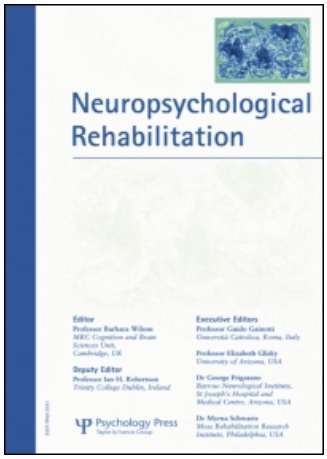

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Apolipoprotein E and Subjective Symptomatology Following Brain Injury Rehabilitation

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The Apolipoprotein E (*APOE*) allele ε4 has been repeatedly demonstrated to be related to the development of Alzheimer's disease. We have investigated its potential significance in stroke and traumatic brain injury as reflected in outcome following neuropsychological rehabilitation of 39 brain injured adults (mean age at injury 33.3 years, range 16–56). Outcome was evaluated by rating scales derived from a questionnaire completed by each brain injured subject and by a close relative. The questionnaire scales covered physical, cognitive, emotional, and social functioning. Ten of the subjects were found to carry the *APOE-ε4* gene and the remaining 29 did not. There were no differences between these two

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groups on the questionnaire scales at the time of entry into the rehabilitation programme. At follow-up, however, on average more than 1 year after completing the rehabilitation programme, scale scores for the *APOE-nonε4* group showed significant improvements in functioning whereas the *APOE-ε4* showed deterioration, the two groups differing on a global scale by 0.87 standard deviations. A battery of attention and memory tests, administered and readministered over a shorter test–retest interval, showed no such deterioration. Within the constraints of the time interval and small sample sizes involved, these findings would suggest that the presence of the *APOE-ε4* may be associated with poorer outcome following neuropsychological rehabilitation.

APOLIPOPROTEIN E AND SUBJECTIVE SYMPTOMATOLOGY FOLLOWING BRAIN INJURY REHABILITATION

Apolipoprotein E (*APOE*) is a protein that has an important function in cholesterol transport in plasma and the brain. It is encoded by a gene located on chromosome 19 for which, in humans, there are three alleles, *APOE-ε2*, *APOE-ε3*, *APOE-ε4*. It is now well established that the allele *APOE-ε4* is associated with an elevated risk for, and earlier onset of, Alzheimer's disease, although the neuropathological mechanism is not yet clearly understood (Strittmatter & Roses, 1996). *APOE-ε4* has also been shown to be related to poorer functioning in activities of daily life and to poorer cognitive test performance in non-Alzheimer's elderly individuals (Albert et al., 1995; Blesa et al., 1996).

APOE polymorphism is also of relevance for acute-onset brain injury. Although it does not appear to be related to the risk of stroke, the presence of *APOE-ε4* is prognostic of cognitive decline following stroke (Kalmijn, Feskens, Launer, & Kromhout, 1996). Similarly, there is evidence to suggest that while traumatic brain injury generally elevates the risk for the subsequent dementia (Rasmusson, Brandt, Martin, & Folstein, 1995; Schofield et al., 1997) this elevation is particularly marked in the presence of *APOE-ε4* Katzman et al., 1996; Mayeux et al., 1995). *APOE-ε4* has also been found to be related to more immediate poorer outcome following traumatic brain injury in terms of mortality and vegetative state (Teasdale, Nicoll, Murray, & Fiddes, 1997) and recovery of consciousness (Sorbi et al., 1995).

Neuropsychological rehabilitation typically seeks to improve the functioning of people who have suffered an acute-onset brain injury, the most common among these being stroke and traumatic brain injury. In view of the above evidence it might therefore be predicted that outcome following rehabilitation would be better for individuals who do not carry the *APOE-ε4* allele than for those who do. It has been the objective of the present study to test this hypothesis. To our knowledge this has not previously been done.

There are a number of means by which outcome following rehabilitation can be assessed. Both Wilson (1997) and Prigatano (1997) have recently

emphasised that the objective of rehabilitation and the evaluation of its effect should focus upon the full spectrum of cognitive, emotional, and social dysfunctions which can arise following injury. Indicators of success in this respect are sometimes obtained by eliciting the subjective reports of brain injured people themselves prior to and following rehabilitation (Teasdale & Caetano, 1995). Self-reports, however, cannot stand alone since a major element of the dysfunctioning can be impaired self-awareness (Hillier & Metzer, 1997; Prigatano, 1991). The reports of close relatives may have greater validity. In the present study we have therefore chosen to focus upon subjective symptomatology as reported by both brain injured people themselves and by their close relatives. We have used the European Brain Injury Questionnaire (EBIQ) which ranges across cognitive, emotional, and social factors and has earlier been shown to be both reliable and valid (Teasdale et al., 1997).

