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Pasquale Calabrese

Neuropsychology of multiple sclerosis

An overview

Abstract Neuropsychological dysfunctions have been well documented in patients with multiple sclerosis. We herein give an overview of the main findings of recent decades. The pros and cons of considering the cognitive deficits of multiple sclerosis patients as a form of 'subcortical dementia' are discussed. By comparing the neuropsychological descriptions of multiple sclerosis patients as given in the literature to other neurological diseases which are also associated with neuropsychological deficiencies, we propose the term 'multiple disconnection syndrome' to describe the variety of neuropsychological deficits encountered in this demyelinating disease. Furthermore, a ' threshold of cerebral tolerance' is assumed which must be crossed before cognitive dysfunctions are manifested clinically.

Key words multiple sclerosis · cognition · tests · neuropsychology

P. Calabrese, Ph.D., M.D.habil. (✉)
Dept. of Neurology
Knappschaftskrankenhaus
Neuropsychology Unit
Ruhr-University Bochum
In der Schornau 23–25
44892 Bochum, Germany
E-Mail: pasquale.calabrese@rub.de

Introduction

Multiple sclerosis (MS) is one of the most common neurological diseases, and compared to other neurological conditions it has an early onset in young adult life. In addition, although a number of descriptions concerning the mental symptoms were given in early studies [13, 53], investigations in this area developed significantly only in the last thirty years. This is partly due to the modern brain-imaging techniques which allow a more precise lesion quantification even in early disease stages [62]. Together with the improvement of neuropsychological methodology, important advances have been made in attempting to relate the behavioral disturbances to structural involvement. From socioepidemiological studies, it is known that MS leads to unemployment in 50 to 80 % of the cases within a ten year disease course [22]. Furthermore, neuropsychological studies indicate that cognitive dysfunctions are present in almost 50 % of patients [36] and result in significant functional impairment at work and at home, sometimes despite minimal physical disability [17].

Given these facts, including its negative psychosocial impact, the study of multiple sclerosis is of importance for many professions both in the medical and in the social sciences. We herein will concentrate on the neuropsychological aspects of this disease, differentiating its neuropsychological features from other brain-involving pathologies with similar performance by postulating a possible explanation for some neuropsychological characteristics.

Neuropsychology of multiple sclerosis

Although psychopathological symptoms in multiple sclerosis have been known since the early descriptions of the disease and mental functions in MS were investigated in some detail already almost 90 years ago (e. g. [51]), essential contributions to the understanding of cognitive deficits were made in the last five decades (e. g., [12, 50]). Whereas Kurtzke and coworkers [29] reported a 3 % prevalence of cognitive and affective disturbances, more recent investigations revealed prevalence rates of about 50 % [36, 45].

More recent research has resulted in a growing field of knowledge on distinct MS-related neuropsychologi-

JON 1103

cal deficiencies. The most frequently impaired cognitive domains are attention, information processing speed, memory, mental flexibility and visuoconstruction.

Attention and information processing

Attention and information processing are important cognitive functions that have been largely neglected [41]. Matthews, Cleeland, and Hopper [34] found a significant impairment of MS-patients compared to controls in tasks requiring cognitive speed. In the same study, the authors showed that the motor performance, e. g., in a finger tapping paradigm, was also substantially slowed in the patient group, thus, making it difficult to decide whether the poor performance is due to a slowed motor or mental processing rate. The same problem remained for the findings of Elsass and Zeeberg [16]. MS-patients manifested definitely delayed reaction times when compared with neurologically healthy patients. The authors could not exclude the effects of motor performance on their reaction time measures and therefore it is not clear which function – pure motor performance or information processing speed – causes the increased reaction times in MS.

Using a two choice reaction time-paradigm separating motor components from mental decision speed, Rao and coworkers [45] failed to show differences between patients and controls and therefore concluded that information processing speed, as measured by this paradigm, may not be impaired in MS.

