Behavior Genetics, Vol. 36, No. 1, January 2006 (© 2006)
DOI: 10.1007/s10519-005-9002-2

Linkage Analyses of Event-Related Potential Slow Wave Phenotypes Recorded in a Working Memory Task

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Received 7 Feb. 2005—Final 20 June 2005

Working memory is an essential component of wide-ranging cognitive functions. It is a complex genetic trait probably influenced by numerous genes that individually have only a small influence. These genes may have an amplified influence on phenotypes closer to the gene action. In this study, event-related potential (ERP) phenotypes recorded during a working-memory task were collected from 656 adolescents from 299 families for whom genotypes were available. Univariate linkage analyses using the MERLIN variance-components method were conducted on slow wave phenotypes recorded at multiple sites while participants were required to remember the location of a target. Suggestive linkage (LOD > 2.2) was found on chromosomes 4, 5, 6, 10, 17, and 20. After correcting for multiple testing, suggestive linkage remained on chromosome 10. Empirical thresholds were computed for the most promising phenotypes. Those on chromosome 10 remained suggestive. A number of genes reported to regulate neural differentiation and function (i.e. NRP1, ANK3, and CHAT) were found under these linkage peaks and may influence the levels of neural activity occurring in individuals participating in a spatial working-memory task.

KEY WORDS: Chromosome 10; MERLIN; spatial working memory; twins; variance components.

INTRODUCTION

Working memory is one of the most intensely studied topics in cognitive psychology and cognitive neuroscience, and deservedly so, as the ability to focus attention in order to maintain and manipulate information from one second to the next is an important component of complex cognitive functioning that includes arithmetic, language (or reading) comprehension, and reasoning (Engle *et al*., 1992; Kyllonen and Christal, 1990; Wilson and Swanson, 2001). The aim of the current study was to identify quantitative trait loci (QTLs) influencing working memory processes in adolescents. As working memory, along with other cognitive processes, may be influenced by numerous genes of small effect (Morley and Montgomery, 2001; Plomin *et al*., 1995), the approach taken was to examine intermediate phenotypes (in this case, electrophysiological event-related potential (ERP) measures recorded from the scalp during a visuospatial working memory task). Single genes may have a larger influence on these endophenotypes than on more complex measures, and thus be more readily detectable (de Geus *et al*., 2001; Greenwood and Parasuraman, 2003).

Genes, through their protein products, may influence brain function in a variety of ways. As outlined by Greenwood and Parasuraman (2003) in their recent review of the role of normal genetic variation in modulating cognitive function, these may include the modulation of neural receptors, neurotransmitter modulation, and neuroprotection. Genes influencing the dopaminergic system (e.g. DRD4,

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COMT, and DBH) have been linked with aspects of attention (particularly frontal network) and working memory (Faraone *et al.*, 2001; Goldberg *et al.*, 2003; Greenwood and Parasuraman, 2003). Similarly, CHRNA4, a gene modulating cholinergic receptor function, has been linked to visuospatial attention (Greenwood and Parasuraman, 2003) and to cortical electrophysiology (Steinlein *et al.*, 1997) and CHRM2, a cholinergic muscarinic receptor gene, has been linked to EEG oscillations underlying amplitude of the cognitive ERP component P300 (Jones *et al.*, 2004). (Note that P300 average amplitude correlates quite highly with the average amplitude of the ERP slow wave component examined in the present study (i.e. $r = 0.67$ at parietal, Hansell, 2003; Hansell *et al.*, 2002)). Neurotrophic genes play an essential role in neuronal differentiation and survival during development (Levi-Montalcini, 1998), and the neurotrophic gene BDNF has been associated with some aspects of human memory function (Egan *et al.*, 2003). Furthermore, genes such as ApoE that influence neuronal health and plasticity may also have effects on cognitive function, particularly in older individuals (Greenwood and Parasuraman, 2003).

Genes with functions such as these may influence the slow wave potentials examined in the current analyses. Slow wave potentials, like all ERPs, reflect the synchronous activity of large numbers of neurons whose geometric arrangement is conducive to the summation and propagation of their electrical activity (Coles and Rugg, 1995). These potentials were recorded during the delay period of a delayed-response task—a period requiring the location of a target stimulus to be remembered. Studies of single cell functioning in monkeys have shown persistent firing of prefrontal and parietal neurons during delay periods in which target location must be remembered (Batuev *et al.*, 1985; Chafee and Goldman-Rakic, 2000). Consistent with these findings, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have shown enhanced activation in the prefrontal and parietal cortices in humans during spatial working-memory tasks (Jonides *et al.*, 1993; Rowe *et al.*, 2000). Furthermore, enhanced activation has been reported for the premotor area and the occipital cortex (Smith and Jonides, 1998). Thus, in the present study slow wave recorded from multiple sites ranging from anterior prefrontal sites to posterior occipital sites was examined.

Previous analyses of slow wave collected from a sub-sample found that genetic factors accounted for 35–37% of the reliable variance of prefrontal slow wave and 51–52% for parietal slow wave (Hansell *et al.*, 2001). Genetic correlations have been found to be high between slow wave phenotypes recorded at adjacent sites (e.g. 0.84–0.93 between frontal sites), but they decrease steadily with increasing distance between sites, ranging 0.00–0.14 between the most distant recording sites (i.e. prefrontal and occipital) (Hansell, 2003). The effect of presenting a distracting stimulus during the delay period has also been examined for frontal slow wave (Hansell *et al.*, 2004). It was found that a common genetic factor influenced slow wave recorded in both distractor and non-distractor conditions ($r_g = 0.91$), although slow wave recorded in the distractor condition was also influenced to a small degree by an independent genetic factor.

In the current analyses, slow wave phenotypes recorded at 15 sites and during both distractor and non-distractor memory conditions were examined using univariate linkage methods. It was expected that robust linkage findings would be replicated among the highly correlated phenotypes.

METHOD

Participants

ERP data and genotypes were available for 656 adolescents (336 females, 320 males) from 299 families (comprising 215 DZ twin pairs with no other siblings, 35 DZ pairs with one sibling, eight DZ pairs with two siblings, one DZ pair with three siblings, 36 non-twin sibling duos, and four non-twin sibling trios). In addition, genotypes were available for both parents in 284 of these families, for one parent in 13 families, and for neither parent in two families. Electrophysiological data were collected as part of a large ongoing study of cognitive function (Wright *et al.*, 2001), with collection occurring as closely as possible to participants' 16th birthdays ($M = 16.4$ years, SD = 0.8 years, range = 15.7–22.3 years). Participants had no history of head injuries, neurological or psychiatric conditions, substance abuse/dependence, and/or taking medications with significant central nervous system effects. They were instructed to avoid caffeine-containing foods and drinks in the 2 hours prior to their visit. Ethics approval was obtained from the Human Research Ethics Committee at the Queensland Institute of Medical Research, and written informed consent was obtained from all participants and their parents.

Working-Memory Task

Testing protocols used in this study have been described previously in Hansell *et al.* (2001). Briefly, ERP data were collected while participants completed a computerized delayed-response task that required them to remember the location of a visual target. During each trial, participants were required to focus on a central fixation dot to reduce eye movement. Two hundred and fifty ms after fixation onset, a single target (checkered dot, 1.5° visual angle) was presented peripherally. Target presentation was brief in memory trials (150 ms), but in sensory control trials, the target remained on-screen until target location was indicated. Target presentation was followed by a 1 or 4 second delay period. In 50% of memory and sensory trials a distracting stimulus (identical to the target, but differing in location) was presented for 150 ms during the delay period. The timing of the presentation of the distracting stimulus was random within the interval 300–700 ms post-target onset. The disappearance of the fixation dot signaled the end of the delay period and was the cue for participants to lift their preferred hand from a touch-sensitive pad and to indicate target location with a rubber-tipped pointer. In total, eight trial type variations were presented (memory/sensory × distractor presence/absence × delay 1 s/4 s). Data examined in the present analyses were recorded during 1 s delay periods in a memory condition (no distractor presented) and a memory distractor condition (distracting stimulus presented). Difference measures were not examined as preliminary analyses have indicated inconsistent reliability.