METHOD

As part of a larger research project participants in the present study were derived from 54 adults who had sustained an acute brain injury and who had completed the rehabilitation programme at the Centre for Rehabilitation of Brain Injury (CRBI) in Copenhagen between the period September 1994 to June 1996. The type of injury was the most commonly traumatic brain injury (TBI) or cerebrovascular accident (CVA). The programme adopts an interdisciplinary, holistic approach which is tailored to the individual in the light of neuropsychological assessments (Diller, 1990). Brain injured people are admitted into the programme in groups of about 15, and the programme runs for about 4 months with day attendance at the centre, followed by close contact and monitoring of progress in the community for at least a further 8 months. Details of the programme are presented elsewhere. (Christensen & Caetano, 1997).

The neuropsychological assessments at the start of the programme include the completion of the European Brain Injury Questionnaire (EBIQ). This instrument has been specifically designed in two parallel versions for use with people with brain injury and their close relatives (Teasdale et al., 1997). It comprises 63 questions relating to "problems or difficulties that people sometimes experience in their lives". People with brain injury are asked to indicate "how much (they) have experienced any of these within the last month", and their responses are coded on a 3-point scale: "not at all" (1), "a little" (2), or "a lot" (3). Relatives complete a version in which they give their perceptions of the brain injured person. From both the brain injured person's and the relative's questionnaires eight scales are calculated corresponding to complaints categorised as somatisation, cognition, motivation, impulsivity, depression, social isolation, physical symptoms, and communication. An additional "core" scale summarises complaints globally. The scales are computed as the simple average of the scores 1, 2, or 3 for the questionnaire items included in them, and

thus the scale scores likewise can range from 1.0 through 3.0. Further details concerning the reliability and validity of the EBIQ are presented elsewhere (Teasdale, et al., 1997).

Both at the beginning of the programme and at the end of the 4-month day attendance, subjects are assessed with neuropsychological test battery. This test battery includes a touch-screen computer-controlled set of seven attention and memory tests designed to be ecologically valid. These comprise:

1. A simulated traffic-light (alternating red/green) response test in which lift time and travel time are recorded (in milliseconds).
2. A divided attention task in which memory for a weather report and a traffic report is tested after also performing the above traffic-light test. Items (out of 21) recalled are scored for both tests.
3. Memory for last names is tested following presentation of a list of (six) first and last names. This is tested on two successive presentations and after 1 hour.
4. Free recall of a "shopping-list" of 15 items is tested five successive times with selective reminding of non-remembered items after each recall attempt. Recall is also tested 1 hour later. In the present study we have employed the first and fifth recall, together with the 1 hour delayed recall.
5. Name recall is tested for 14 video recorded individuals who introduce themselves with first their names and then their place of origin. There are two successive presentations followed by a retest after 1 hour.
6. Identification of a new face is tested where a succession of one, then two, then three, up to 25 faces appear simultaneously on the screen. Number of trails of first error, and total of correct identifications in the 25 presentations is recorded.
7. Recall of the placement (by the subject) of 20 everyday objects throughout a 12-room house is tested. The number correctly recalled on a first attempt, and the total number correct allowing a second attempt, are recorded.

Further details of these tests are presented elsewhere (Crook & Larrabee, 1992; Crook, Youngjohn, & Larrabee, 1992). It should be noted that each of the tests (with the exception of the first) is administered in a different parallel version at the end of the rehabilitation programme.

The 54 brain injured subjects were contacted in the period September 1996 to January 1997 and invited to take part in a follow-up study which would involve a semi-structured interview, a questionnaire (the EBIQ), and the determination of *APOE* genotype.

