**Transcranial magnetic stimulation enhances the specificity of multiple sclerosis diagnostic criteria: A critical narrative review.**

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# **Supplementary Materials**

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**Review Protocol**

**Eligibility Criteria**

* Journal articles,
* English language,
* Original research,
* Not pediatric sample,
* Humans,
* CIS → MS, HC vs. MS,
* MS patient sample size, *n* ≥ 40,
* Validated diagnostic criteria,
* Diagnostic classification data (sensitivity and/or specificity),
* No case reports,
* TMS-EMG of upper or lower extremities,
* No combined evoked potentials scores.

**Search Date**

February 28, 2022

**PubMED**

Terms

("multiple sclerosis"[all fields] OR "clinically isolated syndrome"[all fields]) AND ("transcranial magnetic stimulation"[all fields]) AND (sensitiv\*[all fields] OR specific\*[all fields] OR "predictive value"[all fields] OR "likelihood ratio"[all fields] OR "odds ratio"[all fields] OR "risk ratio"[all fields] OR "hazard ratio"[all fields])

Results

50

**Embase**

Terms

('multiple sclerosis'/exp OR 'multiple sclerosis' OR 'clinically isolated syndrome'/exp OR 'clinically isolated syndrome') AND ('transcranial magnetic stimulation'/exp OR 'transcranial magnetic stimulation') AND (sensitiv\* OR specific\* OR 'predictive value'/exp OR 'predictive value' OR 'likelihood ratio'/exp OR 'likelihood ratio' OR 'odds ratio'/exp OR 'odds ratio' OR 'risk ratio'/exp OR 'risk ratio' OR 'hazard ratio'/exp OR 'hazard ratio')

Results

121

**Web of Science**

Terms

(ALL=("multiple sclerosis") OR ALL=("clinically isolated syndrome")) AND (ALL=("transcranial magnetic stimulation") AND (ALL=(sensitiv\*) OR ALL=(specific\*) OR ALL=("predictive value") OR ALL=("likelihood ratio") OR ALL=("odds ratio") OR ALL=("risk ratio") OR ALL=("hazard ratio"))

Results

90

**Scopus**

Terms

ALL ( ( "multiple sclerosis" [all AND fields] OR "clinically isolated syndrome" [all AND fields] ) AND ( "transcranial magnetic stimulation" [all AND fields] ) AND ( sensitiv\*[all AND fields] OR specific\*[all AND fields] OR "predictive value" [all AND fields] OR "likelihood ratio" [all AND fields] OR "odds ratio" [all AND fields] OR "risk ratio" [all AND fields] OR "hazard ratio" [all AND fields] ) )

Results

676

**Article Inclusion**

Total from Searches

937

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12

Total from Reviews

85

Total from Included Items

51

**Total from All Sources**

1073

Duplicates

109

**For Title Review**

964

For Abstract Review

268

For Full Text Review

201

**Final**

17

**Table S1.** Study characteristics.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Funding source** | **Prospective study** | **Consecutive patients** | **Longitudinal observation** | **Examines subclinical lesions** | **RMS vs. PrMS** | **Low vs. high disability** | **Active vs. inactive MS** |
| (Beer et al. 1995) | Swiss National Science Foundation [Grant No 3.852-1.86] | Y | Y | N | Y | N | N | N |
| (Caramia et al. 2004) | NR | Y | N | Y | N | N | N | Y |
| (Cruz-Martínez et al. 2000) | NR | Y | Y | Y | Y | N | N | N |
| (Facchetti et al. 1997) | NR | N | Y | N | N | Y | N | N |
| (Hess et al. 1987) | UK Multiple Sclerosis Society,  Roche Research Foundation,  Rotary Foundation | N | Y | N | Y | N | N | N |
| (Jung et al. 2006) | Biogen Idec. | N | N | N | Y | N | N | N |
| (Kale et al. 2009) | NR | N | Y | N | Y | N | Y | N |
| (Kale et al. 2010) | NR | N | N | N | N | N | Y | N |
| (Kandler et al. 1991) | NR | N | Y | N | Y | N | N | N |
| (Leocani et al. 2006) | Italian National Ministry of Health [Grant No 96/J/T44] | Y | Y | Y | N | Y | N | N |
| (Magistris et al. 1999) | Swiss National Science Foundation [Grant No 31–43454.95] | Y | Y | N | Y | N | N | N |
| (Mayr et al. 1991) | NR | N | N | N | Y | N | N | N |
| (Pisa et al. 2020) | Fondazione Italiana Sclerosi Multipla [Grant No FISM2012/R/9] | N | Y | N | N | N | N | N |
| (Ravnborg et al. 1992) | Danish Multiple Sclerosis Society, Fondsborsvekselerer Henry Hansen Og Hustru,  Carla Hansen,  Fodt Westergaards Legat, Lykfeldts Legat, Foundation for Experimental Research in Neurology | Y | Y | N | Y | N | N | N |
| (Schmierer et al. 2000) | Charité Forschungsförderung [Grant No 97–209] | N | N | N | N | N | N | N |
| (Schmierer et al. 2002) | NR | Y | N | Y | N | Y | Y | N |
| (Tataroglu et al. 2003) | NR | N | Y | N | Y | Y | N | N |

MS, multiple sclerosis; N, no; NR, not reported; PrMS, progressive multiple sclerosis; RMS, relapsing multiple sclerosis; Y, yes.

