# APOE ϵ4 and the cognitive genetics of multiple sclerosis

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## ABSTRACT

**Background:** Evidence linking *APOE* to myelin repair, neuronal plasticity, and cerebral inflammatory processes suggests that it may be relevant in multiple sclerosis (MS). The purpose of this study was to determine whether the ϵ4 allele of *APOE* is associated with cognitive deficits in patients with MS.

**Method:** Using a case-control design, 50 patients with MS with the ϵ4 allele (ϵ4+) and 50 ϵ4−negative (ϵ4−) patients with MS were tested using a comprehensive battery of tests evaluating the cognitive domains most often affected in MS.

**Results:** The ϵ4+ and ϵ4− patients with MS were well-matched with respect to demographic variables (age, gender, ethnicity, education, employment status, premorbid IQ) and disease variables (disease course, disease duration, Expanded Disability Status Scale, 25-foot timed walk, 9-hole pegboard test). In addition, the groups were similar in depressive symptoms, in the proportion of patients receiving disease-modifying therapy, and in carriage of the *APOE* ϵ2 allele. Results showed that none of the 11 cognitive outcome variables differed between ϵ4+ and ϵ4− patients with MS. Cognitive measures were also unrelated to ϵ4 interactions with age and gender. The incidence of overall cognitive dysfunction did not differ between ϵ4+ and ϵ4− groups, nor did failure on any test, and ϵ4 carriage was not a significant predictor of any adverse cognitive outcome. These negative results endured with the exclusion of ϵ2+ subjects from the analyses.

**Conclusion:** This study does not support a role for the ϵ4 allele in cognitive dysfunction in multiple sclerosis. ***Neurology***® **2010;74:1611–1618**

## GLOSSARY

**9HPT** = 9-hole pegboard test; **AD** = Alzheimer disease; **BRNB** = Brief Repeatable Battery of Neuropsychological Tests; **EDSS** = Expanded Disability Status Scale; **MACFIMS** = Minimal Assessment of Cognitive Function in Multiple Sclerosis; **MANCOVA** = multivariate analysis of covariance; **MANOVA** = multivariate analysis of variance; **MS** = multiple sclerosis; **TWT** = 25-foot timed-walking test.

Forty percent to sixty percent of patients with multiple sclerosis (MS) are affected by cognitive deficits of sufficient severity to impede their daily functioning, relationships, employment, and quality of life.[1-3] Impairments in processing speed, working memory, attention, visual memory, verbal memory, and executive functions are common in MS and may be present at the earliest stages of the disease.[4,5] *APOE*, encoded on chromosome 19q13, has been of significant interest in MS[6] owing in part to its established role as the most important genetic risk factor for sporadic Alzheimer disease (AD).[7] Three common allelic variants—ϵ2, ϵ3, and ϵ4—give rise to 3 distinct protein isoforms. The ϵ4 allele raises the risk of AD in a dose-dependent manner.[7] The possible association between ϵ4 and cognitive dysfunction in MS has been investigated in a handful of studies with conflicting results.[8-13] Two studies, for example, reported a relationship between ϵ4 carriage and verbal memory deficits in patients with MS.[11,12] These findings seemed compelling in part because ϵ4 adversely affects verbal memory in AD and in elderly populations without dementia.[14] On the

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other hand, a study with a robust sample size of over 1,000 patients with MS reported no association of ε4 and cognition, yet only a single cognitive test that did not probe verbal memory was utilized.[13] The remaining 3 studies did not isolate verbal memory performance from composite cognitive scores.[8-10] A potential role of *APOE* ε4 in cognitive dysfunction in MS therefore remains uncertain. We investigated the association between the ε4 allele of *APOE* and cognitive dysfunction in MS using detailed neuropsychological inquiry and a case-control design. We hypothesized that patients with MS carrying the ε4 allele would exhibit poorer cognitive performance than those without the ε4 allele.

## METHODS

**Patient screening, enrollment, and matching.** Patients were recruited from MS clinics at St. Michael's Hospital and Sunnybrook Health Sciences Centre between July 2006 and September 2008.