DNA genotyping at the *APOE* locus in the genome of the participants was performed by polymerase chain reaction of DNA from epithelial cells,

followed by restriction enzyme digestion and size analysis. The method was adapted from that described by Wenham, Price, and Blandell (1991). In this study, however, the DNA was obtained from epithelial cells released during a mouth wash (Main, Jones, MacGillivray, & Banfield, 1991). The mouth wash was stored at −20°C until processed in the laboratory. The thawed cells were concentrated by centrifugation and suspended in an alkaline solution. The DNA within the epithelial cells was released by heat treatment and the suspension neutralised. The dissolved DNA was separated from the remains by centrifugation and subjected to 40 cycles of polymerase chain reaction. The reaction mixture contained the Wenham primers (Wenham et al., 1991), AmpliTaq Gold DNA polymerase, the four common deoxynucleoside triphosphates, 5% dimethyl sulfoxide, and 0.75 mM $MgCl_2$. The AmpliTaq Gold DNA polymerase was activated and the DNA denaturated by an initial high temperature treatment of the reaction mixture (95°C for 5 minutes). Each of the 40 cycles was composed of annealing (65° C for 30 seconds), extension (70°C for 90 seconds), and denaturation (94°C for 30 seconds). After a final prolonged extension (70°C for 10 minutes) the product was digested with the restriction enzyme *Cfo* I. The *Cfo* I digest was analysed on ready-to-use 12% Poly(NAT) gels (Elchrom Scientific) with pBR322 DNA-*Msp* I digest fragments as size markers. The gel was stained by SYBR-green I and the fluorescent bands evaluated in ultraviolet light. The *APOE* genotype was determined from the band pattern. Besides bands composed of only a few basepairs, the *APOE-ε2* allele gave clearly visible fragments of 91 and 81 bp, *APOE-ε3* gave 91 and 48bp, and *APOE-ε4* gave 72 and 48 bp.

Among the 54 potential subjects we have obtained complete EBIQ questionnaires—both prior to the programme start and at follow-up—together with APOE determination for 39 (72%). Drop-out was due to unwillingness to participate ($n = 8$), death ($n = 1$), and the absence of a close relative who could complete the EBIQ ($n = 6$).

In analyses of demographic and medical variables we have employed non-parametric procedures (Chi-squared tests and Mann-Whitney *U* tests) owing to nominal scaling or markedly skewed distributions. However, preliminary inspection of the distributions for the EBIQ scales, and the neuropsychological test data, revealed that they approximated to normal distributions (with typically some small tendency towards positive skew in the EBIQ scales). We have therefore employed parametric statistics (analysis of variance) in analysing them.

RESULTS

Genotype distribution for the 39 subjects is shown in Table 1. It can be seen that the distribution closely corresponds to percentages reported for the general population in Denmark (Gerdes, Klausen, Sihm, & Faergeman, 1992). For

TABLE 1
Distribution of *APOE* Genotypes in Sample and in the Danish Population[1]

Genotype	*N*	*%*	*Population %*
2/2	1	3	2
3/2	6	15	12
3/3	22	56	55
4/2	0	0	2
4/3	9	23	25
4/4	1	3	4
Total	39	100	100

[1] from Gerdes et al., 1992

TABLE 2
Comparison of Included/Excluded Subjects on Demographic and Medical Variables

	In sample		*Not in sample*		*Probability*
	N	*%*	*N*	*%*	
Sex					
Male	25	64	9	60	
Female	14	36	6	40	> .1[1]
Type of injury					
CVA	19	49	6	40	
TBI	18	46	6	40	
Other[3]	2	5	3	20	> .1[1]
Year of programme entry					
1994	9	23	5	33	
1995	19	49	8	53	
1996	11	28	2	13	> .1[1]
	Mean	(*SD*)	*Mean*	(*SD*)	
Education level[4]	2.0	(1.0)	2.6	(0.8)	> 1[2]
Age at Injury	33.3	(11.0)	35.4	(13.5)	> 1[2]
Coma duration (days)	5.7	(10.2)	5.3	(9.2)	> 1[2]
Hospitalisation (days)	69.2	(62.0)	51.7	(47.3)	> 1[2]
Injury to programme entry (years)	1.9	(1.6)	2.2	(1.4)	> 1[2]

[1] Exact significance Chi-squared test (Mehta & Patel, 1996)
[2] Exact significance Mann–Whitney *U* test (Mehta & Patel, 1996)
[3] One case of cerebral infection and one of unilateral hydrocephalus
[4] Scale from 0 = minimum grade school to 5 = academic education

purposes of analysis the genotypes 2/2, 2/3, and 3/3 are combined into a single group (*APOE-nonε4*, $n = 29$) as are the 4/3 and 4/4 genotypes (*APOE-ε4*, $n = 10$).

