PNS abnormalities may be identified earlier using techniques examining motor nerve excitability as mentioned in Boërio et al..[53]

Sarova-Pinhas et al. found electrophysiological abnormalities in 15% of the examined peripheral nerves in PwMS with 10 out of 22 PwMS having at least 2 peripheral nerves with conduction abnormalities.[70] In line, Pogorzelski et al. examined 70 PwMS without clinical signs of motor and sensory neuropathy and found electrophysiological evidence of a motor or sensory PNS lesion in at least one peripheral nerve in 74% of the examined PwMS.[71] Using a somewhat similar approach, Boërio et al. included PwMS who had normal standard ENG examinations in order to find other motor nerve conduction parameters that could be different in PwMS compared to HC, but did not investigate latency.[53] The study argued that, even if demyelinating polyneuropathy was described in MS, PNS involvement probably remains rare and subclinical due to subtle nerve lesions and lack of significant demyelination. Consequently, most neurophysiological outcomes assessing PNS may show normal range findings making other techniques warranted, when investigating peripheral nerve impairments in PwMS.[53] In accordance, another study reported that 5% of the investigated MS sample had demyelinating polyneuropathy, which suggests that it could be caused by epitope spreading evolving as the disease progresses.[72] In a recent study, Jende et al. performed ENG in PwMS and found normal values in all 36 participants (three cases showed marginally reduced sensory amplitudes and in one case the F-wave was non-elicitable).[3] The same study conducted magnetic resonance neurography scans of the PNS of the lower extremities and

found lesions in all PwMS compared to HC. Consequently, this study showed in vivo involvement of PNS in PwMS despite normal standard neurophysiological examinations of the PNS.[3]

Studying motor and sensory NCV, Emad et al. reported that NCV was reduced in PwMS, while Gartzen et al. similarly found motor NCV to be reduced in 7.4% and 5.5% of the peroneal and tibial nerves of the PwMS, respectively.[4,51] Furthermore, a relationship was found between tibial nerve NCV and EDSS.[51] Nonetheless, Emad et al. concluded, that differences in the neurophysiological findings in the PNS between PwMS and HC are small and inconclusive.[51] When summarising their data, Gartzen el al. demonstrated that 29.6% of PwMS had at least one abnormality when undertaking a standard motor and sensory neurophysiological examination.[4] The same study further argued that, despite the myelin is derived from the Schwann cells in the PNS and from oligodendrocytes from the CNS, simultaneous autoimmune reactions in these nervous systems are plausible.[4]

Boërio et al. demonstrated prolongation of *absolute refractory periods* (ARP) and *relative refractory periods* (RRP) in PwMS compared to HC, and that percentage of refractoriness was increased and supernormality highly reduced in PwMS.[53] Elaborating on the reduction of supernormality, Gartzen et al. pointed to a histopathological study by Pollock et al. examining the sensory sural nerves of PwMS with no clinical polyneuropathy and with normal NCV.[4] In this study a 50% reduction in myelin thickness and a high frequency of abnormal teased fibers suggested the involvement of peripheral myelin in MS. Gartzen et al. further argued that these subtle alterations in the peripheral nerves would primarily manifest as changes in the nerve recovery cycles rather than as affected standard nerve conduction. Here, the prolonged refractory period of the nerve is caused by inactivation of the sodium channels in PwMS, which leads to reduction in supernormality.[4]

Central nervous system assessed by voluntary muscle contractions

Reviewed studies presented conflicting results regarding EMG amplitudes, thought to reflect neural activation. Moreover, Scott et al. and Hameau et al. examined knee flexor and extensors and found smaller EMG amplitudes in PwMS during both sub- and maximal muscle contractions,[55,56]. Scott et al., interpreted this as a reflection of reduced firing rates in PwMS.[55] Hameau et al. examined fatigability of knee extensors and reported that PwMS produced 77% of

the MVC of the knee extensors, while HC produced 93% during the first 5 contractions.[56] The authors explain the discrepancy by a reduced voluntary muscle activation of agonists muscles, which cause limitations in muscle activation as reflected by a lower amplitude in PwMS.[56] Reduced firing rates in PwMS were also associated with reduced walking speed and distance.[73] Rice et al. offer some explanation into the underlying mechanisms in a small study examining muscle weakness including 4 PwMS and 16 HC. Here they found reduced maximal motoneuron firing rates in PwMS (17 Hz vs. 24 Hz),[74] which was in line with the study of Scott et al.[55] The conflicting results may also be partly explained by the fact that many studies report absolute EMG amplitudes, an outcome known to vary considerably between individuals. Absolute EMG amplitudes should be normalized to some individual reference value, such as maximal muscle strength.[54]