Some other studies used tests of attention/information processing which (a) were not influenced by motor impairments and (b) examined some other components of attention than reaction time. This research was mainly based on auditory tests such as the Paced Auditory Serial Addition Task (PASAT), although concerns have been raised about the scoring method [14]. In general, MS patients performed inferior to controls in this task [15, 31, 45, 47]. Since arithmetic functions appear to be intact in MS patients and, in addition, performance in the Sternberg Memory Scanning Paradigm is undisturbed (e. g., [31]; but see [45]), the deficits in the PASAT seem to result from the demands on memory load. The most convincing hypothesis proposed to explain these deficits appears to be a working memory impairment [19]. According to Baddeley [3], only a restricted amount of information can be held in short-term memory and therefore rehearsal loops must exist. Recently, Paulesu, Frith, and Frackowiak [38] inferred from their PET data that the Broca area in the left hemisphere should be associated with the subvocal rehearsal system. An interruption of these loops, for instance due to white matter lesions, may cause the observed information processing and attention deficits. Attention deficits in MS were also found in other auditory and visual attention tasks not requiring motor functions [49]. Furthermore, attention deficits were detected also in MS patients with clinically isolated lesions [11].

A preliminary conclusion, which can be drawn from the results obtained in the small number of reports on attention and information processing deficits in MS, is that these impairments seem to occur early in the disease course and may be one reason for subsequent dysfunctions in memory or abstract reasoning.

Memory

Memory disturbances appear to be the most frequent cognitive dysfunction in MS [5, 40, 41, 45, 48]. Specifications on the frequency of these deficits are not completely identical; the range lies between 40 % and 60 % [36, 49, 54].

In 1905, Seiffer [53] concluded from his data that in nine of his ten cases "more or less dramatic intellectual impairments were found, which most frequently were observable in the areas of memory, remote as well as recent, and of associative thinking and information processing" (p. 298; translated by the author). Seiffer made quite extensive memory testing with his patients; he used, for instance, an autobiographical interview and a questionnaire-like procedure to test school- and world-knowledge in order to objectify remote memory functions; furthermore, he applied seven measures of verbal and visual short-term and long-term memory, ranging from seconds to up to 16 days.

More recently, controlled neuropsychological studies give a more variable picture of memory functions in MS. The first data were published early in the 1980s [21, 43, 54]. All these studies found disturbances in short-term memory and delayed recall for verbal as well as spatial material. Since these reports include different groups of patients, i. e., subjects with different disease courses, it can be concluded that memory dysfunctions appear to be a core deficit in MS. Most of the studies report span memory and short-term recognition to be grossly unimpaired (e. g., [2, 10, 25, 41, 43, 49]), although there is counterevidence from some studies (e. g., [5]). Measures on verbal memory, involving more complex material or supraspan tasks, seem to be affected [5, 24, 41, 49, 58]. In Selective Reminding Tasks, MS patients produced less items from long-term memory than controls, whereas the reproduction from short-term storage was undisturbed [45]. Furthermore, story recall seems to be impaired, too [9, 37, 45]. Recognition memory is usually less impaired than recall, indicating that retrieval rather than encoding or storage processes seem to be most easily impaired in MS [9, 46, 58]. As shown by Calabrese and coworkers [10], encoding capacities may also be influenced by MS. These findings of impaired verbal memory functions were also reported for visuo-spatial tasks [9, 43, 59].

Most recently, some research involving tests to measure everyday memory functions found lower scores in MS-patients than in healthy or clinical controls [10, 36]. The main deficits were observed in subtests of long-term memory for verbal as well as visuo-spatial and figural items with and without cueing. Furthermore, prospective memory was also found to be deficient.

The occurrence of remote memory deficits in MS is still a matter of debate. Using a famous faces recognition test, Beatty and colleagues [5] found retrograde memory deficits in a group of patients, while Rao and coworkers [45] could not confirm these results using a similar procedure. Naming deficits or impaired acquisition alone were not sufficient to explain the observed disturbances. Since the patients in these two studies were not comparable in all variables, further research seems necessary.

Some interesting findings were reported from authors using measures of 'frontal dysfunctions'. The investigation of memory for temporal order, metamemory functions and cognitive flexibility in MS-patients revealed deficiencies and the authors proposed that these deficits were the product of damage to temporal lobe or diencephalic memory systems and to fronto-striatal circuits [7, 8, 45].

