

Résumé

Au cours de la dernière décennie, l'évaluation de l'importance et de l'impact fonctionnel de l'altération cognitive dans le cadre de la sclérose en plaques ont suscité un intérêt considérable, de même que ses corrélations en imagerie par résonance magnétique (IRM), et les approches possibles sur le plan de la gestion clinique. Des résultats préliminaires indiquent que les traitements à visée thérapeutique ou symptomatique peuvent avoir une influence positive sur le fonctionnement cognitif du patient. Néanmoins, peu d'études ont évalué

l'efficacité de programmes de réhabilitation cognitive en se basant sur un schéma expérimental. Pour avancer dans le domaine du diagnostic neuropsychologique, il est essentiel de valider des outils de dépistage précis, économiques et fiables. Ils pourront ainsi être utilisés dans les contextes cliniques afin d'identifier les patients adéquats pour une évaluation neuropsychologique poussée et mettre au point des techniques de réhabilitation sur mesure pour les sujets atteints de sclérose en plaques.

Überblick

Während der letzten zehn Jahre bestand ein großes Interesse daran, Bedeutung und funktionelle Auswirkungen kognitiver Störungen bei multipler Sklerose (MS) sowie deren Korrelate mit magnetresonanztomographischen Befunden zu bewerten und mögliche Ansatzpunkte für die klinische Behandlung zu finden. Vorläufige Ergebnisse zeigten, dass die Behandlung mit entweder krankheits- oder symptom-modifizierenden Mitteln die kognitive Leistung der Patienten beeinflussen. Die Wirksamkeit von

Programmen zur Rehabilitation der Kognition wurde jedoch nur in wenigen kontrollierten Studien untersucht. Fortschritte auf dem Gebiet der neuropsychologischen Diagnose erfordern sensitive, kostengünstige und zuverlässige Screening-Instrumente, die unter klinischen Bedingungen eingesetzt werden können, um Patienten zu identifizieren, die für eine umfangreiche neuropsychologische Bewertung geeignet sind, und um individuell angepasste Rehabilitationstechniken für MS-Patienten auszuarbeiten.

Sommario

Nell'ultimo decennio, ha suscitato un notevole interesse la valutazione dell'importanza e dell'impatto funzionale del deterioramento cognitivo nella sclerosi multipla (SM), i suoi correlati clinico-neuroradiologici (mediante risonanza magnetica nucleare) ed i possibili approcci nella gestione clinica. Alcuni dati preliminari indicano che il trattamento sia con farmaci in grado di modificare il decorso di malattia sia con farmaci sintomatici potrebbe presentare degli effetti cognitivi positivi per il paziente, sebbene siano

solo pochi gli studi che hanno valutato l'efficacia dei programmi di riabilitazione cognitiva utilizzando sistemi sperimentali. Per compiere ulteriori progressi nell'ambito delle diagnosi neuropsicologiche è fondamentale validare nuovi strumenti di screening sensibili, economici ed affidabili che possano essere utilizzati, in ambienti clinici, per identificare i pazienti adatti ad una valutazione neuropsicologica estensiva e per finalizzare tecniche di riabilitazione personalizzate per i pazienti affetti da SM.

Reseña

Durante la última década, ha habido un interés considerable por valorar la importancia y el impacto funcional del deterioro cognitivo en la esclerosis múltiple (EM), la correlación entre la clínica y la resonancia magnética y posibles planteamientos de actuación clínica. Existen pruebas preliminares de que el tratamiento tanto con agentes modificadores de la enfermedad como con agentes sintomáticos podría influir positivamente en la evolución cognitiva del paciente, pero en pocos estudios

se ha valorado la eficacia de los programas de rehabilitación cognitiva usando un diseño experimental. Para progresar más en el campo del diagnóstico neuropsicológico, es esencial validar instrumentos de detección precoz sensibles, rentables y fiables que se puedan usar en contextos clínicos para identificar a pacientes en los que es conveniente una valoración neuropsicológica amplia y terminar de desarrollar técnicas de rehabilitación a medida para los pacientes con EM.

Clinical Management of Cognitive Impairment in Multiple Sclerosis: a Review of Current Evidence

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Summary

Over the past decade, there has been considerable interest in assessing the importance and functional impact of cognitive impairment in multiple sclerosis (MS), its clinico-magnetic resonance imaging correlates, and possible approaches to clinical management. There is preliminary evidence that treatment with both disease-modifying and symptomatic agents may positively influence the cognitive outcome of the patient, but few studies have assessed the efficacy of cognitive

rehabilitation programmes using an experimental design. To make further progress in the field of neuropsychological diagnosis, it is essential to validate sensitive, cost-effective and reliable screening instruments that can be used, in clinical settings, to identify patients appropriate for extensive neuropsychological assessment, and finalize tailor-made rehabilitation techniques for MS patients.