Several studies reported reduced VA in PwMS, which can also be explained by the reduced maximal motoneuron firing rates mentioned above.[74] Steens et al. found significantly larger superimposed twitch amplitudes in hand muscles of PwMS using ITT and interpreted this as a measure of central fatigue.[43] This conclusion is in line with the findings of Skurvydas et al. examining leg muscles and Wolkorte et al. examining hand muscles while the latter also found similar changes between RRMS and SPMS.[11,61] In accordance with the majority of studies showing reduced VA in PwMS, a study by Ng et al. examined voluntary and electrically stimulated muscle contractions and observed a 27% lowering of MVC in PwMS when compared to HC.[62] It was also found that force relaxation was slower in PwMS, which was attributed to central activation impairment in MS. Furthermore, this study indicated that at least part of the changes in VA might have been due to disuse and deconditioning, and not just MS.[62] Offering some support to this notion a RCT-study by Dalgas et al., found that surface EMG activity during maximal muscle contractions of quadriceps, increased after 12 weeks of resistance training.[9] Fimland et al. demonstrated a similar result, after 3 weeks of intensive resistance training of the gastrocnemius and soleus muscles.[75]

A fiber-type shift in muscles, with a reduction in type I fibers from 76 to 65%, has been found in PwMS with reduced activity levels.[76] The slow-to-fast transition of fiber type composition after reduced activity among PwMS may change muscle contractile properties.[77] Scott et al. was the only study examining muscle fiber conduction velocity (MFCV) in PwMS in comparison to HC.[55] PwMS produced significantly faster MFCV compared to HC during both sub- and maximal muscle contractions. However, this supports the hypothesis that PwMS have altered

neuromuscular activity during voluntary muscle contractions. In line with de Haan et al., the same study speculated that disuse atrophy may have occurred in PwMS and led to a higher proportion of type II fibers, causing faster MFCV.[55,78] The high MFCV in patients with neuromuscular disorders is also noted by Blijham et al., confirming that conduction velocities in both muscle and nerve depend on fiber diameter, even in myelinated fibers.[78] Hameau et al. further notes that studies are inconclusive regarding muscle fiber-type distribution and that they suggest PwMS to have a higher proportion of type IIa fibers or having no major differences in muscle fiber type distribution compared to HC.[56] In another RCT, Dalgas et al. have examined the effects of resistance training on muscle fiber adaption in PwMS who underwent a 12-week progressive resistance-training program of the lower extremities.[79] This study by Dalgas et al, demonstrated an increase in muscle fiber size of predominantly type II fibers without fiber type transformation and may suggest that MFCV can be affected by targeted training.[79] It should also be of note that glucocorticoid therapy, often used in treatment of relapses in MS, have shown to cause loss of muscle volume,[80] likely due to stimulation of protein breakdown and inhibition of protein synthesis.[81]

CLINICAL IMPLICATIONS

Implementation of neurophysiological examinations in clinical practice, with the aim of monitoring disease activity, may be useful. Several parameters have shown the ability to detect changes correlated to clinical and subclinical symptoms in PwMS, as most clinical symptoms of MS are related to alteration in impulse conduction in the CNS.[82–84] Furthermore, some parameters have proven useful in discriminating between PwMS and HC, but also between MS subtypes. Early *visual evoked potentials* (VEP) and MEP abnormalities can even predict clinical disabilities as much as 20 years later.[85]

As more recent research show involvement of the PNS, future large-scale longitudinal studies that also include broader variety of PNS measures are warranted, to better understand PNS involvement and consequences in MS. Broader neurophysiological studies will contribute to the understanding of the effect MS has on the CNS, PNS and muscle function and could thus potentially aid treatment. Furthermore, studies evaluating exercise and other rehabilitation interventions on neurophysiological outcomes are warranted in PwMS.

