Behavior Genetics, Vol. 35, No. 6, November 2005 (© 2005)
DOI: 10.1007/s10519-005-6188-2

Genetic Covariation Between Event-Related Potential (ERP) and Behavioral Non-ERP Measures of Working-Memory, Processing Speed, and IQ

N. K. Hansell,[1–3] M. J. Wright,[1] M. Luciano,[1] G. M. Geffen,[2] L. B. Geffen,[2] and N. G. Martin[1]

Received 20 Sep. 2004—Final 1 June 2005

The aim of this study was to identify genetic covariants for fundamental measures of brain function (event-related potentials (ERPs): P300 latency and slow wave amplitude recorded in a working-memory task) and more complex cognitive measures (behavioral non-ERP measures: working-memory performance, information processing speed, IQ). Data were collected from 252 monozygotic and 297 dizygotic twin pairs aged 16. Multivariate modeling identified two independent genetic factors associated with processing speed that also influenced working-memory performance (one reflected the duration of neural activity required to evaluate target information, the other reflected more general cognitive and speed-related abilities). However, the allocation of neural resources, as assessed by ERP slow wave amplitude measures, was not associated with the other cognitive measures investigated. Thus, of the ERP measures examined, P300 latency, but not slow wave amplitude, may be an informative measure to include (i.e., with working-memory performance) in future multivariate linkage and association analyses of cognitive function.

KEY WORDS: Cognition; event-related potentials; P300 latency; processing speed; slow wave; twins; working memory.

INTRODUCTION

Working memory function and speed of information processing are factors proposed to influence individual differences in cognitive ability. Working memory is the short term activation, storage, and manipulation of information (Goldman-Rakic, 1992) and working memory capacity has been found to account for between one-third and one-half of the variance in general intelligence (Conway *et al.*, 2003). Furthermore, it has been argued that individual variation in working memory capacity may be due to processing efficiency (or processing speed) (Fry and Hale, 2000). Faster processing may allow more information to be processed before it is lost through decay or interference (Jensen, 1993), and/or faster rehearsal may allow the maintenance of a larger amount of information (Baddeley, 1986). Consistent with this view, working memory and processing speed are correlated measures (e.g., Fry and Hale, 2000; Vernon and Weese, 1993).

Twin studies indicate that common genetic sources influence variation in measures of working memory and general cognitive ability (Ando *et al.*, 2001; Luciano *et al.*, 2004b). Similarly, common genetic factors have been found to influence measures of processing speed and IQ (Baker *et al.*, 1991; Luciano *et al.*, 2004a; Posthuma *et al.*, 2001; Rijsdijk *et al.*, 1998). Furthermore, both working memory and processing speed measures appear to be influenced by common genetic factors (Luciano *et al.*, 2004b; Posthuma *et al.*, 2003).

[1] Genetic Epidemiology Laboratory, Queensland Institute of Medical Research, Brisbane, Australia.
[2] Cognitive Psychophysiology Laboratory, Schools of Psychology and Psychiatry, University of Queensland, Brisbane, Australia.
[3] To whom correspondence should be addressed at Genetic Epidemiology Laboratory, Queensland Institute of Medical Research, Post Office, Royal Brisbane Hospital, Brisbane, Queensland 4029, Australia. Tel: +61-7-3362 0299. Fax: +61-7-3362 0101. e-mail: narelleH@qimr.edu.au

These twin studies examined outcome measures such as reaction time or response accuracy (e.g., Baker *et al*., 1991; Luciano *et al*., 2004b). However, another approach has been to study cognitive processes at a more fundamental level by examining brain activity underlying these processes using techniques such as the recording of electrophysiological data (e.g., event-related potentials (ERPs)). ERP measures of brain activity are recorded from electrodes placed on the scalp. Changes in voltage are time-locked to an event and thus potentials are event-related. ERP scalp topographies indicate rough areas of brain activation, while amplitudes indicate the extent of activation and latencies indicate the duration.

The ERP slow wave component has been recorded in the delay period of a range of delay tasks and is thought to reflect working memory processes (Geffen *et al*., 1997; Rama *et al*., 1995; Ruchkin *et al*., 1995; Ruchkin *et al*., 1997). Studies show that it varies as a function of memory load (Geffen *et al*., 1997; Rama *et al*., 1995; Ruchkin *et al*., 1990). P300 amplitude and latency are thought to be sensitive to individual differences in memory and attentional processes (Polich and Kok, 1995). They are commonly examined as measures of cognitive function in a wide range of clinical populations and have been shown to correlate with independent measures of cognitive ability (e.g., in alcohol-dependent patients (Kim and Lee, 2004) and patients with social phobia (Sachs *et al*., 2004)).