ERP Recording and Phenotypes

Using the Electrocap system, ERPs were recorded from left- and right-hemisphere prefrontal (Fp1, Fp2), fronto-temporal (F7, F8), and occipital sites (O1, O2), and from left-hemisphere, midline, and right-hemisphere frontal (F3, Fz, F4), central (C3, Cz, C4), and parietal sites (P3, Pz, P4). Impedances were kept below 5 kohm and linked ears served as reference. Eye movements and blinks were monitored through the placement of electrodes on the supra-orbital ridge and the outer canthus of the left eye. The electrooculogram (EOG), Fp1 and Fp2 were amplified 5 K times and remaining EEG channels 20 K times by Grass preamplifiers, with a band pass of 0.01–100 Hz. ERPs were sampled at 250 Hz from 100 ms prior to fixation point onset to 200 ms post-fixation point offset and monitored on-line. EEG data exceeding 50 μV RMS were automatically rejected. Eye blink artifacts were removed using a computerized algorithm developed by examining eye blinks during electroencephalogram (EEG) recording and using those records as a digital template to detect and eliminate similar patterns from the recordings.

Following artifact rejection, trials were averaged separately for each trial type using a pre-target baseline of 350 ms. Waveforms were subjected to visual inspection if 40% or more of trials were rejected due to excessive EOG/EEG and/or if 30% or more were lost due to behavioral rejections (responses too slow, too fast, or spatially incorrect). Data were accepted if there was no indication of drift and if the waveforms appeared stable (i.e. waveforms from the 1 s delay trials were comparable to those obtained by collapsing over the 1 and 4 seconds delay trials).

Slow wave average amplitudes recorded during memory trials (both distractor and non-distractor), and computed for the interval 650–1150 ms (post-target onset), were examined in this paper. A total of 96 trials was presented for each trial type and those not rejected due to excessive EOG/EEG or incorrect behavioral responses were averaged. The mean number of trials averaged for each individual included in these analyses was 63.7 (SD = 16.9, range = 10–95) for memory trials and 62.9 (SD = 17.0, range = 11–95) for memory trials in which a distracting stimulus was presented.

Zygosity Determination and Genotyping

Among same-sex twin pairs, zygosity was initially determined with an overall probability of correct assignment of greater than 99.99% by using a commercial kit (AmpFlSTR Profiler Plus Amplification Kit, ABI) and cross checking with blood group and other phenotypic data. This was subsequently confirmed with the genotyped data using GRR and Relpair. MZ pairs were excluded from analyses unless data for a sibling were also available, in which case, data for the first-born MZ co-twin were included in analyses.

Participants were genotyped as a consequence of their participation in a larger ongoing study of melanoma risk factors (Zhu *et al.*, 1999). The genotyping and the cleaning of the data, have been described in detail in Zhu *et al.* (2004). Briefly, three batches of genotyping were performed—two by the Australian Genome Research Facility (AGRF), Melbourne, and

one by the Center for Inherited Disease Research (CIDR), Baltimore. Merging the genome scans resulted in a dense map of 796 markers at an average spacing of 4.8 cM. Scans included both autosomal and X-chromosomal markers with locations determined from the sex-averaged deCODE map (Kong *et al.*, 2002; Leal, 2003). The number of markers obtained per participant in the current study ranged from 211 to 791 ($M = 614$, SD = 190 (participants with fewer than 200 markers were excluded from the study and were not included in the sample numbers given previously)). Genotyped parents of participants had between 1 and 785 markers ($M = 333$, SD = 167), with 481 individual parents having more than 200 markers and the remaining 100 parents having fewer than 40 markers.

Statistical Analyses

Using SPSS 11.5 for Windows (SPSS Inc., 1989–2002), data were screened for univariate outliers and those data with *z*-score values greater than ± 3 (less than 1% of the dataset) were excluded from all analyses. In addition, means, standard deviations, and Pearson phenotypic and twin correlation coefficients were computed.

Linkage Analyses

To test for linkage between marker loci and slow wave phenotypes, univariate multipoint linkage analyses were performed using the variance-components (VC) models in MERLIN (Abecasis *et al.*, 2002) and, for the X-linked variance components, the Abecasis MINX program (http://www.sph.umich.edu/csg/abecasis/Merlin/reference.html). Identity-by-descent (IBD) sharing probabilities are calculated in MERLIN and MINX using the Lander–Green algorithm with sparse gene flow trees. Using the VC method, phenotypic variance explained by the estimated IBD sharing at a chromosomal position is modeled.

Correction for Multiple Testing

All LOD scores peaking at 1.5 or greater are reported. Their theoretical point-wise *p*-values were Bonferroni corrected for multiple testing and LOD scores were adjusted accordingly. These LOD scores were then assessed for significance or suggestiveness against the standard thresholds proposed by Lander and Kruglyak (1995) (i.e. thresholds of 3.6 for significant linkage and 2.2 for suggestive linkage).

To determine the *effective* number of independent traits for Bonferroni correction, a principal components analysis (PCA)(varimax rotation) of the 30 correlated phenotypes was conducted. The number of independent traits was determined as the number of orthogonal factors with eigenvalues greater than one. The PCA method of determining the effective number of independent traits is widely used in animal studies (e.g. de Koning *et al.*, 1998; Spelman *et al.*, 1996). A more exact adjustment for multiple testing could be made using permutation or gene dropping methods. However, these were not used in this instance due to the considerable computation time required.

Deriving Empirical Thresholds

The most promising phenotypes (i.e. those with a high LOD score that was supported by similar findings for correlated phenotypes) were examined further. For these phenotypes, empirical genome-wide significance thresholds were computed using the method employed by Abecasis *et al.* (2004). For each simulation, the dataset contained the original phenotypic data, but new genotypes were simulated with MERLIN under the null hypothesis of no linkage. The allele frequencies, marker spacing, and missing data pattern were unchanged. The highest LOD score for each chromosome was retained and the number of these LOD scores >1, >1.5, >2.0, >3.0, >3.5, and >4.0 was determined for each simulation. Subsequently, the means of these groupings over all simulations were plotted against the respective LOD scores (i.e. 1.0, 1.5, etc.—see Fig. 1 for example plot), thereby indicating the average number of false positives per genome scan one would expect to observe at a given maximum LOD score (MLS) threshold. Five thousand simulations were run for slow wave recorded at Pz in the memory condition and the significance and suggestive levels were compared to those obtained from 500 simulations. In addition, 500 simulations were run for slow wave recorded at Fp1 (memory distractor), F4 (memory), C3 (memory), Cz (memory distractor), and Pz (memory distractor).