LIMITATIONS

Several limitations must be kept in mind when interpreting the results from the studies included in this review. Firstly, studies are generally small and cross-sectional by nature, and not always being matched perfectly to HC. Secondly, only few studies could be located, and particularly the PNS is still poorly studied in PwMS. Thirdly, neurophysiological outcomes are heterogeneous across studies, limiting direct comparison of studies. Finally, only few studies take disability level and MS type into account, despite this is likely to influence the results.

CONCLUSION

Neurophysiological examinations of the CNS, PNS and muscles have shown their use in detecting clinical and subclinical lesions in PwMS compared to HC. MEP assessed by TMS showed impairments that were correlated with the level of disability in PwMS in contrast to ENG in the PNS. ITT demonstrates increased central fatigue in PwMS. However, the vast majority of studies have few participants and base results on cross-sectional data. Large longitudinal studies are needed aiming to elucidate neurophysiological changes in CNS, PNS and muscle in PwMS.

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FIGURE and TABLE LEGENDS

Figure 1. Visualizations of the neurophysiological examinations of the motor pathways related to the central nervous

system (CNS), peripheral nervous system (PNS), and the neuromuscular function included in the present review (for further explanation of outcome variables see table 1). *Abbreviations*: CMCT: central motor conduction time; PMCT: peripheral motor conduction time; CSP: cortical silent period; NCV: nerve conduction velocity; RMS: root mean square; ITT: interpolated twitch technique.

Figure 2. Flowchart of the literature search and the study selection. *: studies identified from the reference list of an included study.

Figure 3. Overview of findings in persons with Multiple Sclerosis (PwMS) compared to healthy controls (HC) in neurophysiological examinations of motor functions. *Abbreviations*: RMT: resting motor threshold; CMCT: central motor conduction time; CSP: cortical silent period; SICI: short intracortical inhibition; NCV: nerve conduction velocity; ARP: absolute refractory period; RRP: relative refractory period; MVC: maximal voluntary contraction; VA: voluntary activation.

Table 2. An overview of studies examining transcranial magnetic stimulation evoked muscle contractions. For further explanation of outcome variables see Table 1. Abbreviations: MS: Multiple Sclerosis; PwMS; persons with Multiple Sclerosis; HC: healthy controls; CMCT: central motor conduction time; RMT; resting motor threshold; SICI: short intracortical inhibition; CSP: cortical silent period; MEP: motor evoked potentials.

Table 3. An overview of studies examining electroneuronographic differences. For further explanation of outcome variables see Table 1. Abbreviations: MS: Multiple Sclerosis; PwMS; persons with Multiple Sclerosis; HC: healthy controls.

Table 4. An overview of studies examining voluntary muscle contractions (electromyography and interpolated twitch technique). For further explanation of outcome variables see Table 1. MS: Multiple Sclerosis; PwMS; persons with Multiple Sclerosis; HC: healthy controls; MVC: maximal voluntary contraction; VA: voluntary activation.

Table 1: Brief explanation of investigations and outcome variables

Method	Description
Motor evoked potentials (MEP)	Evoked potentials elicited by magnetic stimulation of the motor cortex.
Outcome	
Latency	The transmission time from stimulating the cortex to the start of the evoked potential in the EMG of the target muscle.
Amplitude	Voltage difference between minimum to maximum peaks and a measure of the number and size of the depolarized muscle fibers. Decreased amplitude is usually a measure of axonal loss[1] or loss of synchronised arrival of the action potentials due to impaired corticospinal conduction.[2]
Central motor conduction time (CMCT)	The time it takes for the fastest action potentials to travel from the site of cortical stimulation to the spinal motoneuron. It is calculated by subtracting the peripheral motor conduction time (PMCT) from the MEP latency or by the F-wave method (Figure 1).
Cortical silent period (CSP)	A reflection of intracortical inhibition and is calculated from the end of the MEP to the return of voluntary EMG (Figure 1)
Resting motor threshold (RMT)	The minimum intensity of stimulation needed to elicit MEPs of 50 μV in at least 5/10 consecutive stimulations of relaxed muscles.
Electroneuronography (ENG) of motor nerves	Electrical stimulation of peripheral nerves and measuring nerve conduction in motor nerves.
Outcome	
Compound muscle action potential (CMAP)	EMG reflection of the summation of action potentials obtained from activated muscle fibers in a target muscle.
Latency	The transmission time from electrical stimulation to the arrival of the fastest action

