Section 1
Chapter 1

Basic mechanisms

Conduction studies in multiple sclerosis

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Evoked potentials in the diagnosis of multiple sclerosis

The diagnosis of multiple sclerosis (MS) is based on the detection of multiple inflammatory demyelinating white matter lesions, which are disseminated in space and time. Traditionally, evoked potential (EP) studies have been employed to reveal dissemination of lesions in equivocal clinical situations. This is achieved by demonstration of clinically silent lesions. In the 1980s–1990s, a wealth of studies described the technical aspects of evoked potentials and their application in MS. Many of these studies were aimed at optimizing the yield of the EP studies, by refinement of the technical parameters or by increasing the number of stimulation modalities. These efforts resulted in sensitivities (i.e., frequencies of abnormal results) as high as 80% in some studies [1–4]. It is noteworthy that specificities (i.e., how many abnormal results are found in patients not suffering from MS) were rarely specified. Moreover, high sensitivity of a test in MS does not equal high diagnostic yield. For instance, a test that tends to confirm clinically detectable signs is not very likely to improve the diagnostic certainty in a patient, even though it might be very sensitive in terms of yielding a high proportion of abnormal results. An analysis of the diagnostic yield was done by Beer and co-workers [4], by calculating the number of patients with suspected MS who could be reclassified after the clinical examination according to the Poser Committee Criteria [5]. In their study, MRI and analysis of cerebrospinal fluid for oligoclonal banding largely outperformed EP studies (Fig. 1.1).

The introduction of magnetic resonance imaging (MRI) had a dramatic impact on the use of conduction studies in the diagnostic work-up of MS patients. Lesions and their spatial distribution in the central nervous system (CNS) can directly be demonstrated using MRI. Dissemination of lesions in time is easily assessed using serial MRIs or by demonstration of different acuity by uptake of contrast agents in a single MRI. Moreover, MRI has the advantage of being fast and painless, while EP studies are often considered cumbersome for the examiner and painful by the patient. Thus, conduction studies are not considered in the actual diagnostic criteria for MS [6], with the exception of visually evoked potentials (VEPs) in some situations with primary progressive MS, as they demonstrate subclinical lesions relatively often [4].

Despite their diminished importance in the diagnostic work-up of patients, evoked potentials may serve as **surrogate markers for the progression of the disease**, and may be of interest for the prognosis of patients. In these areas, MRI parameters have been found to be remarkably weak. The MR lesion load may not correlate with the clinical deficit of the patient [7, 8]. Furthermore, the number of gadolinium-enhancing lesions in the baseline MR scan was not found to be a strong predictive parameter for the relapse rate in the first year after diagnosis, and monthly MR scans over 6 months were not predictive of the change in the expanded disability status scale (EDSS) in the subsequent 12 and 24 months [9]. In contrast, a number of evoked potential studies demonstrated a correlation between clinical deficit and EP findings [10–12]. Evoked potentials were found useful to monitor the effect of steroid treatment of acute bouts of MS [13]. Direct comparisons between MRI parameters and EP results suggested a better relation between EP and clinical status (EDSS) than between

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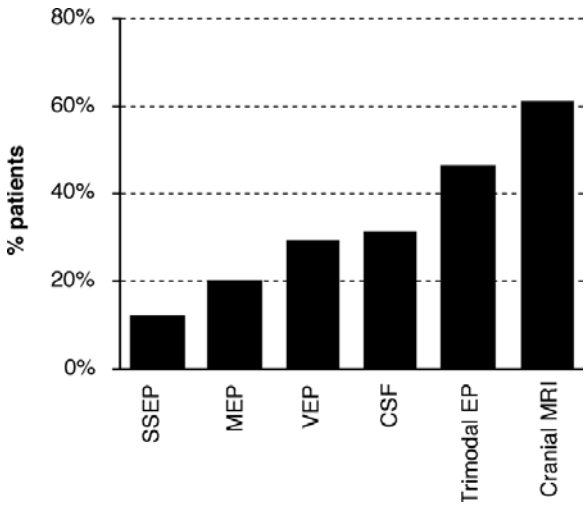

Fig. 1.1. Reclassification sensitivity (i.e., the percentage of reclassified patients according to Poser criteria) of evoked potentials studies, cerebrospinal fluid (CSF) analysis, and magnetic resonance imaging, SSEP, somatosensory evoked potentials; MEP, motor evoked potentials; VEP, visually evoked potentials. Data extracted from Beer *et al.* [4].

MRI and EDSS [10, 11]. Evoked potentials may thus serve to follow the disease during therapeutic interventions [11–13]. They may also serve as prognostic parameters: Fuhr and co-workers reported that the combined result of MEP and VEP at onset would predict the EDSS after 2 years [12].