The genetic relationship between biological ERP measures of neural activity and behavioral non-ERP measures of working memory function, processing speed, and general cognitive ability is yet to be fully explored. However, there are indications that common genetic sources may influence variation in some cognitive processes ranging from basic neural activity to more complex behaviors. Previous analyses in our laboratory examined the relationship between P300 amplitude, P300 latency, working-memory performance and IQ (Wright *et al*., 2002). These analyses found little evidence of a genetic association between P300 amplitude and working-memory performance, but a modest association was found between working-memory performance and P300 latency recorded over frontal brain regions. Neither P300 amplitude nor latency was associated with IQ (Wright *et al*., 2002).

The present study examined an extended range of both ERP and behavioral non-ERP measures of working memory function and information processing speed, with the aim of identifying further genetic covariants of cognitive function. (A long-term aim is to examine genetic covariants in multivariate linkage and association analyses.) The working memory measures included in multivariate analyses were ERP slow wave measures and a non-ERP measure of working-memory performance based on response speed and accuracy. P300 amplitude was not included due to our previous findings (i.e., a lack of association with IQ and working-memory performance (Wright *et al*., 2002)). The measures of processing speed examined were P300 latency, and non-ERP measures of choice-reaction time, and inspection time. IQ was included as a measure of general cognitive ability. ERP measures recorded over prefrontal and parietal brain regions were examined as these regions are commonly reported to show enhanced activation during visuo-spatial working memory tasks (Batuev *et al*., 1985; Fuster, 2001). Data were collected from a sample of 16 year-old adolescent twins and examined using structural equation modeling based on the classical twin method (Neale and Cardon, 1992).

As measures of working memory function, we hypothesized that ERP slow wave and a behavioral non-ERP measure of working-memory performance would covary genetically. Furthermore, because working-memory performance has been shown to covary with IQ (Luciano *et al*., 2004b; Wright *et al*., 2002), we hypothesized that these genetic influences may also influence IQ. It was further expected that the ERP measure P300 latency would covary genetically with the behavioral non-ERP speed of processing measures (choice-reaction time and inspection time) and, as has been shown previously, covary genetically with working-memory performance (Wright *et al*., 2002). However, genetic covariation between ERP and non-ERP speed of processing measures was expected to be moderate as P300 latency in this sample has not been found to covary genetically with IQ (Wright *et al*., 2002), while choice-reaction time and inspection time measures have been found to covary quite substantially with IQ (Luciano *et al*., 2004b). Finally, analyses were expected to replicate previous findings by Luciano *et al*. (2004b) by showing a common source of genetic influence on the behavioral non-ERP measures of working-memory performance, choice-reaction time, inspection time, and IQ.

METHOD

Participants

Data were collected from 549 twin pairs, with testing occurring as closely as possible to their 16th

birthdays ($M = 16.2$, SD = 0.3, range = 15.4–18.1 with 47 pairs aged 15, 484 pairs aged 16, 17 pairs aged 17 and 1 pair aged 18 years). This is the largest sample examined to date as part of an ongoing study of the genetics of cognition (Wright *et al*., 2001). Pairs comprised 135 female and 117 male MZ pairs, 75 female and 70 male DZ pairs, and 152 opposite sex pairs. Twin pairs were excluded if parental report indicated either had a history of head injuries, neurological or psychiatric conditions, substance abuse/dependence, and/or taking medications with significant central nervous system effects. Zygosity was 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. Written, informed consent was obtained from all participants and their parents and ethics approval was obtained from the Human Research Ethics Committee at the Queensland Institute of Medical Research.

