

Genome-wide Scan for Prospective Memory Suggests Linkage to Chromosome 12q22

Jamie J. Singer,^{1,3} Mario Falchi,¹ Alex J. MacGregor,^{1,2} Lynn F. Cherkas,¹ and Tim D. Spector¹

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Prospective memory slips (forgetting to do something) are as part of everyday memory failure as retrospective complaints (forgetting a past event). The extent to which genes influence prospective and retrospective memory is so far unclear. This study aims to quantify the relative genetic and environmental influences on such memory slips and seeks to identify QTL's with the first genome-wide scan for such traits. A classic twin design was implemented: comprising 896 monozygotic (MZ) and 1008 dizygotic (DZ) female twin pairs aged between 19 and 85 (mean age, 51) participated. The prospective and retrospective memory questionnaire (PRMQ) consists of 16 items, eight asking about prospective memory failures and eight concerning retrospective failures. Heritability for prospective memory and retrospective memory were found to be 44% and 41%, respectively. A genome-wide scan of 489 female DZ twin pairs suggested a QTL on chromosome 12q22 for prospective memory (LOD 2.76, empirical *p*-value 0.0006). Within this QTL lies an obvious candidate—the SCAD gene. These results suggest that large-scale gene discovery studies are possible with self-report memory questionnaires.

KEY WORDS: Linkage; LOD; prospective memory; QTL; SCAD gene; self-report questionnaire; twin study.

INTRODUCTION

Most of us think of memory as a past event, a face learnt, or a skill trained in. We forget that predominantly, our lives are concerned with the task ahead: from remembering to attach a document in an email to taking medication. We need to remember to do things in the future. This aspect of memory is known as *prospective memory* and has received little attention in psychology (Eysenck and Keane, 2000).

The distinction between retrospective memory and prospective memory has been well demonstrated:

those who are good at remembering to pass on a message are no better at remembering the message content than those who tend to forget to pass on information at all (Kvavilashvili, 1987).

Generally speaking we remember to carry out intended tasks (Marsh *et al.*, 1998) though it has been reported this becomes more difficult as we become older (Cockburn and Smith, 1991). Prospective memory tasks can either be time-based (e.g. making a telephone call at a certain time) or event-based (making a telephone call once an email has arrived). Performance on event-based tasks has been shown to be better than on time-based tasks. This implies intended actions are more likely to be triggered by external cues (Sellen *et al.*, 1997). Such cues, however, do not need to be specific to the intended act. For example, a poster detailing a psychology experiment might remind an individual to attend a lecture (Morris, 1992). Motivation to remember has also

¹ Twin Research and Genetic Epidemiology Unit, St Thomas Hospital, London, SE1 7EH, UK.

² School of Medicine, University of East Anglia, Norwich, UK.

³ To whom Correspondence should be addressed at Twin Research and Genetic Epidemiology Unit, St Thomas Hospital, London, SE1 7EH, UK. Tel.: +44-20-71886728; Fax: +44-20-71886761; e-mail: jamie.singer@kcl.ac.uk

been shown to be important (Meacham and Singer, 1977).

Our intention to remember something is likely to be influenced by the same modules that enable us to attend to different stimuli and make executive decisions—those which help us form strategies and plan ahead (McDaniel *et al.*, 1998). Indeed, subjects that are asked to perform tasks that involve executive processes, perform less well on prospective memory tasks. Furthermore, short distracting visual cues and phonological cues, did not disrupt prospective remembering (Marsh and Hicks, 1998).

Clearly, environmental effects influence our ability to remember to act—some use reminders, diaries, or routine. Although genetic influences on retrospective memory (using self-report questionnaires) have been demonstrated (Singer *et al.*, 2005), the extent to which genetic factors play a role in prospective memory ability is unknown. One association study found a significant deficit in prospective memory for epsilon4 allele (of apolipoprotein E (APOE)) carriers (Driscoll *et al.*, 2005), which suggests genetic influences do play a role.

We report here both a classical twin study and we believe the first reported genome-wide scan for prospective memory. To do so, we use The Prospective and Retrospective Memory Questionnaire (PRMQ): a self-report memory rating tool (Crawford *et al.*, 2003). However, the relationship between objective and subjective measures of memory is not clear-cut. Though weak correlations are described in the literature (Little *et al.*, 1986; Rabbitt and Abson, 1990), self-report measures have been shown to predict subsequent memory decline (Jonker *et al.*, 1996) and interestingly, reports of prospective memory failures have been demonstrated to be a more sensitive measure of true memory performance than memory for past events (Mantyla, 2003). We assess this relationship with the cognitive neuropsychological battery, CANTAB (Robbins *et al.*, 1994).