Pathophysiology of central conduction in multiple sclerosis

Traditionally, evoked potentials have rarely been interpreted in view of the pathophysiological significance of their abnormality. Theoretically, conduction along central pathways can be altered in various ways. Acute demyelination may induce conduction block, i.e., action potentials do not propagate across the lesion. The conduction velocity across the lesion may be reduced due to myelin abnormalities. Clinically, conduction block will cause a neurological deficit (i.e., a paresis or a sensory deficit), while conduction slowing will not necessarily cause deficits and may therefore point towards a clinically silent lesion [12, 14–16]. Not only demyelination but also remyelination of a previously demyelinated axon may cause reduction of the propagation velocity. In MS, axonal damage may occur along with demyelination. While axonal death will not change conduction velocity, it will reduce the number of conducting axons, causing central conduction failure and inducing clinical deficits. The situation may be complicated by alternative routes of transmission within the CNS, which are used to compensate for interrupted routes. Furthermore, in motor evoked potentials, a loss of central motor neurons will decrease the number of axons converging on the anterior horn cell, increasing the need for temporal summation of incoming excitatory postsynaptic potentials, resulting in an increased central conduction time [14].

Evoked potentials are most often used to measure **central conduction time**. In MS prolonged central conduction times are usually interpreted as markers of demyelination. However, this simple notion is probably not entirely true. In a retrospective study, Humm and co-workers analyzed the central motor conduction time (CMCT) in a large sample of MS patients and observed that the CMCT was mainly increased in patients with progressive forms of MS while it was normal or only slightly prolonged in patients with acute relapsing–remitting forms of MS [16]. Interestingly, this prolongation was not related to the clinical motor deficit or to the electrophysiologically measured central conduction failure, and it was not related to the duration of the disease. Hence while a patient with a relapsing–remitting form of MS would have a normal central motor conduction time, a patient with a primary (or secondary) progressive form of MS with the same disease duration would have a greatly prolonged CMCT. The finding of particularly long CMCTs in patients with progressive forms of MS was also made in a subsequent, prospective study [17]. CMCT was also found to be particularly prolonged in MS patients with marked temperature vulnerability (Uhthoff phenomenon), while it was normal in patients without temperature vulnerability [18]. Thus it appeared that a prolonged CMCT increased the likelihood of a patient to develop a transient conduction block during warming [16]. A similar observation was made using VEPs: in a study of exercise induced changes in 15 MS patients, Persson and Sachs observed an association between the degree of induced changes of visual acuity and the extent of VEP latency prolongation [19]. These observations may suggest that prolongations of CMCT are indicative for a myelin disturbance which may be typical for chronic MS, and which makes conduction vulnerable to temperature changes. Humm and co-workers speculated that these prolongations could relate to incomplete remyelination rather than to acute demyelination [16].

Assessment of central conduction failures

Theoretically, amplitudes of evoked potentials are markers of the amount of conducting fibers. Reduced amplitudes would thus indicate loss of conduction by axonal death or central conduction block within the pathway that is studied. Unfortunately, amplitudes of somatosensory evoked potentials and motor evoked potentials vary considerably between normal subjects, and therefore normal limits are broad [20, 21]. This impedes interpretation of amplitudes of evoked potential to such an extent that the only robust amplitude criterion is "lack of response." It is thus impossible with most EP protocols to demonstrate partial central conduction blocks or gradual loss of conducting axons over time. In the recent years we have developed a method to quantify central motor conduction, allowing for a meaningful interpretation of potential amplitudes. In the following, we will describe this triple stimulation technique (TST) and some of the results obtained with it.

Central motor conduction in multiple sclerosis: the triple stimulation technique

Motor evoked potentials (MEPs) are elicited by transcranial magnetic stimulation (TMS), which is a noninvasive, painless method to stimulate the human brain. Serious adverse effects were not described with single pulses. The technical implications and the basic methodology have been covered broadly and are not repeated here [22, 23]. Theoretically, the size of an MEP should reflect the number of conducting central motor neurons, but this relation is obscured, mainly by two factors. First, in healthy subjects as well as in patients, MEPs are smaller than compound muscle action potentials (CMAPs) evoked by peripheral nerve stimulation, and their size varies from one stimulus to the next and between subjects [14, 21, 24–7]. These MEP characteristics are caused by varying synchronization of the descending action potentials in response to TMS. The resulting phase cancellation phenomenon impedes direct conclusions on the number of activated motor neurons [21]. Size parameters of MEPs are thus insensitive for the detection of small to moderate central conduction failures, which may cause clinically significant deficits [2, 14, 28, 29].

To eliminate the problem of discharge desynchronization, Magistris and co-workers developed a triple stimulation technique (TST) [21]. This collision technique suppresses the effects of central action potential desynchronization, which occurs in MEPs of healthy subjects and patients. As a consequence, the TST provides a quantitative measure of the percentage of spinal motor neurons that can be brought to discharge by TMS. In healthy subjects, this percentage is always near 100%. In patients with central motor disorders, this percentage is often smaller, as a result of the corticospinal conduction failure. The term "conduction failure" is used here to describe the situation in which the brain stimulus does not lead to excitation of all motor units of the target muscle, reducing the TST amplitude ratio below normal limits. It can be due to loss of corticospinal neurons, to central axonal lesions, to conduction block, or to reduced excitability of the motor cortex to TMS.