Table 2 shows basic demographic and medical data for those not included in the study versus those included (*APOE-nonε4* and *APOE-ε4* combined), and Table 3 shows the latter group divided into *APOE-nonε4* and *APOE-ε4*. It can be seen that there are no significant differences between those included in the study and those not included in terms of distributions for sex, injury type (CVA versus TBI), or year in which the subject had been in the CRBI programme. Nor are there any significant differences between the *APOE-nonε4* and *APOE-ε4* groups with respect to any of these medical and demographic variables.

Table 4 shows means for nine EBIQ scales, separately for own and relative's report, and as a function of *APOE* and time in relation to the rehabilitation programme. The mean changes from preprogramme to follow-up (together

TABLE 3
Comparison of *APOE-nonε4* and *APOE-ε4* Groups on Demographic and Medical Variables

	APOE-nonε4		*APOE-ε4*		*Probability*
	N	%	*N*	%	
Sex					
Male	19	65	6	60	
Female	10	35	4	40	> .1[1]
Type of injury					
CVA	13	45	6	60	
TBI	14	48	4	40	
Other	2	7	0	0	> .1[1]
Year of programme entry					
1994	7	24	2	20	
1995	15	52	4	40	
1996	7	24	4	40	> .1[1]
	Mean	(*SD*)	*Mean*	(*SD*)	
Education level[3]	1.9	(1)	2.3	(1)	> .1[2]
Age at Injury	31.4	(10)	38.6	(12.5)	> .1[2]
Coma duration (days)	7.4	(12)	1.6	(2.4)	> .1[2]
Hospitalisation (days)	71.7	(69)	62.7	(39.5)	> .1[2]
Injury to programme entry (years)	2.1	(1.6)	1.3	(1.2)	> .1[2]
Programme entry to follow-up (years)	1.5	(0.5)	1.3	(0.6)	> .1[2]

[1] Exact significance Chi-squared test (Mehta & Patel, 1996)
[2] Exact significance Mann–Whitney *U* test (Mehta & Patel, 1996)
[3] Scale from 0 = minimum grade school to 5 = academic education

TABLE 4
Means for Own and Relative Scale, at Preprogramme and at Follow-up, as a Function of *APOE* Genotype

	APOE-nonε4 (n = 29)				*APOE-ε4 (n = 10)*			
	Preprogramme		*Follow-up*		*Preprogramme*		*Follow-up*	
	Mean	*(SD)*	*Mean*	*(SD)*	*Mean*	*(SD)*	*Mean*	*(SD)*
Own								
Somatisation	1.69	(0.4)	1.5	(0.3)	1.64	(0.4)	1.84	(0.6)
Cognition	1.71	(0.4)	1.56	(0.3)	1.65	(0.3)	1.74	(0.3)
Motivation	1.55	(0.4)	1.43	(0.3)	1.76	(0.5)	1.68	(0.4)
Impulsivity	1.62	(0.4)	1.58	(0.4)	1.45	(0.5)	1.58	(0.4)
Depression	1.61	(0.4)	1.54	(0.4)	1.67	(0.5)	1.86	(0.6)
Isolation	1.54	(0.3)	1.43	(0.4)	1.43	(0.3)	1.53	(0.3)
Physical symptoms	1.29	(0.3)	1.18	(0.2)	1.38	(0.3)	1.4	(0.3)
Communication	1.68	(0.5)	1.54	(0.5)	1.58	(0.6)	1.75	(0.7)
Core	1.6	(0.3)	1.48	(0.3)	1.56	(0.3)	1.74	(0.4)
Relative								
Somatisation	1.61	(0.3)	1.41	(0.3)	1.66	(0.3)	1.74	(0.3)
Cognition	1.85	(0.4)	1.65	(0.4)	1.69	(0.4)	1.81	(0.3)
Motivation	1.73	(0.4)	1.48	(0.4)	1.72	(0.5)	1.82	(0.4)
Impulsivity	1.62	(0.4)	1.53	(0.4)	1.62	(0.5)	1.68	(0.4)
Depression	1.56	(0.4)	1.42	(0.4)	1.52	(0.5)	1.7	(0.6)
Isolation	1.47	(0.4)	1.45	(0.4)	1.4	(0.4)	1.53	(0.4)
Physical symptoms	1.51	(0.2)	1.45	(0.2)	1.53	(0.2)	1.55	(0.2)
Communication	1.72	(0.5)	1.53	(0.5)	1.48	(0.5)	1.63	(0.5)
Core	1.67	(0.3)	1.5	(0.3)	1.61	(0.3)	1.76	(0.3)