Participation in this study was solicited from 421 patients, of whom 362 (86%) enrolled. Reasons for nonenrollment were as follows: did not meet inclusion/exclusion criteria specified below (n = 33), refusal due to transportation issues (n = 11), refusal due to work or family obligations (n = 8), and refusal for other or unspecified reasons (n = 7). Inclusion criteria consisted of a diagnosis of MS by the Macdonald criteria,[15] fluency in English, and the ability to provide informed consent. Exclusion criteria consisted of age >65 years, corticosteroid treatment in the 4 weeks preceding cognitive testing, history of any other neurologic illness or medical illness that could influence cognition including head injury with loss of consciousness of any duration, alcohol abuse, and history of major mental illness with the exception of major depressive disorder. Demographic (age, gender, years of education, self-reported ethnicity) and disease variables (duration of MS, disease course) were collected at initial screening with information corroborated by medical records. Genetic material was acquired from each patient via buccal swab. Of 362 subjects screened, 75 were ε4+ (21%). Genotypic frequencies were in accordance with Hardy-Weinberg equilibrium ($p = 0.16$). The ε4+ patients were contacted by telephone and invited for cognitive testing. Fifty ε4+ patients with MS agreed; they underwent cognitive testing as described below. Of the remaining 25 ε4+ patients, 4 were unable to participate due to current MS exacerbation or steroid treatment, 2 were hospitalized, 11 were unable to be subsequently contacted, 7 withdrew from the study after agreeing to participate, and 3 were unable to attend due to inclement weather. There were no demographic or disease variable differences between 50 ε4+ patients with MS who participated and the 25 who did not.

The ε4+ patients with MS were group-matched to 50 consecutive ε4− patients with MS on age and gender. ε4− Patients with MS underwent the same testing protocol as ε4+ subjects described below.

**Genetic testing.** *APOE* genotype was determined by the methods described in appendix e-1 on the *Neurology*® Web site at www.neurology.org.

**Neuropsychological evaluation.** All 100 patients with MS (50 ε4+ and 50 ε4−) were evaluated by a researcher who was blind to their genetic status. The 2 groups did not differ with respect to the proportion of subjects tested in the morning vs afternoon ($p > 0.05$). Ethnicity did not differ between the groups (white European vs minority, $p > 0.05$). On the day of neuropsychological testing, the following variables were collected: employment status, medications, visual acuity, Expanded Disability Status Scale (EDSS),[16] 9-hole pegboard test (9HPT), and 25-foot timed walking test (TWT). 9HPT and TWT were administered and scored according to guidelines for the Multiple Sclerosis Functional Composite Scale.[17] All subjects had near vision of at least 20/70 corrected. Premorbid IQ was estimated using the Adult National Reading Test.[18] To assess depressive symptoms, the Beck Depression Inventory was administered.[19]

Subjects underwent cognitive testing using the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) battery.[20] This 90-minute test battery was developed by expert consensus with each constituent test meeting the criteria of having standardized test materials and instructions, published data from large normative samples, and minimization of potentially confounding motor and sensory deficits. The MACFIMS evaluates the 5 cognitive domains most often affected in MS (processing speed/working memory; verbal/visual memory; executive functions; visual perception/spatial orientation; and language/other) with 7 tests (Paced Auditory Serial Addition Task; California Verbal Learning Test–II; Brief Visual Memory Test–Revised; Delis-Kaplan Executive Function System; Controlled Oral Word Association Test) that collectively yield 11 cognitive measures.[20-21] Each test is described in detail in appendix e-2. Constituent tests of the MACFIMS were administered using standard materials in the order recommended by the MACFIMS guidelines.[20] Scoring was completed by a researcher blind to subjects' genetic status.

**Statistics.** Statistical analyses were performed using SPSS 16.0 with $\alpha$ set at 0.05.

Demographic and disease variables were compared between ε4+ and ε4− patients with MS using 2-sided *t* tests for continuous, parametric data (reported as mean ± SD); Mann-Whitney tests for continuous, nonparametric data (reported as median [interquartile range 25th–75th percentile values]); and Pearson $\chi^2$ tests for categorical data.

Cognitive comparisons between ε4+ and ε4− subjects were performed by multivariate analysis of variance (MANOVA). Age, gender, and education were entered as covariates in a multivariate analysis of covariance (MANCOVA). These variables were chosen due to their reliability and known influence on cognition.

To investigate the presence of possible ε4 × age[22] and ε4 × gender[23] interactions, a customized MANOVA was carried out on the 11 cognitive outcome variables with age, gender, ε4, ε4 × age, and ε4 × gender entered as fixed factors.

Cognitive impairment was defined a priori as per MACFIMS guidelines as failure on 2 or more tests with failure being defined as scoring ≤5th percentile on any test index compared to recommended age-, gender-, and education-matched normative values.[20,21] Proportions of ε4+ vs ε4− subjects with MS failing an individual index or meeting criteria for cognitive impairment were compared by Pearson $\chi^2$ analyses.

Logistic regression analyses were used to determine whether ε4 carriage was a predictor of failure on any cognitive index or overall cognitive dysfunction using the forced entry method with ε4 status, age, gender, and education entered as predictors.