METHODS

Subjects

Nineteen thousand and four Caucasian female–female twin pairs participated in the study; comprising 896 MZ and 1008 DZ pairs. The subjects were recruited from the Twins UK (St Thomas' Adult UK Twin Registry) (Spector and MacGregor, 2002) and had a mean age of 51 with a range from 19 to 85. All are healthy volunteers who were originally

recruited through a national media campaign and from twin registers, and were unaware of any hypothesis (Spector *et al.*, 1996). The zygosity of the twins was assessed by questionnaire, which has an accuracy of over 95% (Martin and Martin, 1975) and validated by multiplex DNA fingerprinting using variable tandem repeats where necessary (i.e., when zygosity determination was unclear), thus giving 99.7% accuracy. Four hundred and eighty nine female DZ twin pairs had genome scans.

The Prospective and Retrospective Memory Questionnaire (PRMQ)

The PRMQ (Crawford *et al.*, 2003), in Table I, was developed to provide a self-report measure of prospective and retrospective memory slips in every day life. It contains 16 items, split equally between items asking about retrospective and prospective memory failures. The scale has been shown to be reliable with Chronbach's α 0.84 and 0.80 for prospective and retrospective scales, respectively (Crawford *et al.*, 2003).

A total score was calculated by summing individual responses so that a high score indicates that subjects are responding positively about their memory. Separate scores were calculated for prospective and retrospective items. A log transformation was performed on the total PMRQ score so that the distribution of scores was as close to a normal distribution as possible.

The CANTAB Tests

The Cambridge Neuropsychological Test Automated Battery (CANTAB) is a series of computerised tests of cognition that run on a personal computer fitted with a touch sensitive screen. It has been standardised on a large sample of 787 normal elderly volunteers (Robbins *et al.*, 1994) and test–retest reliability studies demonstrate correlations for individual test items range between 0.56 and 0.86 (Lowe and Rabbitt, 1998). The CANTAB includes: Pattern recognition memory (discriminating between a previously seen pattern and a novel pattern); paired associated learning (choosing a matching pair from face down cards which had been previously shown); delayed matching to sample (choosing a previously seen item from four items after a delay); spatial span (recall of the order by which a series of boxes are opened); and spatial working memory (a game in which the subject is required to locate boxes with blue

Table 1. The Prospective and Retrospective Memory Questionnaire

Memory Questionnaire	1	2	3	4	5
1. Do you decide to do something in a few minutes' time and then forget to do it? (PROSPECTIVE)	1	2	3	4	5
2. Do you fail to recognise a place you have visited before? (RETRO)	1	2	3	4	5
3. Do you fail to do something you were supposed to do a few minutes later even though it's there in front of you, like take a pill or turn off the kettle? (PROSPECTIVE)	1	2	3	4	5
4. Do you forget to do something that you were told a few minutes before? (RETRO)	1	2	3	4	5
5. Do you forget appointments if you are not prompted by someone else or by a reminder such as a calendar or diary? (PROSPECTIVE)	1	2	3	4	5
6. Do you fail to recognise a character in a radio or television show from scene to scene? (RETRO)	1	2	3	4	5
7. Do you forget to buy something you planned to buy, like a birthday card, even when you see the shop? (PROSPECTIVE)	1	2	3	4	5
8. Do you fail to recall things that have happened to you in the last few days? (RETRO)	1	2	3	4	5
9. Do you repeat the same story to the same person on different occasions? (RETRO)	1	2	3	4	5
10. Do you intend to take something with you, before leaving the room or going out, but minutes later leave it behind, even though it's there in front of you? (PROSPECTIVE)	1	2	3	4	5
11. Do you mislay something that you have just put down, like a magazine or glasses? (RETRO)	1	2	3	4	5
12. Do you fail to mention or give something to a visitor that you were asked to pass on? (PROSPECTIVE)	1	2	3	4	5
13. Do you look at something without realising you have seen it moments before? (RETRO)	1	2	3	4	5
14. If you tried to contact a friend or relative who was out, would you forget to try again later? (PROSPECTIVE)	1	2	3	4	5
15. Do you forget what you watched on television the previous day? (RETRO)	1	2	3	4	5
16. Do you forget to mention to tell something to someone you had meant to mention a few minutes ago? (PROSPECTIVE)	1	2	3	4	5

1, Very often; 2, Quite often; 3, Sometimes; 4, Rarely; 5, Never.

square inside without reopening boxes they have previously selected).