KEY WORDS:

MULTIPLE SCLEROSIS; COGNITIVE IMPAIRMENT; NEUROPSYCHOLOGICAL TEST BATTERY; DISEASE-MODIFYING AGENTS; SYMPTOMATIC AGENTS; REHABILITATION PROGRAMMES

Introduction

For decades, clinicians have rarely performed accurate assessments of neuropsychological (NP) deficits in multiple sclerosis (MS) patients. Only during the past 20 years have they become aware of the prevalence of MS-related cognitive impairment and its profound functional impact. Approaches to clinical management are in their infancy, however.

The first unresolved issue is assessment of cognitive function. Routine neurological examination and mental-state assessment will not detect cognitive dysfunction in the majority of MS patients, hence the need for sensitive, cost-effective and reliable screening procedures that can be applied in everyday clinical practice.

Cognitive dysfunction, as with other symptoms of MS, is highly variable – estimates of its frequency range from 43% to 72%.¹ Severe dementia is observed in 20–30% of cognitively impaired MS patients.¹ The domains of cognitive function most commonly impaired are episodic memory,

attention/concentration, processing speed and verbal fluency. Domains often compromised are executive functions such as concept formation, abstract reasoning, planning, monitoring and visual perception. Language, semantic memory and attention span are less frequently involved.²

Cognitive dysfunction can have a dramatic impact on several aspects of quality of life, and independently on degree of physical disability. Cognitive impairment significantly affects the ability to maintain employment, and cognitively impaired patients require greater assistance with daily living activities and are less likely to socialize than cognitively intact MS patients.^{3–5} The capacity of a patient to benefit from in-patient rehabilitation can also be limited by cognitive impairment.⁶

Few authors have studied the natural history of cognitive dysfunction in MS patients. In a 3-year follow-up study, incipient cognitive decline seemed to be widespread and progressive,⁷ while in another

study, the percentage of patients with cognitive impairment increased from 26% to 56% over a 10-year follow-up period, and the profile of cognitive deficits tended to expand.⁸

The frequency of cognitive dysfunction in MS, and its severity and impact on everyday functioning, leads to increasing consensus that NP assessment should accompany the neurological examination and become a factor in therapeutic decision-making. This article deals with current approaches to clinical assessment and management of cognitive dysfunction, and reviews existing data on treatment with pharmacological therapies and rehabilitative programmes.

Assessment of Cognitive Impairment

Patients may often underestimate their deficits because of metamemory impairment, or overestimate them due to depression. It is therefore difficult to evaluate the cognitive status of an MS patient without formal NP assessment. Since it is impractical to refer all MS patients seen in clinical practice for comprehensive NP evaluation, clinicians should have at their disposal a brief, cost-effective and reliable NP screening test.

Several screening methods have been evaluated in MS. The Mini-Mental State Examination (MMSE)⁹ is insensitive to MS-related cognitive impairment, except in the most severely impaired patients,^{10,11} with sensitivity ranging from 28% to 36% and specificity

ranging from 89% to 100%. Variants of the MMSE have similar disadvantages or have been scarcely validated.¹² To avoid problems with screening tests, several brief batteries of NP tests have been developed (Table 1) which cover the functions that are most often compromised in MS. One of these, the Screening Examination for Cognitive Impairment (SEFCI),¹³ has a 74–86% sensitivity, 90–91% specificity, and an estimated administration time of 25–30 min. The Brief NP Battery (BRB) proposed by Rao, or a variant proposed by the USA MS Society's Cognitive Functions Group,¹⁴ has a 68% sensitivity, 85% specificity and an estimated administration time of 30–35 min. Two articles directly compared these two methods and found them equally sensitive for detecting cognitive impairment in MS patients, but the SEFCI required less time to administer (a reduction of about 27%).^{15,16} Significantly, due to its difficulty, the Paced Auditory Serial Addition Test (PASAT) included in the BRB is sometimes not well accepted by patients with moderate–severe impairment, and causes a substantial drop-out rate. Finally, the Basso Screening Battery¹⁷ is 100% sensitive and 80% specific, with an estimated administration time of 15–25 min.