Power analyses were conducted with G*Power v3.1.[24]

**Table 1** Demographic and disease variables

| | *APOE* ϵ4 status | | | |
|---|---|---|---|---|
| | ϵ4+ (n = 50) | ϵ4− (n = 50) | Statistic | *p* Value |
| Age, y, mean ± SD[a] | 43.7 ± 10.4 | 44.2 ± 9.5 | *t*, *df* = 0.26, 98 | 0.80 |
| Gender, n (%) female[b] | 29 (58) | 37 (74) | $\chi^2 = 2.85$ | 0.09 |
| Education, y, median (IQR)[c] | 15.0 (13.0–16.0) | 16.0 (13.0–17.0) | *U* = 1110.50 | 0.33 |
| Employment status, n (%) employed[b] | 28 (56) | 26 (52) | $\chi^2 = 0.16$ | 0.69 |
| Disease course, n (%)[b] | | | | |
| Relapsing-remitting | 36 (72) | 37 (74) | $\chi^2 = 2.10$ | 0.35 |
| Secondary progressive | 12 (24) | 8 (16) | | |
| Primary progressive | 2 (4) | 5 (10) | | |
| Disease duration, y, median (IQR)[c] | 8 (2.9–15.3) | 7.3 (3.5–12.0) | *U* = 1171.50 | 0.84 |
| EDSS, median (IQR)[c] | 4.0 (2.9–6.0) | 4.0 (3.0–6.0) | *U* = 1175.50 | 0.61 |
| 9HPT, median score (IQR)[c] | 23.0 (19.6–27.3) | 20.9 (18.0–27.6) | *U* = 1058.00 | 0.24 |
| TWT, median score (IQR)[c] | 4.2 (3.6–6.9) | 5.0 (4.0–8.0) | *U* = 798.00 | 0.17 |
| Disease-modifying medication, n (%)[a] | 21 (42.0) | 25 (50.0) | $\chi^2 = 0.64$ | 0.42 |
| Beck Depression Inventory, median score (IQR)[c] | 12.0 (6.5–22.5) | 11.0 (5.0–23.0) | *U* = 1085.00 | 0.90 |
| ANART, median errors (IQR)[c] | 12.0 (7.3–19.8) | 9.0 (6.0–18.0) | *U* = 935.50 | 0.43 |

Abbreviations: 9HPT = 9-hole pegboard test; ANART = Adult National Reading Test; EDSS = Expanded Disability Status Scale; IQR = interquartile range; TWT = 25-foot timed walking test.
[a] *t* Test.
[b] Pearson $\chi^2$ test.
[c] Mann-Whitney *U* test.

**Standard protocol approvals, registrations, and patient consents.** This study was approved by the Research Ethics Boards of the 2 university hospitals. All participants provided informed, written consent.

**RESULTS Sample demographics and disease variables.** Demographic characteristics and disease variables for the entire sample of patients with MS (n = 100) are described in appendix e-3. Table 1 shows demographic and disease variables for the 50 ϵ4+ and 50 ϵ4− patients with MS. Genotypic frequencies were as follows: 7 ϵ2/ϵ4, 39 ϵ3/ϵ4, 4 ϵ4/ϵ4, 8 ϵ2/ϵ3, and 42 ϵ3/ϵ3. The ϵ4+ and ϵ4− groups did not differ with respect to carriage of the ϵ2 allele (14% vs 16%, $\chi^2 = 0.078$, $p = 0.799$, odds ratio [95% confidence interval] = 0.86 [0.29–2.60]).