RESULTS

All slow wave data were normally or near-normally distributed, with minor positive kurtosis found for some variables. None required transformation. Waveforms are shown in Figure 2. For the slow wave interval examined (i.e. 650–1150 ms post target

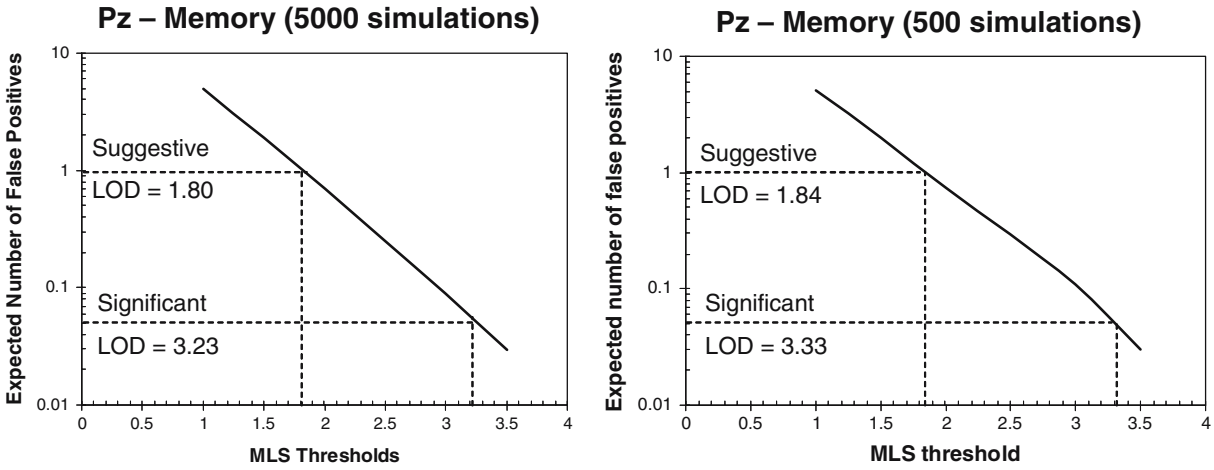

Fig. 1. Empirical thresholds for suggestive linkage (one expected false positive per genome scan) and significant linkage (one expected false positive per 20 genome scans) obtained from simulations (5000 vs. 500) for slow wave amplitude recorded at midline parietal during memory non-distractor trials (plotted on a log scale).

onset), the waveform for memory distractor trials appears to be overlaid with processing related to the distracting stimulus (as suggested by the reduced amplitudes) when compared to the waveform for memory trials in which no distracting stimulus was presented. In general, amplitudes for both trial types have returned to similar levels by the end of the delay period (i.e. 1 s post-target onset). The waveforms show a very high similarity between the left and right hemispheres. In addition, the frontal (F3, Fz, F4), central (C3, Cz, C4), and parietal (P3, Pz, P4) waveforms are very similar, as are the prefrontal (Fp1, Fp2) and fronto-temporal (F7, F8) waveforms. Mean, standard deviation, and range is shown for each slow wave phenotype in Table I.

Broad-sense heritabilities (and twin correlations) are shown in Table II. Heritabilities range from 0.16 to 0.53. The lowest heritabilities were found at the fronto-temporal sites (F7, F8).

Phenotypic correlations (Fig. 3) were high for slow wave recorded across hemisphere for the same trial type (r ranged 0.84–0.92), with the exception of slow wave recorded at F7 and F8 ($r = 0.58$ for memory trials and 0.61 for memory distractor trials). Also high, were correlations between the two trial types for slow wave recorded at the same site (r ranged 0.74–0.83). In general, correlations were high between slow wave phenotypes recorded at adjacent scalp locations and decreased as the distance between recording sites increased.

A PCA with varimax rotation was run on all phenotypes and five orthogonal factors with eigenvalues greater than one, and accounting for a cumulative 86.4% of the variance, were identified. Thus Bonferroni corrections for multiple testing were based on five effective traits.

Linkage

Univariate multi-point linkage analyses were conducted for 30 slow wave phenotypes (two conditions × 15 scalp locations). The plotted results are shown in Figure 4, with the most notable region of linkage appearing on chromosome 10 for slow wave amplitude recorded over frontal, central, and parietal scalp locations. As expected, the results were very similar for highly correlated phenotypes (e.g. Fp1/Fp2, P3/Pz). LOD scores peaking greater than 1.5 are shown in Table III. These estimates are also shown corrected for multiple testing, using a Bonferroni adjustment for five effective traits. All were assessed in terms of the theoretical thresholds suggested by Lander and Kruglyak (1995) and accordingly, LODs greater than 2.2 (the threshold for suggestive linkage) are highlighted.

LOD scores adjusted for multiple testing were found to be suggestive at four markers on chromosome 10, with considerable overlap between peaks indicated (see Fig. 5—note that plots are unadjusted for multiple testing). At marker D10S547, position 27.8 cM (between D10S189 at 19.8 cM and D10S2325 at 31.1 cM), a LOD score of 2.77 was found for slow wave recorded during memory trials at right-hemisphere frontal (F4). Also peaking at this

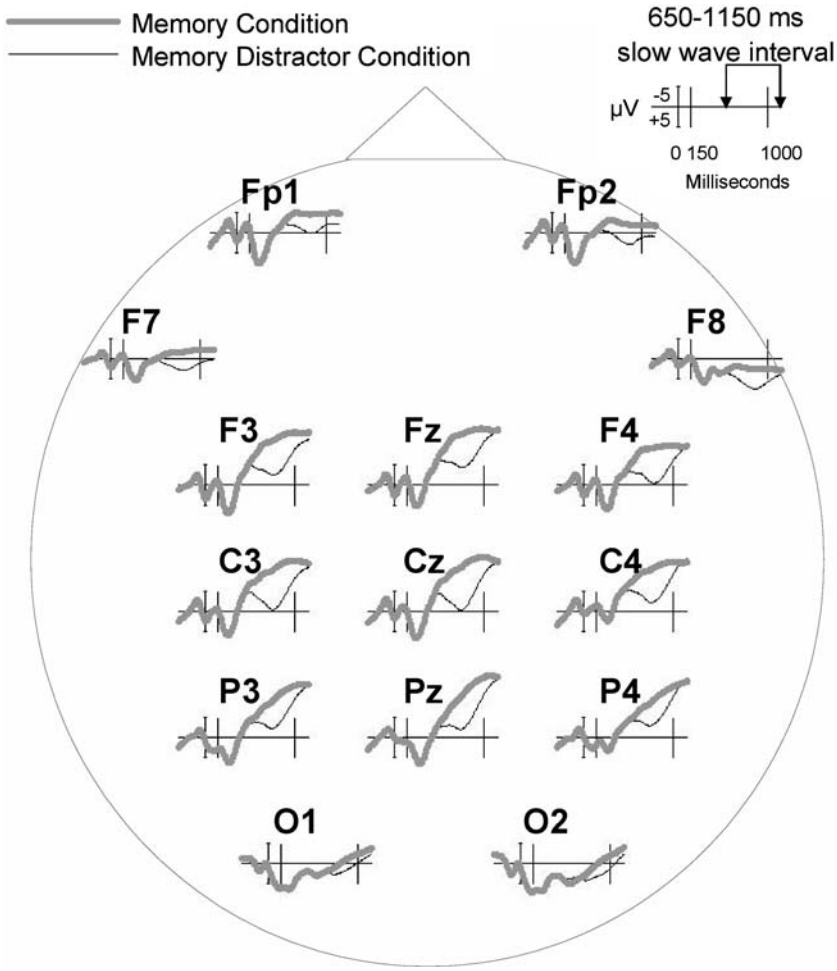

Fig. 2. Waveforms (averaged over 100 participants to show ERP components) recorded during the memory and memory distractor conditions at left- and right-hemisphere prefrontal (Fp1, Fp2), fronto-temporal (F7, F8), and occipital sites (O1, O2) and left-hemisphere, midline, and right-hemisphere frontal (F3, Fz, F4), central (C3, Cz, C4), and parietal (P3, Pz, P4) sites. Vertical lines at 0 and 150 ms indicate target onset and offset. In memory distractor trials, a distracting stimulus was presented for 150 ms randomly within the 300–700 ms interval.