Genetic Modelling

The details of fitting models to data on twins have been described elsewhere (Neale and Cardon, 1992). In summary, an individual's phenotype is influenced by both genotype and environment. Using twins, the relative contribution of genetic and environmental variation to a trait can be assessed quantitatively by variance components analysis based on the pattern of correlation among the twins. The genetic contribution to variation has a potential contribution from additive (A) and non-additive or dominance (D) variation. Environmental variation has a potential contribution from variation in the common family environment of the twins (C) and variation that is unique to individual twins (E). The twin model stipulates that the phenotypic covariance (Cov) among twins can be expressed in terms of these variance components such that:

$$\text{Cov (MZ)} = A + D + C$$

$$\text{Cov (DZ)} = 0.5A + 0.25D + C$$

The extent to which the observed pattern of variation and covariation among traits measured in MZ and DZ twin pairs can be accounted for by contributions from A, D, C and E can be assessed by comparing the fit of a set of nested models from which variance components are sequentially removed. The significance of the contribution of individual variance components is assessed by the change in model χ^2 statistics.

Model fitting to twin data is based on either variance-covariance matrices or raw data. In this case variance-covariance matrices of MZ and DZ twins were used with the maximum likelihood approach implemented. Structural equation model fitting of this kind is performed using the statistical package Mx (Neale *et al.*, 1999).

Age influences cognitive functioning and thus the similarity in age within pairs has the potential to inflate correlations for cognitive traits in both monozygotic and dizygotic twins. If unaccounted for in modelling, this might lead to an overestimate of the contribution of the common environment (Snieder, 1999). In this analysis, we eliminated the effect of age by conducting modelling on the residuals of the regression analysis in which age was included. The PRMQ total score and the two subscale scores were included in the modelling.

Linkage Methods

The software package Merlin (Abecasis *et al.*, 2002) was used for multipoint variance components (VC) linkage analysis. In the variance components approach a linear mixed model is fit to the data so that the phenotypic variance about the trait mean is partitioned into a monogenic component (σ_{QTL}^2), representing the contribution of a QTL with additive effect, a polygenic component (σ_{G}^2), attributable to residual additive genetic variance, and a residual component (σ_{E}^2), attributable to environmental effects unique to the individual. The phenotypic variance-covariance among sibs trait values may be written as $\Omega = \hat{\Pi}\sigma_{\text{QTL}}^2 + 2\Phi\sigma_{\text{G}}^2 + I\sigma_{\text{E}}^2$, where $\hat{\Pi}$ is a matrix of the proportion of alleles shared IBD estimated from the genotypic data at a point in the genome, 2Φ is a matrix of the expected proportion of alleles shared IBD over the genome, and I is an identity matrix. LOD scores are calculated as the difference between the maximum of the \log_{10} likelihood of the full model, including estimates of σ_{QTL}^2 , σ_{G}^2 , and σ_{E}^2 , and the maximum of the \log_{10} likelihood of the reduced model in which σ_{QTL}^2 is constrained to equal 0.

We assessed the empirical significance on our most significant linkage result through a permutation test. The permutation test, first proposed by Fisher (1935), generates a random sample from an appropriate null distribution. Indeed, since the procedure is based on the observed traits and genetic markers, it well reflects the characteristics of the particular experiment to which it is applied. We randomly permuted the IBD-state between sib-paris and evaluated a variance component linkage analysis after each cycle. Since the multipoint IBD-matrix is calculated once, the procedure is faster than a gene dropping simulation test, and the IBD-states distribution is exactly the same observed in the studied sample.

The empirical significance for our most significant linkage peak was assessed through 10,000 permutations. Empirical p values were estimated from

the proportion of replicates giving a LOD score equal or greater than that observed. Empirical p values adjusted to account for the scanning of the whole genome were not obtained, since it would have required prohibitively time-consuming simulations.