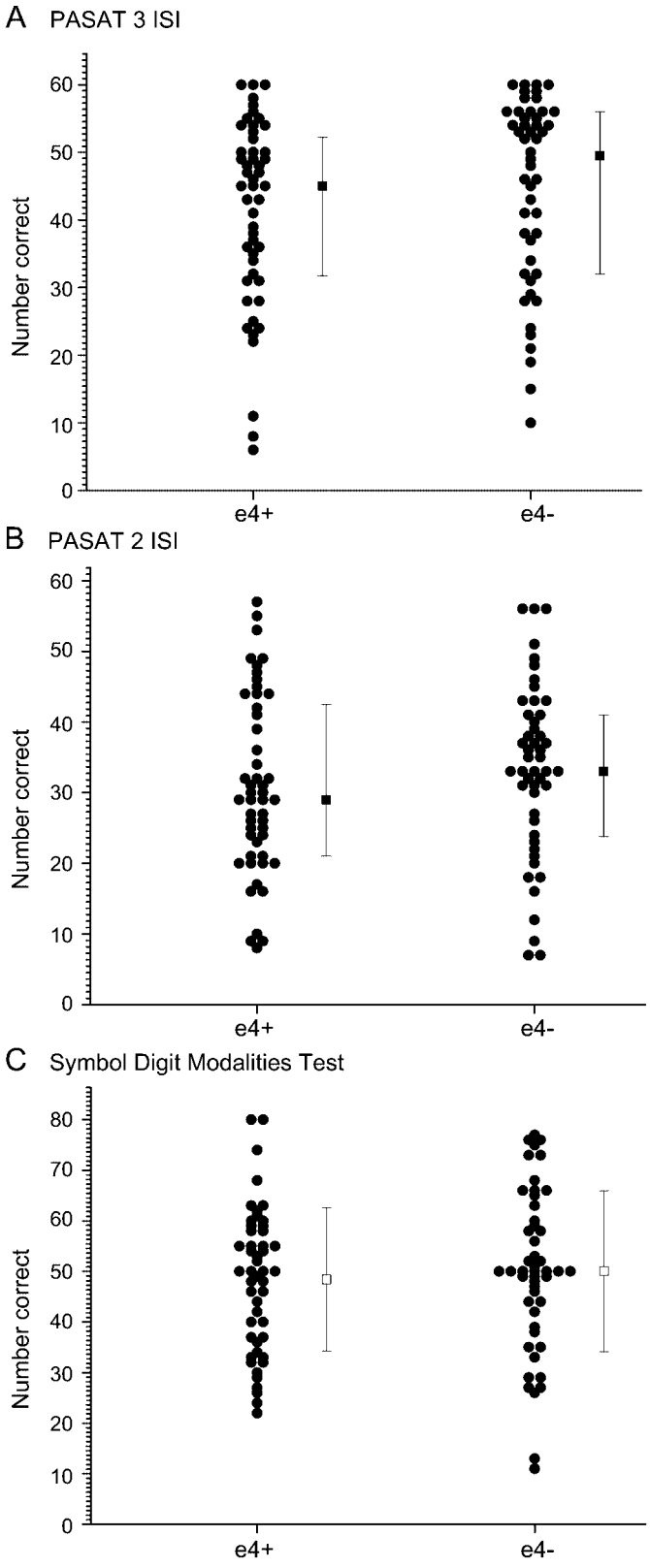
**Neuropsychological variables in *APOE* ϵ4+ and ϵ4− patients with MS.** The raw scores for cognitive indices that probed processing speed/working memory (figure 1), learning and memory in verbal and visual modalities (figure 2), executive functions, visual perception and spatial orientation, and language/other (figure 3) are shown for ϵ4+ and ϵ4− patients with MS. Between-group MANOVA was performed with ϵ4 status as the independent variable and the 11 cognitive indices as dependent variables. The combined dependent variables were not affected by ϵ4 status (Wilks $\lambda = 0.869$; $F_{11,88} = 0.927$; $p = 0.518$; partial $\eta^2 = 0.104$). No ϵ4 main effect was detected when age, gender, and education were added as covariates in a MANCOVA (Wilks $\lambda = 0.917$; $F_{11,85} = 0.701$; $p = 0.734$; partial $\eta^2 = 0.083$).

To investigate a possible age and gender interaction, the sample was dichotomized based on a mean age of 44 (age <44, n = 44, mean ± SD age of this group = 34.6 ± 5.4 years). A between-subjects MANOVA was performed on the 11 cognitive variables with ϵ4 status, age (< or ≥44), and gender as independent variables and ϵ4 × age and ϵ4 × gender as custom factors. The ϵ4 × age interaction yielded no main effect on the combined dependent variables (Wilks $\lambda = 0.917$; $F_{11,84} = 0.691$; $p = 0.744$; partial $\eta^2 = 0.083$). Similar negative results were obtained for the ϵ4 × gender interaction (Wilks $\lambda = 0.915$; $F_{11,84} = 0.708$; $p = 0.727$; partial $\eta^2 = 0.085$).

**Global and domain-specific cognitive dysfunction in ϵ4+ and ϵ4− patients with MS.** Forty-one percent of the entire sample was cognitively-impaired. There was no difference in the proportion of ϵ4+ vs ϵ4− patients with MS with cognitive impairment (48% vs 34%, $\chi^2 = 2.03$, $p = 0.155$, odds ratio [95% confidence interval] = 1.79 [0.80–4.01]). As table 2 shows, ϵ4+ patients with MS did not have higher rates of failure on any of the 11 cognitive indices evaluated.

Logistic regression analyses were performed with overall cognitive dysfunction and failure on any of 11 cognitive indices as outcomes. There were 4 predic-

**Figure 1** Processing speed and working memory




ISI = interstimulus interval; PASAT = Paced Auditory Serial Addition Task; ● = scores of individual patients with multiple sclerosis; ■ = median ± interquartile range; □ = mean ± SD.

tors: age, gender, education, and ϵ4 status. Collinearity diagnostics yielded variable inflation factors less than 1.1 which were deemed acceptable. ϵ4 carriage was not a predictor of any outcome investigated (table e-1).