with standard errors) for each of the nine scales are also shown in Fig. 1 (for own report) and Fig. 2 (for relative's report). The EBIQ data were analysed using a repeated-measure analysis of variance with genotype as a between-group factor and scale, report (self versus relative) and time (preprogramme versus follow-up) as within-group factors. The overall comparison of genotypes was not significant [$F(1,37) = 1.17$, $P > .2$]. There was, however, a significant interaction between genotype and time [$F(1,37) = 10.2$, $P < .01$]. Other significant effects were overall differences between scales [$F(8,296) = 5.08$, $P < .01$] and an interaction between scales and report [$F(8,296) = 5,65$, $P < .01$]. Mauchly's test of sphericity was significant for these latter two terms ($P < .01$) but correcting the degrees of freedom using Greenhouse-Geisser Epsilon (Howell, 1997) did not diminish their significance. No other main terms or interactions were significant ($P > .2$).

Separate analyses of the differences between scales and their interaction with report showed that, for both reports, cognitive difficulties are the most

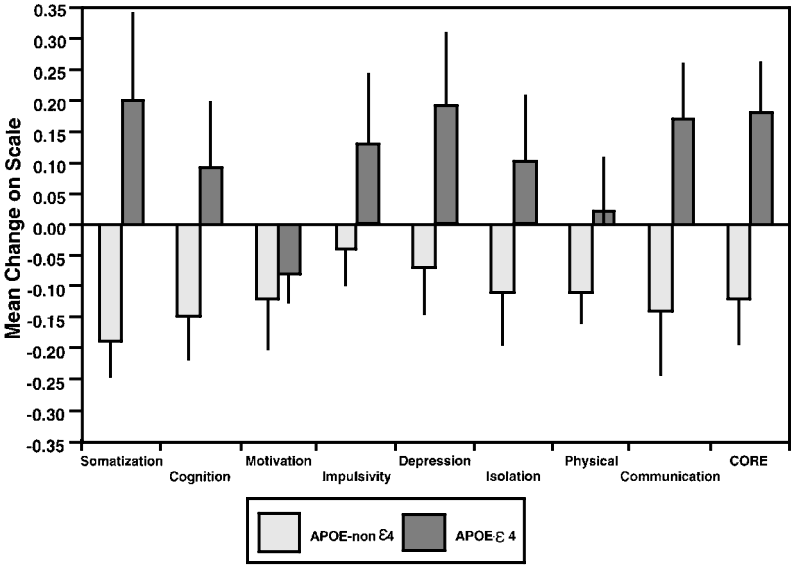

FIG. 1. Mean changes (and standard errors) for own scales from preprogramme to follow-up, as a function of *APOE* genotype.

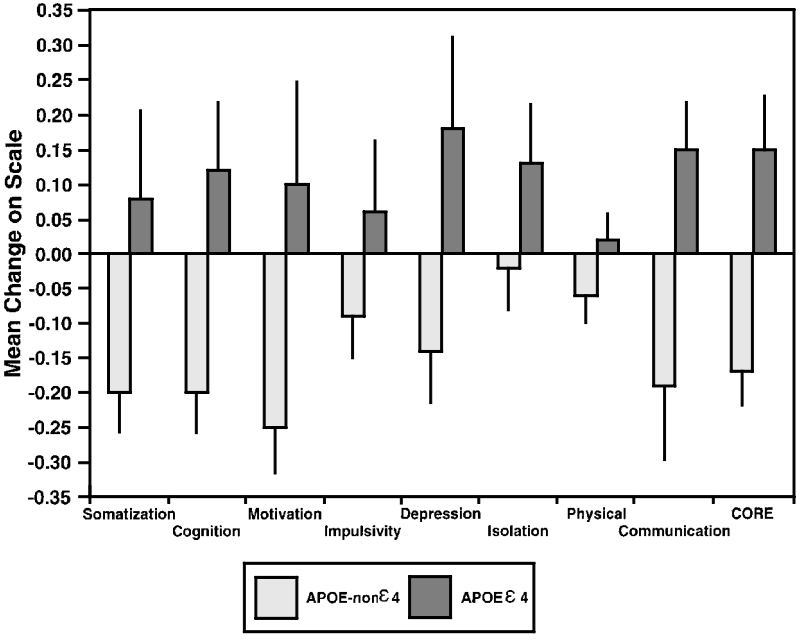

FIG. 2. Mean changes (and standard errors) for relative scales from preprogramme to follow-up, as a function of *APOE* genotype.

commonly endorsed and physical consequences that least common. However, whereas for both of these scales the relatives report more difficulties than brain injured subjects themselves, the reverse was true for the somatisation, depression, social isolation, and communication scales.