A common distinction in the neuropsychology of memory is that of explicit and implicit learning and memory domains [18, 23]. Whereas standard recall and recognition memory tasks demand explicit and conscious recollection of facts, implicit learning may occur without awareness. Studies in MS showed normal implicit memory functions in skill learning, word stem (lexical) and semantic priming [4, 6]. In this aspect, the performance of MS-patients differed from that reported for subjects with Alzheimer's and Huntington's disease. Cognitive dysfunctions in MS seem to be different from those seen in subcortical or cortical dementia and thus may better be explained on a basis of a multiple disconnection.

Grafman, Rao, Bernardin, and Leo (1991) used different tasks to study effortful and automatic memory processes. MS-patients showed disturbances on tasks demanding effortful operations (free and cued recall), but not on tasks demanding automatic processing (monitoring frequency and modality). An explanation for these findings may be that the processing of verbal information within working memory would be impaired [32], thus, causing deficits in processing information at the level of the articulatory loop (see [3]), i. e., in retrieving and in rapidly processing verbal information. Automatic processing which demands intact semantic activation, independent from working memory, appears to be unaffected in MS (cf. [6]).

In conclusion, memory appears to be the most frequently disturbed cognitive function in MS. But when studying unselected groups of patients, a strong variability in test performance between patients is found [10, 37, 43]. However, several typical memory impairments in MS have been described. The capacity of short-term memory, recognition memory and implicit learning seems to be relatively undisturbed, whereas working memory functions, at least for verbal material, can be deficient. Retrieval strategies from short-term and long-term memory are impaired as well. The existence of disturbances in remote memory functions and encoding processes is not yet clear and needs further investigation. Research strategies controlling processing capacities and, in addition, more studies using ecologically valid instruments investigating everyday memory functions should be undertaken to obtain more information on the problems to be expected in daily living and to introduce a basis for intervention.

Cognitive flexibility

According to Vowels and Gates (1984), one-third of the MS-patients show deficits in tests requiring planning, problem solving, concept formation and utilization of feedback. Furthermore, these patients display additional memory impairment and flattening of affect; but some patients may fail on these tests without having impaired memory functions or affective flattening. Beside the commonly observed memory problems, conceptual reasoning seems to be a frequent deficit in MS (e. g., (39–41]).

Concept formation tasks, such as the Wisconsin Card Sorting Task, revealed significant differences between normal controls and MS-patients [44, 45] or scores within the same range as brain-damaged patients [34]. The MS-group, especially chronic-progressive patients, performed less well and produced a greater number of perseveration errors.

Rao and coworkers [44] used a two-choice visual discrimination task to investigate the abilities to formulate hypotheses or to use feedback to shift from or to stay with the hypothesis. Results showed that MS-patients performed worse than non-neurologic patients. The MS-group was less able to eliminate irrelevant hypotheses and tended to perseverate despite negative feedback.

Taken together, it can be concluded that MS-patients appear to be frequently impaired in conceptual reasoning. They have difficulties in responding to environmental feedback, in forming concepts and in shifting sets. These deficits are not necessarily related to attentional, memory or affective factors.

Visuospatial and visuoconstructive abilities

Research on visuoconstructive, visuospatial and visuoattentional abilities is rare, although some authors report domain-specific deficits [30]. These deficits were

not necessarily attributable to cognitive dysfunctions, as motor deficits influenced these tasks, too.

The use of non-motor visuospatial/visuoconstructive tasks revealed different results. Jennekens-Schinkel et al. [26] used the Raven Standard Progressive Matrices to measure non-verbal, visuospatial intellectual abilities and found no differences between MS-patients and controls. On the other hand, Rao and colleagues [45] found that some visuospatial skills were impaired in MS-patients. One possible interpretation for these findings is that the tests used in these investigations, measure (at least, in part) additional functions besides visual abilities (e. g., conceptual functions, logical reasoning and organizational skills).

Presently the published data are inconclusive and more research on MS-patients is needed to obtain detailed information on this cognitive domain.