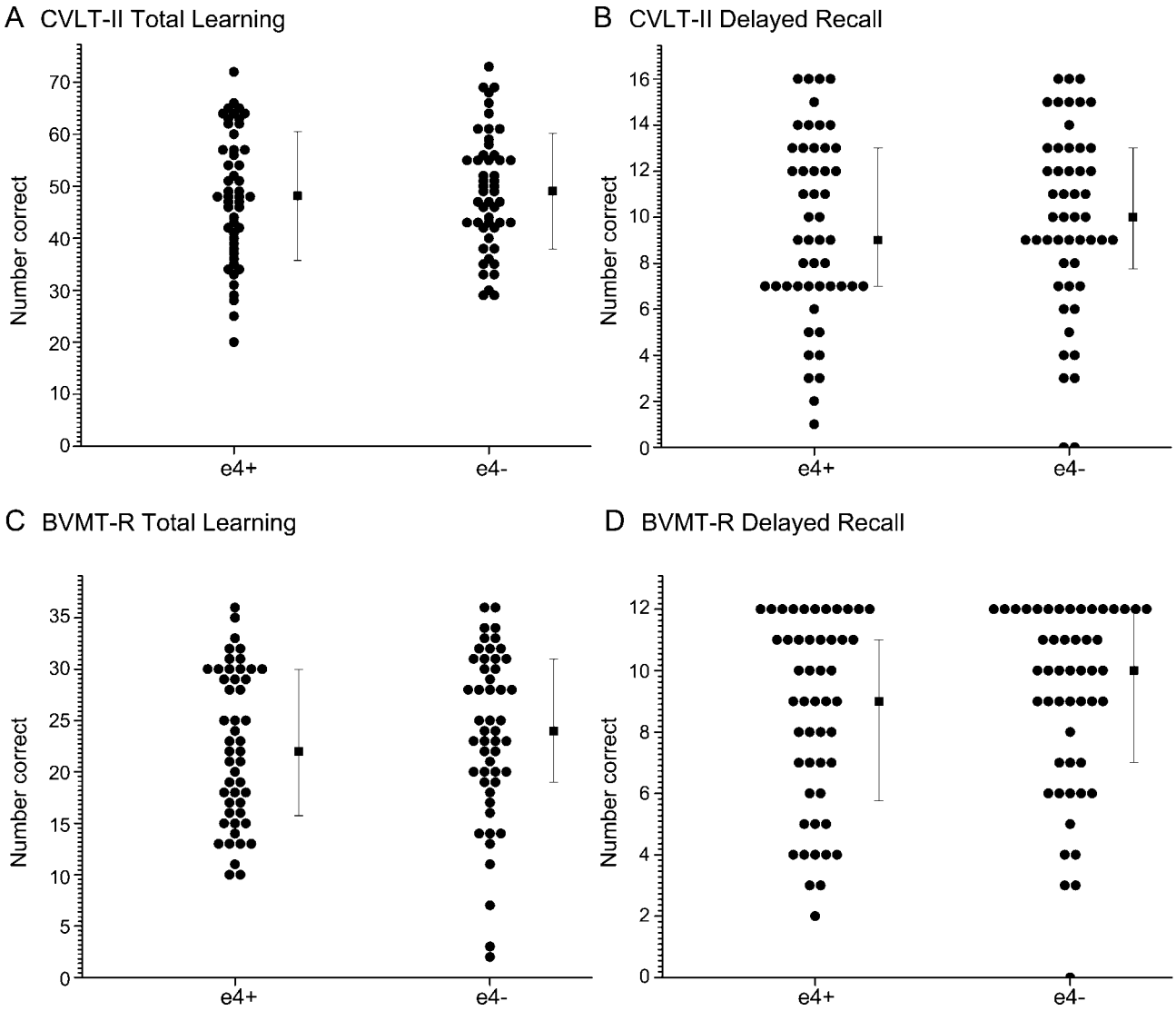
Post hoc analyses are shown in appendix e-4.

**DISCUSSION** Our objective was to compare the neuropsychological performance of 100 patients with MS, 50 with and 50 without the *APOE* ϵ4 allele, in a single, prospective sample. We found that attention, processing speed, working memory, verbal memory, visual memory, visual-spatial processing, verbal fluency, and executive functions were no worse in ϵ4+ patients with MS than in those without the allele. These negative results endured irrespective of whether group comparisons were made between scores on individual cognitive indices, between subjects failing a given cognitive index, or between subjects with overall cognitive impairment. In addition, no age or gender interactions with the ϵ4 allele were detected on cognitive outcome measures. The inclusion of relevant covariates did not alter the results, nor did changing the criteria for test failure or cognitive impairment to capture either milder or more severe dysfunction that may have been masked by cutoff effects.