Of more central interest for the present study was the overall significant interaction between genotype and time point. It is striking that all of the scale means for the *APOE-nonε4* group decline between preprogramme and follow-up, whereas, with only one exception, they increase among the *APOE-ε4* group (see Table 4 and Figs. 1 and 2). In order to disentangle the interaction of genotype and time point we conducted separate analyses for the *APOEnon-ε4* and *APOE-ε4* groups. Among the *APOE-nonε4* group there was a significant overall effect of time-point [$F(1,28) = 10.78$, $P < .01$] indicating a uniform significant *reduction* in scale scores from preprogramme to follow-up. For the *APOE-ε4* group the time-point comparison approached statistical significance [$F(1,9) = 4.06$, $P < .075$] notwithstanding the small group size. To the extent that this effect may be considered as real, it comprises a broadly uniform *increase* in scale scores from preprogramme to follow-up.

The apparent lack of difference between the genotype groups at preprogramme is confirmed by a separate analysis of variance [$F(1,37) = 0.17$, $P = .68$]. Nor does this analysis reveal any interactions between genotype and any other factor ($P > .1$).

The interaction between genotype and time is robust. It remained significant after covarying simultaneously for the possible effects of type of injury (using only the CVA and TBI groups), age at injury, and time between injury and programme entry [$F(1,32) = 9.26$, $P < .01$]. It was also significant for the TBI group statistically tested alone [$F(1,16) = 6.09$, $P < .025$] and approaches significance for the CVA group statistically tested alone [$F(1,17) = 3.44$, $P < .08$].

For the two groups combined there were moderate correlations for each of the nine scales between the brain injured subjects and their relatives prior to the programme (median $r = .46$, range .25–.67) and these rose somewhat at follow-up (median $r = .59$, range .51–.69). Correspondingly the preprogramme to follow-up correlations were moderate for both the brain injured subjects (median $r = .51$, range .25–.62) and the relatives (median $r = .55$, range .32–.60).

Figure 3 shows the distribution of scores on the global Core scale at follow-up for the brain injured subjects and their relatives, as a function of genotype. The degree of discrimination between the two groups is indicated, for instance, by the fact that a cut-off at 1.8 on both scales would identify four (40%) of the *APOE-ε4* group but only two (7%) of the *APOE-nonε4* group, and that a cut-off at 1.4 on both scales would identify 8 (80%) of the *APOE-ε4* group but only 11 (38%) of the *APOE-nonε4* group.

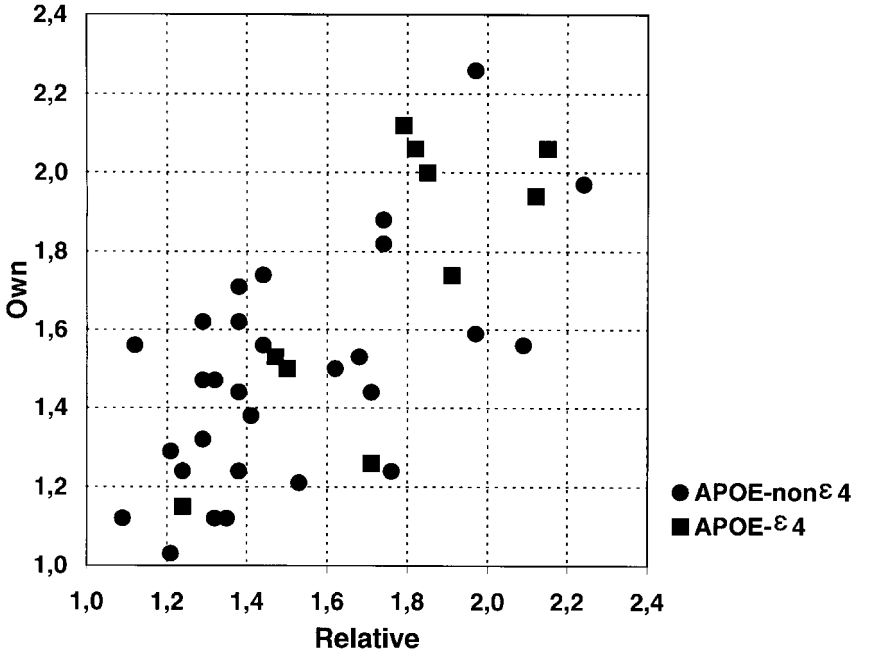

FIG. 3. Distribution of Core scale scores at follow-up, as a function of *APOE* genotype.