Genotyping

DNA was extracted at the Twin Research Unit Laboratory using the BACC2 DNA extraction kit (Nucleon Biosciences) from 10 mL of venous blood collected on 1.6 mg/mL EDTA. Genome-wide linkage analysis included 737 genotypic markers equivalent to highly polymorphic microsatellite markers spaced every 10 cM using standard fluorescence-based genotyping methodologies (Pritchard *et al.*, 1995; Reed *et al.*, 1994) from the ABI Prism linkage mapping set (Applied Biosystems) and Genethon Genetic Linkage Map (Dib *et al.*, 1996) and described in more detail previously (Wilson *et al.*, 2003). The estimated genotyping error rate was <1%.

RESULTS

Descriptive Statistics

Nineteen hundred and eight twin pairs, comprising 896 pairs of MZ and 1008 pairs of DZ twins, returned the prospective and retrospective memory questionnaire. Details of the sample are compared by zygosity in Table II. The MZ and DZ twin groups are well matched for age (51.4 and 51.8, respectively), for PRMQ scores both on the total scale (61.8 and 61.4, respectively), and separately for the prospective scale (29.3 and 29.1, respectively) and retrospective scale (32.5 and 32.2, respectively).

A weak, negative relationship between PRMQ scores and age ($r = -0.08$, $p < 0.01$) was found. This was also the case for prospective memory score ($r = -0.13$, $p < 0.001$) and a non-significant, negative relationship was identified for retrospective memory score and age ($r = -0.01$, $p > 0.05$). The

Table II. Details of Twins Studied by Zygosity

	Monozygotic twins	Dizygotic twins	p Value ^a
Characteristic of sample	($n = 900$ pairs)	($n = 1000$ pairs)	
Mean age (range)	51.4 (19–85)	51.8 (20–85)	0.36
PRMQ total score (range, s.d.)	61.8 (21–80, 9.7)	61.4 (19–80, 9.9)	0.15
Prospective memory score (range, s.d.)	29.3 (8–40, 5.6)	29.1 (8–40, 5.6)	0.35
Retrospective score (range, s.d.)	32.5 (11–40, 4.8)	32.2(11–40, 4.9)	0.06

^a p -Value generated from a paired t -test.

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trend was that older subjects tended to respond negatively about their memory.

Table III revealed correlations for individual PRMQ items of between 0.17 and 0.62 ($p < 0.001$). The overall correlation between prospective and retrospective scores was strong and positive ($r = 0.77$, $p < 0.001$). The relationships between the PRMQ score and prospective and retrospective scores were 0.95 and 0.93 ($p < 0.001$).

Relationship with CANTAB

Three hundred and seventy two subjects had previously taken part in a computerised cognitive test battery. A low but significant, negative relationship was found between a working memory strategic task score and prospective memory ($r = -0.12$, $p = 0.02$). A moderate, positive relationship was found between two prospective items raw scores

(e5 and e15) and the working memory task score ($r = 0.22$, $p < 0.001$).

Heritability and Model Fitting

The results of genetic modeling analyses are shown in Table IV. Model fitting to prospective and retrospective scales separately revealed that in both cases, the effects of the shared environment (C) and dominant genetic effects (D) could be dropped from the model without significant loss of fit but additive genetic effects (A) could not be eliminated ($p < 0.001$). This suggests that variance in prospective and retrospective memory ability in this population is best explained by the effects of additive genetic factors and unique environmental factors, an AE model. Estimates from this model produce a heritability for retrospective memory of 41% (95% confidence interval, 35% to 47%) and for prospective memory of 44% (95% confidence interval, 39% to 49%).