The technical principle of TST has already been described in detail [21, 30]. It consists of a transcranial magnetic stimulus followed by two maximal electrical stimuli, one to the ulnar nerve at the wrist, and one to the brachial plexus at Erb's point, with appropriate delays. The TST test curve (TST_{test} = stimuli: brain–wrist–Erb) is compared to a TST control curve ($TST_{control}$ = stimuli: Erb–wrist–Erb). The ratio TST_{test} : $TST_{control}$ (termed "TST amplitude ratio") reflects the percentage of activated spinal motor neurons. An overview of the technique is given in Fig. 1.2. Since the original description of the technique, an adaptation has been worked out for use on the lower extremities [31]. Here, recordings are done from abductor hallucis, the distal stimulus is given to the tibial nerve at the ankle, and a proximal stimulus is given through a monopolar needle electrode placed close to the sciatic nerve [31]. Normal values and sensitivities are similar for the TST of upper and lower limbs.

Central conduction failure in multiple sclerosis

In a large collective of MS patients, Magistris *et al.* found reduced TST amplitude ratios in 106 of 221 arms, indicating central conduction failure in 48%. In the same sample of patients, prolonged central motor conduction times were only found in 48 of 221 arms (= 22%). There was a significant quantitative relationship between the TST amplitude ratio and the force