Working-Memory Task

The computerized delayed-response task and testing protocols used in this study have been described previously in Hansell *et al*. (2001). Briefly, the computer screen was hooded to show a circular screen with a diameter of 250 mm. Participants were required to focus on a central fixation point throughout the task in order to reduce eye movement. A target (checkered dot) was presented peripherally, 250 ms after fixation onset, and on an annulus (9.25°). There were eight trial type variations (memory/sensory × distractor presence/absence × delay 1 second/4 seconds). In sensory trials, the target remained on-screen until a response indicating target location was enacted, but in memory trials the target was presented only briefly (150 ms). A delay period of 1 or 4 seconds followed target presentation. In 50% of sensory and memory trials, a distracting stimulus identical to the target, but presented in a different (random) location, was presented for 150 ms in the window 300–700 ms post-target onset. At the end of the delay period, the fixation point disappeared and this was the cue for participants to lift their preferred hand from a touch-sensitive pad, where it had been resting, to indicate target location with a rubber-tipped pointer.

ERP Recording

Although only ERPs recorded at Fp2 and P4 were examined in the present study, ERP data were collected from 15 sites (Fp1, Fp2, F3, Fz, F4, F7, F8, C3, Cz, C4, P3, Pz, P4, O1, O2) using the Electrocap system, with linked ears as reference and impedances kept below 5 kohms. Electrodes placed on the supra-orbital ridge and the outer canthus of the left eye monitored eye movements and blinks. The electro-oculogram (EOG), Fp1 and Fp2 were amplified 5 K times and all other 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. Electroencephalogram (EEG) and EOG data exceeding 50 μV RMS were automatically rejected. Eye 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.

ERP Measures: Slow Wave Average Amplitude, P300 Latency

Following artifact rejection, trials were averaged separately for each trial type using a pre-target baseline of 350 ms. Approximately 4% of data did not meet acceptance criteria and were excluded from analyses. The acceptance criteria required that EOG/EEG rejections be less than 40% and that behavioral rejections (too slow, too fast, or spatially incorrect) be less than 30%. Data not meeting these criteria were visually inspected and accepted if the waveforms did not show significant drift and appeared stable (i.e., waveforms from the 1 second delay trials were comparable to those collapsed over the 1 and 4 seconds delay trials). Purpose written software was used to quantify amplitudes and latencies.

Slow wave average amplitude was examined for the interval 650–1150 ms (post-target onset) in memory trials in which a distracting stimulus was presented. Distractor trials were used as they may be a better measure of working memory processes than non distractor trials (Engle *et al*., 1999) and as they appear to be more heritable than non-distractor trials (Hansell *et al*., 2004). The mean number of trials averaged for each individual was 64.3 (SD = 16.5, range = 10–96). Note that longer trials were required to record the slow wave over delay periods and that

the possibility of trial rejection due to eye blinks and other artifacts was therefore increased.

P300 was measured from waveforms collapsed over trial type. The delay task was not designed to differentiate P300 measures by trial type and visual inspection of waveforms and preliminary analyses of memory and sensory P300 data collected from the first 50 twin pairs indicated no amplitude or latency differences for trial type (Wright *et al.*, 2002).

P300 latency was defined as the maximum peak within the interval 150–450 ms (post-target onset). To aid latency detection, averaged waveforms ($M = 279.5$ trials, SD = 56.3, range = 40–376) were digitally filtered with a low-pass triangular filter (5 Hz). The selected interval was chosen as waveforms averaged over a large number of participants showed a positive component at approximately 300 ms and no other positive peaks within the window. The window was divided into 10 ms sub-windows and the slope of each sub-window was determined by fitting a line of best fit (least squares approximation) to the data points. A peak was identified as a change in slope from positive to negative in successive sub-windows. Up to three peaks were computer selected within the 150–450 ms window and then subjected to direct visual inspection by a research assistant who was blind to zygosity. Where peaks could not be selected with a high degree of certainty (approximately 6% of prefrontal data and 8% of parietal data), latency was coded as missing. P300 amplitude was not examined as previous analyses have shown that it does not correlate well with working-memory performance (phenotypic $r = 0.04$ at frontal and 0.14 at parietal) or IQ (0.08 at frontal, 0.05 at parietal) (Wright *et al.*, 2002).

Behavioral Non-ERP Measures: Working-Memory Performance, Psychometric IQ, Choice-Reaction Time, Inspection Time

Luciano and colleagues (e.g., 2004a; 2004b) have comprehensively investigated a range of working memory, IQ, and information processing measures, some of which are included in the present study. They are working-memory performance (response accuracy or amount won in the delayed-response task), full-scale IQ (from the Multidimensional Aptitude Battery, Jackson, 1984), mean reaction time obtained from correct responses in a 2-choice condition of a computerized choice reaction-time task (CRT), and inspection time (IT) obtained from a computerized line discrimination task (the measure of interest being the standard deviation of the IT curve). For each of the non-ERP variables, computer or experimenter error resulted in the loss of up to 1% of the collected data. In addition, approximately 4% of the IT data were excluded due to the data having a poor fit to the cumulative normal curve.