**Table S2.** Control participant characteristics.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Control group** | **Other neurologic disorders** | **Sample size** | **# Females** | **Age** | **Age-matched to MS** | **Sex-matched to MS** |
| (Beer et al. 1995) | Other neurologic disorders | Functional neurologic symptoms, Stroke, Non inflammatory myelopathy, Other neurologic disorders | 47 | 27 | 41 (19-67) | NR | NR |
| (Caramia et al. 2004) | Healthy controls | NA | 20 | 12 | 36.2 (18-52) | Y | NR |
| (Cruz-Martínez et al. 2000) | Healthy controls | NA | 38 | 23 | 32.7 (14-56) | Y | NR |
| (Facchetti et al. 1997) | Healthy controls | NA | 20 | 10 | 30.1 ± 5.5 | NR | NR |
| (Hess et al. 1987) | Healthy controls | NA | 32 | 5 | 36.8 (21-78) | NR | NR |
| (Jung et al. 2006) | Healthy controls | NA | 20 | 7 | 29 (18-44) | NR | NR |
| (Kale et al. 2009) | Healthy controls | NA | 53 | 35 | 39 ± 9.5 | NR | NR |
| (Kale et al. 2010) | Healthy controls | NA | 50 | 31 | 35.4 ± 10.4 | Y | Y |
| (Kandler et al. 1991) | Healthy controls | NA | 30 | 12 | 38 (22-74) | NR | NR |
| (Leocani et al. 2006) | Healthy controls | NA | NR | NR | NR | NR | NR |
| (Magistris et al. 1999) | Other neurologic disorders | Stroke, Neurodegenerative disorders, ALS, Myelopathy, Peripheral nerve disorders, Functional neurologic symptoms, Other neurologic disorders,  Non neurologic disorders | 155 | NR | 51 (17-90) | NR | NR |
| (Mayr et al. 1991) | Healthy controls | NA | 86 | 49 | 38.2 (17-72) | NR | NR |
| (Pisa et al. 2020) | Healthy controls | NA | 10 | NR | NR | Y | Y |
| (Ravnborg et al. 1992) | Healthy controls | NA | 50 | 25 | 18-60 | NR | NR |
| (Schmierer et al. 2000) | Healthy controls | NA | 25 | 14 | 31.8 (23-46) | NR | NR |
| (Schmierer et al. 2002) | Healthy controls | NA | 35 | 18 | 36 (20-62) | Y | Y |
| (Tataroglu et al. 2003) | Healthy controls | NA | 31 | 18 | 33.4 (22-49) | NR | NR |

Note: age and disease duration are reported in years. Continuous data are expressed as median (range) or mean ± standard deviation. ALS, amyotrophic lateral sclerosis; MS, multiple sclerosis; N, no; NA, not applicable; NR, not reported; Y, yes.

**Table S3.** Transcranial magnetic stimulation characteristics.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Handedness** | **CNS drugs** | **TMS measure** | **MT** | **Target** | **Side** | **Electrodes** | **Contraction of target muscle** | **Muscle activity monitoring** | **Type of stimulator** | **Pulse shape** | **Coil type** | **Coil orientation** | **Current direction** | **Coil location** | **Hotspot** | **Intensity** | **Attention** | **# Trials** | **Inter-trial interval** | **MEP size** | **Room temperature** |
| (Beer et al. 1995) | NR | NR | CMCT (NR) | RMT | ADM, BB, TA | Both | Bipolar | Relaxed | EMG monitored | Custom | Monophasic | 9 cm C | Tangential to scalp | Clockwise, Anticlockwise | Marked using pen | Motor mapping (2 cm steps) | > RMT | NR | NR | NR | NR | NR |
| (Caramia et al. 2004) | MS: 7 Lt weak, 16 Rt weak, 2 both weak, 54 not weak Control: NR | No | CMCT (F-wave) | RMT | OPB | More clinically affected | Bipolar | 40% of maximum | Auditory EMG feedback | Magstim 200 | Monophasic | 9.5 cm F8 | Tangential to scalp, handle 45o to sagittal plane | Posterior-anterior | Over hotspot | NR | 105% RMT | EMG feedback | 3 | 7 s | NR | NR |
| (Cruz-Martínez et al. 2000) | NR | NR | RMT, MEP (Amplitude), CMCT (F-wave) | RMT | OPB, TA | Both | Bipolar | Slight | NR | Magstim 200 | Monophasic | C | Tangential to scalp | Clockwise, Anticlockwise | Over vertex or just anterior | NR | 130% RMT | NR | 6-10 | NR | Normalized to CMAP | NR |
| (Facchetti et al. 1997) | NR | NR | CMCT (Nerve root) | RMT | ADM, TA | Both | Bipolar | Slight | NR | Cadwell MS10 | Monophasic | NR | NR | NR | NR | NR | 130% RMT | NR | 4 | NR | NA | NR |
| (Hess et al. 1987) | NR | NR | MEP (Amplitude), CMCT (Nerve root) | AMT | ADM | Both | Bipolar | 5-10% of maximum | EMG monitored | Custom | Monophasic | 9 cm C | Tangential to scalp | Clockwise, Anticlockwise | Over vertex | NR | > AMT | NR | 4 | NR | Normalized to CMAP | NR |
| (Jung et al. 2006) | NR | NR | CMCT (Nerve root), iSP ([automated] Latency, duration, depth, TCT [iSP-MEP]) | RMT | APB, TA | Both | Bipolar | Maximal | Auditory EMG feedback | Magstim 200 | Monophasic | 9 cm F8 | Tangential to scalp, handle 0-45° from sagittal plane | Posterior-anterior | Over hotspot | Location of reproducible MEPs | 80% MSO | EMG feedback | 15 | 5-7 s | iSP normalized to pre-stimulus EMG | NR |
| (Kale et al. 2009) | NR | NR | MEP (Amplitude, latency), CMCT (Nerve root) | RMT | APB | Both | Bipolar | Relaxed | EMG monitored | Magstim 200 | Monophasic | C | Tangential to scalp | Clockwise, Anticlockwise | Over hotspot | Location of reproducible MEPs | NR | NR | 5 | NR | Amplitude of raw MEP | Air-conditioned |
| (Kale et al. 2010) | NR | NR | MEP (Area, latency), CMCT (Nerve root) | RMT | APB | Both | Bipolar | Relaxed | EMG monitored | Magstim 200 | Monophasic | C | Tangential to scalp | Clockwise, Anticlockwise | Over hotspot | Location of reproducible MEPs | NR | NR | 5 | NR | Raw MEP | Air-conditioned |
| (Kandler et al. 1991) | NR | NR | MEP (Amplitude), CMCT (Nerve root) | NR | ADM, AH | Both | Bipolar | Relaxed | Auditory EMG feedback | Magstim 200 | Monophasic | C | Tangential to scalp | Clockwise, Anticlockwise | Over vertex or just anterior | NR | 90-100% MSO | EMG feedback | 6 | NR | Raw MEP | NR |
| (Leocani et al. 2006) | NR | NR | CMCT (Nerve root) | NR | APB, AH | Both | NR | 20% of maximum | NR | Cadwell MS10 | Monophasic | 12 cm C | Tangential to scalp | Clockwise, Anticlockwise | Over vertex | NR | NR | NR | NR | NR | NR | NR |
| (Magistris et al. 1999) | NR | NR | CMCT (F-wave), TST (Amplitude, area) | AMT | ADM | Both | Bipolar | Slight | Auditory EMG feedback | Magstim 200 | Monophasic | 9 cm C | Tangential to scalp | Clockwise, Anticlockwise | Over vertex or just lateral | Location of lowest AMT | NR | EMG feedback | 8 | NR | TST normalized to control curve | NR |
| (Mayr et al. 1991) | NR | NR | MEP (Amplitude), CMCT (F-wave) | RMT | OPB, AH | Both | Bipolar | Slight | Auditory EMG feedback | Magstim 200 | Monophasic | 8.5 cm C | Tangential to scalp | Clockwise, Anticlockwise | Over vertex or 1-2 cm anterior | NR | 120% RMT | EMG feedback | 4 | NR | Raw MEP | NR |
| (Pisa et al. 2020) | MS: 9 unilaterally weak, 11 both weak, 17 not weak, 13 NR, Control: NR | NR | MEP (Latency) | RMT | FDI, TA | Dominant | Bipolar | Relaxed | NR | Magstim 200 | Monophasic | 7 cm F8 | Tangential to scalp | NR | Marked with pen | NR | 120% RMT | NR | 10 | NR | NR | NR |
| (Ravnborg et al. 1992) | NR | NR | MEP (Amplitude), CMCT (Nerve root) | AMT | BB, FCR, FDI, TA, AH | Both | Bipolar | 10-15% of maximum | Visual EMG feedback | Dantec | Monophasic | 14 cm C | Tangential to scalp, handle in sagittal plane | Clockwise, Anticlockwise | 1 cm anterior to vertex | NR | 120% AMT | EMG feedback | 3 | NR | Normalized to spine root MEP | 22oC |
| (Schmierer et al. 2000) | NR | NR | MEP (Amplitude), CMCT (Nerve root), iSP ([visual] latency, duration, TCT [iSP-MEP]) | AMT | FDI, TA | Both | Bipolar | Maximal | EMG monitored | Magstim 200 | Monophasic | 8.5 cm F8 | Tangential to scalp, handle anterior-posterior | Posterior-anterior | Over hotspot | Location of maximal MEP | 80% MSO | NR | 20 | 2-3 s | Raw MEP | NR |
| (Schmierer et al. 2002) | NR | NR | RMT (Relative frequency), CMCT (Nerve root), iSP ([visual] latency, duration, TCT [iSP-MEP]) | RMT | FDI, TA | Both | Bipolar | Maximal | EMG monitored | Magstim 200 | Monophasic | 8.5 cm F8 | Tangential to scalp, with handle anterior-posterior | Posterior-anterior | Over hotspot | Location of maximal MEP | 80% MSO | NR | 20 | 3 s | NA | NR |
| (Tataroglu et al. 2003) | NR | NR | MEP (Amplitude, latency) CMCT (Nerve root), CSP (Duration, latency; method)\* | RMT | FDI, TA | Both | NR | 50% of maximum | Visual EMG feedback | Magstim 200 | Monophasic | 9 cm C | Tangential to scalp | Clockwise, Anticlockwise | Over vertex or 2-3 cm anterior | NR | 150% RMT | EMG feedback | 5 | NR | Normalized to CMAP | NR |