The absence of an ϵ4 effect on cognitive outcomes cannot be attributed to confounding external variables between ϵ4+ and ϵ4− MS groups in this study. The 2 groups were well-matched on demographic (age, gender, ethnicity, education) and disease characteristics (disease duration, disease course, EDSS, 9HPT, TWT). In addition, ϵ4+ and ϵ4− groups did not differ with respect to estimates of premorbid IQ, depressive symptoms, or the proportion of patients taking disease-modifying medication. The ϵ2 allele, suggested to be a protective factor for AD,[25] was also similar in frequency in the 2 groups, and additional analyses excluding the 15 ϵ2 carriers did not reveal cognitive differences between ϵ4+ and ϵ4− patients with MS. This study was not, however, powered to detect a possible protective effect of ϵ2. In the present study, distributions of gender, ethnicity, education, and disease course were representative of the local, community-dwelling MS population. Consistent with previous studies of *APOE*, the prevalence of the ϵ4 allele was 21%.[26] The prevalence of cognitive impairment in our sample, 41%, also fits with the published literature.[1]

The 90-minute cognitive battery employed in this study, the MACFIMS, is more comprehensive than the Brief Repeatable Battery of Neuropsychological Tests (BRNB), which was used in 3 previous studies of ϵ4 in MS. The MACFIMS addresses 2 shortcom-

**Figure 2** Verbal and visual memory

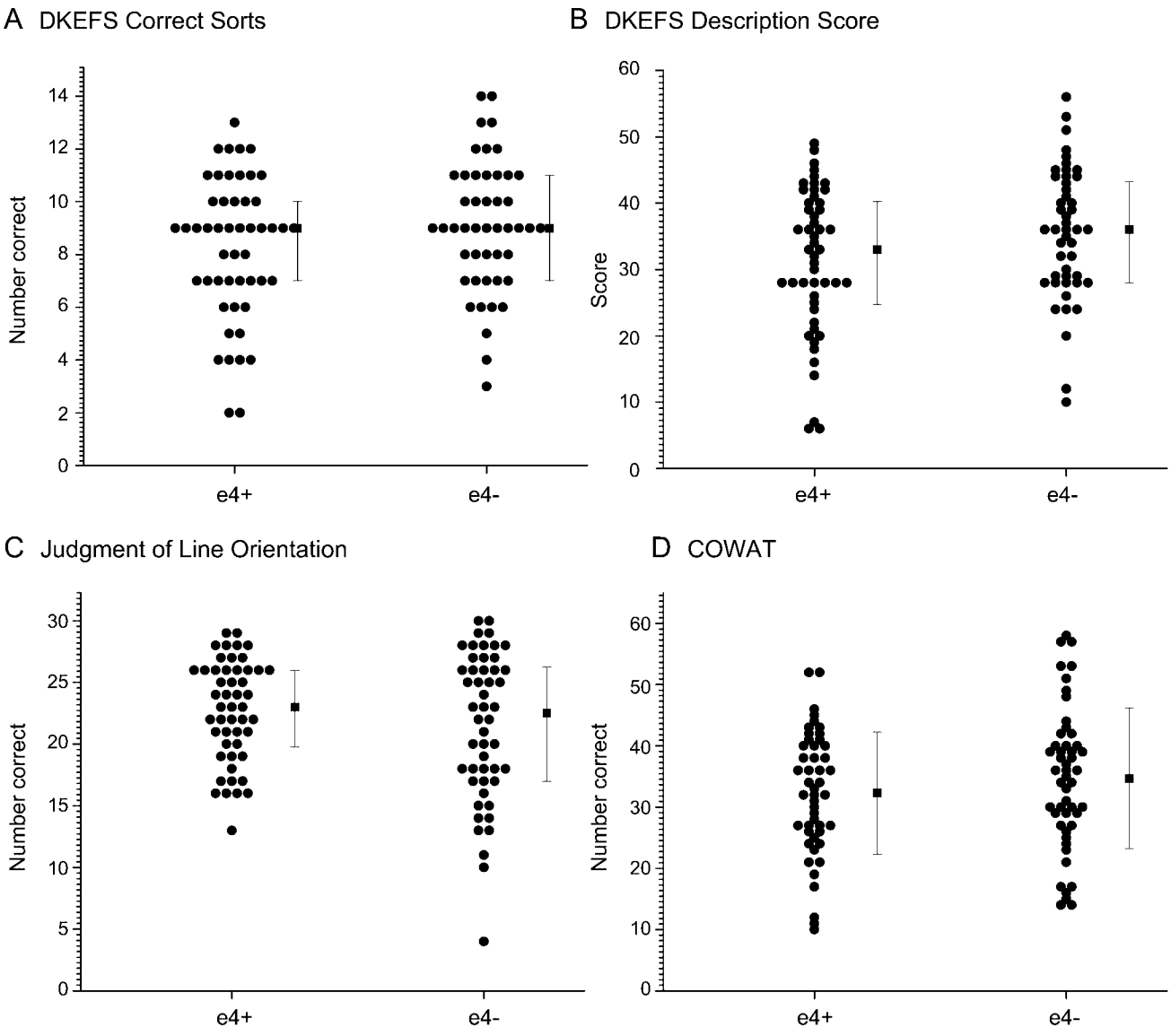



CVLT-II = California Verbal Learning Test-II; BVMT-R = Brief Visual Memory Test-Revised; ● = scores of individual patients with multiple sclerosis; ■ = median ± interquartile range.