Effects of disease characteristics on cognitive functioning

The influence of disease characteristics on cognitive processes in MS is a matter of controversy. While some studies report no correlation between disease duration and cognition (e. g., [19, 37, 45, 46]), a trend for a higher frequency of poor scores in a memory test in patients with a longer disease duration was reported by McIntosh-Michaelis et al. [36]. Conflicting results are also reported regarding the role of physical disability (in most cases measured with the Extended Disability Status Scale). Some studies reported significant correlations between physical disability and cognitive functioning [10, 32, 36, 45, 56, 58]; other studies were negative [5, 35, 37, 46]. More recently, Lynch and coworkers reported a strong association between cognitive impairment and the rate of disability progression. Since this study represents one of the few larger studies, including 253 inpatients, the authors argue cognitive impairment to be more closely associated with physical disability than most previous studies indicate. Further research is necessary to decide the question on the relationship between these two variables, but it must be noted that the studies with the greatest number of patients belongs to the first group [45, 56].

A third characteristic of MS would be the disease course. Most authors found a relation between disease course and cognitive functioning [10, 19, 37]. When comparing patients with primary progressive MS (PPMS) to patients with relapsing-remitting disease activity (RRMS) and individuals with a secondary-progressive (SPMS) course, most studies find PPMS patients to be more impaired in their cognitive abilities (e. g., [60]). Unfortunately, disease course might be confounded with several other variables (age, disease duration) and, thus, might be of limited value as an independent predictor for cognitive decline. Recently, Kraus and coworkers [38] were able to correctly identify 87.7 % of patients' courses in general and about 90 % of patients with chronic progressive MS by using discriminant analysis on the basis of cognitive test results.

Related to these findings on the disease course are studies on cognitive functioning early in MS course. Summing up, it may be said that subtle deficits can also be found in this group of patients. For instance, Stenager and coworkers [56] reported that deficits in a specific memory test (story recall) could be found in patients with only the mildest physical impairments. Furthermore, Klonoff and colleagues [27] as well as Grant and coworkers [20] reported learning and memory deficits in early and mild MS. Calabrese et al. [10] found no deficits compared to control subjects in MS-patients with the first manifestation of the disease.

In a longitudinal study, after an average interval of two years before follow-up, Mariani et al. [33] re-tested their 19 moderately impaired MS-patients with an initially relapsing-remitting course. The group of patients showed no evidence of cognitive decline at re-testing and, in addition, no significant change in MRI lesions. Jennekens-Schinkel and colleagues [26] concluded after a four year follow-up that "a uniform MS-related development of cognitive deficits could not be identified, improvement, stability and further deterioration being found at reassessment" (p. 229). Feinstein and coworkers (1993) tested their patients over a period of six months every two weeks. Five patients with early relapsing-remitting and five with long-standing benign multiple sclerosis were involved. Controls and those patients with stable MRI lesion scores showed no cognitive decline over this period or improved even due to practice effects. Though patients with increasing lesion load either performed less well over time or did not benefit from practice effects in this particular study, cognitive measures were not consistently correlated to structural damage as visualized by conventional MRI. While some studies failed to establish correlations between lesion load and cognitive functions [52], other investigations found high correlations to lesion load but not without topographic specificity [60]. By separating total brain volume from neocortical volume, Amato and coworkers [1] were able to demonstrate a relationship between neocortical atrophy and cognitive speed. It may be argued that there is a threshold of cerebral tolerance which must be trespassed before cognitive disturbances achieve clinical relevance. However, since cognitive disturbances might reflect neuroinflammation as well as degenerative processes, further studies need to consider these cumulative effects by adopting dynamic and structural methods representing different levels of analysis to shed some new light on these relationships.

Summary

Today, a uniform pattern of cognitive impairments in MS does not seem to be observable, but some main areas of deficits can be identified. Primary language functions, immediate and implicit memory and verbal intellectual skills appear to be unaffected. Information processing abilities, complex visuo-spatial tasks, conceptual reasoning as well as sustained attention are often impaired. However, the greatest deficits could be identified in the area of memory. Working memory and retrieval functions in short-term and long-term memory seem to be the most essential cognitive deficits in MS. Emotional disturbances often accompany cognitive decline, but seem not to be causally linked.

Although there is a growing awareness of these neuropsychological deficits in MS, some deficits are subtle and therefore might be missed during routine neurological evaluation. However, since it becomes clear that cognitive impairment is a major indicator of psychological distress as well as a source of vocational disability, social impairment and quality of life, a thorough neurocognitive evaluation should be mandatory.