Brief batteries cannot substitute for comprehensive NP assessment, as, for example, they do not explore executive functions that are critical to the subject's everyday function. They are a useful tool to determine if further and more thorough evaluation is

Table 1: Brief Neuropsychological Batteries

Battery	Cognitive domain	Tests
Screening Examination for Cognitive Impairment	Verbal memory General verbal ability Attention–concentration	10-item word list × 3 trials (with delay) Shipley Institute of Living Scale Oral Symbol Digit Modalities Test
Brief Repeatable Battery	Verbal memory Spatial memory Attention–concentration Verbal fluency	Selective Reminding Test × 12 trials Spatial Recall Test (7/24) Paced Auditory Serial Addition Test Controlled Oral Word Association Test
Brief Repeatable Battery Revised	Verbal memory Spatial memory Attention–concentration Attention–concentration Verbal fluency	Selective Reminding Test 10/36 Spatial Recall Test Oral Symbol Digit Modalities Test Paced Auditory Serial Addition Test Word List Generation
Basso Screening Battery	Verbal learning Verbal fluency Auditory attention	Wechsler Memory Scale-Revised Logical Memory Controlled Oral Word Association Test Seashore Rhythm Test

needed, however. A comprehensive NP examination, such as that proposed by Peyser,¹⁸ may take 2–6 h, and it may be necessary to address questions associated with rehabilitation programmes, disability and employment issues. Peyser proposed a core group of tests that would serve as a minimal basis for comparison of findings across centres and studies, but would be brief enough to give individual investigators the opportunity to explore their own specific research questions adding other NP measures. The proposed core battery assesses all major areas of cognitive functioning, includes tests with demonstrated reliability and validity for which alternative versions for longitudinal assessment are available, and excludes tests heavily dependent on fine visual acuity, motor speed or co-ordination.

Finally, to identify patients appropriate for NP referral, the clinician may rely on a comprehensive clinical interview and assessment, focusing on memory, concentration and performance in everyday tasks at home and work. Such an approach may miss patients with subtle cognitive changes, however. Other factors, as well as patient or family member complaints regarding cognitive difficulties, should alert the neurologist, including: brain magnetic resonance imaging (MRI) with a large lesion load and/or significant atrophy of the corpus callosum or generalized brain atrophy; presence of frontal release signs; recent relapse or evidence of clinical progression; secondary–progressive course; treatment-resistant depression; severe fatigue; and early employment retirement decisions. NP evaluation is also appropriate for patients entering a rehabilitation programme or clinical trial.¹⁹ Conversely, a clear contraindication to testing is the severely disabled patient in a low-demand environment, and in whom cognitive assessment is unlikely to provide further insight or lead to changes in care.

Management of Cognitive Impairment

Very little is known about effective strategies for managing cognitive impairment in MS. Tentative approaches include pharmacological therapies using disease-modifying or symptomatic agents, and rehabilitation programmes.

Key Points

- Multiple sclerosis (MS)-related cognitive impairment is highly prevalent (43–72% of patients), and its impact on a subject's work and social functioning is increasingly appreciated
- No single sensitive, cost-effective and reliable screening test for MS cognitive impairment has been identified. Brief neuropsychological batteries, which cover the functions most often compromised in MS are largely used, although they cannot substitute for comprehensive neuropsychological assessment
- There is preliminary evidence that treatment with both disease-modifying and symptomatic agents may positively influence the cognitive outcome of the patient
- There is a need to develop tailor-made rehabilitation techniques for MS subjects that take into account the course and stage of the disease.

Disease-modifying Agents

Assessment of NP outcomes in trials of disease-modifying agents is a recent phenomenon and scant data comes from pivotal trials on interferon beta-1b, interferon beta-1a and glatiramer acetate (Table 2). A trial on cyclosporin²⁰ showed no beneficial effect on cognitive outcome, but a small trial with methotrexate²¹ showed an improvement using tests of attention/processing speed.

Interferon beta-1b

A randomized, double-blind, placebo-controlled, Phase-III trial²² with interferon beta-1b demonstrated its efficacy in treating relapsing–remitting MS (RRMS). Cognitive assessment was only performed on 30 of the 372 patients who entered the trial, however.²³ Two years after trial entry, and again after a 2-year follow-up, these 30 subjects underwent a brief NP evaluation, P300 testing, MRI and Expanded Disability Status Scale Scoring.

The NP test battery included Logical Memory and Visual Reproduction (VR) subsets of the Wechsler Memory Scale (WMS) form I and II, Trailmaking Test part B and Stroop Color-Word Test, Purdue Pegboard, and the Beck Depression Inventory (BDI). These evaluated immediate and delayed recall