	potentials to a recording electrode in the target muscle.
Amplitude of CMAP	A reflection of the number and the size of depolarized muscle fibers. It is measured by the voltage difference between minimum to maximum peaks. Decreased amplitude is a measure of axonal loss and desynchronization along the efferent motor pathways.
Nerve conduction velocity (NCV) of motor nerve	Velocity of motor nerve signal carried by the fastest nerve fibers and is measured by dividing distance between the site of stimulation and electrode on target muscle with the time difference between stimulation electrode on motor nerve and recording electrodes on muscle.
Interstimuli intervals (ISI)	Time interval between consecutive stimulations. In Boërio et al. various ISI are utilized, where it was initially set at 1 ms and then gradually increased.[53]
Absolute refractory periods (ARP)	In Boërio et al. it was measured as the shortest ISI for which a response to the second pulse occurred.[53]
Relative refractory period (RRP)	In Boërio et al. defined as the first ISI, where the amplitude of the response to the conditioned test stimulus was equal to the unconditioned stimulus.[53]
Supernormality	Hyperexcitable phase following the refractory period of a stimulated nerve.
Electromyography (EMG) during voluntary muscle contraction	Measure of the translation of neural input to a given muscle through recruitment and firing frequency of motor units.
Outcome Amplitude	Measure of the number and frequency of motor unit potentials in the measured muscle. The amplitude of the EMG signal can be measured by the root mean square (RMS).

Table 2: An overview of studies examining transcranial magnetic stimulation evoked muscle contractions.

Author (year)	**Reference number**	**Persons with MS (PwMS) / healthy controls (HC)**	**Central motor conduction time (CMCT)**	**Motor evoked potential latencies and target muscle**	**Resting motor threshold (RMT)**	**Short interval intracortical inhibition (SICI)**	**Cortical silent period (CSP)**	**Amplitude**	**Comments**
Gagliardo et al. (2007)	25	32 /20	CMCT ↑ in PwMS compared to HC ($p = 0.001$) and ↑ in disabled compared to non-disabled PwMS ($p = 0.001$).	*Latency*: not specified. *Muscle*: tibialis anterior.	RMT ↑ in PwMS compared to HC ($p = 0.0011$) and ↑ in disabled compared to non-disabled PwMS ($p = 0.001$).	Not specified.	Not specified.	Amplitude ↓ in PwMS compared to HC ($p < 0.0001$) .	Of 32 PwMS, 17 are non-disabled and 15 disabled.
Neva et al. (2016)	26	26/11	Not specified.	*Latency* ↑ in PwMS compared to HC ($p = 0.02$).	RMT ↑ in PwMS compared to HC ($p = 0.22$).	Not specified.	CSP duration not specified. CSP onset is	Not specified.	

				Muscle: extensor carpi radialis.			prolonged in PwMS (p = 0.11).		
Firmin et al. (2012)	41	16/29	Intergroup differences in CMCT not specified. However, CMCT distributions were compared showing significant differences between PMS and HC, while there were no intergroup difference between RRMS and HC in distributions.	Latency: Not specified. However, there were wider latency distributions in PwMS compared to HC. *Muscle*: abductor digiti minimi.	Not specified.	Not specified.	Not specified.	Not specified.	Survival functions of amplitude decay showed slower decrease of amplitude in PwMS compared to HC.
Morgante et al. (2011)	30	33/12	CMCT ↑ in PwMS (both fatigued and non fatigued) compared to HC (p = 0.003). CMCT did not differ between	*Latency*: not specified. *Muscle*: first dorsal interosseus and	No intergroup difference.	No intergroup difference (p = 0.4).	Not specified.	Amplitude ↓ in PwMS compared (p = 0.001).	Of 33 PwMS, 16 had fatigue and 17 were without fatigue.