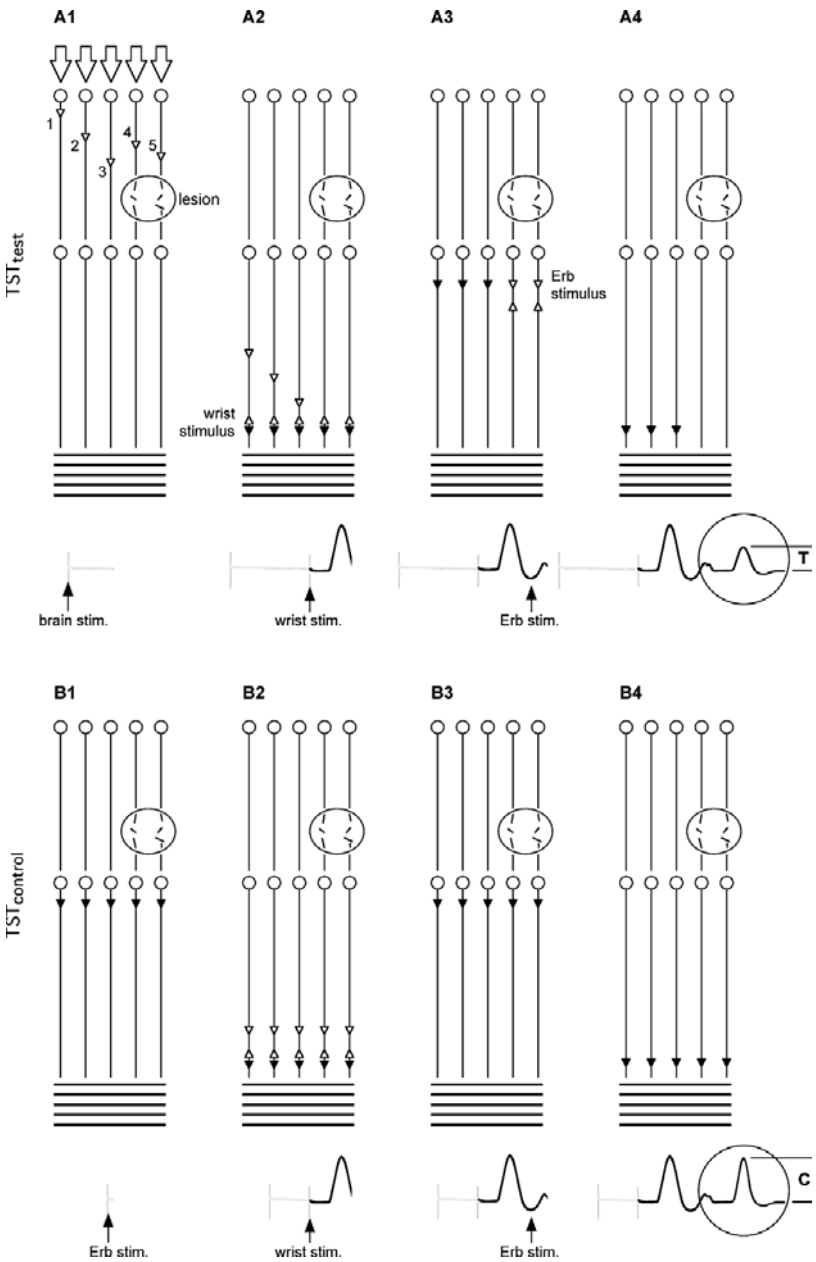

Fig. 1.2. Triple stimulation technique (TST) principle. In this scheme the motor tract is simplified to five corticospinal axons with monosynaptic connections to five peripheral axons (a simplification which does not account for complexity of corticospinal connections); horizontal lines represent the muscle fibers of the five motor units. Black arrows depict action potentials that cause a trace deflection, open arrows those that do not. Below, the trace recordings are given at each time point. **A1**: A maximal transcranial stimulation excites 100% of the axons. Action potentials (APs) are not synchronized. Conduction fails on axons 4 and 5 because of a lesion. **A2:** The APs descending on axons 1–3 excite the peripheral axons 1–3. After a delay, a maximal stimulation performed at the wrist is recorded as the first negative deflection of TST test trace. On axons 1–3, a collision occurs. On axons 4 and 5, the antidromic APs from the wrist stimulus ascend. **A3:** After a delay a maximal stimulation is performed at Erb's point. The descending APs collide on axons 4 and 5, while they continue to descend on axons 1–3. **A4:** A synchronized response from the three axons excited initially by the transcranial stimulation is recorded as the second deflection of TST test trace; T is the amplitude measured in the TST_{test} trace. **B1:** A maximal stimulation is performed at Erb's point. **B2:** After a delay a maximal stimulation performed at the wrist is recorded as the first deflection of TST control trace; antidromic APs ascend on all five axons, and collisions occur on all five axons. **B3:** After a delay a maximal stimulation is performed at Erb's point; **B4:** A synchronized response from the five axons is recorded as the second deflection of TST control trace; C is the amplitude measured in this $TST_{control}$ trace. The ratio of T : C is the TST amplitude ratio; here it is 3 : 5 = 60%, indicating intact central conduction on 60% of the axons, and central conduction failure on 40% of the axons.

(measured clinically using a four-step scale), and a reduction of the TST amplitude ratio was always associated with a reduction of muscle force. This suggests that muscle weakness was related to the proportion of central motor neurons that could not be activated by the transcranial stimulus as assessed by the TST [30]. Magistris and co-workers concluded that the TST was a highly sensitive method measuring a clinically relevant conduction parameter, linked to the clinical deficit. A relation between force, signs of pyramidal dysfunction, and TST amplitude ratio was also found in a study recording from a leg muscle (Fig. 1.3) [31], confirming that the TST measures a clinically relevant parameter. Subsequently, a prospective study was conducted to monitor treatment with methylprednisolone during acute exacerbations

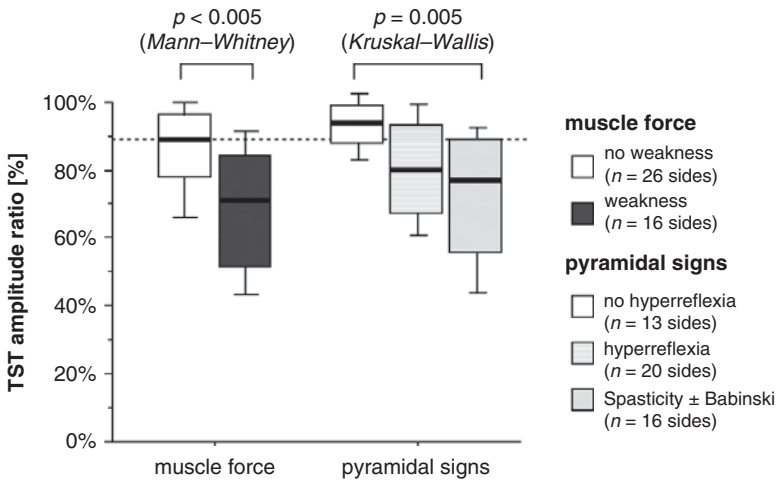

Fig. 1.3. Relation between muscle force and pyramidal signs and the TST results in 49 legs of 43 patients with MS, cervical myelopathy, or amyotropic lateral sclerosis (ALS). Muscle weakness is related to decreased TST amplitude ratio (left; ALS patients excluded because of the possibility of weakness due to lower motor neuron lesion). Presence of hyperreflexia and spasticity is associated with decreased TST amplitude ratio (right). Data extracted from Bühler *et al.* [31].

in MS [17]. The study demonstrated marked reductions of the TST amplitude ratio in MS at baseline. After 5 days of treatment with methylprednisolone, the TST amplitude increased significantly in patients with relapsing–remitting MS and secondary chronic MS, paralleled by an increase of muscle force. Methylprednisolone treatment did not improve muscle force and TST amplitude ratio in patients with primary chronic forms of MS. There was no change in CMCT with treatment in any of the three MS patient groups [17]. The increase of TST amplitude ratio during methylprednisolone treatment is most likely explained by the reduction of a central motor conduction block. As mentioned above, conduction block is an important cause of conduction failure and clinical deficit in acute demyelination [15, 32]. It can result from segmental demyelination (which would not immediately respond to steroid treatment), but may also be the consequence of edema and of inflammatory cytokines [15, 33]. Methylprednisolone has marked anti-edematous and anti-inflammatory as well as membrane stabilizing properties [34]. The lack of electroclinical improvement in patients with primary progressive MS can be attributed to the more substantial axonal loss in this patient group. Summarized, the TST allowed quantifying the functional improvement induced by treatment in this group of MS patients. It is noteworthy that a number of earlier studies concentrated mainly on measuring the CMCT, given the lack of reliable MEP amplitude measurements. Several authors have reported CMCT reductions after intravenous methylprednisolone treatment [35–37]. While these studies generally found an association between overall disease severity and CMCT, a relationship between the improvement of the clinical motor deficit of the studied limb and of the corresponding CMCT could not be demonstrated in any of these studies.