Table III. Correlations of Individual Test Items*

	pr1	re2	pr3	re4	pr5	re6	pr7
pr1	1.0000						
re2	0.2795	1.0000					
pr3	0.6089	0.3017	1.0000				
re4	0.5234	0.3056	0.5263	1.0000			
pr5	0.4018	0.2583	0.3996	0.3999	1.0000		
re6	0.1739	0.3360	0.2655	0.2897	0.2094	1.0000	
pr7	0.4708	0.2585	0.4803	0.4257	0.4496	0.2619	1.0000
re8	0.4451	0.3456	0.4703	0.5402	0.4140	0.3566	0.4697
re9	0.3485	0.2451	0.3700	0.3838	0.3232	0.2301	0.3883
pr10	0.5651	0.2511	0.5520	0.4947	0.4342	0.2227	0.5647
re11	0.4824	0.2531	0.4994	0.4454	0.3789	0.2422	0.4692
pr12	0.4745	0.2675	0.4800	0.4511	0.4527	0.2465	0.5036
re13	0.3428	0.3928	0.4262	0.4004	0.3094	0.4265	0.3789
pr14	0.3996	0.2425	0.4007	0.3607	0.4032	0.2333	0.4487
re15	0.3376	0.3367	0.3674	0.4306	0.3316	0.3603	0.3834
pr16	0.5646	0.2915	0.5268	0.5497	0.4384	0.2606	0.5324
	re8	re9	pr10	re11	pr12	re13	pr14
re8	1.0000						
re9	0.4300	1.0000					
pr10	0.4627	0.4409	1.0000				
re11	0.4419	0.3812	0.6254	1.0000			
pr12	0.4632	0.4075	0.5367	0.4937	1.0000		
re13	0.4706	0.3768	0.4016	0.4010	0.4514	1.0000	
pr14	0.3818	0.3416	0.4487	0.3701	0.5043	0.3977	1.0000
re15	0.5449	0.3449	0.3827	0.3798	0.3828	0.4368	0.4173
pr16	0.5125	0.4251	0.5857	0.5163	0.5779	0.4531	0.5193
	re15	pr16					
re15	1.0000						
pr16	0.5223	1.0000					

*All correlations are significant ($p < 0.001$).

Linkage

Figure 1 shows the results of the genome wide scan for retrospective and prospective memory. Analysis showed the highest linkage peak was for the prospective score on chromosome 12 (Fig. 2), covering a region between ~132 cM and ~155 cM (markers D12S86 to D12S1659), with the maximum peak at 153 cM, marker D12S1679 (LOD 2.76). The highest linkage peak for retrospective memory score was on chromosome 18 (peak LOD score 1.85 on marker D8S462; see Table V).

The empirical significance of our best result on chromosome 12, assessed by 10,000 permutations, yielded a pointwise p value of 0.0006.

DISCUSSION

Summary

The Prospective and Retrospective Memory Questionnaire has demonstrated the potential of a simple tool such as a self-report questionnaire, to identify chromosomal locations and possibly, candidate genes for cognitive behaviour.

This study on female twin pairs has revealed that prospective memory, an ability that engages executive thought processes (Marsh and Hicks, 1998), is likely to be influenced by genetic factors. Forty four percent of variation in prospective memory scores and 41% of variation in retrospective memory scores among women, was explained

Table IV. Univariate Modelling Statistics

	a 95% CI's	c 95% CI's	e 95% CI's	d 95% CI's	χ^2	Df	p	AIC
<i>Prospective memory</i>								
ACE	44 32, 49	0 0, 9	56 51, 61	—	1.63	3	0.65	-4.36
AE	44 39, 49	—	56 51, 62	—	1.63	4	0.8	-6.36
CE	—	32 27, 36	68 64, 73	—	34.43	4	0	26.43
E	—	—	1 1, 1	—	196.6	5	0	186.64
ADE	35 8, 49	—	55 50, 61	10 0, 39	1.13	3	0.77	-4.87
<i>Retrospective memory</i>								
ACE	41 31, 47	0 0, 8	59 53, 64	—	5.18	3	0.159	-0.819
AE	41 35, 47	—	59 53, 64	—	5.18	4	0.269	-2.819
CE	—	29 24, 33	71 67, 76	—	36.34	4	0	28.34
E	—	—	1 1, 1	—	164.16	5	0	154.16
ADE	25 0, 45	—	57 52, 63	17 0, 46	3.703	3	0.157	-0.297
<i>Total PRMQ</i>								
ACE	44 33, 50	0 0, 9	56 50, 62	—	2.92	3	0.4	-3.1
AE	44 38, 50	—	56 50, 62	—	2.92	4	0.57	-5.1
CE	—	31 26, 36	69 64, 74	—	33.56	4	0	25.56
E	—	—	1 1, 1	—	163.37	5	0	153.37
ADE	28 0, 49	—	55 49, 61	17 0, 48	1.76	3	0.62	-4.24

Note: Bold typed models were the best fitting models.

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by underlying genetic variation with no need to include shared environmental influences.