			fatigued and non fatigued PwMS (p = 0.5).	abductor pollicis brevis.					
Steens et al. (2012)	31	20/20	CMCT ↑ in PwMS (p = 0.02)	*Latency*: not specified. *Muscle*: right first dorsal interosseus.	No intergroup difference (p = 0.18).	Not specified.	Not specified.	Not specified.	
Schubert et al. (1998)	32	11/10	CMCT ↑ in PwMS.	*Latency*: not specified. *Muscle*: flexor hallucis brevis and tibialis anterior.	No intergroup difference.	Not specified.	Not specified.	MEP area ↓ in PwMS compared to HC. 42% reduced in flexor hallucis brevis and 19% in tibialis anterior.	
Sheean et al. (2012)	33	21/19	CMCT ↑ in PwMS (p < 0.01).	*Latency*: ↑ in PwMS compared to HC (p < 0.05).	No intergroup difference.	Not specified.	Not specified.	No intergroup difference.	

				Muscle: Adductor pollicis.					
Mainero et al. (2004)	44	12/12	CMCT ↑ in PwMS ($p < 0.0001$).	*Latency*: not specified. *Muscle*: first dorsal interosseus.	Not specified.	Not specified.	Not specified.	Not specified.	No differences in MEP amplitude, latency of CSP duration in PwMS after Fampridine 3,4-aminopyridine and placebo.
Di Sapio et al. (2014)	34	28/28	CMCT ↑ in PwMS ($p < 0.0001$).	*Latency*: not specified. *Muscle*: vastus medialis, tibialis anterior and flexor hallucis brevis.	No intergroup difference.	Not specified.	Not specified.	Not specified.	
Nantes et al. (2016)	35	43/29	Not specified.	*Latency*: ↑ in PwMS during rest and muscle contraction ($p < 0.001$). Impaired PwMS had ↑	No intergroup difference ($p = 0.08$).	No intergroup difference ($p > 0.05$).	CSP ↑ in PwMS ($p < 0.01$). Impaired PwMS had ↑ CSP than	Amplitude ↓ in PwMS during rest compared to HC ($p < 0.001$).	PwMS who performed within two standard deviations of HC were classified as performing and the slower PwMS were

				latencies than performing PwMS. *Muscle*: first dorsal interosseus.			performing PwMS.	Impaired PwMS had ↓ amplitudes than performing PwMS. No difference in amplitude during contraction.	classified as impaired.
Bridoux et al. (2015)	46	12/12	Not specified.	*Latency*: not specified. *Muscle*: extensor carpi radialis.	Not specified.	Not specified.	Not specified.	Amplitude ↓ in PwMS (p = 0.03).	
Conte et al. (2009)	39	30/17	CMCT ↑ in PwMS (p = 0.002). Also significantly ↑ in progressive PwMS compared to relapse-remitting PwMS.	*Latency*: ↑ in PwMS. *Muscle*: first dorsal interosseus.	Not specified.	SICI ↓ in secondary progressive PwMS compared to relapse remitting PwMS (p = 0.014) and	Not specified.	Amplitude ↓ in secondary progressive PwMS compared to relapse remitting PwMS) and HC (p =	Three groups studied: secondary progressive PwMS, relapse remitting PwMS and HC.

						HC (p = 0.008).		0.0001).	
Von Meyenburg et al. (2013)	42	41/28	CMCT ↑ in PwMS (p < 0.001).	*Latency*: not specified. *Muscle*: abductor digiti minimi and tibialis anterior.	Not specified.	Not specified.	Not specified.	Not specified.	Asymmetry index for CMCT studied showing strongly increased indices for PwMS compared to HC.
Liepert et al. (2005)	47	16/6	Not specified.	*Latency*: not specified. *Muscle*: superficial flexor digitorum.	Not specified.	SICI ↓ in PwMS with fatigue compared to non-fatigued PwMS and HC (p < 0.01).	Not specified.	No intergroup difference. After exercise amplitudes ↓ without intergroup effect.	Three groups examined: 8 PwMS with fatigue, 8 PwMS without fatigue and 6 HC.
Thickbroom et al. (2008)	38	10/13	CMCT ↑ in PwMS.	*Latency*: ↑ in PwMS (p < 0.05). *Muscle*: tibialis anterior.	Not specified.	Not specified.	Not specified.	No intergroup difference (p < 0.05).	