Note: no study reported history of repetitive motor activity or level of relaxation of non-target muscles; thus, these criteria are omitted from the table. ADM, abductor digiti minimi; AH, abductor hallucis; AMT, active motor threshold; APB, abductor pollicis brevis; BB, biceps brachii; C, circular; CMAP, compound muscle action potential; CMCT, central motor conduction time; CNS, central nervous system; CSP, corticospinal silent period; Delt, deltoid; EMG, electromyography; F8, figure-of-eight; FCR, flexor carpi radialis; FDI, first dorsal interosseus; iSP, ipsilateral silent period; Lt, left; MEP, motor evoked potential; MSO, maximum stimulator output; NR, not reported; OPB, opponens pollicis brevis; RMT, resting motor threshold; Rt, right; TA, tibialis anterior; TCT, transcallosal conduction time; TST, triple stimulation technique. \*, method for CSP determination not reported. See ref: (Chipchase et al. 2012).

**Table S4.** Detailed transcranial magnetic stimulation results.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Abnormal result criterion** | **2 × 2 contingency result** | **Sensitivity (95% CI)** | **Specificity (95% CI)** | **Diagnostic odds ratio (95% CI)** | **Associations with disease-related outcomes** |
| ***Resting motor threshold (RMT), one study (6%)*** | | | | | | |
| (Cruz-Martínez et al. 2000) | > 2 SD above mean of controls | **Upper extremity:** TP = 34/88 limbs, FP = 0/38 participants, TN = 38/38 participants, FN = 54/88 limbs  **Lower extremity:** TP = 15/35 limbs, FP = 0/38 participants, TN = 38/38 participants, FN = 20/35 limbs | **Upper extremity:** 39%  **Lower extremity:**  43% | **Upper extremity:** 100% (98-100%)  **Lower extremity:** 100% (98-100%) | **Upper extremity:** 23.30 (13.66-39.75)  **Lower extremity:** 27.75 (13.22-58.23) | RMT was correlated with EDSS (*p* < .02), ataxia (*p* < .04), and central motor pathway MRI lesions (*p* < .05).  Magnitude not reported. |
| (Schmierer et al. 2002) | > 2.5 SD above mean of controls | **RMS (upper + lower extremity):** TP = 7/38 limbs, FP = NR, TN = NR, FN = 31/38 limbs  **PPMS (upper + lower extremity):** TP = 4/38 limbs, FP = NR, TN = NR, FN = 34/38 limbs | **RMS (upper + lower extremity):** 18%  **PPMS (upper + lower extremity):** 10% | NR | NR | RMT was not significantly correlated with EDSS. |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| ***Motor evoked potential (MEP), 10 studies (59%)*** | | | | | | |
| *MEP size (amplitude, area), nine studies (53%)* | | | | | | |
| (Cruz-Martínez et al. 2000) | > 2 SD below mean of controls | **Upper extremity:** TP = 21/88 limbs, FP = 0/38 participants, TN = 38/38 participants, FN = 67/88 limbs  **Lower extremity:** TP = 10/35 limbs, FP = 0/38 participants, TN = 38/38 participants, FN = 25/35 limbs | **Upper extremity:** 24%  **Lower extremity:** 29% | **Upper extremity:** 100% (98-100%)  **Lower extremity:** 100% (98-100%) | **Upper extremity:** 11.60 (6.47-20.81)  **Lower extremity:** 14.80 (6.65-32.92) | MEP amplitude was correlated with EDSS (*p* < .03), ataxia (*p* < .007), and MRI lesions in the pons (*p* < .009) and cervical cord (*p* < .03).  Magnitude not reported. |
| (Hess et al. 1987) | < 15% of CMAP amplitude | **Upper extremity:** TP = 39/83 participants, FP = 0/32 participants, TN = 32/32 participants, FN = 44/83 participants | **Upper extremity:** 47% | **Upper extremity:** 100% (94-100%) | **Upper extremity:** 27.48 (15.81-47.78) | NR |
| (Kale et al. 2009) | > 2.5 SD below mean of controls | **Upper extremity:** TP = 109/131 participants, FP = NR, TN = NR, FN = 22/131 participants | **Upper extremity:** 83% (82-84%) | NR | NR | MEP amplitude was correlated with EDSS (*p* < .001).  Magnitude not reported. |
| (Kale et al. 2010) | > 2.5 SD below mean of controls | **Upper extremity:** TP = 67/79 participants, FP = NR, TN = NR, FN = 12/79 participants | **Upper extremity:** 85% (83-87%) | NR | NR | MEP amplitude was correlated with EDSS (*p* < .05) and corpus callosum atrophy (*p* not reported).  Magnitude not reported. |
| (Kandler et al. 1991) | Below mean of controls | **Upper extremity:** TP = 14/162 limbs, FP = NR, TN = NR, FN = 148/162 limbs  **Lower extremity:** TP = 16/63 limbs, FP = NR, TN = NR, FN = 47/63 limbs | **Upper extremity:** 9%  **Lower extremity:** 25% | NR | NR | MEP amplitude was correlated with pyramidal dysfunction (hyperreflexia, weakness, spasticity, plantar reflex) (*p* not reported).  Magnitude not reported. |
| (Mayr et al. 1991) | < 1 %ile of controls | **Upper extremity:** TP = 5/44 participants, FP = 4/86 participants, TN = 82/86 participants, FN = 39/44 participants  **Lower extremity:** TP = 12/44 participants, FP = 4/86 participants, TN = 82/86 participants, FN = 32/44 participants | **Upper extremity:** 11%  **Lower extremity:** 28% | **Upper extremity:** 99% (97-100%)  **Lower extremity:** 100% (98-100%) | **Upper extremity:** 2.63 (0.67-10.34)\*  **Lower extremity:** 7.69 (2.31-25.61) | MEP amplitude was not significantly correlated with pyramidal dysfunction (hyperreflexia, weakness, spasticity, plantar reflex). |