Table 2: Clinical trials with disease-modifying agents

	Interferon beta-1b (IFNβ-1b)	Interferon beta-1a (IFNβ-1a)	Glatiramer acetate
Study and design	Pliskin, 1996 ²³ Randomized, double-blind, placebo-controlled	Fischer, 2000 ²⁹ Randomized, double-blind, placebo-controlled	Weinstein, 1999 ²⁷ Randomized, double-blind, placebo-controlled
Intervention	Injected subcutaneously on alternate days Placebo or 1.6 MIU IFNβ-1b or 8 MIU IFNβ-1b	Injected intramuscularly once weekly Placebo or 30 µg IFNβ-1a	Injected subcutaneously once daily Placebo or 20 mg glatiramer acetate
Duration	2 years	2 years	2 years
Patients	Patients' subgroup from the pivotal IFNβ-1b clinical trial Total, n=30 Placebo, n=13 Low-dose IFNβ-1b, n=8 High-dose IFNβ-1b, n=9 Age, 25–50 years Relapsing–remitting MS	Patients' subgroup from the pivotal IFNβ-1a clinical trial Total, n=276 Completed, n=166 Placebo, n=83 IFNβ-1a, n=83 Age, 18–55 years Relapsing–remitting MS	The whole patient group included in the pivotal trial Total, n=251 Placebo, n=126 Glatiramer acetate, n=125 Age, 18–45 years Relapsing–remitting MS
Outcome measures	Wechsler Memory Scale Logical Memory Wechsler Memory Scale Visual Reproduction Trailmaking Test part B Stroop Color-Word Test Purdue Pegboard Beck Depression Inventory Cognitive evoked potentials (P300) Magnetic resonance imaging Expanded Disability Status Scale Baseline and after 2 years	Comprehensive Neuropsychological Battery • California Computerized Assessment Package • Ruff Figural Fluency Test • California Verbal Learning Test • Wechsler Memory Scale-revised Visual Memory • Wisconsin Card Sorting Test • Visual search • Tower of London • 20 Questions • Wechsler Adult Intelligence Scale-Revised Baseline and after 2 years Brief Neuropsychological Battery • Ruff Figural Fluency Test • California Verbal Learning Test • Paced Auditory Serial Addition Test Baseline and every 26 weeks	Brief Repeatable Battery of Neuropsychological Tests Baseline, after 1 year and after 2 years
Results	Delayed Visual Reproduction Test improved in the high-dose group	Variables included in Set A improved significantly in the IFNβ-1a group; similar trend was observed for variables included in Set B but not for variables in Set C ^a	No statistically significant difference

^aSet A: learning, recent memory and information processing tested by the California Computerized Assessment package, Ruff Figural Fluency Test and California Verbal Learning Test; Set B: visuospatial abilities and executive functions tested by Wechsler Memory Scale-revised Visual Memory, Wisconsin Card Sorting Test, Visual Scanning, Tower of London and 20 Questions; Set C: verbal abilities tested by Wechsler Adult Intelligence Scale-Revised, Wechsler Memory Scale-Revised and Digit Span-Forward.

memory, attention and mental speed, dominant and non-dominant motor function, and depression, respectively. The total cohort improved significantly on WMS VR-Immediate Recall and Stroop Word Reading, probably due to a practice effect. The improvement was greater in the group receiving high-dose (8 MIU) interferon beta-1b, but the difference was not statistically significant. Follow-up pairwise comparison indicated a significant

($P=0.023$) improvement in WMS VR-Delayed Recall in the high-dose group and a trend for improvement in the Trailmaking Test part B, while the cognitive performance of the placebo and low-dose (1.6 MIU) groups did not change significantly. There was a correlation between MRI changes in total cerebral lesion load and NP performance with the VR-Delayed Recall task.

The study sample was small, however, meaning

that possible chance effects due to multiple comparisons cannot be ruled out, and no information on the patients' cognitive performances at the beginning of treatment is available. Finally, although the authors suggest that the VR test may be particularly sensitive to cognitive changes, it is difficult to explain such a selective effect as a consequence of interferon therapy. Results from this study should be considered as explorative because of these limitations.

In a pilot, uncontrolled study of 10 patients with secondary-progressive MS treated for 2 years with a combination of interferon beta-1b and azathioprine, Fernandez *et al.*²⁴ found a significant improvement in mean IQ scores on the Wechsler Adult Intelligence Scale compared with baseline scores. Given the uncontrolled design of the study, however, a learning effect cannot be ruled out.

Finally, in a preliminary report, Barak and Achiron²⁵ found a significant improvement in tests of complex attention, concentration and visual memory in a group of 23 patients with RRMS treated for 1 year with interferon beta-1b, compared with 23 untreated control patients.

Glatiramer acetate

A randomized, double-blind, placebo-controlled, Phase-III trial of glatiramer acetate²⁶ demonstrated that this treatment reduced the relapse rate by 29% over 2 years in RRMS, and effects on neuropsychological outcome were published later.²⁷ Two hundred and fifty-one RRMS patients were randomized to receive glatiramer acetate ($n=125$) or placebo ($n=126$). Nineteen patients from the glatiramer acetate-treated group and 17 from the placebo-treated group dropped out. Cognitive functions were evaluated using the BRB, administered to all patients at the screening visit, and after 12 months and 24 months of treatment. NP performance at the end of the study was greater in both groups, and the improvement was statistically significant for all tests except the PASAT and Symbol Digit Modality Test. This improvement in both groups was probably accounted for by a practice effect, and this study therefore found no effect of glatiramer acetate on cognitive impairment. There was no opportunity to demonstrate a therapeutic effect on cognitive

functions, however. The cognitive performance of all patients at baseline was in the normal range, and during the 24 months there was no decline in cognitive function, even in the placebo group. Moreover, 2 years may not be a sufficient follow-up period to detect a significant change in RRMS patients with preserved cognitive functioning.^{5,28}