ings of the BRNB. First, it includes tests of executive function and visuospatial orientation, cognitive functions that may each be compromised in up to one quarter of patients with MS[21,27] and, in some elderly and AD populations, have been associated with ϵ4.[28-31] Second, the MACFIMS replaced the verbal and visual memory tests used in the BRNB with tests possessing better psychometric properties and larger normative samples.[20] When compared in patients with MS, the MACFIMS and the BRNB had similar sensitivity with respect to verbal learning tests but the visual memory test in the former possessed greater discriminative validity.[32] Criterion validity of the MACFIMS has been amply demonstrated; each constituent test differentiated patients with MS from normal controls with medium to very large effect sizes.[21] Finally, it is important to note that the recommended cutoff for a patient to be designated cognitively impaired using the MACFIMS has ecological validity; cognitive impairment defined by the MACFIMS sensitively predicted the employment status of patients with MS.[21]

Six studies to date have examined the relationship between *APOE* and cognition and the results are equivocal. In part, this may reflect methodologic limitations. The first report[8] found no association between ϵ4 and cognitive impairment but with only 12 ϵ4+ subjects, type II error was a distinct possibility. A subsequent study[9] tested 503 patients with MS—of whom 74 were ϵ4+—using the Mental Deterioration Battery.[33] The sensitivity of this battery to cognitive dysfunction in MS is not clear and the ecological validity of cutoffs for impairment are likewise untested.[34] No association was found be-

Figure 3 Executive functions, visuospatial orientation, and language




COWAT = Controlled Oral Word Association Test; DKEFS = Delis-Kaplan Executive Function System; ● = scores of individual patients with multiple sclerosis; ■ = median ± interquartile range.

tween ϵ4 and overall cognitive impairment. A series of post hoc subgroup analyses revealed an association between severe cognitive impairment and ϵ4 in males only, but age, education, and disability were potential confounders in this result. Cognitive impairment in females did not correlate with any variable investigated including age and education. The authors conceded that they could not explain the gender effect, a finding that that raises the possibility of sampling problems. A third study used a variation of the BRNB for cognitive evaluation in ϵ4+ and ϵ4− patients with MS matched on demographic and disease variables. A single cognitive composite score did not differ between the groups. In further analyses a more stringent threshold for cognitive impairment found a correlation with ϵ4. In a fourth study, the BRNB was used with validated cutoffs for failure on individual cognitive tests (i.e., below the fifth percentile of scores obtained by healthy controls).[1,2,34] ϵ4 carriage emerged as a predictor of verbal learning impairment. This finding was limited in part by a modest sample of 23 ϵ4+ patients and by the absence of data on the potentially confounding variable of premorbid IQ. The latter omission may lead to overestimating memory deficits in individuals with low-average IQ.[35] Another group[12] used the Neuropsychological Screening Battery for MS (BRNB minus the SDMT) to study ϵ4+ subjects who were slightly older than ϵ4− subjects. Estimates of premorbid IQ and frequency of the ϵ2 allele were not reported. The odds ratio of failing the verbal memory test in ϵ4+ vs ϵ4− patients was 2.1 ($p = 0.035$). There were no other

**Table 2** Failure in cognitive indices in ε4+ vs ε4− patients with multiple sclerosis

| Test | *APOE* ε4 status: ε4+ (% failed) (n = 50) | ε4− (% failed) (n = 50) | $\chi^2$ | *p* Value | Odds ratio (confidence interval) |
|---|---|---|---|---|---|
| PASAT-3 | 28 | 27 | 0.03 | 0.87 | 1.08 (0.44–2.61) |
| PASAT-2 | 26 | 25 | 0.83 | 0.36 | 1.56 (0.60–4.08) |
| SDMT | 16 | 14 | 0.19 | 0.66 | 1.21 (0.51–2.87) |
| CVLT-II TL | 14 | 10 | 0.38 | 0.54 | 1.47 (0.43–4.97) |
| CVLT-II DR | 32 | 24 | 0.79 | 0.37 | 1.49 (0.62–3.59) |
| BVMT-R TL | 33 | 22 | 1.42 | 0.23 | 1.72 (0.70–4.21) |
| BVMT-R DR | 29 | 26 | 0.08 | 0.77 | 1.14 (0.47–2.76) |
| DKEFS CS | 14 | 10 | 0.38 | 0.54 | 1.47 (0.43–4.97) |
| DKEFS DESC | 12 | 10 | 0.1 | 0.75 | 1.23 (0.35–4.32) |
| JLO | 18 | 36 | 4.11 | 0.04 | 0.39 (0.15–0.98) |
| COWAT | 33 | 22 | 1.43 | 0.232 | 1.73 (0.70–4.25) |