| (Ravnborg et al. 1992) | < lower 99% confidence limit of controls | **Upper + lower extremity:** TP = 20/40 participants, FP = 4/28 participants, TN = 24/28 participants, FN = 20/40 participants | **Upper + lower extremity:** 50% (38-63%) | **Upper + lower extremity:** 86% (81-100%) | **Upper + lower extremity:** 6.00 (1.76-20.46) | MEP amplitude was correlated with MRI lesion number (McNemar’s = 0.85, *p* not reported) but not pyramidal dysfunction (hyperreflexia, weakness, spasticity, plantar reflex). |
| (Schmierer et al. 2000) | Below lowest value of controls | **Upper extremity:** TP = 17/50 participants, FP = 0/25 participants, TN = 25/25 participants, FN = 33/50 participants  **Lower extremity:** TP = 3/50 participants, FP = 0/25 participants, TN = 25/25 participants, FN = 47/50 participants | **Upper extremity:** 34%  **Lower extremity:** 6% | **Upper extremity:** 100% (92-100%)  **Lower extremity:** 100% (92-100%) | **Upper extremity:** 12.36 (6.11-25.00)  **Lower extremity:** 1.53 (0.45-5.24)\* | MEP amplitude was not significantly correlated with MRI lesion location or burden. |
| (Tataroglu et al. 2003) | > 2.5 SD below mean of controls,  Asymmetry > 2.5 SD above mean of controls | **Upper + lower extremity:** TP = 38/58 participants, FP = 2/31 participants, TN = 29/31 participants, FN = 20/58 participants | **Upper + lower extremity:** 66% (64-68%) | **Upper + lower extremity:** 94% (88-100%) | **Upper + lower extremity:** 27.55 (5.95-127.46) | MEP amplitude was not significantly correlated with EDSS. |
| *MEP latency, four studies (24%)* | | | | | | |
| (Kale et al. 2009) | > 2.5 SD above mean of controls | **Upper extremity:** TP = 68/131 participants, FP = NR, TN = NR, FN = 63/131 participants | **Upper extremity:** 52% (52-52%) | NR | NR | MEP latency was correlated with EDSS (*p* < .001).  Magnitude not reported. |
| (Kale et al. 2010) | > 2.5 SD above mean of controls | **Upper extremity:** TP = 34/79 participants, FP = NR, TN = NR, FN = 45/79 participants | **Upper extremity:** 43% | NR | NR | MEP latency was correlated with corpus callosum atrophy (*p* not reported) but not EDSS.  Magnitude not reported. |
| (Pisa et al. 2020) | Upper extremity > 24.3 ms,  Lower extremity > 36.5 ms | **Upper extremity:** TP = 41/50 participants, FP = NR, TN = NR, FN = 9/50 participants  **Lower extremity:** TP = 49/50 participants, FP = NR, TN = NR, FN = 1/50 participants | **Upper extremity:** 82% (79-85%)  **Lower extremity:** 98% (94-100%) | NR | NR | Upper extremity MEP latency was correlated with EDSS (Rho = 0.296, *p* < .05) and walking performance (Rho = 0.6, *p* < .0001).  Lower extremity MEP latency not reported. |
| (Tataroglu et al. 2003) | > 2.5 SD above mean of controls,  Asymmetry > 2.5 SD above mean of controls | **Upper + lower extremity:** TP = 40/58 participants, FP = 6/31 participants, TN = 25/31 participants, FN = 18/58 participants | **Upper + lower extremity:** 69% (67-71%) | **Upper + lower extremity:** 80% (75-85%) | **Upper + lower extremity:** 9.26 (3.24-26.47) | MEP latency was not significantly correlated with EDSS. |
| ***Central motor conduction time (CMCT), 16 studies (94%)*** | | | | | | |
| (Beer et al. 1995) | > 2.5 SD above mean of entire sample,  Asymmetry > 2.5 SD above mean of entire sample | **Upper + lower extremity:** TP = 96/142 participants, FP = 11/47 participants, TN = 36/47 participants, FN = 46/142 participants | **Upper + lower extremity:** 68% (67-69%) | **Upper + lower extremity:** 77% (74-80%) | **Upper + lower extremity:** 6.83 (3.19-14.62) | NR |
| (Caramia et al. 2004) | > 2 SD above mean of controls | **Upper extremity:** TP = 13/79 participants, FP = NR, TN = NR, FN = 66 participants | **Upper extremity:** 16% | NR | NR | NR |
| (Cruz-Martínez et al. 2000) | > 2 SD above mean of controls | **Upper extremity:** TP = 54/88 limbs, FP = 0/38 participants, TN = 38/38 participants, FN = 34/88 limbs  **Lower extremity:** TP = 18/35 limbs, FP = 0/38 participants, TN = 38/38 participants, FN = 17/35 limbs | **Upper extremity:** 61% (60-62%)  **Lower extremity:** 51% (50-52%) | **Upper extremity:** 100% (98-100%)  **Lower extremity:** 100% (98-100%) | **Upper extremity:** 58.76 (34.45-100.24)  **Lower extremity:** 39.17 (18.78-81.70) | CMCT was correlated with EDSS (*p* < .01), pyramidal dysfunction (hyperreflexia, weakness, spasticity, plantar reflex) (*p* < .02), ataxia (*p* < .02), and MRI lesions in the pons (*p* < .03) and central motor pathway (*p* < .04).  Magnitude not reported. |
| (Facchetti et al. 1997) | > 2.5 SD above mean of controls | **RMS (upper extremity):** TP = 12/40 participants, TN = NR, FP = NR, FN = 28/40 participants  **SPMS (upper extremity):**  TP = 13/13 participants, FP = NR, TN = NR, FN = 0/13 participants  **RMS (lower extremity):** TP = 17/40 participants, FP = NR, TN = NR, FN = 23/40 participants  **SPMS (lower extremity):** TP SPMS = 13/13 participants, FP = NR, TN = NR, FN SPMS = 0/13 participants | **RMS (upper extremity):** 30%  **SPMS (upper extremity):**  100% (85-100%)  **RMS (lower extremity):** 43%  **SPMS (lower extremity):** 100% (85-100%) | NR | NR | CMCT was not significantly correlated with EDSS or number or area of MRI lesions. |
| (Hess et al. 1987) | > 2.5 SD above mean of controls  Asymmetry > 2.5 SD above mean of controls | **Upper extremity:** TP = 60/83 participants, FP = 0/32 participants, TN = 32/32 participants, FN = 23/83 participants | **Upper extremity:** 72% (70-74%) | **Upper extremity:** 100% (94-100%) | **Upper extremity:** 80.87 (44.71-146.26) | CMCT was correlated with hyperreflexia (*p* < .001), weakness (*p* < .05), and ataxia (*p* < .05), but not impaired fine movements or sensory deficits.  Magnitude not reported. |