Genetic factors have been found previously to explain variation in objective memory tasks with

heritability estimates between 30 and 60% (Thapar *et al.*, 1994) but few studies have looked at self-reported memory abilities. Our previous study, using 2000 female twin pairs, has demonstrated similar

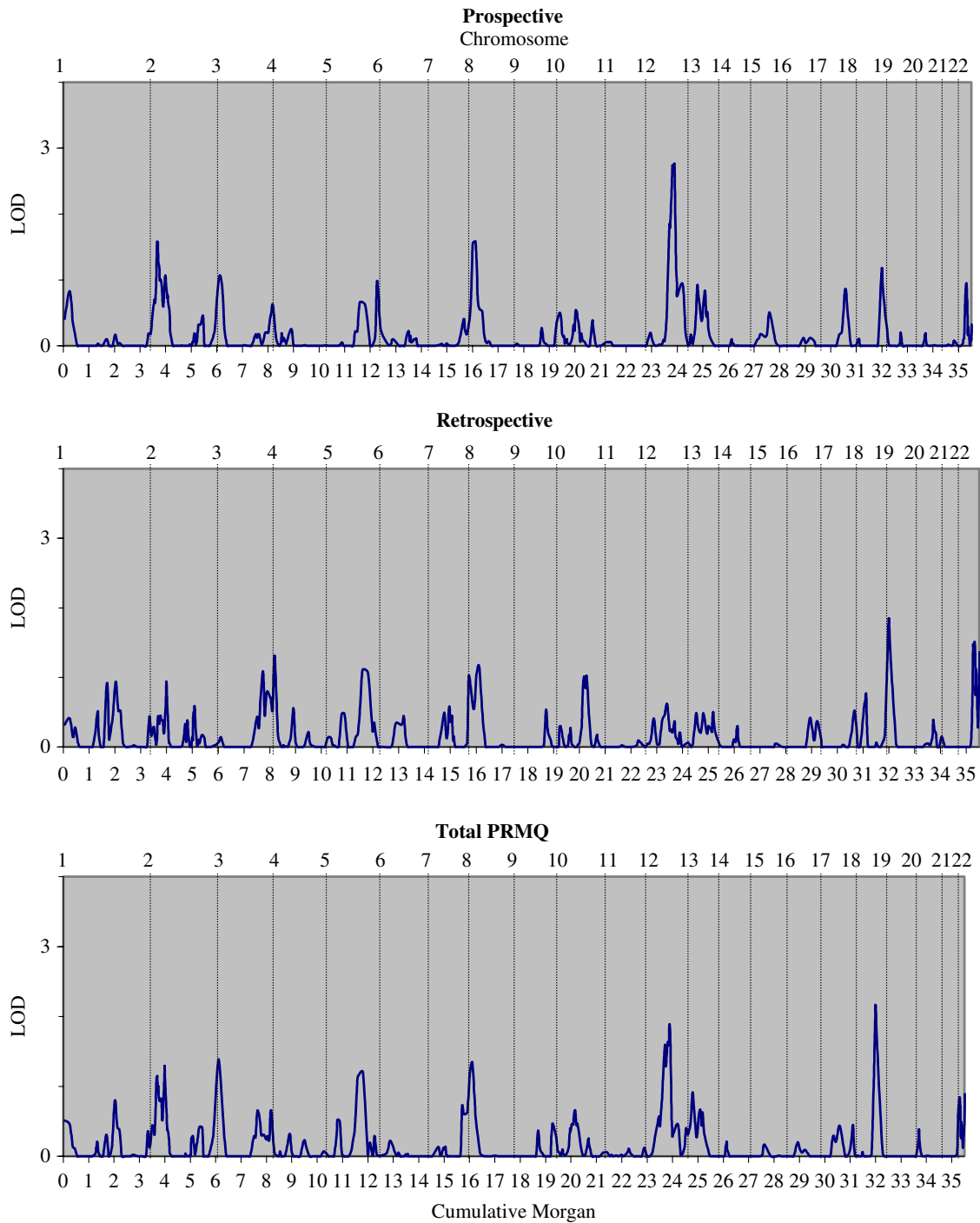


Fig. 1. Linkage analysis for prospective and retrospective memory.