References

1. Amato MP, Bartolozzi ML, Zipoli V, Portaccio E, Mortella M, Guidi L, Siracusa G, Sorbi S, Federico A, De Stefano N (2004) Neocortical volume decrease in relapsing-remitting MS patients with mild cognitive impairment. Neurology 63:89–93
2. Anzola GP, Bevilacqua L, Cappa SF, Capra R, Faglia L, Farina E, Frisoni G, Mariani C, Pasolini MP, Vignolo LA (1990) Neuropsychological assessment in patients with relapsing-remitting multiple sclerosis and mild functional impairment: correlation with magnetic resonance imaging. J Neurol Neurosurg Psychiatry 53:142–145
3. Baddeley A (1986) Working memory. Oxford: Oxford University Press
4. Beatty WW, Goodkin DE, Monson N, Beatty PA (1989) Cognitive disturbances in patients with relapsing remitting multiple sclerosis. Arch Neurol 46:1113–1119
5. Beatty WW, Goodkin DE, Monson N, Beatty PA (1990a) Implicit learning in patients with chronic progressive multiple sclerosis. Int J Clin Neuropsychol 12:166–172
6. Beatty WW, Goodkin DE, Monson N, Beatty PA, Hertsgaard D (1988) Anterograde and retrograde amnesia in patients with chronic progressive multiple sclerosis. Arch Neurol 45:611–619
7. Beatty WW, Monson N (1990) Semantic priming in multiple sclerosis. Bulletin of the Psychonomic Society 28: 397–400
8. Beatty, WW, Monson, N (1991a). Memory for temporal order in multiple sclerosis. Bulletin of the Psychonomic Society 29:10–12
9. Beatty WW, Monson N (1991b) Metamemory in multiple sclerosis. J Clin Exp Neuropsychol 13:309–327
10. Caine ED, Bamford KA, Schiffer RB, Shoulson I, Levy S (1986) A controlled neuropsychological comparison of Huntington's disease and multiple sclerosis. Arch Neurol 43:249–254
11. Calabrese P, Haupts M, Babinsky R, Markowitsch HJ, Gehlen W (1993) Alltagsgedächtnisleistungen bei Multipler Sklerose. Zeitschrift für Neuropsychologie 4:4–16
12. Callanan MM, Logsdail SJ, Ron MA, Warrington EK (1989) Cognitive impairment in patients with clinically isolated lesions of the type seen in multiple sclerosis. A psychometric and MRI study. In: Jensen K, Knudsen L, Stenager E, Grant I (eds) Mental disorders and cognitive deficits in multiple sclerosis. London: Libbey, pp 63–75
13. Canter AH (1951) Direct and indirect measures of psychological deficit in multiple sclerosis. J Gen Psychol 44: 3–50
14. Charcot JM (1877) Lectures on the diseases of the nervous system delivered at La Salpetrière. London: New Sydenham Society
15. Coo H, Hopman WM, Edgar CM, McBride EV, Brunet DG (2005) The paced auditory serial addition test (PASAT): to what extent is it performed as instructed, and is it associated with disease course? Multiple Sclerosis 11:85–89
16. DeLuca J, Johnson SK, Natelson BH (1993) Information processing efficiency in chronic fatigue syndrome and multiple sclerosis. Arch Neurol 50:301–304
17. Elsass P, Zeeberg I (1983) Reaction time deficits in multiple sclerosis. Acta Neurol Scand 68:257–261
18. Franklin GM, Nelson LN, Filley CM, Heaton RK (1989) Cognitive loss in multiple sclerosis. Case reports and review of the literature. Arch Neurol 46:162–167
19. Graf P, Squire LR, Mandler G (1987) The information that amnesic patients do not forget. J Exp Psychol Learn Mem Cogn 10:164–178
20. Grafman J, Rao SM, Litvan I (1990) Disorders of memory. In: Rao SM (ed) Neurobehavioral aspects of multiple sclerosis. New York: Oxford University Press, pp 102–117
21. Grant I, McDonald WI, Trimble MR (1989b) Neuropsychological impairment in early multiple sclerosis. In: Jensen K, Knudsen L, Stenager E, Grant I (eds) Mental disorders and cognitive deficits in multiple sclerosis. London: Libbey, pp 17–26
22. Grant I, McDonald WI, Trimble MR, Smith E, Reed R (1984) Deficient learning and memory in early and middle phases of multiple sclerosis. J Neurol Neurosurg Psychiatry 47: 250–255
23. Gronning M, Hannisdal E, Mellgren SI (1990) Multivariate analyses of factors associated with onemployment in people with multiple sclerosis. J Neurol Neurosurg Psychiatry 53:388–390
24. Heindel WC, Butters N, Salmon DP (1988) Impaired learning of a motor skill in patients with Huntington's disease. Behav Neurosci 102:141–147
25. Huber SJ, Paulson GW, Shuttleworth EW, Chakeres D, Clapp LE, Pakalnis A, Weiss K, Rammohan K (1987) Magnetic resonance imaging correlates of dementia in multiple sclerosis. Arch Neurol 44:732–736
26. Jambor K (1969) Cognitive functioning in multiple sclerosis. Br J Psychiatry 115:765–775
27. Jennekens-Schinkel A, Laboyrie PM, Lanser JBK, van der Velde EA (1990) Cognition in patients with multiple sclerosis. After four years. J Neurol Sci 99:229–247
28. Klonoff H, Clark C, Oger J, Paty D, Li D (1991) Neuropsychological performance in patients with mild multiple sclerosis. J Nerv Ment Dis 179:127–131
29. Kurtzke JF (1983) Rating neurologic impairment in multiple sclerosis: an extended disability status scale (EDSS). Neurology 33:1444–1452