A further indication of the effect size may be computed by expressing the difference between the means of two groups on the Core scale at follow-up as a proportion of their (identical) standard deviations (see Table 4). Following Howell (1997, p. 217) this yields (1.76–1.50)/0.3 = 0.87 which would be classified as a large effect size.

Table 5 presents the means for the 17 scores that are derived from the seven tests in the neuropsychological test battery administered prior to and immediately on completion of the 4-month day programme. Data were available for 22 of the *APOE-nonε4* and 8 of the *APOE-ε4* group. We performed analyses of variance on each of the seven groups of tests separately, using repeated measures for the test item (two of three items depending on the test) and for time of testing, pre- or postprogramme. In these seven analyses, one (for the First/Last Names test) showed a significant overall effect for genotypes [$F(1,28) = 4.28$, $P < .05$] with the *APOE-ε4* group performing *better* than the *APOE-nonε4* group. Five of the analyses showed significant effects of test item with, as was to be expected, significantly more items being recalled on a successive testing and fewer thereafter at delayed recall. There were no other significant main effects or interactions among the analyses ($P > .1$).

TABLE 5
Means for Neuropsychological Tests, at Preprogramme and at Follow-up, as a Function of *APOE* Genotype

	APOE-nonε4 (n = 22)				*APOE-ε4 (n = 8)*			
	Preprogramme		*Follow-up*		*Preprogramme*		*Follow-up*	
	Mean	*(SD)*	*Mean*	*(SD)*	*Mean*	*(SD)*	*Mean*	*(SD)*
Reaction Time—Mean Lift	245.5	(57.4)	224.5	(44.0)	298.4	(176.5)	251.3	(94.2)
Reaction Time—Mean Travel	268.4	(76.2)	249.1	(73.6)	254.3	(160.1)	268.4	(138.9)
Radio report (weather) recall	8.1	(5.1)	8.6	(3.9)	8.0	(7.3)	10.4	(4.8)
Radio report (traffic) recall	7.7	(4.6)	9.5	(3.8)	10.5	(8.3)	11.3	(3.6)
First/Last Names Trial 1 recall	1.3	(1.2)	1.0	(1.0)	1.4	(2.1)	2.1	(1.0)
First/Last Names Trial 2 recall	2.5	(1.2)	2.6	(1.4)	3.1	(2.1)	3.9	(1.1)
First/Last Names Delayed recall	2.0	(1.4)	2.0	(1.6)	2.6	(2.3)	3.8	(1.5)
Groceries List Trial 1 recall	7.2	(2.4)	7.3	(2.5)	7.8	(3.2)	8.6	(2.2)
Groceries List Trial 5 recall	11.7	(2.6)	12.3	(2.4)	13.0	(1.7)	13.3	(2.0)
Groceries List Delayed recall	11.0	(2.8)	12.0	(2.4)	11.3	(2.9)	13.4	(1.9)
Name–Face Trial 1 recall	3.4	(1.9)	3.0	(1.9)	3.8	(2.3)	4.4	(2.1)
Name–Face Trial 2 recall	7.0	(3.1)	6.6	(2.8)	8.4	(2.9)	9.5	(3.0)
Name–Face Delayed recall	6.1	(3.4)	6.0	(3.2)	7.9	(3.8)	8.4	(4.5)
New-Face number to first error	10.9	(6.7)	10.7	(5.5)	10.7	(3.8)	11.7	(7.5)
New-Face total correct	17.7	(4.8)	18.0	(5.3)	17.0	(4.8)	18.1	(4.4)
Misplaced Objects Trial 1 recall	11.3	(3.8)	11.7	(3.3)	11.3	(3.9)	12.2	(4.2)
Misplaced Objects Total recall	14.1	(3.1)	24.9	(2.6)	14.6	(3.0)	15.2	(3.3)

DISCUSSION

The results from this study need to be interpreted with caution. The sample size is comparatively small and although we have been unable to identify any bias in the drop-out from the study this cannot be taken to mean that none is present. Furthermore, the small sample size has compelled us to combine homozygotic and heterozygotic conditions although there is evidence to suggest that, for instance, *APOE-ε4* is more potentially deleterious in its effect when present in homozygous form than when appearing in a heterozygous combination (Strittmatter & Roses, 1996). For the same reason we have been unable here to investigate the separate influence of the *APOE-ε2* gene that has been reported to be protective against dementia (Corder et al., 1994).