Uhthoff phenomenon is a characteristic symptom of MS patients. It describes a worsening of deficits (or development of new deficits) after increasing the body temperature, or an amelioration of deficits by cooling. Computer model calculations [38] and animal preparations [39] suggest that the main neurophysiological mechanism underlying Uhthoff's phenomenon is a temperature-dependent central conduction block of partially demyelinated axons. Humm and co-workers immersed 20 MS patient in cold or warm water and assessed the clinical and electrophysiological consequences of this temperature manipulation [18]. They observed significant changes in TST amplitude ratio in some (but not all) patients. These changes significantly correlated with the change in walking velocity. Hence, the TST measured the conduction failure (and changes of the conduction failure) responsible for the clinical deficit of the patient. The rapid amelioration after cooling (and the rapid worsening after warming) are well compatible with transient changes of central conduction blocks, which could be quantified by using the TST. Interestingly, temperature vulnerability (as seen clinically, electrophysiologically, and in a self-assessment of the patients) was significantly more marked in patients with a prolonged CMCT [18]. These observations may suggest that prolongations of CMCT are indicative for the type of myelin disturbance that makes conduction vulnerable to temperature changes. It could be

speculated that these prolongations often relate to incomplete remyelination rather than to acute demyelination. While acute demyelinization leads to conduction block, incomplete remyelination is characterized by slow and unsafe conduction, which may be more vulnerable to pertubations [15, 39].

Conclusions

Today, EP studies are largely replaced by MR imaging for the diagnostic work-up of patients with suspected MS. Magnetic resonance imaging provides an easier and more comprehensive way of assessing dissemination of lesions in space and time. EP studies may, however, be of value to follow the development of disease, since EP measurements relate better to the clinical status of the patient than imaging studies. It is of interest to analyze the pathophysiological basis of abnormal EP results. In MS, prolonged conduction times are particularly characteristic of chronic progressive forms, and prolonged conduction times are associated with increased temperature vulnerability of a patient. Both observations point to a specific type of myelin damage, possibly related to remyelination with instable and unsafe conduction. Improving the method of transcranial magnetic stimulation by the triple stimulation technique improves the detection and quantification of central conduction failures, pointing to central conduction block or loss of central neurons. The time course of conduction failure in MS patients, e.g., during methylprednisolone treatment or temperature exposure, may hint at transient central conduction block, while stable deficits may relate more to central axonal death. A refined analysis of EP results may thus allow pinpointing the abnormality of a given MS patient, and thereby provide important prognostic clues.

References

1. Chiappa K H, Ropper A H. Evoked potentials in clinical medicine (first of two parts). *N Engl J Med* 1982;**306**:1140–50
2. Mayr N, Baumgartner C, Zeitlhofer J, Deecke L. The sensitivity of transcranial cortical magnetic stimulation in detecting pyramidal tract lesions in clinically definite multiple sclerosis. *Neurology* 1991;**41**:566–9
3. Ravnborg M, Liguori R, Christiansen P, Larsson H, Sorensen P S. The diagnostic reliability of magnetically evoked motor potentials in multiple sclerosis. *Neurology* 1992;**42**:1296–301
4. Beer S, Rösler K M, Hess C W. Diagnostic value of paraclinical tests in multiple sclerosis: relative sensitivities and specificities for reclassification according to the Poser Committee criteria. *J Neurol Neurosurg Psychiatry* 1995;**59**:152–9
5. Poser C M, Paty D W, Scheinberg L, *et al.* New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983;**13**:227–31
6. McDonald W I, Compston A, Edan G, *et al.* Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol* 2001;**50**:121–7
7. Simon J H, Jacobs L D, Campion M, *et al.* Magnetic resonance studies of intramuscular interferon beta-1a for relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group. *Ann Neurol* 1998;**43**:79–87
8. Kappos L, Moeri D, Radue E W, *et al.* Predictive value of gadolinium-enhanced magnetic resonance imaging for relapse rate and changes in disability or impairment in multiple sclerosis: a meta-analysis. Gadolinium MRI Meta-analysis Group. *Lancet* 1999;**353**:964–9
9. Facchetti D, Mai R, Micheli A, *et al.* Motor evoked potentials and disability in secondary progressive multiple sclerosis. *Can J Neurol Sci* 1997;**24**:332–7
10. O'Connor P, Marchetti P, Lee L, Perera M. Evoked potential abnormality scores are a useful measure of disease burden in relapsing–remitting multiple sclerosis. *Ann Neurol* 1998;**44**:404–7
11. Fuhr P, Borggrefe-Chappuis A, Schindler C, Kappos L. Visual and motor evoked potentials in the course of multiple sclerosis. *Brain* 2001;**124**:2162–8
12. Brusa A, Jones S J, Plant G T. 2001; Long-term remyelination after optic neuritis: a 2-year visual evoked potential and psychophysical serial study. *Brain* 2001;**124**:468–79
13. La Mantia L, Riti F, Milanese C, *et al.* Serial evoked potentials in multiple sclerosis bouts: relation to steroid treatment. *Ital J Neurol Sci* 1994;**15**:333–40
14. Hess C W, Mills K R, Murray N M, Schriefer T N. Magnetic brain stimulation: central motor conduction studies in multiple sclerosis. *Ann Neurol* 1987;**22**:744–52
15. Smith K J, McDonald W I. The pathophysiology of multiple sclerosis: the mechanisms underlying the production of symptoms and the natural history of the disease. *Phil Trans R Soc Lond B* 1999;**354**:1649–73
16. Humm A M, Magistris M R, Truffert A, Hess C W, Rösler K M. Central motor conduction differs between acute relapsing–remitting and chronic progressive multiple sclerosis. *Clin Neurophysiol* 2003;**114**:2196–203