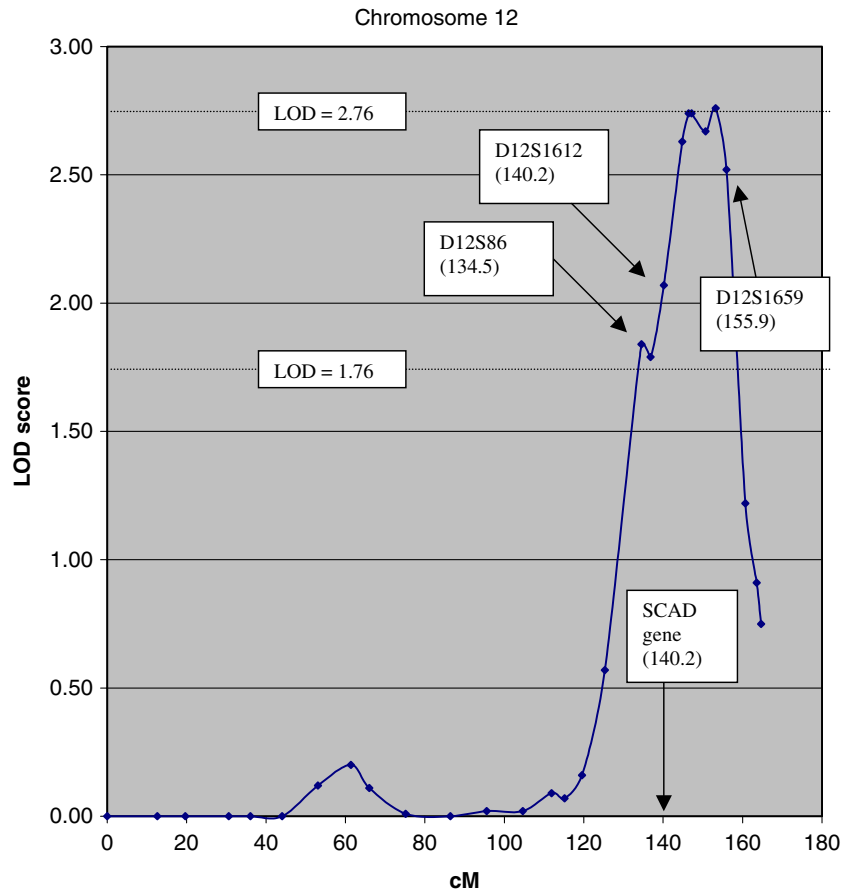


Fig. 2. Linkage map for prospective memory score on Chromosome 12.

findings to the current report suggesting between 36% and 45% of variation in self-report memory problems are due to genetic factors. (Singer *et al.*, 2005). The study asked several questions of a retrospective nature taken from the contentment and ability scales of The Multifactorial Memory Questionnaire (Troyer and Rich, 2002).

Although we found a QTL with a LOD of 2.76 (empirical p value 0.0006 which is equivalent to LOD 2.6), a LOD score of over 3.6 is usually considered necessary to conform to conventional guidelines for significant genome-wide linkage and a LOD greater than 2.2 is considered to be suggestive of linkage (Lander and Kruglyak, 1995). The two QTL peaks identified on chromosomes 12 and 18 may represent genuine QTLs that could be confirmed by further studies, or they may still be false positive signals.

Compared to VC methods, regression methods are computationally less demanding and more robust

to violation of normality of the trait distribution. Nonetheless they are more suited to the analysis of selected samples. When the distribution of the trait is approximately normal, VC linkage methods are more powerful than regression based methods (Fulker and Cherny, 1996). In this study, the trait has been measured in a random sample, and values of skewness and kurtosis were 0.50 and 0.35 for prospective memory. Some work has shown that kurtosis, and not skewness, of the phenotypic distribution is the critical factor affecting the robusticity of the multivariate normal model to distributional violations (Allison *et al.*, 1999; Blangero *et al.*, 2001). We support our results through a permutation study. The procedure is statistically valid when used in conjunction with likelihood based statistics and for any distribution of the quantitative trait. Through 10,000 permutations we obtained a p value of 0.0006, which confirmed the suggestive linkage signal on chromosome 12.

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The QTL peak on chromosome 12 does harbour one obvious candidate gene of interest: the short-chain acyl-coA Dehydrogenase (SCAD) gene at 140.2 cM at marker D12S1612. The role of theta oscillations (5–9 Hz) in learning and memory has been demonstrated by the finding that its elimination blocks and facilitation enhances LTP induction and memory (Mizumori *et al.*, 1990; Winson, 1978). It has been shown that expression of the SCAD gene in brain regions, most pertinently the hippocampus, is involved in theta generation (Tafti *et al.*, 2003). This finding was further explored in a study of healthy patients using a memory scanning task (Schack *et al.*, 2005), in which it was demonstrated that theta reflects central executive functions.

