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

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# **Supplementary Materials**

1. Review protocol.
2. **Table S1.** Study characteristics.
3. **Table S2.** Control participant characteristics.
4. **Table S3.** Transcranial magnetic stimulation characteristics.
5. **Table S4.** Detailed transcranial magnetic stimulation results.
6. **Table S5.** Detailed risk of bias assessment.
7. **Table S6.** Detailed biomarker assessment.
8. References.
9. **Table S7.** Document tracking spreadsheet (separate document).
10. **Table S8.** Data transcription spreadsheet (separate document).

**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

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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

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109

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964

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268

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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 weakControl: 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 controlsAsymmetry > 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 patientselectionDescribe included patients(previous testing,presentation, intendeduse of index test, andsetting) | Describe the index test andhow it was conducted andinterpreted | Describe the reference standardand how it was conductedand interpreted | Describe any patients who didnot receive the index testsor reference standard orwho were excluded fromthe 2 × 2 table (refer toflow diagram)Describe the interval and anyinterventions between indextests and the referencestandard | NA |
| Signaling Questions (Y / N / U) | Was a consecutive orrandom sample ofpatients enrolled? | Were the index test resultsinterpreted without knowledgeof the results of thereference standard? | Is the reference standard likelyto correctly classify the targetcondition? | Was there an appropriateinterval between index testsand reference standard? |
| Was a case–control designavoided? | Did all patients receive areference standard? |
| Did the study avoidinappropriate exclusions? | If a threshold was used, was itprespecified? | Were the reference standardresults interpreted withoutknowledge of the results ofthe index test? | Did all patients receive thesame reference standard? |
| Were all patients included inthe analysis? |
| Risk of Bias (H / L / U) | Could the selection ofpatients have introducedbias? | Could the conduct orinterpretation of the index testhave introduced bias? | Could the reference standard,its conduct, or itsinterpretation haveintroduced bias? | Could the patient flow haveintroduced 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 theincluded patients do notmatch the reviewquestion? | Are there concerns that theindex test, its conduct, or itsinterpretation differ from thereview question? | Are there concerns that thetarget condition as definedby the reference standarddoes not match the reviewquestion? | 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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