Thickbroom et al. (2006)	40	23/15	Not specified.	*Latency*: No intergroup difference. *Muscle*: first dorsal interosseus.	No intergroup difference.	Not specified.	No intergroup difference ($p > 0.05$).	Amplitude ↓ in PwMS ($p < 0.01$).	
Cabib et al. (2015)	37	20/13	Not specified.	*Latency*: ↑ in PwMS ($p = 0.005$). *Muscle*: first dorsal interosseus.	Not specified.	Not specified.	Not specified.	Not specified.	Studies cortical ipsilateral silent period duration and latency, where both are ↑ in PwMS.
Stampanoni Bassi et al. (2020)	28	18/18	Not specified.	*Latency:* Not specified *Muscle*: first dorsal interosseus.	RMT ↑ in PwMS compared to HC ($p = 0.009$).	SICI ↓ in PwMS compared to HC ($p = 0.007$).	Not specified.	Baseline amplitude difference not specified. Amplitude ↓ after 600 abductions of index finger in PwMS	

								compared to HC.	
Mordillo-Mateos et al. (2019)	29	17/16	CMCT ↑ in PwMS ($p = 0.0093$).	*Latency*: Not specified. *Muscle*: first dorsal interosseus.	RMT ↑ in PwMS compared to HC ($p = 0.0139$).	Not specified.	Not specified	Amplitude ↓ in PwMS ($p = 0.0241$).	
Zipser et al. (2018)	27	13/16	Not specified.	*Latency:* Not specified. *Muscle*: abductor pollicis brevis.	RMT ↑ in PwMS compared to HC ($p < 0.05$).	Not specified.	Not specified.	Not specified.	TMS coupled with electroencephalography (EEG) in order to examine spatiotemporal dynamics of TMS neural activity.

Table 3: An overview of studies examining electroneurographic differences.

Author (year)	**Reference number**	**Persons with MS (PwMS) / healthy controls (HC)**	**Nerve and latency**	**Conduction velocity**	**Amplitude**	**Comments**
Hidasi et al. (2009)	5	13/13	*Latency*: no intergroup difference at baseline ($p = 0.09$) and 3 years after ($p = 0.06$). *Nerve*: right median nerve.	No intergroup difference.	No intergroup difference.	
Emad et al. (2017)	51	20/20	*Latency*: No intergroup differences ($p > 0.05$). *Nerves*: median and	Conduction velocity ↓ in PwMS compared to HC in the median ($p = 0.008$) and tibial	No intergroup difference ($p > 0.05$).	

			tibial nerves.	nerves (0.003).		
Gartzen et al. (2011)	4	54/21	*Latency*: No intergroup difference. *Nerves*: peroneal and tibial nerves.	Conduction velocities ↓ in 7.4% of peroneal and 5.5% of tibial nerves in PwMS.	Amplitudes ↓ in 18.5% of peroneal and 18.5% in tibial nerves in PwMS.	Overall standard nerve conduction abnormalities found in 14.2% PwMS. In 7.4% PwMS more than one abnormality found.
Boërio et al. (2007)	53	20/20	*Latency*: Not specified. *Nerve*: right ulnar nerve.	Not specified.	Not specified.	Absolute refractive period ↑ ($p = 0.0022$), relative refractive period ↑ ($p = 0.0373$) and supernormality ↓ ($p = 0.0002$) in PwMS.
Görgülü et al. (2020)	52	33/25	*Latency*: ↑ in right peroneal, left median nerve ($p < 0.05$). *Nerve*: median, ulnar, peroneal and tibial nerves.	Conduction velocity ↓ in left peroneal nerve in PwMS compared to HC ($p < 0.05$).	No intergroup difference ($p > 0.05$).	

Table 4: An overview of studies examining voluntary muscle contractions (electromyography and interpolated twitch technique).