Within these limitations, however, the results are not inconsistent with what might have been predicted. Following an intensive neuropsychological rehabilitation programme there is improved functioning among brain injured people phenotypically characterised as *APOE-nonε4*, at least as registered by subjective report. This improvement appears to a greater or lesser extent across the broad range of cognitive, emotional, and social scales which the EBIQ registers and it appears not only in self-report but also in the reports of close relatives. The reverse is true for brain injured people phenotypically characterised as *APOE-ε4*. According to both self-report and relative's report, function declines over the same time period. Furthermore these findings appear to hold true for both traumatic brain injury cases and for stroke cases.

This study has an unusual characteristic within the field of neuropsychological rehabilitation in that it is akin to a double-blind methodology. The subjects' genotypes were unknown to themselves and to the professional therapists both during the rehabilitation programme and at the time of follow-up. The study suffers, however, from the same methodological limitation that is present among most other research in rehabilitation, with the notable exception of studies by Prigatano (Prigatano, 1986; Prigatano et al., 1995), namely that of lacking a "non-rehabilitated" control group. It could therefore be that the improvement of the *APOE-nonε4* group and the decline of the *APOE-ε4* group are simply manifestations of a natural course of development following injury, i.e. so-called "spontaneous recovery" and the lack of it, respectively. Even if that were the case our findings would still have relevance for rehabilitation efforts, but there are reasons to suppose that they have not arisen from a natural course of development.

Principally, there is extensive evidence to suggest that post-injury symptomatology, as observed by brain injured people themselves and their relatives, does not remit spontaneously in the long term following medical recovery (Brooks, 1992; Oddy, Coughlan, Tyerman, & Jenkins, 1985; Engberg, 1995; Teasdale et al., 1997). A second reason is that the two groups had not differed at the time of programme entry, but did so only at follow-up. It

seems plausible therefore to attribute the improved condition of the *APOE-nonε4* group to a direct effect of the rehabilitation programme itself. By the same token, however, it would appear that the programme has been unable to reverse a post-injury decline among the *APOE-ε4* group, a decline which is consistent with the body of evidence on the deleterious effects of this genotype.

The lack of any significant interaction between genotype and EBIQ scale, and the consistency with which virtually all scales showed some difference between the two groups at follow-up, point to a very diffuse effect of *APOE-ε4* across somatic, cognitive, emotional, and social functioning. This should perhaps not be surprising for a gene that is so clearly associated with general decline manifesting itself in dementia.

The only genotype-related effect among neuropsychological tests was marginal in significance and in the reverse direction with the *APOE-ε4* group performing significantly better on the First/Last Name test. This finding is not readily explained, being inconsistent with other findings here and elsewhere in the literature. It may therefore be due to chance alone and it should be noted that a Bonferroni correction for the number of *F*-ratios tested would eliminate the significance.

There are two possible explanations for the lack of any significant findings among the neuropsychological test battery consistent with the EBIQ findings. It could be that the effect had not manifested itself in the relatively shorter time interval involved. The follow-up EBIQ was completed on average more than 1 year after subjects had finished the day programme, whereas the post-programme neuropsychological testing was conducted immediately on completing the programme. It was not possible within practical and economic constraints to include neuropsychological testing in the follow-up procedure. It is therefore conceivable that testing at that time would have shown an effect parallel to that appearing in the EBIQ scales.

A second explanation is, however, that since gains in neuropsychological tests are generally modest following rehabilitation (Wilson, 1997; Prigatano, 1997), and are of little predictive value in terms of practical outcomes (Teasdale, Skovdahl Hansen, Gade, & Christensen, 1997), they might not have been expected to relate to *APOE* genotype.

On balance, the relation of *APOE* to post-acute neuropsychological rehabilitation would appear to merit further research. Even at this stage, however, it may be wise to sound a note of caution that has also been heard in relation to *APOE* as a predictor of dementia (Post et al., 1997), namely, that the effect sizes, although not insubstantial here, may prove to be too modest to warrant genetic screening in the assessment of suitability for rehabilitation.

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