17. Humm A M, Z'Graggen W J, Buhler R, Magistris M R, Rösler K M. Quantification of central motor conduction deficits in multiple sclerosis patients before and after treatment of acute exacerbation by methylprednisolone. *J Neurol Neurosurg Psychiatry* 2006;**77**:345–50
18. Humm A M, Beer S, Kool J, *et al.* Quantification of Uhthoff's phenomenon in multiple sclerosis: a magnetic stimulation study. *Clin Neurophysiol* 2004;**115**:2493–501
19. Persson H E, Sachs C. Visual evoked potentials elicited by pattern reversal during provoked visual impairment in multiple sclerosis. *Brain* 1981;**104**:369–82
20. Stöhr M. Somatosensorisch evozierte Potentiale SEP. In: Maurer K, Lowitzsch K, Stöhr M, eds. *Evozierte Potentiale AEP – VEP – SEP*. Stuttgart: Ferdinand Enke Verlag, 1990;183–4
21. Magistris M R, Rösler K M, Truffert A, Myers J P. Transcranial stimulation excites virtually all motor neurons supplying the target muscle: a demonstration and a method improving the study of motor evoked potentials. *Brain* 1998;**121**(3):437–50
22. Rösler K M. Transcranial magnetic brain stimulation: a tool to investigate central motor pathways. *News Physiol Sci* 2001;**16**:297–302
23. Chen R, Cros D, Curra A, *et al.* The clinical diagnostic utility of transcranial magnetic stimulation: report of an IFCN committee. *Clin Neurophysiol* 2008;**119**:504–32
24. Amassian V E, Cracco R Q, Maccabee P J. Focal stimulation of human cerebral cortex with the magnetic coil: a comparison with electrical stimulation. *Electroencephalogr Clin Neurophysiol* 1989;**74**:401–16
25. Kiers L, Cros D, Chiappa K H, Fang J. Variability of motor potentials evoked by transcranial magnetic stimulation. *Electroencephalogr Clin Neurophysiol* 1993;**89**:415–23
26. Rösler K M, Petrow E, Mathis J, *et al.* Effect of discharge desynchronization on the size of motor evoked potentials: an analysis. *Clin Neurophysiol* 2002;**113**:1680–7
27. Rösler K M, Roth D M, Magistris M R. Trial-to-trial size variability of motor-evoked potentials: a study using the triple stimulation technique. *Exp Brain Res* 2008;**187**:51–9
28. Britton T C, Meyer B U, Benecke R. Variability of cortically evoked motor responses in multiple sclerosis. *Electroencephalogr Clin Neurophysiol* 1991;**81**:186–94
29. Zentner J, Meyer B. Diagnostic significance of MEP elicited by electrical and magnetoelectric stimulation in acute/subacute supratentorial lesions. *Electromyogr Clin Neurophysiol* 1998;**38**:33–40
30. Magistris M R, Rösler K M, Truffert A, Landis T, Hess C W. A clinical study of motor evoked potentials using a triple stimulation technique. *Brain* 1999;**122**(2):265–79
31. Bühler R, Magistris M R, Truffert A, Hess C W, Rösler K M. The triple stimulation technique to study central motor conduction to the lower limbs. *Clin Neurophysiol* 2001;**112**:938–49
32. Jones S J, Brusa A. Neurophysiological markers of relapse, remission and long-term recovery processes in MS. *Electroencephalogr Clin Neurophysiol Suppl* 1999;**50**:584–90
33. Smith K J. Conduction properties of central demyelinated and remyelinated axons, and their relation to symptom production in demyelinating disorders. *Eye* 1994;**8**(2):224–37
34. Andersson P B, Goodkin D E. Glucocorticosteroid therapy for multiple sclerosis: a critical review. *J Neurol Sci* 1998;**160**:16–25
35. Kandler R H, Jarratt J A, Davies-Jones G A, *et al.* The role of magnetic stimulation as a quantifier of motor disability in patients with multiple sclerosis. *J Neurol Sci* 1991;**106**:31–4
36. Salle J Y, Hugon J, Tabaraud F, *et al.* Improvement in motor evoked potentials and clinical course post-steroid therapy in multiple sclerosis. *J Neurol Sci* 1992;**108**:184–8
37. Fierro B, Salemi G, Brighina F, *et al.* A transcranial magnetic stimulation study evaluating methylprednisolone treatment in multiple sclerosis. *Acta Neurol Scand* 2002;**105**:152–7
38. Schauf C L, Davis F A. Impulse conduction in multiple sclerosis: a theoretical basis for modification by temperature and pharmacological agents. *J Neurol Neurosurg Psychiatry* 1974;**37**:152–61
39. Felts P A, Baker T A, Smith K J. Conduction in segmentally demyelinated mammalian central axons. *J Neurosci* 1997;**17**:7267–77