Interferon beta-1a

The study published by Fischer *et al.*²⁹ provides the most convincing evidence of a potential beneficial effect of interferon therapy on cognitive outcome in MS. Two hundred and seventy-six patients from the original cohort in the pivotal interferon beta-1a trial³⁰ were tested using a comprehensive NP battery (at baseline and after 2 years) and a Brief NP Battery (at baseline and every 26 weeks over 2 years). One hundred and sixty-six patients completed the comprehensive NP battery at 2 years. The principle NP outcome analysis dealt with performance change on the comprehensive NP battery, while secondary outcome analysis dealt with the Brief NP Battery composite scores (Ruff Figural Fluency Test and California Verbal Learning Test) and the PASAT processing rate. Statistical analysis of the comprehensive NP battery concentrated on three main cognitive domains characterized by different frequencies of involvement in MS: learning, recent memory and information processing (tested by the California Computerized Assessment Package, Ruff Figural Fluency Test and California Verbal Learning Test [Set A]); visuospatial abilities and executive functions (tested by Wechsler Memory Scale-Revised Visual Memory, Wisconsin Card Sorting Test, Visual Scanning, Tower of London and 20 Questions [Set B]); and verbal abilities (assessed by Wechsler Adult Intelligence Scale-Revised, Wechsler Memory Scale-Revised and Digit Span-Forward [Set C]). After correction for baseline cognitive performance, patients in the group receiving interferon did significantly better than placebo patients on the variables included in Set A, a similar trend was observed for variables included in Set B, but no difference was seen for variables in Set C. The active treatment and placebo groups also differed significantly in their mean slope on the Brief NP Battery composite, with a better performance

observed in the treated group. Similarly, the PASAT processing rate was significantly ($P=0.023$) better in the active treatment group, and only 19.5% of patients on interferon had sustained worsening of their PASAT performance by the end of the study, compared with 36.6% of placebo patients (a 46.7% reduction in the risk of cognitive deterioration). Beneficial treatment effects were most apparent in those cognitive areas most commonly involved in the disease. It is hypothesized that beneficial effects of interferon beta-1a might occur in the short term due to the anti-inflammatory effects of the therapy, and in the long term due to the protective effects on tissue damage in the brain.

Symptomatic Agents

Most trials on symptomatic agents have focused on therapies for fatigue (Table 3). Due to short re-test intervals and follow-up periods in these studies, a significant re-test or practice effect has often been observed.

Effects of amantadine have been studied in a crossover trial and, more recently, in a parallel-group trial. The primary outcome was fatigue in the former study,³¹ with changes in cognitive performance being the secondary outcome. After 4 weeks' treatment a single effect was noted on tests of executive functions. In the latter trial,³² cognitive functions were the main outcome measure. Patients were treated for 6 weeks with amantadine, pemoline or placebo, using a parallel-group design. A significant difference between treatment groups was seen for attention/concentration tests, with a better performance observed in the amantadine-treated group.

Smits *et al.*³³ used the BRB in a crossover study with 4-aminopyridine. This battery was administered 2 weeks before starting treatment (to minimize the practice effect), at the beginning of the first treatment period, at the crossover period, and at the end of the second treatment period. There was a trend for improved performance during the 4-aminopyridine treatment period. No significant treatment-related changes in NP performance were seen in a different crossover trial with 4-aminopyridine over a 1-year follow-up.³⁴ A crossover trial looking at 3,4-diaminopyridine has also been carried out,³⁵ with

two 30-day treatment periods separated by a 30-day washout. No significant beneficial effect on cognitive functioning was observed.

Cognitive Rehabilitation

To date, most of the work on rehabilitation techniques for cognitive disorders has been done with stroke or head-injury patients, and there is a dearth of research focusing on specific rehabilitation techniques for MS patients.

Rehabilitation approaches

Cognitive rehabilitation should be one part of a comprehensive treatment strategy that begins the moment MS is diagnosed. It should focus primarily on the patient, but include family members and caregivers, and embrace cognitive strategies, pharmacological treatments, psychopathology and help for psychosocial difficulties.