30. Kurtzke JF, Beebe GW, Nagler B, Auth TL, Kurland LT, Nefzger MD (1972) Studies on the natural history of multiple sclerosis. 6. Clinical and laboratory findings at first diagnosis. Acta Neurol Scand 48:19–46
31. LaPointe LL, Maitland CG, Blanchard AA, Kemker BE, Stierwalt JA, Heald GR (2005) The effect of auditory distraction on visual cognitive performance in multiple sclerosis. J Neuroophthalmol 25:92–94
32. Litvan I, Grafman J, Vendrell P, Martinez JM (1988a) Slowed information processing in multiple sclerosis. Arch Neurol 45:281–285
33. Litvan I, Grafman J, Vendrell P, Martinez JM, Junqué C, Vendrell JM, Barraquer-Bordas JL (1988b) Multiple memory deficits in patients with multiple sclerosis. Exploring the working memory system. Arch Neurol 45:607–610
34. Mariani C, Farina E, Cappa SF, Anzola GP, Faglia L, Bevilacqua L, Capra R, Mattiolo F, Vignolo LA (1991) Neuropsychological assessment in multiple sclerosis: a follow-up study with magnetic resonance imaging. J Neurol 238:395–400
35. Matthews CG, Cleeland CS, Hopper CL (1970) Neuropsychological patterns in multiple sclerosis. Diseases of the Nervous System, 31:161–170
36. Maurelli M, Marchioni E, Cerretano R, Bosone D, Bergamaschi R, Citterio A, Martelli A, Sibilla L, Savoldi F (1992) Neuropsychological assessment in MS: clinical, neuropsychological and neuroradiological relationships. Acta Neurol Scand 86:124–128
37. McIntosh-Michaelis SA, Roberts MH, Wilkinson SM, Diamond ID, McLellan DL, Martin JP, Spackman AJ (1991) The prevalence of cognitive impairment in a community survey of multiple sclerosis. Br J Clin Psychol 30: 333–348
38. Minden SL, Moes EJ, Orav J, Kaplan E, Reich P (1990) Memory impairment in multiple sclerosis. J Clin Exp Neuropsychol 12:566–586
39. Paulesu E, Frith CD, Frackowiak RSJ (1993) The neural correlates of the verbal component of working memory. Nature 362:342–344
40. Penman M-F (1991) Assessing the prevalence of cognitive impairment in multiple sclerosis: implications for patient management. Axon 13:45–49
41. Petersen RC, Kokmen E (1989) Cognitive and psychiatric abnormalities in multiple sclerosis. Mayo Clin Proc 64: 657–663
42. Rao SM (1986) Neuropsychology of multiple sclerosis: a critical review. J Clin Exp Neuropsychol 8:503–542
43. Rao SM (1990) (ed) Neurobehavioral aspects of multiple sclerosis. New York: Oxford University Press
44. Rao SM, Hammeke TA, McQuillen MP, Khatri BO, Lloyd D (1984) Memory disturbance in chronic progressive multiple sclerosis. Arch Neurol 41: 625–631
45. Rao SM, Hammeke TA, Speech TJ (1987) Wisconsing Card Sorting Test performance in relapsing-remitting and chronic-progressive multiple sclerosis. Journal of Clinical and Consulting Psychology, 55:263–265
46. Rao SM, Leo GJ, Bernardin L, Unverzagt F (1991a) Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns and prediction. Neurology 41:685–691