marker, with a LOD of 1.84, was slow wave recorded at left-hemisphere frontal (F3) in the memory condition. For slow wave recorded during memory distractor trials, a LOD of 2.38 was found for midline parietal (Pz)—with lesser LODs of 1.94 and 2.09 at left-hemisphere parietal (P3) and left-hemisphere central (C3), respectively—at marker D10S1208, position 62.05 cM (between D10S1426 at 57.7 cM and D10S1227 at 74.9 cM). In addition, at marker D10S196, position 70.07 cM (between D10S208 at 59.94 cM and D10S1227 at 74.9 cM), a LOD score of 2.67 was found for slow wave recorded during memory distractor trials at midline central (Cz). Furthermore, for slow wave recorded during memory trials at midline parietal (Pz), a LOD score of 2.31 was found for marker D10S1652, position 80.7 cM (between D10S1227 at 74.9 cM and D10S537 at 89.2 cM).

Although no longer suggestive after correction for multiple testing, LOD scores for a number of frontal and prefrontal slow wave phenotypes showed an interesting convergence at marker D5S1503, position 110.3 cM (between D5S1725 at 103.2 cM and ATA4F06 at 114.6 cM). Corrected LOD scores of 1.94 and 1.64 were found for slow wave recorded during memory distractor trials at left- and right-hemisphere prefrontal (Fp1, Fp2), respectively, while scores of 1.01 and 0.83 were found for slow wave

Table I. Means, Standard Deviations (SD), Minimum Amplitudes, and Maximum Amplitudes (in μV) for Slow Wave Recorded from *N* Individuals During Memory and Memory Distractor Conditions at Left- and Right-Hemisphere Prefrontal (Fp1, Fp2), Fronto-temporal (F7, F8), and Occipital Sites (O1, O2) and Left-Hemisphere, Midline, and Right-Hemisphere Frontal (F3, Fz, F4), Central (C3, Cz, C4), and Parietal Sites (P3, Pz, P4)

	Memory					Memory with distractor				
	N	Min	Max	Mean	SD	*N*	Min	Max	Mean	SD
Fp1	653	−30.7	26.2	−2.2	8.2	655	−30.1	27.5	−0.6	8.6
Fp2	654	−27.8	22.1	−1.3	7.8	655	−26.7	26.3	0.6	8.1
F7	648	−16.7	18.7	−0.8	5.3	649	−14.7	20.8	0.8	5.5
F8	649	−16.1	19.6	0.7	5.1	650	−16.2	21.2	2.5	5.3
F3	653	−25.5	15.7	−5.4	6.6	654	−23.7	21.2	−2.1	7.0
Fz	654	−25.7	11.5	−6.1	6.0	656	−22.9	17.4	−3.0	6.4
F4	654	−24.3	14.9	−4.5	6.2	653	−19.1	18.8	−1.2	6.5
C3	650	−23.5	15.2	−5.1	6.3	652	−21.9	22.0	−1.6	6.9
Cz	652	−27.5	15.2	−5.8	6.6	653	−23.1	20.1	−1.9	7.1
C4	644	−26.8	25.4	−5.5	6.4	641	−22.0	17.8	−2.6	6.5
P3	651	−28.0	18.8	−5.0	6.8	653	−27.0	24.0	−2.6	7.5
Pz	648	−28.6	20.6	−5.9	7.1	651	−28.3	25.0	−2.8	7.9
P4	651	−24.3	15.2	−5.0	5.7	653	−21.3	17.1	−2.8	6.2
O1	651	−18.4	18.5	−0.2	5.4	653	−18.8	20.5	0.5	5.7
O2	648	−19.3	24.2	0.2	6.6	649	−21.0	24.4	−24.4	6.9

Note: Means are not adjusted for twin relatedness.

Table II. Twin Correlations[a] and Broad-Sense Heritabilities (h^2)[b] for Slow Wave Amplitudes Recorded During Memory and Memory Distractor Conditions at Left- and Right-Hemisphere Prefrontal (Fp1, Fp2), Fronto-temporal (F7, F8), and Occipital Sites (O1, O2) and Left-Hemisphere, Midline, and Right-Hemisphere Frontal (F3, Fz, F4), Central (C3, Cz, C4), and Parietal Sites(P3, Pz, P4)

	Memory condition			Memory distractor condition		
Slow wave site	r_{MZ} (212–216 pairs)	r_{DZ} (282–287 pairs)	h^2	r_{MZ} (212–215 pairs)	r_{DZ} (281–287 pairs)	h^2
Fp1	0.27	0.08	0.27	0.28	0.17	0.38
Fp2	0.31	0.13	0.38	0.34	0.16	0.34
F7	0.23	0.08	0.19	0.27	0.16	0.31
F8	0.18	0.09	0.16	0.26	0.05	0.09
F3	0.35	0.18	0.46	0.37	0.24	0.43
Fz	0.40	0.24	0.51	0.37	0.23	0.42
F4	0.37	0.19	0.47	0.40	0.23	0.43
C3	0.48	0.11	0.32	0.49	0.20	0.41
Cz	0.43	0.18	0.44	0.45	0.24	0.49
C4	0.44	0.21	0.53	0.49	0.28	0.57
P3	0.42	0.15	0.35	0.48	0.21	0.43
Pz	0.45	0.24	0.51	0.53	0.25	0.52
P4	0.41	0.25	0.52	0.49	0.32	0.63
O1	0.42	0.30	0.47	0.45	0.22	0.35
O2	0.42	0.31	0.49	0.47	0.25	0.41

[a]Computed in SPSS from the pair numbers shown (all other analyses used the genotyped sample described in the method section, which excludes MZ pairs).
[b]Computed in MERLIN.

recorded in memory trials at right- and left-hemisphere frontal (F4, F3), respectively (for plot see Fig. 6).

Empirical Significance

Empirical significant and suggestive LOD thresholds for selected phenotypes of interest were