| (Jung et al. 2006) | > 2.5 SD above mean of controls | **Upper extremity:** TP = 24/98 limbs, FP = NR, TN = NR, FN = 74/98 limbs  **Lower extremity:** TP = 68/98 limbs, FP = NR, TN = NR, FN = /98 limbs | **Upper extremity:** 25%  **Lower extremity:** 69% (68-70%) | NR | NR | Upper extremity, but not lower extremity, CMCT was correlated with pyramidal dysfunction (hyperreflexia, weakness, spasticity, plantar reflex) (*p* < .005), but not corpus callosum atrophy or MRI lesion volume or number.  Magnitude not reported. |
| (Kale et al. 2009) | > 2.5 SD above mean of controls | **Upper extremity:** TP = 64/131 participants, FP = NR, TN = NR, FN = 67/131 participants | **Upper extremity:** 49% | NR | NR | CMCT was correlated with EDSS (*p* < .001).  Magnitude not reported. |
| (Kale et al. 2010) | > 2.5 SD above mean of controls | **Upper extremity:** TP = 32/79 participants, FP = NR, TN = NR, FN = 47/79 participants | **Upper extremity:** 41% | NR | NR | CMCT was correlated with corpus callosum atrophy (*p* not reported) but not EDSS.  Magnitude not reported. |
| (Kandler et al. 1991) | > upper 99% confidence limit of controls,  Asymmetry > upper 99% confidence limit of controls | **Upper extremity:** TP = 27/63 participants, FP = NR, TN = NR, FN = 36/63 participant  **Lower extremity:** TP = 42/63 participants, FP = NR, TN = NR, FN = 21/63 participants | **Upper extremity:** 43%  **Lower extremity:** 67% (66-68%) | NR | NR | NR |
| (Leocani et al. 2006) | > 2.5 SD above mean of controls,  Asymmetry > 2.5 SD above mean of controls | **RMS (upper extremity):** TP = 24/43 participants, FP = NR, TN = NR, FN = 19/43 participants, **SPMS (upper extremity):** TP = 26/28 participants, FP = NR, TN = NR, FN = 2/28 participants, **PPMS (upper extremity):** TP = 11/13 participants, FP = NR, TN = NR, FN = 2/13 participants, **RMS (lower extremity):** TP = 26/43 participants, FP = NR, TN = NR, FN = 17/43 participants, **SPMS (lower extremity):** TP = 27/28 participants, FP = NR, TN = NR, FN = 1/28 participants, **PPMS (lower extremity):** TP = 12/13 participants, FP = NR, TN = NR, FN = 1/13 participants | **RMS (upper extremity):** 56% (54-58%)  **SPMS (upper extremity):** 93% (87-99%)  **PPMS (upper extremity):** 85% (72-98%)  **RMS (lower extremity):** 61% RMS (59-63%)  **SPMS (lower extremity):** 96% SPMS (89-100%)  **PPMS (lower extremity):** 92% PPMS (78-100%) | NR | NR | CMCT was correlated with EDSS (Rho = 0.6, *p* < .001). |
| (Magistris et al. 1999) | > 2.5 SD above lab normative values | **Upper extremity:** TP = 60/221 limbs, FP = 112/268 limbs, TN = 156/268 limbs, FN = 161/221 limbs | **Upper extremity:** 27% | **Upper extremity:** 58% (58-58%) | **Upper extremity:** 0.52 (0.35-0.76)ꝉ | CMCT was not significantly correlated with weakness. |
| (Mayr et al. 1991) | > 99 %ile of controls | **Upper extremity:** TP = 31/44 participants, FP = 0/86 participants, TN = 86/86 participants, FN = 13/44 participants  **Lower extremity:** TP = 27/44 participants, FP = 0/86 participants, TN = 86/86 participants, FN = 17/44 participants | **Upper extremity:** 71% (68-74%)  **Lower extremity:** 61% (59-63%) | **Upper extremity:** 99% (97-100%)  **Lower extremity:** 100% (98-100%) | **Upper extremity:** 202.69 (102.56-400.59)  **Lower extremity:** 135.00 (71.00-256.69) | CMCT was correlated with pyramidal dysfunction (hyperreflexia, weakness, spasticity, plantar reflex) (*p* not reported).  Magnitude not reported. |
| (Ravnborg et al. 1992) | > upper 99% confidence limit of controls | **Upper + lower extremity:** TP = 33/40 participants, FP = 7/28 participants, TN = 21/28 participants, FN = 7/40 participants | **Upper + lower extremity:** 83% (73-93%) | **Upper + lower extremity:** 75% (61-89%) | **Upper + lower extremity:** 14.14 (4.34-46.11) | CMCT was correlated with MRI lesion number (McNemar’s = 0.85, *p* not reported) but not pyramidal dysfunction (hyperreflexia, weakness, spasticity, plantar reflex). |
| (Schmierer et al. 2000) | > 2.5 SD above mean of controls | **Upper extremity:** TP = 7/50 participants, FP = 0/25 participants, TN = 25/25 participants, FN = 43/50 participants  **Lower extremity:** TP = 24/50 participants, FP = 0/25 participants, TN = 25/25 participants, FN = 26/50 participants | **Upper extremity:** 14%  **Lower extremity:** 48% | **Upper extremity:** 100% (92-100%)  **Lower extremity:** 100% (92-100%) | **Upper extremity:** 3.91 (1.61-9.52)  **Lower extremity:** 22.15 (11.23-43.69) | CMCT was not significantly correlated with MRI lesion burden or location. |
| (Schmierer et al. 2002) | > 2.5 SD above mean of controls | **RMS (upper extremity):** TP = 12/38 limbs, FP = NR, TN = NR, FN = 26/38 limbs  **PPMS (upper extremity):** TP = 14/38 limbs, FP = NR, TN = NR, FN = 24/38 limbs  **RMS (lower extremity):** TP = 24/38 limbs, FP = NR, TN = NR, FN = 14/38 limbs  **PPMS (lower extremity):** TP = 22/38 limbs, FP = NR, TN = NR, FN = 16/38 limbs | **RMS (upper extremity):** 32%  **PPMS (upper extremity):** 37%  **RMS (lower extremity):** 63% (60-66%)  **PPMS (lower extremity):** 58% (56-60%) | NR | NR | Upper and lower extremity CMCT was correlated with EDSS (*r* = 0.4-0.5, *p* < .01). |