47. Rao SM, Leo GJ, St. Aubin-Faubert P (1989a) On the nature of memory disturbances in multiple sclerosis. J Clin Exp Neuropsychol 11:699–712
48. Rao SM, St. Aubin-Faubert P, Leo GJ (1989b) Information processing speed in patients with multiple sclerosis. J Clin Exp Neuropsychol 11:471–477
49. Ron MA (1986) Multiple sclerosis: psychiatric and psychometric abnormalities. J Psychosom Res 30:3–11
50. Ron MA, Callanan MM, Warrington EK (1991) Cognitive abnormalities in multiple sclerosis: a psychometric and MRI study. Psychol Med 21:59–68
51. Ross AT, Reitan RM (1955) Intellectual and affective functions in multiple sclerosis. Arch Neurol Psychiatry 73: 663–677
52. Ross DM (1917) The mental symptoms in disseminated sclerosis. Rev Neurol Psychiatry 13:361–373
53. Rovaris DM (1917) The mental symptoms in disseminated sclerosis. Rev Neurol Psychiatry 13:361–373
54. Seiffer W (1905) Über psychische, insbesondere Intelligenzstörungen bei multipler Sklerose. Archiv für Psychiatrie und Nervenkrankrankheiten 40:252–303
55. Staples D, Lincoln NB (1979) Intellectual impairment in multiple sclerosis and its relation to functional abilities. Rheumatology and Rehabilitation 18:153–160
56. Stenager E, Knudsen L, Jensen K (1989a) Correlation of Beck Depression Inventory score, Kurtzke Disability Status Scale and cognitive functioning in multiple sclerosis. In: Jensen K, Knudsen L, Stenager E, Grant I (eds) Mental disorders and cognitive deficits in multiple sclerosis. London: Libbey, pp 147–151
57. Stenager E, Knudsen L, Jensen K (1989b) Multiple sclerosos: correlation of cognitive dysfunction with Kurtzke Disability Status Scale. In:Jensen K, Knudsen L, Stenager E, Grant I (eds) Mental disorders and cognitive deficits in multiple sclerosis. London: Libbey, pp 27–37
58. Swirsky-Sacchetti T, Mitchell DR, Seward J, Gonzales C, Lublin F, Knobler R, Field HL (1992) Neuropsychological and structural brain lesions in multiple sclerosis: a regional analysis. Neurology 42:1291–1295
59. Van den Burg W, van Zomeren AH, Minderhoud JM, Prange AJA, Meijer NSA (1987) Cognitive impairment in patients with multiple sclerosis and mild physical disability. Arch Neurol 44:494–501
60. Vowels LM (1979) Memory impairment in multiple sclerosis. In: Molloy M, Stanley GV, Walsh KW (eds) Brain impairment: Proceedings of the 1978 brain impairment workshop. Melbourne: University of Melbourne, pp 10–22
61. Wachowius U, Talley M, Silver N, Heinze HJ, Sailer M (2005) Cognitive impairment in primary and secondary progressive multiple sclerosis. J Clin Exp Neuropsychol 27:65–77
62. Vowels LM, Gates GR (1984) Neuropsychological findings. In: Simons AF (ed) Multiple sclerosis: psychological and social aspects. London: Heinemann, pp 82–90
63. Young IR, Hall AS, Pallis CA, Bydder GM, Legg NJ, Steiner RE (1981) Nuclear magnetic resonance imaging of the brain in multiple sclerosis. Lancet 2:1063–1066