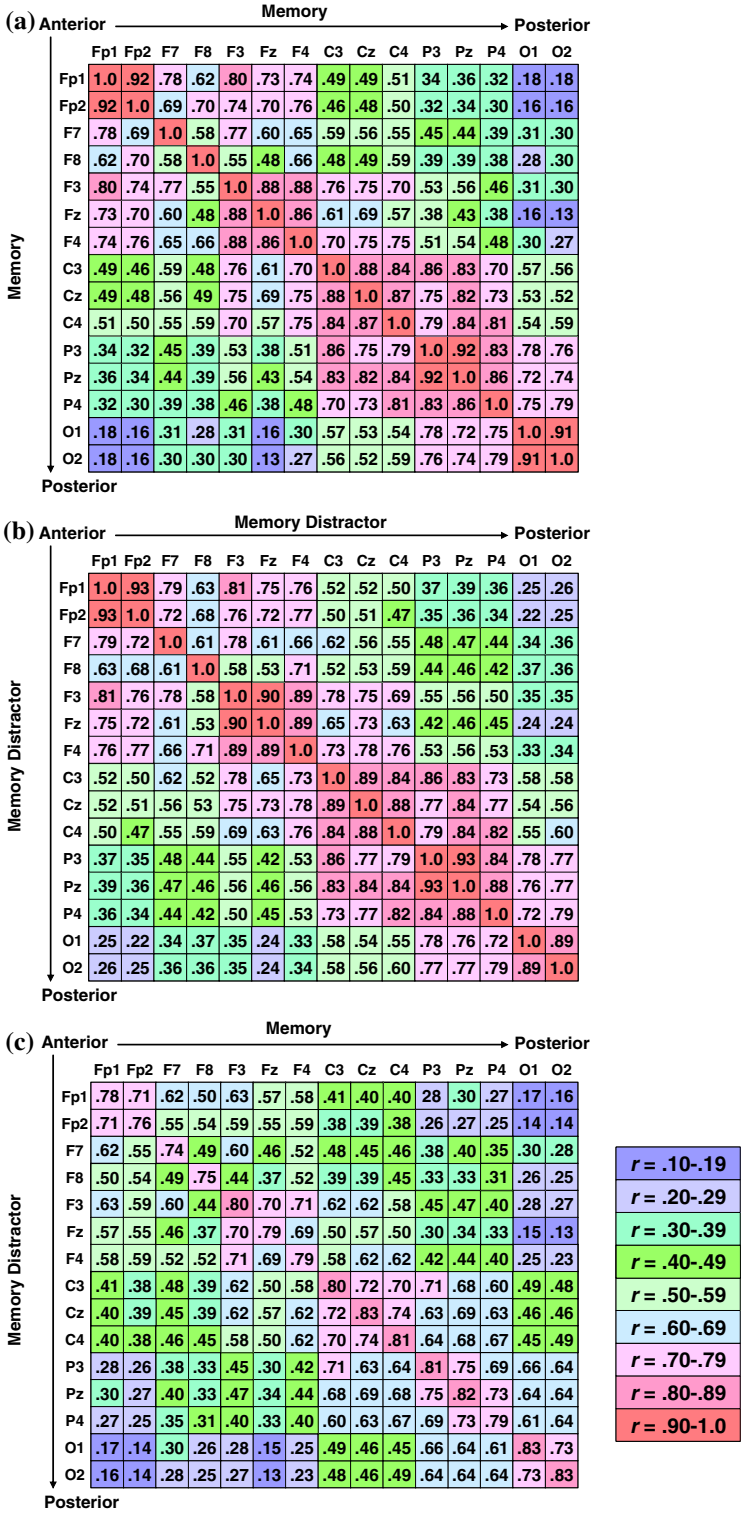

Fig. 3. Pearson correlation coefficients between sites (i.e. left- and right- hemisphere prefrontal (Fp1, Fp2), fronto-temporal (F7, F8), and occipital (O1, O1) and left-hemisphere, midline, and right-hemisphere frontal (F3, Fz, F4), central (C3, Cz, C4), and parietal (P3, Pz, P4)) are shown for slow wave average amplitude recorded during (a) the memory condition, (b) the memory distractor condition, and (c) between the memory and memory distractor conditions. All correlations are significant at the 0.01 level.

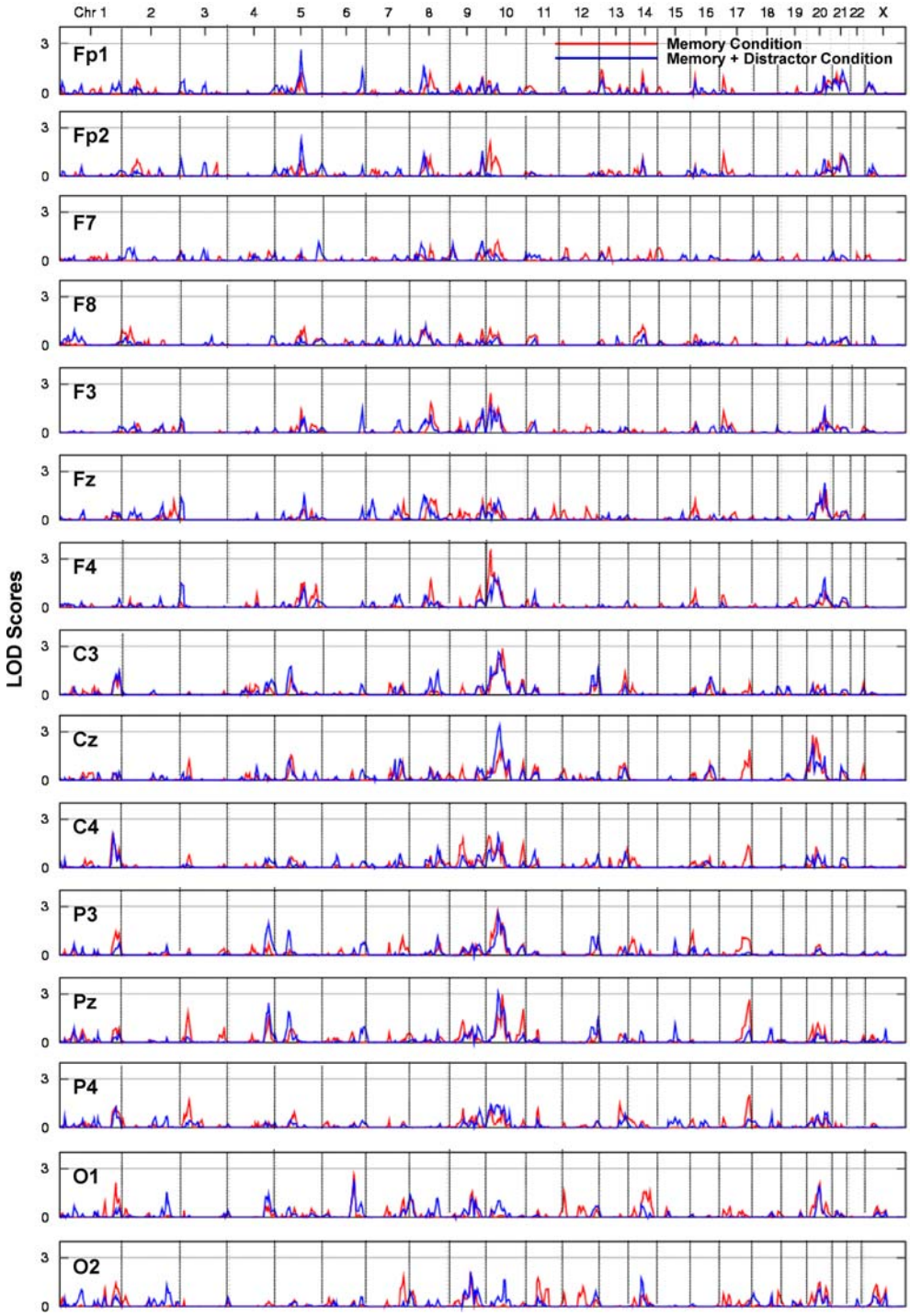

Fig. 4. Results of genome-wide linkage analyses (uncorrected for multiple testing) for slow wave recorded at left- and right-hemisphere prefrontal (Fp1, Fp2), fronto-temporal (F7, F8), and occipital (O1, O2) and left-hemisphere, midline, and right-hemisphere frontal (F3, Fz, F4), central (C3, Cz, C4), and parietal (P3, Pz, P4) sites.