| (Tataroglu et al. 2003) | > 2.5 SD above mean of controls | **Upper + lower extremity:** TP = 44/58 participants, FP = 4/31 participants, TN = 27/31 participants, FN = 14/58 participants | **Upper + lower extremity:** 76% (74-78%) | **Upper + lower extremity:** 87% (82-92%) | **Upper + lower extremity:** 21.21 (6.32-71.14) | CMCT was not significantly correlated with EDSS. |
| ***Triple stimulation technique (TST), one study (6%)*** | | | | | | |
| (Magistris et al. 1999) | > 2.5 SD below laboratory normative values | **Upper extremity:** TP = 106/221 limbs, FP = 106/268 limbs, TN = 162/268 limbs, FN = 115/221 limbs, | **Upper extremity:** 48% | **Upper extremity:** 60% (60-60%) | **Upper extremity:** 0.60 (0.42-0.86)ꝉ | TST amplitude ratio was correlated with weakness (*p* < .0001).  Magnitude not reported. |
| ***Corticospinal silent period (CSP), one study (6%)*** | | | | | | |
| (Tataroglu et al. 2003) | > 2.5 SD above mean of controls,  Asymmetry > 2.5 SD above mean of controls | **Upper + lower extremity:** TP = 40/58 participants, FP = 9/31 participants, TN = 22/31 participants, FN = 18/58 participants | **Upper + lower extremity:** 69% (67-71%) | **Upper + lower extremity:** 70% (66-74%) | **Upper + lower extremity:** 5.43 (2.09-14.10) | CSP duration was correlated with ataxia (*r* = 0.3, *p* < .001) but not EDSS. |
| ***Ipsilateral silent period (iSP), three studies (16%)*** | | | | | | |
| *iSP latency, three studies (16%)* | | | | | | |
| (Jung et al. 2006) | > 2.5 SD above mean of controls,  Asymmetry > 2.5 SD above mean of controls | TP = 4/98 limbs, FP = NR, TN = NR, FN = 94/98 limbs | **Upper extremity:** 4% | NR | NR | iSP latency was not significantly correlated with pyramidal dysfunction (hyperreflexia, weakness, spasticity, plantar reflex), corpus callosum atrophy, or MRI lesion volume or number. |
| (Schmierer et al. 2000) | > 2.5 SD above mean of controls | TP = 9/50 participants, FP = 0/25 participants, TN = 25/25 participants, FN = 41/50 participants | **Upper extremity:** 18% | **Upper extremity:** 100% (92-100%) | **Upper extremity:** 5.27 (2.32-11.98) | iSP latency was not significantly correlated with MRI lesion burden or location. |
| (Schmierer et al. 2002) | > 2.5 SD above mean of controls | **RMS:** TP = 6/38 limbs, FP = NR, TN = NR, FN = 32/38 limbs  **PPMS:** TP = 13/38 limbs, FP = NR, TN = NR, FN = 25/38 limbs | **Upper extremity RMS:** 16%  **Upper extremity PPMS:** 34% | NR | NR | iSP latency was correlated with EDSS in PPMS (*r* = 0.4, *p* < .01) but not RMS. |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| *iSP duration, three studies (18%)* | | | | | | |
| (Jung et al. 2006) | > 2.5 SD above mean of controls,  Asymmetry > 2.5 SD above mean of controls | TP = 22/98 limbs, FP = NR, TN = NR, FN = 76/98 limbs | **Upper extremity:** 22% | NR | NR | iSP duration was not significantly correlated with pyramidal dysfunction (hyperreflexia, weakness, spasticity, plantar reflex), corpus callosum atrophy, or MRI lesion volume or number. |
| (Schmierer et al. 2000) | > 2.5 SD above mean of controls | TP = 36/50 participants, FP = 0/25 participants, TN = 25/25 participants, FN = 14/50 participants | **Upper extremity:** 72% (69-75%) | **Upper extremity:** 100% (92-100%) | **Upper extremity:** 61.71 (29.70-128.22) | iSP duration was with MRI lesion burden (*r* = 0.4, *p* < .01) but not MRI lesion location. |
| (Schmierer et al. 2002) | > 2.5 SD above mean of controls | **RMS:** TP = 13/38 limbs, FP = NR, TN = NR, FN = 25/38 limbs  **PPMS:** TP = 19/38 limbs, FP = NR, TN = NR, FN = 19/38 limbs | **Upper extremity RMS:** 16%  **Upper extremity PPMS:** 34% | NR | NR | iSP duration was not significantly correlated with EDSS. |
| *iSP depth, one study (6%)* | | | | | | |
| (Jung et al. 2006) | > 2.5 SD above mean of controls | TP = 6/98 limbs, FP = NR, TN = NR, FN = 92/98 limbs | **Upper extremity:** 6% | NR | NR | iSP depth was not significantly correlated with pyramidal dysfunction (hyperreflexia, weakness, spasticity, plantar reflex), corpus callosum atrophy, or MRI lesion volume or number. |
| *Transcallosal conduction time (TCT), three studies (18%)* | | | | | | |
| (Jung et al. 2006) | > 2.5 SD above mean of controls,  Asymmetry > 2.5 SD above mean of controls | TP = 6/98 limbs, FP = NR, TN = NR, FN = 92/98 limbs | **Upper extremity:** 6% | NR | NR | TCT was not significantly correlated with pyramidal dysfunction (hyperreflexia, weakness, spasticity, plantar reflex), corpus callosum atrophy, or MRI lesion volume or number. |
| (Schmierer et al. 2000) | > 2.5 SD above mean of controls | TP = 2/50 participants, FP = 0/25 participants, TN = 25/25 participants, FN = 48/50 participants | **Upper extremity:** 4% | **Upper extremity:** 100% (92-100%) | **Upper extremity:** 1.00 (0.23-4.34)\* | TCT was not significantly correlated with MRI lesion burden or location. |
| (Schmierer et al. 2002) | > 2.5 SD above mean of controls | **RMS:** TP = 5/38 limbs, FP = NR, TN = NR, FN = 33/38 limbs  **PPMS:** TP = 9/38 limbs, FP = NR, TN = NR, FN = 29/38 limbs | **Upper extremity RMS:** 13%  **Upper extremity PPMS:** 24% | NR | NR | TCT was not significantly correlated with EDSS. |