Limitations and Implications for Future Research

Self-report data must be interpreted with careful consideration. Anxiety, depression and personality factors may influence responses. Also, there is a reliance on recall and perhaps a variability due to individual's expectation (the elderly may have a negative impression of their memory abilities) (Derouesne *et al.*, 1999; Jonker *et al.*, 2000). Accounting for these variables was beyond the scope of the present study. Despite this, subjective testing has been shown to predict memory decline in elderly patients (Schofield *et al.*, 1997). In one study, 2537 non-depressed individuals were questioned about their memory-related problems. It was found that such self-report data was predictive of subsequent memory impairment (Jonker *et al.*, 1996) thus showing support for a strong relationship between objective and subjective tests of memory. In our study, prospective item (5) in the PRMQ correlated positively ($n = 372$, $r = 0.22$, $p < 0.001$) with a strategic working memory task in The Cambridge Neuropsychological Test Automated Battery (CANTAB) (Robbins *et al.*, 1994). This implies that the worse your ability to plan ahead (on a computerised

memory task), the less likely you are to remember an appointment (without the use of a diary or calendar). A weaker, yet significant, relationship was found between the same objective test and the total (transformed) PRMQ score. This adds weight to the finding by Marsh *et al.* (1998), that the executive processes that make up our every-day working memory influence prospective memory (Marsh and Hicks, 1998). Furthermore, if the subjective memory tests were just so poor as to be only generating random noise—we would not expect to detect heritability or any linkage signals.

A small, yet significant negative relationship was found between the PRMQ total score, prospective memory and age. For the most part, self-memory complaints mirror objective tests of ageing and memory decline but this is not always the case as demonstrated by the relationship found between age and retrospective memory. It is quite possible that the elderly forget how much they forget (see Rabbitt *et al.*, 1995, for a review).

Interestingly, our study suggests that those who report prospective memory slips are just as likely to report retrospective memory slips. Whilst previous studies have used objective tests of memory (Kvavilashvili, 1987), the current study does not agree with the suggestion that the two are unrelated. Though it is important to note that, whilst a correlation of 0.77 was found, a previous analysis of the PRMQ has found the two dimensions to be independent (Crawford *et al.*, 2003). Given this relationship, one would expect the linkage peaks to be closely matched. However, it is possible that the underlying gene does not have a pleotropic effect on both phenotypes.

All twin studies assume that the environments of MZ and DZ twins are equal and hence, greater phenotypic similarity among MZ than DZ twins simply a result of the two-fold greater genetic similarity. If the equal environment assumption (EEA) does not hold, then heritability may be overestimated (Hopper, 2000). However, the EEA has been shown

Table V. Genomic Regions with Evidence of Linkage to Memory

Genomic region and measure	Peak LOD score	Peak marker	Location (cM from pter)	1-LOD drop area
12q24.2-24.3:				
Prospective score	2.76	D12S1679	153.19	D12S86–D12S1659
Total PRMQ	1.29			
18q22.3-23:				
Retrospective score	1.85	D8S462	120.05	D18S1161–D18S70
Total PRMQ	2.16			

to hold for many behavioural studies of this nature (Kyvik, 1999) and in the current study, age and reported memory scores were well matched between MA and DZ twins.

In addition, the results are likely to be generalizable to singletons based on the nature and size of the sample, as well as the reasonableness of the results. This twin population used has already been shown to be representative of the overall British population for a wide variety of medical, psychological and social traits (Andrew *et al.*, 2001).

However, it is not clear as to whether the results could be generalizable to males. Sex differences in the brain are well established (Aartsen *et al.*, 2004; Guillem and Mograss, 2005; Maitland *et al.*, 2004) so it would certainly be interesting to look at a male population.

CONCLUSION

A suggestive QTL with a LOD of 2.76 for prospective memory, was located on chromosome 12. Whilst this QTL ideally needs to be replicated before a full scale fine mapping project is undertaken, the results suggest that QTLs for memory can be obtained via simple self administered questions that make it practical to study the large numbers needed for adequate power in family studies.

The PRMQ can be administered easily to thousands of individuals—a property that could prove to be extremely useful in the search for QTLs for cognition. Whilst it has been acknowledged that self-report questionnaire results can be marred by confounding variables, the current study suggests, by comparison with objective measures, that respondents are accurately reflecting their true memory abilities.

Losing one's memory can be devastating: from the triviality of forgetting to pay an invoice to the importance of remembering to take a pill, yet the study of prospective memory has been severely overlooked. Further genetic studies using tools such as the PRMQ, together with objective tests of prospective memory, are required to enable us to further unwrap the mysteries of human memory.

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