The key principles of NP rehabilitation are as follows:

- Remediation or restoration (complete or partial restitution of a disturbed function by therapy, e.g. speech therapy);
- Compensation (residual or undisturbed functions used as a basis for compensatory strategies);
- Adaptation (by means of external aids).³⁶

Multiple sclerosis-related cognitive changes have highly variable and unpredictable courses, and so compensatory strategies, such as cognitive coping strategies like cognitive reframing, are therefore particularly useful. Cognitive reframing is a way of reconceptualizing a problem from one considered impossible to solve, to one for which other coping strategies may be helpful.³⁶ For example, if an intractable memory disorder can be reframed as an organizational problem, this can allow the patient to utilize other strategies such as information gathering, planning and goal setting (e.g. develop systems of reminders, use an organizer, keep a 'to do' list).^{37,38} Positive reframing, a special form of cognitive coping, seems to be associated with better adaptation in MS.³⁹

Table 3: Clinical trials with symptomatic agents

	Amantadine	Amantadine/ Pemoline	4-aminopyridine (4-AP)		3,4-diaminopyridine (3,4-DAP)
Study and design	Cohen, 1989 ³¹ Double-blind, placebo-controlled, randomized, crossover	Geisler, 1996 ³² Single-blind, placebo-controlled, randomized, parallel-group	Smits, 1994 ³³ Double-blind, placebo-controlled, randomized, crossover	Rossini, 2001 ³⁴ Double-blind, placebo-controlled, randomized, crossover	Bever, 1996 ³⁵ Double-blind, placebo-controlled, randomized, crossover
Intervention	Amantadine (100 mg/day) or placebo for 4 weeks; 2-week washout; crossover and treatment for other 4 weeks	Pemoline 18.75 mg–56.25 mg (titrated in 3 weeks) Amantadine 200 mg Placebo	4-AP (20–40 mg/day) for 2 weeks followed by placebo for 2 weeks or placebo for 2 weeks followed by 4-AP for 2 weeks	4-AP (32 mg/day) for 6 months followed by placebo for 6 months or placebo for 6 months followed by 4-AP (32 mg/day) for 6 months	3,4-DAP 100 mg or nicotinic acid 10 mg daily Two 30-day treatment periods separated by a 30-day washout period
Duration	10 weeks	6 weeks	4 weeks	1 year	90 days
Patients	Total, n=29 Mean age, 44.5 years Relapsing–remitting MS, n=16 Chronic progressive MS, n=13 Expanded Disability Status Scale ≤5.5	Total, n=45 Placebo, n=16 Pemoline, n=13 Amantadine, n=16 Age, 18–50 years Fatigue Severity Scale ≥4.0 Expanded Disability Status Scale ≤6.5 Center for Epidemiological Studies Depression Scale ≤35 Mini Mental State Evaluation ≥15	Total, n=20 Age, 18–65 years Relapsing–remitting MS, n=2 Chronic progressive MS, n=18 Expanded Disability Status Scale P/4AP=4.75 Expanded Disability Status Scale 4AP/P=7.25	Total, n=62, Completed, n=49 Mean age, 43.9 years Primary progressive MS, n=6 Chronic progressive MS, n=43 Mean Expanded Disability Status Scale, 6.2 Mean disease duration, 13.2 years	Total, n=36 Mean age, 44 years (range, 21–65) Relapsing–remitting MS, n=7 Chronic progressive MS, n=29 Mean Expanded Disability Status Scale, 6.0 (range, 2.5–9.0) Mean disease duration, 15.6 years (range, 2–29)
Outcome measures	Daily fatigue diary Fatigue assessment inventory Grooved Pegboard Task Symbol Digit Modalities Test Trailmaking Test Stroop Interference Test Controlled Word Generation Test Continuous Performance Task Digit Span Task	Symbol Digit Modalities Test Wechsler Adult Intelligence Scale Revised Digit Span Trailmaking Test Selective Reminding Test Benton Visual Retention Test Finger Tapping Test Expanded Disability Status Scale Fatigue Severity Scale Center for Epidemiological Studies Depression Scale Mini Mental State Evaluation	Brief Repeatable Neuropsychological Battery	Expanded Disability Status Scale Fatigue Severity Scale Evoked Potentials Neuropsychological battery: • Auditory Attention Test • Forward Digit • Corsi's Block Span Test • 15' delayed recall of the Rey's 15-Words List • Phonological Word Fluency • Benton's Line Orientation Test • Token Test • Wisconsin Card Sorting Test • Raven's Progressive Matrices • Hamilton's Scale	Patient subjective response Manual motor testing of leg strength Scored videotaped neurological examination Quadriceps and hamstrings strength measured by isometric dynamometry Brief Repeatable Neuropsychological Battery Ambulation Index Expanded Disability Status Scale
Effect on cognitive outcome	Significant improvement in the Stroop Interference Test in the treated group	Significant improvement in written Symbol Digit Modalities Test in the amantadine group	Trend for improved performance with 4-AP	No significant treatment-related changes	No significant treatment-related changes