Abbreviations: BVMT-R = Brief Visual Memory Test–Revised; COWAT = Controlled Oral Word Association Test; CVLT-II = California Verbal Learning Test–II; DKEFS = Delis-Kaplan Executive Function System; JLO = Judgment of Line Orientation; PASAT = Paced Auditory Serial Addition Task; SDMT = Symbol Digit Modalities Test.

cognitive differences. In a secondary analysis, the young cohort of ε4+ patients (age 31–40) was found to be especially susceptible to verbal learning deficits. These secondary results are difficult to interpret, however, since the statistical tests employed and the subgroup sample sizes were not provided. Finally, a recent study[13] found no difference between ε4+ and ε4− patients with MS on a single cognitive index, the SDMT.

The limitations of previous studies preclude any firm conclusions. Our study, in contrast, controlled for many of these problems with an adequate sample size; detailed, validated neuropsychological inquiry; close group matching; and analyses that took into account any modifying effect of demographic variables. Our negative result therefore presents the most robust evidence to date that presence of the ε4 allele has no effect on cognition in MS. Notwithstanding these conclusions, this study is not without its drawbacks. Like previous studies, our investigation was cross-sectional in design. An effect of ε4 on the rate of cognitive decline therefore cannot be excluded. In addition, our sample of 100 patients with MS had statistical power to detect a medium but not a small effect size. The clinical relevance of a small effect size may, however, be questionable and would challenge routine screening of patients with MS for possession of the ε4 allele. In the present study, patients with MS older than 65 years were excluded due to the possible confounding influence of age-related cognitive decline. The presence of an ε4 effect on cognition in older patients with MS therefore remains to be determined. It is also possible that ε4 is associated with cognitive deficits in subgroups of patients with MS that were not highly represented in our community-based sample; for example, in individuals with severe physical disability. An additional limitation of this study was that we were unable to determine a possible dose effect of the ε4 allele.

The search for heritable underpinnings of MS is not new.[36] Using cognitive dysfunction as a phenotype in genetic studies of MS is, however, a more recent development.[37] Our negative results should not limit this line of inquiry. Longitudinal data relating to putative ε4 effects are needed. Furthermore, research exploring the potential relationship between other genes and cognitive dysfunction may prove more fruitful.

## AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Omar Ghaffar.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## DISCLOSURE

Dr. Ghaffar served as a consultant to Cerebrio (a continuing medical education company); has received travel expenses and/or honoraria for lectures or educational activities not funded by industry; and has received salary and research support from the CIHR. Dr. Reis and Dr. Pennell report no disclosures. Dr. O'Connor has served on scientific advisory boards for Novartis, Sanofi-Aventis, Bayer Schering Pharma, Genentech, Inc., and Roche; has received travel funding from Biogen Idec and Teva Pharmaceutical Industries Ltd.; has received honoraria for speaking engagements or educational events from Biogen Idec and Novartis; has served as a consultant for Biogen Idec, Bayer Schering Pharma, EMD Serono, Teva Pharmaceutical Industries Ltd., Genentech, Inc., and Warburg Pincus; has received research support from Bayer Schering Pharma, Novartis, BioMS Medical, Sanofi-Aventis, and Roche; and served as the National Scientific and Clinical Advisor to the Multiple Sclerosis Society of Canada. Dr. Feinstein has served on scientific advisory boards for Merck Serono and Avanir Pharmaceuticals; has received travel funding from Merck Serono, Teva Pharmaceutical Industries Ltd., Bayer Schering Pharma, and Biogen Idec; served on the editorial boards of *Multiple Sclerosis* and the *African Journal of Psychiatry*; received royalties from the publication of *The Clinical Neuropsychiatry of Multiple Sclerosis* (Cambridge University Press, 2007); has received honoraria for speaking engagements or educational activities from Merck Serono, Teva Pharmaceutical Industries Ltd., Bayer Schering Pharma, and Biogen Idec; served on the Medical Advisory Committee of the Multiple Sclerosis Society of Canada; performs neuropsychiatric evaluation including cognitive testing and brain imaging in clinical practice (20% of effort); and has received research support from Teva Pharmaceutical Industries Ltd., Merck Serono, the Canadian Institutes of Health Research, the University of Toronto, and the Multiple Sclerosis Society of Canada.


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