Chapter 2

The physiopathology of multiple sclerosis

Giancarlo Comi

Introduction

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system, predominantly, but not exclusively, involving the normal-appearing white matter. From an immunological point of view, chronic inflammation in MS can be thought of as an inflammatory process with a disordered resolution phase. We still do not know why inflammation in MS does not resolve, but there are several possible explanations. The persistence of inflammatory central nervous system (CNS) infiltrates could be caused by long-lasting "danger signals." Although many viruses have been implicated as possible danger signals in MS, there is no conclusive evidence that any pathogens have such a role. The most recent and perhaps attractive candidate is the Epstein–Barr virus, which has been found to be associated with MS both in children [1, 2] and in adults [3, 4]. Moreover, Aloisi and colleagues [5] found in CNS elevated numbers of B cells infected by the virus, an observation that, if confirmed, would indicate a pathogenic role of the virus.

The pathological substrates of neurological dysfunction in MS are demyelination and axonal loss [6–8]. In myelinated fibers, saltatory conduction of action potentials is determined by clustering of voltage-sensitive sodium channels within axon membranes at nodes of Ranvier and, to a much lesser extent, beneath the myelin sheaf [9]. Demyelination may produce multiple functional alterations, reported in Table 2.1. Conduction block almost invariably occurs if the length of the demyelinated area exceeds 5 mm [10]. Conduction block may also be caused by soluble mediators of inflammation, such as nitroxide, especially in demyelinated axons [11–14]. The rapid improvement of neurological deficits during an attack is in fact mostly due to the resolution of inflammation because remyelination requires some weeks to be completed and to have functional consequences. In areas with partial demyelination, slowing of conduction velocity and a prolonged refractory period may result in failure in transmitting high-frequency impulses [10]. Moreover in multi-synaptic pathways, multifocal demyelination may induce a desynchronized afferent volley that compromises the temporal and spatial summation of synaptic potentials with a failure to elicit the next response in the pathway. Neurological dysfunction resulting from conduction block is usually transitory; however, the possibility of persistent conduction block cannot be excluded. On the other hand the functional consequences due to axonal loss are irreversible if not compensated by CNS plasticity and axonal regeneration which seems to be quite modest at the best.

Dynamic of multiple sclerosis damage

In about 85% of the MS patients, defined relapsing–remitting (RR) MS, the early phase of the disease, is marked by acute attacks characterized by unifocal (two-thirds of patients) or multifocal white matter lesions [15]; gray matter lesions are not frequent in the early phase of the disease. Attacks in the early phase of the disease are usually followed by an apparent complete recovery; however, careful neurological examination reveals deterioration of neurological functions in about a quarter of patients [16]. Intervals between attacks can be as long as 20 years or as short as a few days. Magnetic resonance imaging (MRI) has revealed the frequent occurrence of new lesions or the reactivation of old lesions during the clinically stable phases of the disease. For example in the European–Canadian clinical trial testing the efficacy of glatiramer acetate in the placebo arm, during a 9-month

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Table 2.1 Functional effects of demyelination

Slowing of conduction
Temporal dispersion
Increased refractory period
Conduction block
Secondary axonal degeneration

period, there was a mean of 36.8 new lesions per patient compared to 0.75 relapses per patient [17]. About 90% of RRMS patients enter a progressive course of the disease, the so-called secondary progressive course (SPMS), characterized by a continuous neurological deterioration, sometimes with more or less prolonged phases of stability; relapses become rare in SPMS and also the MRI activity is substantially reduced [18–20]. In approximately 15% of patients, the disease has a progressive course from the onset, which is called primary progressive multiple sclerosis (PPMS) [18, 21]. Patients with PPMS typically have few MRI active lesions [22]. This finding may correspond to the lesser degree of inflammation seen by histopathology [23].

In a quite simplified manner the nervous damage in MS may be attributed to the white and gray matter lesions and to the diffuse white and grey matter involvement.