%ile, percentile; 95% CI, 95% confidence interval; CMAP, compound muscle action potential; EDSS, Expanded Disability Status Scale; FN, false negative; FP, false positive; MRI, magnetic resonance imaging; NR, not reported; PPMS, primary progressive multiple sclerosis RMS, relapsing multiple sclerosis; SD, standard deviation; SPMS, secondary progressive multiple sclerosis; TN, true negative; TP, true positive. \*, 95% CI of diagnostic odds ratio (DOR) crossed zero, suggesting no change in odds of MS. ꝉ, DOR < 1 indicated decreased odds of MS.

**Table S5.** Detailed risk of bias assessment.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Domain** | **Patient Selection** | **Index Test** | **Reference Standard** | **Flow and Timing** | **Risk of Bias** |
| **Article** | Description | Describe methods of patient selection Describe included patients (previous testing, presentation, intended use of index test, and setting) | Describe the index test and how it was conducted and interpreted | Describe the reference standard and how it was conducted and interpreted | Describe any patients who did not receive the index tests or reference standard or who were excluded from the 2 × 2 table (refer to flow diagram) Describe the interval and any interventions between index tests and the reference standard | NA |
| Signaling Questions (Y / N / U) | Was a consecutive or random sample of patients enrolled? | Were the index test results interpreted without knowledge of the results of the reference standard? | Is the reference standard likely to correctly classify the target condition? | Was there an appropriate interval between index tests and reference standard? |
| Was a case–control design avoided? | Did all patients receive a reference standard? |
| Did the study avoid inappropriate exclusions? | If a threshold was used, was it prespecified? | Were the reference standard results interpreted without knowledge of the results of the index test? | Did all patients receive the same reference standard? |
| Were all patients included in the analysis? |
| Risk of Bias (H / L / U) | Could the selection of patients have introduced bias? | Could the conduct or interpretation of the index test have introduced bias? | Could the reference standard, its conduct, or its interpretation have introduced bias? | Could the patient flow have introduced bias? (Was the patient flow free of bias?) | What was the study's overall risk of bias? |
| Concerns About Applicability (H / L / U) | Are there concerns that the included patients do not match the review question? | Are there concerns that the index test, its conduct, or its interpretation differ from the review question? | Are there concerns that the target condition as defined by the reference standard does not match the review question? | NA | Were there concerns for applicability of the overall study methods? |
| (Beer et al. 1995) | Signaling Questions (Y / N / U) | Y | Y | Y | Y | NA |
| Y | Y |
| Y | Y | Y | Y |
| Y |
| Risk of Bias (H / L / U) | L | L | L | L | L |
| Concerns About Applicability (H / L / U) | L | L | L | NA | L |
| (Caramia et al. 2004) | Signaling Questions (Y / N / U) | U | N | Y | Y | NA |
| Y | Y |
| U | Y | N | N |
| Y |
| Risk of Bias (H / L / U) | U | H | H | H | H |
| Concerns About Applicability (H / L / U) | U | L | L | NA | U |
| (Cruz-Martínez et al. 2000) | Signaling Questions (Y / N / U) | Y | Y | Y | Y | NA |
| Y | Y |
| U | Y | Y | Y |
| U |
| Risk of Bias (H / L / U) | U | L | L | U | U |
| Concerns About Applicability (H / L / U) | U | L | L | NA | U |
| (Facchetti et al. 1997) | Signaling Questions (Y / N / U) | Y | Y | Y | Y | NA |
| N | Y |
| N | Y | Y | Y |
| Y |
| Risk of Bias (H / L / U) | H | L | L | L | H |
| Concerns About Applicability (H / L / U) | H | L | L | NA | H |
| (Hess et al. 1987) | Signaling Questions (Y / N / U) | N | N | Y | Y | NA |
| N | Y |
| Y | Y | N | N |
| Y |
| Risk of Bias (H / L / U) | H | H | H | H | H |
| Concerns About Applicability (H / L / U) | L | L | L | NA | L |
| (Jung et al. 2006) | Signaling Questions (Y / N / U) | U | U | Y | Y | NA |
| N | Y |
| U | Y | U | Y |
| Y |
| Risk of Bias (H / L / U) | H | U | U | L | H |
| Concerns About Applicability (H / L / U) | U | L | L | NA | U |
| (Kale et al. 2009) | Signaling Questions (Y / N / U) | Y | U | Y | Y | NA |
| N | Y |
| N | Y | U | Y |
| Y |
| Risk of Bias (H / L / U) | H | U | U | L | H |
| Concerns About Applicability (H / L / U) | H | L | L | NA | H |
| (Kale et al. 2010) | Signaling Questions (Y / N / U) | N | U | Y | Y | NA |
| N | Y |
| N | Y | U | Y |
| Y |
| Risk of Bias (H / L / U) | H | U | U | L | H |
| Concerns About Applicability (H / L / U) | H | L | L | NA | H |
| (Kandler et al. 1991) | Signaling Questions (Y / N / U) | Y | U | Y | Y | NA |
| N | Y |
| Y | Y | U | Y |
| N |
| Risk of Bias (H / L / U) | H | U | U | H | H |
| Concerns About Applicability (H / L / U) | L | L | L | NA | U |
| (Leocani et al. 2006) | Signaling Questions (Y / N / U) | Y | Y | Y | Y | NA |
| Y | Y |
| N | Y | Y | Y |
| Y |
| Risk of Bias (H / L / U) | H | L | L | L | H |
| Concerns About Applicability (H / L / U) | H | L | L | NA | H |
| (Magistris et al. 1999) | Signaling Questions (Y / N / U) | Y | U | Y | Y | NA |
| Y | Y |
| Y | Y | U | Y |
| Y |
| Risk of Bias (H / L / U) | L | U | U | L | U |
| Concerns About Applicability (H / L / U) | L | L | L | NA | L |
| (Mayr et al. 1991) | Signaling Questions (Y / N / U) | U | U | Y | Y | NA |
| N | Y |
| N | Y | U | Y |
| Y |
| Risk of Bias (H / L / U) | H | U | U | L | H |
| Concerns About Applicability (H / L / U) | H | L | L | NA | H |
| (Pisa et al. 2020) | Signaling Questions (Y / N / U) | Y | U | Y | Y | NA |
| N | Y |
| Y | Y | U | Y |
| Y |
| Risk of Bias (H / L / U) | H | U | U | L | H |
| Concerns About Applicability (H / L / U) | L | L | L | NA | L |
| (Ravnborg et al. 1992) | Signaling Questions (Y / N / U) | Y | Y | Y | Y | NA |
| Y | Y |
| Y | Y | Y | Y |
| Y |
| Risk of Bias (H / L / U) | L | L | L | L | L |
| Concerns About Applicability (H / L / U) | L | L | L | NA | L |
| (Schmierer et al. 2000) | Signaling Questions (Y / N / U) | U | U | Y | Y | NA |
| N | Y |
| N | Y | U | Y |
| Y |
| Risk of Bias (H / L / U) | H | U | U | L | H |
| Concerns About Applicability (H / L / U) | H | L | L | NA | H |
| (Schmierer et al. 2002) | Signaling Questions (Y / N / U) | U | U | Y | Y | NA |
| Y | Y |
| N | Y | U | Y |
| N |
| Risk of Bias (H / L / U) | H | U | U | H | H |
| Concerns About Applicability (H / L / U) | H | L | L | NA | H |
| (Tataroglu et al. 2003) | Signaling Questions (Y / N / U) | Y | U | Y | Y | NA |
| N | Y |
| N | Y | U | Y |
| U |
| Risk of Bias (H / L / U) | H | U | U | U | H |
| Concerns About Applicability (H / L / U) | H | L | L | NA | H |