Table III. LOD Scores > 1.5 (Scores > the Suggestive Threshold of 2.2 are bolded)

				Uncorrected for multiple testing				Corrected for multiple testing			
				Memory cond		Mem + Dist cond		Memory cond		Mem + Dist cond	
Chr	Marker	Pos(cM)	Slow wave site	LOD	*p*	LOD	*p*	LOD	*p*	LOD	*p*
1	D1S235	244.4	C4	2.09	0.001	1.99	0.0012	1.44	0.005	1.37	0.006
	D1S2785	257.46	O1	2.13	0.0009			1.48	0.0045		
2	XRCC5	209.01	O1			1.56	0.004			0.92	0.02
3	D3S2338	37.49	Pz	1.89	0.002			1.12	0.01		
	D3S3038	43.38	P4	1.67	0.007			0.71	0.035		
4	D4S2417	176.31	P3			2.01	0.0012			1.37	0.006
			Pz	1.69	0.003	**2.45**	**0.0004**	1.02	0.015	1.8	0.002
5	D5S1470	53.87	Pz			1.89	0.002			1.12	0.01
	D5S418	64.56	C3			1.75	0.002			1.12	0.01
			Cz	1.58	0.004			0.92	0.02		
	D5S1503	110.29	**Fp1**			**2.63**	**0.0003**			1.91	0.0015
			Fp2			**2.25**	**0.0006**			1.58	0.0035
			F4	1.51	0.004			0.92	0.02		
	D5S471	124.98	F4	1.53	0.004			0.92	0.02		
6	D6S292	137.13	**O1**	**2.63**	**0.0003**			1.91	0.0015		
7	D7S3070	165.57	O2	1.83	0.002			1.12	0.01		
8	D8S1110	65.47	Fp1			1.63	0.003			1.02	0.015
			Fz			1.52	0.004			0.92	0.02
	D8S270	97.29	F3	1.83	0.002			1.12	0.01		
			F4	1.7	0.003			1.02	0.015		
9	D9S175	70.64	C4	1.76	0.002			1.12	0.01		
	D9S938	105.89	O2	2.12	0.0009	1.97	0.0013	1.48	0.0045	1.34	0.0065
	D9S1677	112.85	O1	1.58	0.004			0.92	0.02		
	D9S158	158.64	Fp2			1.59	0.003			1.02	0.015
	D9S1838	159.36	F3			1.54	0.004			0.92	0.02
10	D10S189	19.78	C4	1.96	0.0013			1.34	0.0065		
	AD10S189	19.88	C4	1.96	0.0013			1.34	0.0065		
	D10S1412	25.56	Fp2	2.06	0.001			1.44	0.005		
	D10S547	27.79	**F3**	**2.45**	**0.0004**	1.61	0.003	1.8	0.002	1.11	0.015
			F4	**3.49**	**0.00003**			**2.84**	**0.00015**		
			C3			1.79	0.002			1.12	0.01
	D10S548	43.40	F4	2.19	0.0008	1.79	0.002	1.53	0.004	1.12	0.01
	D10S208	59.94	**P3**	**2.71**	**0.0002**			2.07	0.001		
			Pz	1.57	0.004			0.92	0.02		
	D10S1208	62.05	F4	1.58	0.004	1.8	0.002	0.92	0.02	1.12	0.01
			C3			**2.65**	**0.0002**			2.07	0.001
			C4			2.01	0.0012			1.37	0.006
			P3			**2.57**	**0.0003**			1.91	0.0015
			Pz			**3.07**	**0.00009**			**2.39**	**0.00045**
	D10S196	70.07	**C3**	**2.28**	**0.0006**			1.58	0.0035		
			Cz	1.74	0.002	**3.42**	**0.00004**	1.12	0.01	**2.72**	**0.0002**
	D10S1225	80.61	C4	1.61	0.003			1.02	0.015		
	D10S1652	80.71	**C3**	**2.87**	**0.00014**			**2.22**	**0.0007**		
			Cz	2	0.002			1.12	0.01		
			C4	1.61	0.003			1.02	0.015		
			P3	2.03	0.0011	1.79	0.002	1.4	0.0055	1.12	0.01
			Pz	**2.95**	**0.00011**			**2.31**	**0.00055**		
	D10S537	89.16	O2			1.66	0.003			1.02	0.015
	D10S212	177.19	C4	1.51	0.004			0.92	0.02		
			Pz	2.09	0.001			1.44	0.005		
	AD10S212	177.29	C4	1.51	0.004			0.92	0.02		
			Pz	2.09	0.001			1.44	0.005		
11	D11S905	57.39	O2	1.74	0.002			1.12	0.01		

Table III. Continued

				Uncorrected for multiple testing				Corrected for multiple testing			
				Memory cond		Mem + Dist cond		Memory cond		Mem + Dist cond	
Chr	Marker	Pos(cM)	Slow wave site	LOD	*p*	LOD	*p*	LOD	*p*	LOD	*p*
12	D12S99	15.20	O1	1.52	0.004			0.92	0.02		
	D12S1723	169.54	C3	1.64	0.003	1.64	0.003	1.02	0.015	1.02	0.015
14	D14S276	53.25	O2			1.76	0.002			1.12	0.01
	D14S258	68.54	O1	1.6	0.003			1.02	0.015		
	D14S280	94.42	O1	1.58	0.004			0.92	0.02		
	D14S617	94.47	O1	1.58	0.004			0.92	0.02		
17	AD17S928	135.77	**Pz**	**2.68**	**0.0002**			2.07	0.001		
			P4	2.04	0.0011			1.4	0.0055		
			Cz	1.9	0.002			1.12	0.01		
20	D20S851	28.49	**Cz**	**2.79**	**0.0002**	**2.28**	**0.0006**	2.07	0.001	1.58	0.0035
	D20S470	44.09	**Cz**	**2.67**	**0.0002**			2.07	0.001		
	D20S195	56.77	O1			1.89	0.002			1.12	0.01
	D20S478	60.72	O1	2.07	0.001			1.44	0.005		
	D20S107	61.78	Fz	1.51	0.004			0.92	0.02		
	D20S480	83.19	**Fz**			**2.29**	**0.0006**			1.58	0.0035
			F4			1.80	0.002			1.12	0.01
	D20S100	88.96	Fz	1.87	0.002			1.12	0.01		

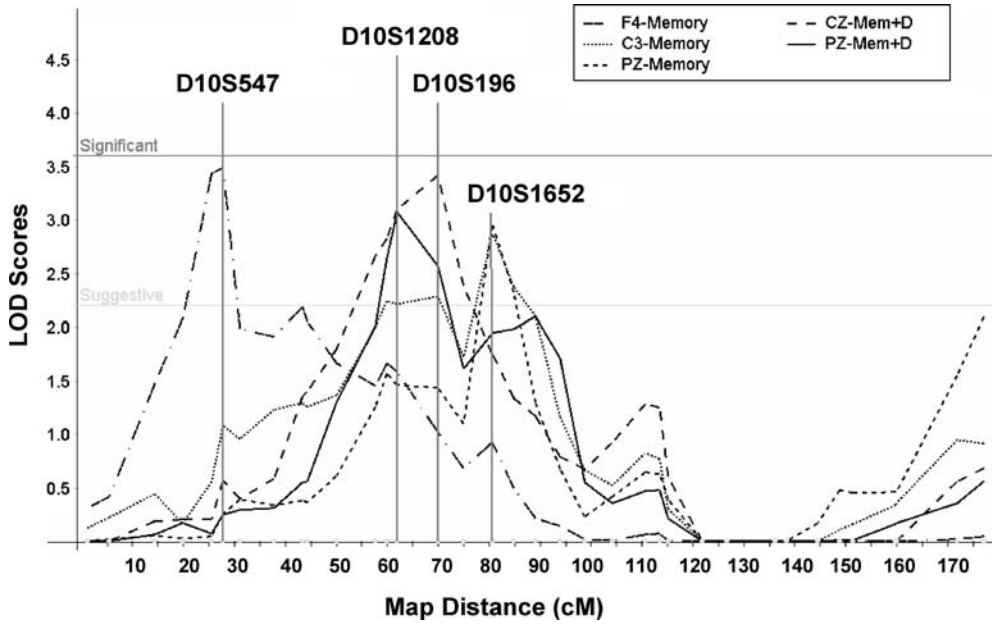

Fig. 5. Genome scan results for Chromosome 10 showing variables with LOD scores peaking at markers D10S547 (slow wave recorded at F4 in the memory condition), D10S1208 (Pz, memory with distractor (Mem + D) condition), D10S196 (Cz, memory with distractor condition), and D10S1652 (Pz, memory condition and C3, memory condition). These results are uncorrected for multiple testing and significance and suggestive thresholds are based on Lander and Kruglyak (1995).