Lesion-related nervous damage

There is epidemiological evidence that attacks produce irreversible CNS damage. About 50% of attacks leave a residual irreversible disability [24]. The number of attacks in the first 2 years of the disease is predictive of future disability [25–28]; interestingly enough, relapses influence the speed of accumulation of disability only until the patient reaches a moderate disability (expanded disability status scale [EDSS] score of 4), the subsequent accumulation of disability (time from EDSS 4 to EDSS 6) being independent of what happened in the RR phase of the disease [26]. A recent study indicated that a shorter time from disease onset and onset of the SPMS course was associated with a faster accumulation of disability during the SPMS phase of the disease [21]. The MRI lesion load seen in the brain at the onset of disease predicts the evolution to clinically definite multiple sclerosis [17, 29, 30]. In a recent multinational study, in patients with an irreversible tissue injury first attacks suggestive of MS were already found; macroscopic focal lesions but not "diffuse" brain damage measured by magnetization transfer ratio (MTR) resulted in an increased risk of subsequent development of definite MS in clinically isolated syndrome (CIS) patients [31]. The degree of brain MRI abnormalities seen in the early phase of the disease predicts the disability that will accumulate many years later [29, 30, 32]. In a recent long-term study, the T2 lesions seen with brain MRI in RRMS correlate strongly with brain tissue loss and with clinical disease severity 13 years later [33]. Finally, clinical trials performed in CIS and early RRMS patients have demonstrated that with reduced numbers of inflammatory lesions there was a decrease in the progression of brain atrophy [34–36]. All these observations indicate that the amount of tissue damage produced by lesions contributes to long-term disability.

Pathological studies demonstrate an important axonal transection inside the acute lesion, already occurring in the early phases of the disease [7, 37, 38]. Acute axonal loss is predominant in lesions appearing in the early phases of the disease and decreases over time [39]. The axonal transection occurs electively in the acute lesion where it is associated with large infiltration of T lymphocytes (especially CD8+ T cells) and macrophages [39] indicating a correlation between inflammation and axonal damage, a relationship also demonstrated by MRI studies. For a very long time, little attention has been paid to the occurrence of extensive axonal damage during the early phases of the disease. More recently many studies, using various MRI techniques, have shown irreversible nervous damage in CIS and early RRMS patients (Table 2.2). Magnetization transfer ratio, a measure of tissue damage, is significantly decreased in the lesions of CIS patients [40]. The same technique has been used to evaluate the longitudinal changes taking place in the white matter when a lesion occurs [41]. The appearance of the lesion is associated with a drop of MTR, due to edema, demyelination, and axonal loss variably combined. After a few days or weeks the MTR values usually increase because of the resolution of edema and remyelination [42–46]. Changes are quite variable from patient to patient and in the same patient from lesion to lesion, meaning a large intraindividual and interindividual variability of the recovery processes. Stabilization of the lesion is usually reached after 6–12 months [41, 45]; however in some lesions demyelination and remyelination, as

Table 2.2 MRI findings in CIS and early RRMS

1997 Prince *et al.*	Early spinal cord atrophy
1999 Liu *et al.*	Brain, spinal cord atrophy in RRMS
1999 De Stefano *et al.*	NAA reduced in early RRMS
1999 Rudick *et al.*	Brain atrophy in mild RRMS
2000 Simon *et al.*	Black holes in mild RRMS
2001 Iannucci *et al.*	NAWM abnormality in CIS
2001 Brex *et al.*	Brain atrophy in CIS
2003 Filippi *et al.*	NAA reduced in CIS
2004 Dalton *et al.*	Gray but not white matter atrophy in CIS
2004 Paoillo *et al.*	Brain atrophy in those with CIS who developed CDMS
2004 Filippi *et al.*	Brain atrophy in CIS partially related to inflammation
2005 Fernando *et al.*	MTR of NAWM–NAGM is abnormal in CIS

NAA, *N*-acetylaspantic acid; NAGM, normal-appearing gray matter; NAWM, normal-appearing white matter.

Table 2.3a Relation between baseline lesion characteristics and evolution to black holes at 6 months

	Characteristics	Evolution rate
Lesion size	<6 mm	35%
	>6 mm	52%
Duration of enhancement	<1	36%
	>2	54%
Re-enhancement	yes	44%
	no	43%
Type of enhancement	nodular	41%
	ring	72%

Table 2.3b Relation between location of baseline lesion characteristics and evolution to black holes at 6 months

Deep white matter	38%
Periventricular	56%
Juxtacortical	32%
Infratentorial	29%

indicated by the MTR changes, are ongoing for months and years after lesion formation [41]. The main factors influencing the residual nervous damage inside the acute lesions are lesion size, enhancement duration, and the periventricular location [47] (Tables 2.3a and 2.3b). The preferential location of MS lesions is in the periventricular area, as it is also in mice with experimental allergic encephalomyelitis (EAE) [48] (Fig. 2.1). This location could depend on the attraction of inflammatory cells in the subventricular area by chemokines, such as CXCL10 produced by multipotent stem/precursor cells (NPCs), resident in the subventricular zone [49, 50]. From the other side the recruitment of the progenitors to contribute to the reparative mechanisms orchestrated by inflammatory cells (lymphocytes and microglia) is impaired (L. Muzio, personal comunication), giving poor reparation of the new lesions occurring in this area.

Progressive brain atrophy, mostly explained by axonal loss, is already detectable in CIS patients and is significantly correlated with the number of active lesions accumulated in the same period [34, 51]. Interestingly enough, the progression of brain atrophy is only observed in patients with evolution to clinically definite MS [52]. Corpus callosum atrophy appears over a period of 1 year after a diagnosis of CIS [53]. The acute axonal damage also occurs because of the products of inflammation, such as nitric oxide and tumor necrosis factor [54]. A high electrical activity