In a rehabilitative programme, the first step is an accurate and comprehensive evaluation focusing on three areas: neuropsychological functioning (to assess the individual residual capacities and difficulties); pre-morbid IQ (to obtain an estimate of the patient's intellectual abilities before the onset of MS); and deficits in activities of daily living, environment and family support (to get information on the daily demands confronting the patient). After this phase, implementation can begin. Treatment of the patient's deficits should take place in a 'real-life situation'. For instance, for a patient with a constructional dyspraxia who has difficulty in dressing himself/herself, the ability to put on a shirt should be the main treatment goal, rather than constructional deficits *per se*.⁴⁰

Review of the literature

Several authors have assessed the efficacy of cognitive rehabilitation in MS, using an experimental design. Jonsson *et al.*⁴¹ randomized 40 MS patients with mild-to-moderate cognitive and behavioural impairment equally to receive one of two therapeutic approaches: specific cognitive treatment by a direct training programme based on the patient's individual neuropsychological test profile, and by compensatory strategies and psychotherapy; and non-specific, deliberately diffused mental stimulation, such as seeing and discussing different kinds of films, reading newspaper articles, and playing games. Treatment lasted an average of 46 days. Short-term effects were assessed immediately after treatment, and long-term effects after 6 months. As a whole group, patients improved significantly for several cognitive variables immediately after the end of treatment, and on fewer variables 6 months later. This could be explained by a re-test effect, or a non-specific treatment effect. Short-term effects on cognitive measures were not significant, but the specific cognitive treatment group reported significantly less depression on the BDI. After 6 months, only this group showed a significant effect on the visuo-spatial memory task. The effects on depression ratings were maintained in the cognitive treatment group after 6 months, while subjects in the non-specific treatment group rated themselves as significantly more depressed. The authors concluded

that self-rating, measuring different aspects of quality of life such as depression, may be a relevant instrument for measuring NP treatment effects.

The effectiveness of multimodal cognitive therapy, using a quasi-experimental wait-list control design was assessed by Rodgers *et al.*⁴² Multimodal cognitive therapy consisted of group psychotherapy, expressive therapy (art and music), mind-body approaches using training in self-regulation, visualization techniques, guided imagery, meditation, relaxation, and mental and physical exercises. These techniques were presented in 24 3-h sessions occurring once per week. Patients were also given homework assignments that lasted 1–1.5 h per day. Twelve of 14 patients in the treatment group and 10 of 13 in the wait-list control group completed the treatment and all assessments. The main outcome measures were NP measures of verbal learning and memory, abstraction, vocabulary, and information processing speed, as well as the BDI and tests of tactile sensitivity of the hands, grip strength and visual acuity. Patients who received therapy showed significantly greater improvement in verbal learning, verbal abstraction, depression and measures of grip strength and tactile sensitivity than patients in the untreated control group. Many of these differences, however, can be accounted for by self-selection of subjects due to non-random assignment, as the two groups differed in baseline characteristics. There was also no follow-up to assess persistency of the therapeutic effects.

The efficacy of computer-based retraining for specific impairment of four different attention domains (focused attention, divided attention, alertness and sustained attention), has also been investigated.⁴³ Twenty-two out-patients with MS received a training programme that was individually generated and that included 12 sessions concentrating on the two most impaired attention domains. A computerized attention test battery was used to test performance at baseline, after each training period, and in the following 9 weeks, and any effects on activities of daily living were assessed using a self-rating inventory. Significant improvements in performance, which remained stable for 9 weeks, could be achieved by the specific training programmes, and patients reported fewer

attention-related problems. Besides attention, possible improvements in other cognitive domains were not assessed. Since significant improvement was selectively seen in the specifically trained functions, improvement could not have been due solely to practice effect, spontaneous recovery or improved mood. These findings point to the necessity to treat different aspects of attentional impairment specifically.

The efficacy and specificity of direct computer-assisted memory retraining compared with non-specific retraining was assessed by Mendozzi *et al.*⁴⁴ Sixty patients were divided into three matched groups to receive: an 8-week specific computer-assisted memory retraining programme; a non-specific, 8-week, computer-assisted memory retraining programme to retrain attention; or no treatment (control group). All patients were neuropsychologically assessed at baseline and after programme completion. Patients were impaired for all 11 memory and attention tests at baseline, but after treatment, the group who received specific training showed a significant improvement in seven of 11 outcome measures. The group who received non-specific training improved in only one test, and the control group remained stable. These results indicate that direct memory training is effective and specific in the short term.

Benedict *et al.*⁴⁵ studied the effectiveness of cognitive-behavioural intervention in 15 patients in whom cognitive impairment was associated with marked personality and behavioural changes. Patients were randomly assigned to receive neuropsychological counselling or standard, non-specific, supportive psychotherapy. The active 12-week treatment programme, in the group receiving neuropsychological counselling, emphasized enhancement of insight through education, social skills training and behavioural modifications. All patients were re-examined within 2 weeks of the end of treatment by neuropsychologists blinded to treatment assignment. Subjects in the active treatment group showed significant improvement in disinhibition and socially aggressive behaviour compared with patients assigned to standard psychological counselling.