determined. These phenotypes were selected as they had the highest LOD scores (shown in Figs. 5 and 6) for markers on which multiple correlated variables had unadjusted LOD scores greater than 2.2, as shown in Table III. The slow wave phenotypes are F4 (memory), Cz (memory distractor), Pz (memory

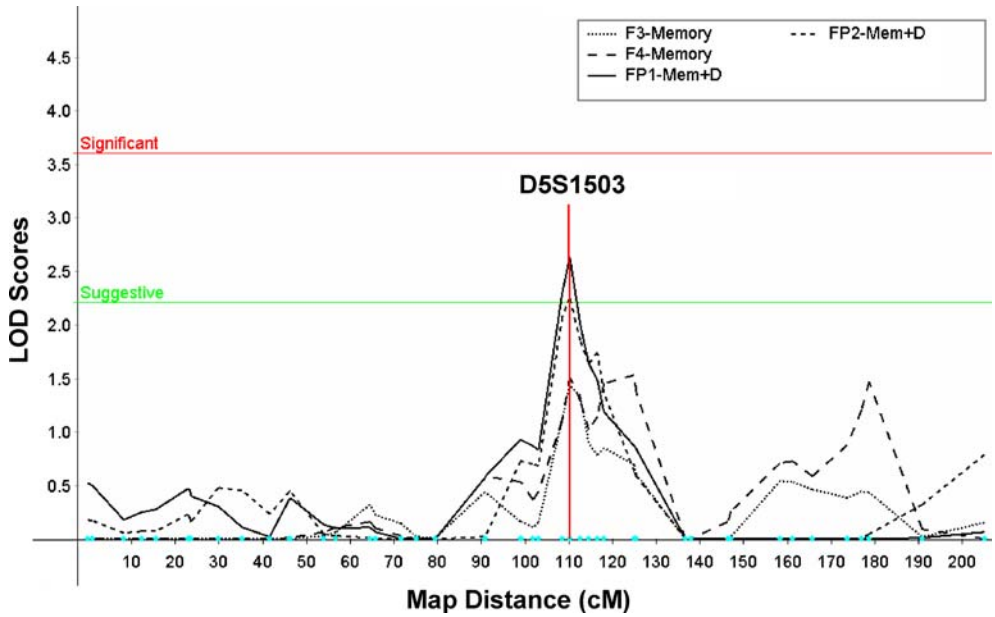

Fig. 6. Genome scan results for Chromosome 5 showing prefrontal (Fp1, Fp2) and frontal (F3, F4) variables, recorded in memory and memory distractor (Mem + D) conditions, peaking at marker D5S1503. These results are uncorrected for multiple testing and significance and suggestive thresholds are based on Lander and Kruglyak (1995).

Table IV. Empirical LOD Thresholds for Significance and Suggestiveness for Selected Slow Wave Phenotypes Recorded During Memory Non-Distractor (Mem) Trials at Right-Hemisphere Frontal (F4), Left-Hemisphere Central (C3), and Midline Parietal (Pz) Sites and During Memory Distractor (M + D) Trials at Left-Hemisphere Prefrontal (Fp1), Midline Central (C3), and Midline Parietal (Pz) Sites

			Empirical LOD thresholds for significance and suggestiveness (based on 500 simulations)	
Slow wave site (& condition)	Marker	LOD score[a]	Significant	Suggestive
F4 (Mem)	D10S547	2.84	3.14	1.78
Cz (M + D)	D10S196	2.72	3.66	2.02
Pz (M + D)	D10S1208	2.39	3.59	1.96
Pz (Mem)	D10S1652	2.31	3.33	1.84
C3 (Mem)	D10S1652	2.22	2.97	1.70
Fp1 (M + D)	D5S1503	1.91	3.27	1.87

[a]Adjusted for multiple testing.

distractor), Pz (memory), C3 (memory), and Fp1 (memory distractor).

The results from running 5000 simulations were comparable to those found for 500 simulations. For Pz (memory), minimum LOD scores indicating significance and suggestiveness were 3.23 and 1.80, respectively, for 5000 simulations and 3.33 and 1.84 for 500 simulations (see Fig. 1). Consequently, only 500 simulations were run on the remaining selected phenotypes, the results of which are shown in Table IV. These empirically derived thresholds of significance and suggestiveness indicate suggestive LODs for the slow wave phenotypes F4 (memory), Cz (memory distractor), Pz (memory distractor), Pz (memory), and C3 (memory). For the slow wave phenotype Fp1 (memory distractor), a borderline suggestive LOD was indicated.

DISCUSSION

These are the first linkage analyses of ERP slow wave measures of brain function. In this instance, the

slow wave was recorded during a visuospatial working memory task. Suggestive linkage (i.e. LOD > 2.2, Lander and Kruglyak, 1995)) was found on chromosomes 4, 5, 6, 10, 17, and 20. After correction for multiple testing, suggestive linkage remained on chromosome 10. Linkage remained suggestive when adjusted LOD scores were compared to empirically derived thresholds. In addition, the empirically derived thresholds indicated a region of interest on chromosome 5, where borderline suggestive linkage was observed.

On chromosome 10, multiple suggestive peaks (at markers D10S1208, D10S196, and D10S1652) were found in a region of approximately 40 cM (50–90 cM on the deCODE map). Two genes mapping to this region, which may plausibly influence slow wave phenotypes, are neuropilin-1 (NRP1—human map locus 10p12 (Rossignol *et al*., 1999), at approx. 60.5 cM, near markers D10S208 at 59.94 cM and D10S1208 at 62.05 cM) and ankyrin-G (ANK3—human map locus 10q21 (Kapfhamer *et al*., 1995), at approx. 78.3 cM, near marker D10S1652 at 80.71 cM). Neuropilin receptors are implicated in the control of neuronal migration within the developing central nervous system—more specifically, in the segregation of migrating cortical and striatal interneurons (Marin *et al*., 2001). ANK3 is characteristically present in central and peripheral nervous system neurons at the axonal initial segment and nodes of Ranvier (Kapfhamer *et al*., 1995) where it may play a role in the maintenance/targeting of ion channels and cell adhesion molecules, and consequently, may play a role in the initiation and propagation of the saltatory action potential (Kordeli, 1995).