H, high; L, low; N, no; NA, not applicable; U, unclear; Y, yes. See ref: (Whiting et al. 2011).

**Table S6.** Detailed biomarker assessment.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Process-specific classification** | | | | | | | **Methodologic quality** | | | | | **Clinical utility** | | | | | **Clinical usefulness** | | | | **Biomarker validity** |
| **Immune alteration** | **BBB disruption** | **Demyelination** | **Excitotoxicity** | **Axonal damage** | **Gliosis** | **Remyelination** | **Raw data** | **Reference standard** | **Appropriate patient spectrum** | **Valid methods** | **Safeguards against bias** | **Biological rationale** | **Clinical relevance** | **Practicality** | **Correlation with disease** | **Correlation with disability** | **Sensitivity** | **Specificity** | **Reliability** | **Epidemiologic evaluation** |
| (Beer et al. 1995) | U | U | U | U | U | U | U | N | Y | Y | Y | Y | U | Y | U | U | U | N | N | U | N | N |
| (Caramia et al. 2004) | U | U | Y | U | Y | U | N | N | Y | U | Y | N | Y | U | U | N | U | N | U | Y | N | N |
| (Cruz-Martínez et al. 2000) | U | U | Y | U | Y | U | U | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | U | N | N |
| (Facchetti et al. 1997) | U | U | Y | U | Y | U | U | N | Y | Y | U | Y | Y | Y | Y | Y | U | Y | U | U | U | N |
| (Hess et al. 1987) | U | U | Y | U | Y | U | U | N | Y | Y | Y | N | Y | Y | Y | U | U | N | Y | Y | N | N |
| (Jung et al. 2006) | U | U | Y | U | Y | U | U | N | Y | U | Y | U | Y | N | N | N | U | N | U | U | N | N |
| (Kale et al. 2009) | U | U | Y | U | Y | U | U | N | Y | Y | U | U | Y | Y | Y | U | Y | N | U | U | N | N |
| (Kale et al. 2010) | U | U | Y | U | Y | U | U | N | Y | U | U | U | Y | U | U | U | Y | Y | U | U | U | N |
| (Kandler et al. 1991) | U | U | Y | U | U | U | U | N | Y | Y | Y | U | Y | U | U | U | U | N | U | U | N | N |
| (Leocani et al. 2006) | U | U | Y | U | Y | U | Y | N | Y | Y | U | Y | Y | Y | Y | U | Y | Y | U | Y | U | N |
| (Magistris et al. 1999) | U | U | Y | U | Y | U | U | N | Y | Y | Y | U | Y | Y | Y | U | U | N | N | Y | N | N |
| (Mayr et al. 1991) | U | U | Y | U | U | U | U | Y | Y | U | Y | U | Y | U | Y | U | U | N | Y | U | N | N |
| (Pisa et al. 2020) | U | U | Y | U | U | U | U | N | Y | Y | Y | U | Y | U | U | U | Y | Y | U | U | U | N |
| (Ravnborg et al. 1992) | U | U | Y | U | U | U | U | N | Y | Y | Y | Y | Y | U | U | Y | N | N | Y | U | N | N |
| (Schmierer et al. 2000) | U | U | Y | U | Y | U | U | N | Y | U | Y | U | Y | Y | Y | Y | U | N | Y | U | N | N |
| (Schmierer et al. 2002) | U | U | Y | U | Y | U | U | N | Y | U | Y | U | Y | U | U | U | Y | N | U | Y | N | N |
| (Tataroglu et al. 2003) | U | U | Y | Y | Y | U | U | N | Y | Y | U | U | Y | Y | Y | U | Y | N | Y | U | N | N |

Note: criteria related to treatment efficacy are omitted. BBB, blood-brain barrier; H, high; L, low; N, no; U, uncertain. See ref: (Bielekova & Martin 2004).

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