Author (year)	Reference number	Persons with MS (PwMS) / healthy controls (HC)	Muscle studied	Electromyography amplitudes	Maximal voluntary contraction (MVC) of muscle	Voluntary activation (VA) of muscle	Comments
Scott et al. (2011)	55	15/14	Vastus lateralis.	Amplitude ↓ during isometric contraction at 60-100% of MVC in PwMS ($p < 0.05$).	MVC ↓ during isometric contraction in PwMS ($p < 0.05$).	Not specified.	Muscle fibre conduction velocity ↑ in PwMS ($p < 0.05$). Rate of force development ↓ in PwMS ($p < 0.05$).
Hameau et al. (2017)	56	38/14	Rectus femoris, vastus lateralis, biceps femoris and semitendinosus.	Amplitude ↓ in vastus lateralis and rectus femoralis during maximal voluntary isometric contraction in PwMS ($p < 0.001$).	MVC ↓ during isometric contraction in PwMS ($p < 0.001$).	Not specified.	
Steens et al. (2012)	31	20/20	First dorsal interosseus.	Not specified.	No intergroup difference ($p >$	Estimated VA ↓ in PwMS ($p = 0.03$).	Superimposed twitch amplitude ↑ in PwMS

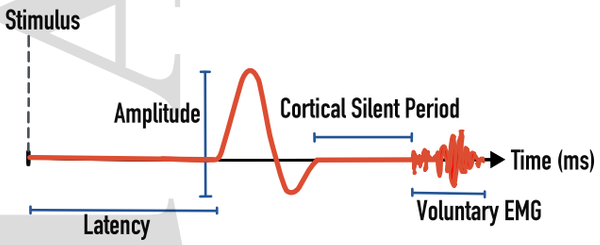
					0.1).		($p < 0.001$).
Kiselka et al. (2013)	57	25/28	Triceps brachii.	PwMS and HC produced similar muscle activity measures as % of EMG during MVC.	No intergroup difference.	Not specified.	
Heller et al. (2016)	58	28/28	Triceps brachii.	PwMS produced higher muscle activity measured as % of EMG during MVC.	Intergroup differences in MVC not specified. %MVC ↑ in PwMS.	Not specified.	
Severijns et al. (2016)	59	19/19	Extensor carpi radialis longus and brevis and flexor carpi radialis.	No intergroup difference..	Not specified.	VA ↓ in PwMS ($p < 0.05$).	
Wolkorte et al. (2016)	61	25/25	Right first dorsal interosseus.	Not specified.	MVC ↓ in PwMS ($p < 0.05$).	VA ↓ in PwMS during brief maximal contractions ($p < 0.05$).	The PwMS in this study consisted of only SPMS.
Skurvydas et al. (2011)	11	18/19	Quadriceps femoris.	Not specified.	MVC ↓ in PwMS ($p < 0.001$).	VA ↓ in PwMS ($p < 0.05$).	

Ng et al. (2004)	62	18/18	Tibialis anterior.	Not specified.	MVC ↓ in PwMS ($p = 0.03$).	Not specified.	Central activation ratio ↓ in PwMS ($p = 0.04$).
Steens et al. (2012)	43	20/20	First dorsal interosseus.	Not specified.	MVC (converted into z-score) ↓ in PwMS ($p = 0.03$)	Not specified.	VA ↓ in PwMS ($p < 0.05$) during sustained contraction.