Also in this region of chromosome 10 is the CHAT gene (locus 10q11.2 (Viegas-Pequignot *et al*., 1991), at approx. 69.4 cM, near marker D10S196 at 70.07 cM), which encodes choline acetyltransferase proteins. The cholinergic system has been associated with the modulation of visuospatial attentional processes (Greenwood and Parasuraman, 2003), and notably, has been implicated in the generation of the cognitive ERP component P300 (i.e. CHRM2, chromosome 7, Jones *et al*., 2004). Dysfunction of the cholinergic system has been associated with cognitive decline in Alzheimer's disease (Davies and Maloney, 1976). Evidence of linkage has been found for the region around the CHAT locus and late-onset alzheimer's disease (Bertram *et al*., 2000; Myers *et al*., 2000). In addition, a single nucleotide polymorphism in the CHAT gene has been associated with late-onset alzheimer's. However, Harold *et al*. (2003) found no association in their investigation of CHAT sequence variants. Mutations of the gene have been shown to cause a congenital myasthenic syndrome associated with often fatal episodes of apnea (Ohno *et al*., 2001).

In addition, LOD scores below the suggestive threshold of 2.2 proposed by Lander and Kruglyak (1995) were found for a marker on chromosome 10 in a region previously associated with dopamine D1 receptor interaction (i.e. dopamine receptor D1 interacting protein (DRD1IP, also designated calcyon Lezcano *et al*., 2000), human map locus 10q26.3, at approx. 177.2 cM, near marker D10S212 at 177.19 cM). Prefrontal D1 receptors appear to have a role in modulating visuospatial working memory in humans (Muller *et al*., 1998) and non-human primates (Goldman-Rakic, 1996). Furthermore, activation of D1-dopamine receptors appears to modulate preparatory processes in the monkey premotor cortex that are related to reaching (Sawaguchi, 1997). In the current study, slow wave was recorded during the delay period of a delayed-response task, following which participants were required to indicate target location by reaching and touching the location on a computer screen. Thus, similar processes may have occurred. At D10S212, for slow wave recorded in the memory condition, LOD scores corrected for multiple testing ranging 0.80–1.44 (uncorrected ranging 1.14–2.09) were found for central and parietal sites (Cz, C4, Pz). Central recording sites are located roughly over the motor/premotor cortex. Linkage at these sites, should it be real, may reflect allelic variation influencing preparatory motor processes that are expressed in the slow wave. No linkage was found at this marker for slow wave recorded at prefrontal or frontal sites.

On chromosome 5, linkage peaks were found at marker D5S1503 for both prefrontal and frontal slow wave. The highest of these peaks, for slow wave recorded at left-hemisphere prefrontal (Fp1) was found to be borderline suggestive when compared to the empirical threshold (i.e. LOD adjusted for multiple testing = 1.91, empirical suggestive threshold = 1.87). This region on chromosome 5 is an interesting one for a memory-related study. Marker D5S1503 maps to 5q21, as does the PST gene (Angata *et al*., 1997), which is located at approximately 111.5 cM based on the deCODE map (vs. D5S1503 at 110.29 cM). The PST gene is expressed moderately in human adult brain tissue (more generally in forebrain derivatives), and may play a role in

neural cell development and regeneration (Nakayama *et al.*, 1995). PST is a polysialyltransferase that forms polysialic acid (PSA). In adult rat brains, choline acetyltransferase (ChAT)-positive fibers have been found to express PSA during regeneration in the hippocampal formation and it has been posited that PSA may provide an environment conducive to axonal growth (Aubert *et al.*, 1998). PSA appears to regulate the function of the neural cell adhesion molecule (N-CAM) (e.g. Kadmon *et al.*, 1990; Rutishauser *et al.*, 1988; Tang *et al.*, 1994), and interestingly, N-CAM knockout mice show deficits in spatial learning and memory (Tomasiewicz *et al.*, 1993; Cremer *et al.*, 1994).

DRD4, COMT, and DBH are genes that have been linked with aspects of attention and working memory through their influence on the dopaminergic system (Daly *et al.*, 1999; Faraone *et al.*, 2001; Goldberg *et al.*, 2003). However, the present results show no evidence of linkage in relation to these genes and the slow wave phenotypes examined. Similarly, no evidence of linkage was found for CHRNA4, CHRM2, BDNF, or ApoE-genes that have also been linked with processes of cognitive function (Egan *et al.*, 2003; Flory *et al.*, 2000; Greenwood and Parasuraman, 2003; Jones *et al.*, 2004). These genes may influence memory and other cognitive functions not expressed in the phenotypes examined in the current analyses.

In general, the linkage results did not differ substantially for slow wave recorded during memory trials with no distracting stimulus and slow wave recorded in memory trials in which a distracting stimulus was presented. This was not unexpected, as the two phenotypes are highly correlated, and previous analyses have found them to be largely influenced by a common genetic factor, although a small specific genetic influence was found for distractor compared to non-distractor slow wave (Hansell *et al.*, 2004). None of the most promising markers (i.e. those where LOD scores remained suggestive after correcting for multiple testing—D10S547, D10S1208, D10S196, D10S1652) was associated with just one slow wave trial type. That is, LOD scores of at least 1.5 (unadjusted) were found for slow wave recorded during both distractor and non-distractor trials at each of these markers.

Correcting the theoretical point-wise *p*-values for multiple testing resulted in the reclassification of 14 linkage peaks from suggestive to non-suggestive. Five linkage peaks, all on chromosome 10, retained their suggestive classification. Empirical LOD thresholds for significant and suggestive linkage were estimated for promising slow wave phenotypes (i.e. slow wave recorded at right-hemisphere frontal (F4), left-hemisphere central (C3), and midline parietal (Pz) during the memory condition and at left-hemisphere prefrontal (Fp1), midline central (Cz), and midline parietal (Pz) in the memory distractor condition). Based on 500 simulations, levels ranged from 2.97 to 3.66 for significant linkage and 1.70–2.02 for suggestive linkage. (Note that thresholds estimated from 5000 simulations were found to be comparable to those estimated from 500 simulations.) LOD scores for each of the promising phenotypes were found to be suggestive in relation to the empirical thresholds (although suggestiveness was borderline for slow wave recorded at left-hemisphere prefrontal (Fp1) in the memory distractor condition). The highest LOD was found for slow wave recorded at right-hemisphere frontal (F4), but no plausible genes of influence were found under this peak.

The present results offer hints of genes that may be influencing variation in the neural processes activated in a delayed-response working-memory task. To illuminate these pathways further, association analyses must be undertaken. Of the genes discussed here, the NRP1 and ANK3 genes are plausible candidates for association analyses. In addition, the CHAT gene is a possible candidate and, to a lesser extent, the DRD1IP gene. The PST gene is also of interest, for although it was associated with relatively low linkage peaks, there was some linkage consistency for slow wave recorded at frontal and prefrontal sites and previous studies suggest that this gene may play a role in memory function.

ACKNOWLEDGMENTS

Phenotype collection was supported by the Australian Research Council (Grant Numbers: A79600334, A79906588, A79801419) and the Human Frontier Science Program (Grant Number: RG0154.1998-B). The genome scans were supported by the Australian NHMRC's Program in Medical Genomics (NHMRC-219178: NGM, GWM, DLD) and a grant to Dr. Jeff Trent for genotyping at the Center for Inherited Disease Research (CIDR: Director, Dr Jerry Roberts) at The Johns Hopkins University. CIDR is fully funded through a federal contract from the National Institutes of Health to The John Hopkins University (Contract Number N01-HG-65403). We thank Dr Cathy Hyland of the

Australian Red Cross Blood Service, Brisbane, for initiating blood grouping; Ann Eldridge, Marlene Grace, and Kathleen Moore for twin recruitment and data collection; and the twins and their families for their participation. Harry Beeby wrote software to display linkage peaks and Kate Morley provided helpful advice in navigating the NCBI Map Viewer. We also thank Peter Visscher for statistical advice.

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Edited by Danielle Posthuma