Finally, Lincoln *et al.*⁴⁶ conducted a single-blind, randomized, controlled trial involving 240 patients recruited from an MS Management Clinic and

assessed on a brief screening battery. They were randomized into three groups: detailed cognitive assessment, the result of which was fed back to staff involved in the patients' care; the same detailed cognitive assessment and a treatment cognitive rehabilitation programme for any deficit identified to help reduce the impact of their NP problems; and no further psychological assessment. Patients were followed up 4 months and 8 months later using the general health questionnaire (GHQ-28), extended activities of daily living scale, short form 36 (SF-36) health survey questionnaire, everyday memory questionnaire, dysexecutive syndrome questionnaire, and memory aids questionnaire. The three groups were compared on outcome measures at 4 months and 8 months after recruitment. Overall, the results showed no significant benefits of intervention on mood, quality of life, subjective cognitive impairment, or independence. The study therefore failed to detect any significant effects of cognitive assessment or cognitive intervention in this cohort of patients. There may have been some benefit from treatment in individual patients, but it was not effective for most patients allocated to receive intervention. It may be hypothesized that some patients were already coping with their cognitive problems in daily life, while for others the cognitive problems were relatively trivial compared with their physical disabilities. Treatment was not intensive and most was carried out at home, which may partially account for its lack of effectiveness. A further possible problem is that the sample size was small relative to the heterogeneity of the general population of MS subjects.

Conclusions

Disease-modifying agents may positively influence cognitive outcome by containing lesions within the CNS, and the efficacy of interferon beta-1a on cognitive measures has been demonstrated in a Phase-III trial. Existing studies on pharmacological therapies suffer from several methodological limitations, however – they were conducted on heterogeneous clinical samples, sample sizes were small, and follow-up periods were generally short. Interpretation of results is complicated by the so-called 'practice effect' that is particularly evident in

trials with symptomatic agents due to brief re-test intervals. Data on disease-modifying agents cannot be extrapolated to the general patient population since they come from highly selected samples of subjects admitted to clinical trials. Finally, when cognitive changes are documented, there is insufficient evidence of their functional impact on everyday life.

Most studies of symptomatic therapy have investigated drugs used to treat fatigue, and may be relevant when cognitive dysfunction is associated with significant fatigue. The effectiveness of amantadine and aminopyridine as fatigue treatments is debatable, while more convincing results have been obtained with modafinil.⁴⁷ Research in this area should be further extended to assess the possible effect of this agent on cognitive functioning.

In the few studies performed with cognitive rehabilitation programmes, small sample size, short follow-up periods and generic treatment effects render it difficult to draw any firm conclusions on effectiveness. New research in this area should therefore be an urgent priority. In order to further progress in the field of NP diagnosis and treatment in MS, the following research seems to be especially important:

- Brief assessment instruments for clinical screening, as well as scales reflecting the impact of cognitive deficits on activities of daily living and social skills;
- Natural history of deficits during the course of the disease and clinico-MRI correlates of deficits;
- Identification of predictors of cognitive disability to select 'at risk' patients for early treatment;
- Trials of disease-modifying and symptomatic agents that have cognitive assessment as the main end-point;
- Tailor-made rehabilitation techniques which take into account the course and stage of the disease.

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Key Paper

TREATMENT WITH METALLOTHIONEIN PREVENTS DEMYELINATION AND AXONAL DAMAGE AND INCREASES OLIGODENDROCYTE PRECURSORS AND TISSUE REPAIR DURING EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS

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Experimental autoimmune encephalomyelitis (EAE) is an animal model for the human demyelinating disease multiple sclerosis (MS). EAE and MS are characterized by significant inflammation, demyelination, neuroglial damage and cell death. Metallothionein-I and -II (MT-I + -II) are anti-inflammatory and neuroprotective proteins that are expressed during EAE and MS. We have shown

recently that exogenous administration of Zn-MT-II to Lewis rats with EAE significantly reduced clinical symptoms and the inflammatory response, oxidative stress and apoptosis of the infiltrated central nervous system areas. We show for the first time that Zn-MT-II treatment during EAE significantly prevents demyelination and axonal damage and transection, and stimulates oligodendroglial regeneration from precursor cells, as well as the expression of the growth factors basic fibroblast growth factor, transforming growth factor beta, neurotrophin (NT)-3, NT-4/5 and nerve growth factor. These beneficial effects of Zn-MT-II treatment could not be attributable to its zinc content *per se*. The present results support further the use of Zn-MT-II as a safe and successful therapy for multiple sclerosis.