Evoked muscle contraction

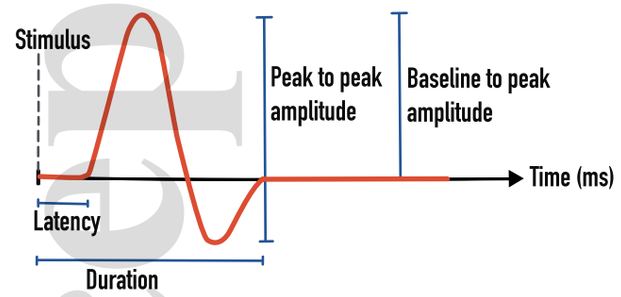
Motor Evoked Potentials

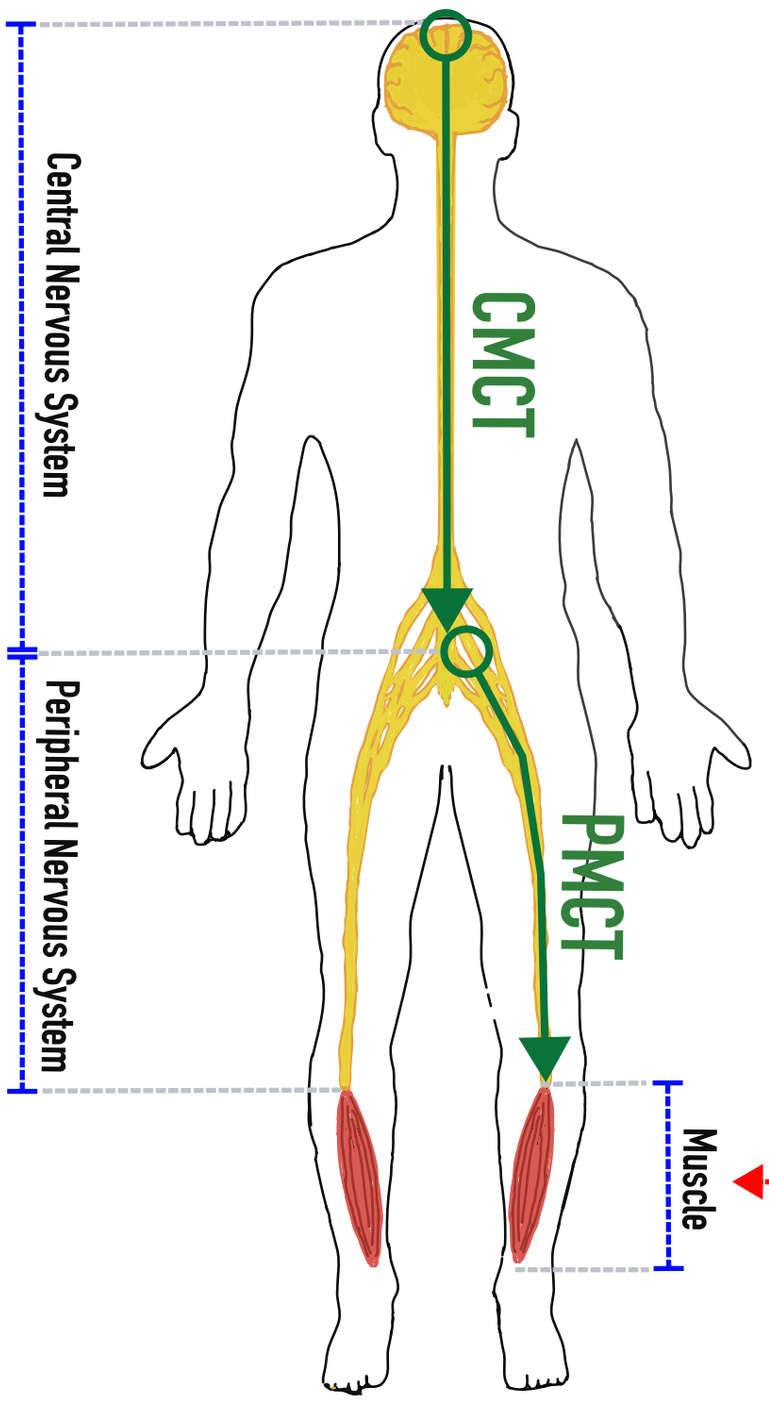
Method: Transcranial Magnetic Stimulation
Outcomes: latency, central motor conduction time (CMCT), and cortical silent period (CSP)



Nerve Conduction Studies

Method: Electroneuronography
Outcomes: latency, nerve conduction velocity (NCV), and amplitude.

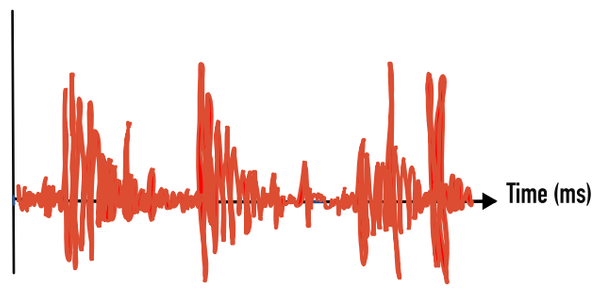




Voluntary muscle contraction

Neuromuscular activity

Method: Electromyography (Voluntary)
Outcomes: amplitude



Voluntary and evoked muscle contraction

Neuromuscular activation

Method: Interpolated twitch technique (ITT)
Outcomes: percentage of voluntary muscle activation