Statistical Analyses

Given the range of variables examined, all were standardized to have a mean of zero and a variance of one (i.e., *z*-scores, also known as standardized scores (Purcell, 2001), were used) to facilitate comparisons of variance. Raw data were analyzed using the maximum likelihood based model-fitting approach of the statistical package Mx (Neale *et al.*, 2003). For all variables, means and variances were examined for birth order, zygosity, and sex effects by comparing the fit of constrained models that did not allow for these effects, with fully saturated models that did. In the same manner, reaction time means were examined for speed-accuracy trade-off effects as described by Neubauer and colleagues (1992). In each case, the more restricted model was compared to the model within which it was nested by likelihood ratio test.

Twin correlations were estimated for 6 zygosity groups (MZ female (MZF), MZ male (MZM), DZ female (DZF), DZ male (DZM), DZ opposite-sex (female first-born—DZFM), and DZ opposite-sex (male first-born—DZMF). For each variable, a constrained model in which the MZF correlation was set equal to the MZM correlation, and similarly, the DZF to the DZM, and the DZFM to the DZMF, was compared to the fully saturated model. A further constraint, which set the DZ same-sex correlation equal to the DZ opposite sex (DZO) correlation, was tested by likelihood ratio.

Multivariate models were then employed to partition the variance into that influenced by additive genes (A), common environment (C), and non-shared environment (E). Data were initially examined in a Cholesky triangular decomposition of variance (Neale and Cardon, 1992). To determine the most parsimonious model, nested sub-models containing only AE, CE, or E sources of influence were compared to the fully saturated ACE model. To simplify the structure of additive genetic influences, a varimax rotation of the genetic correlations obtained from the best fitting Cholesky model was performed using SAS System for Windows 8.02 (SAS Institute Inc. 1999–2001). The resulting genetic factor structure was then modeled using independent pathway

modeling (Neale and Cardon, 1992), which allows for genetic influences specific to each variable in addition to independent genetic factors that influence multiple variables. The identification of the final model was explored by generating data with particular fixed values for the variable model parameters and then ensuring that optimization from different sets of starting values provided a solution of the original values (Neale *et al*., 2003).

Univariate and multivariate outlying families were identified using the %P option in Mx, which provided a likelihood statistic for each family conditional on the genetic model. Data for an entire family were dropped if the *z*-score value for the family was greater than ± 3 and the analyses were rerun.

RESULTS

All ERP variables, working-memory performance, and IQ were normally distributed and did not require transformation. CRT and IT were positively skewed and this was corrected in both cases by log transformation (Tabachnick and Fidell, 1989). Up to 3% of the data collected for each variable were dropped as outlying.

Waveform Description

Individual waveforms from an MZ and a DZ twin pair are shown in Figure 1, by way of illustration. Waveforms generally appeared more similar for MZ co-twins than DZ co-twins. However, twin zygosity was not always obvious from the waveforms and those shown in Figure 1 were specifically chosen for similarity in the case of the MZ pair and for dissimilarity in the case of the DZ pair. The waveforms indicate that individual differences were considerable, even between MZ co-twins. However, there were general trends. Target presentation elicited a P300 that peaked at approximately 300 ms. This is somewhat fast for a visual P300, but not wholly unexpected given that a salient fixation stimulus, marking the beginning of each trial, was presented 250 ms pre-target. The P300 was followed by a slow wave component.

Homogeneity of Means and Variances

Means and variances for each variable are shown in Table I. No effects of zygosity were found. However, inconsistent birth-order effects were found for IQ and choice-reaction time. The mean IQ score for first-born MZ male co-twins was higher than for second-born MZ males, but this effect was not found for MZ female co-twins or same-sex DZ co-twins. Similarly, variability was greater for second-born MZ male co-twins than for first-born co-twins, but this effect was not found for other same-sex pairs. These inconsistencies suggest sampling error rather than real effects. Mean differences found for sex indicated

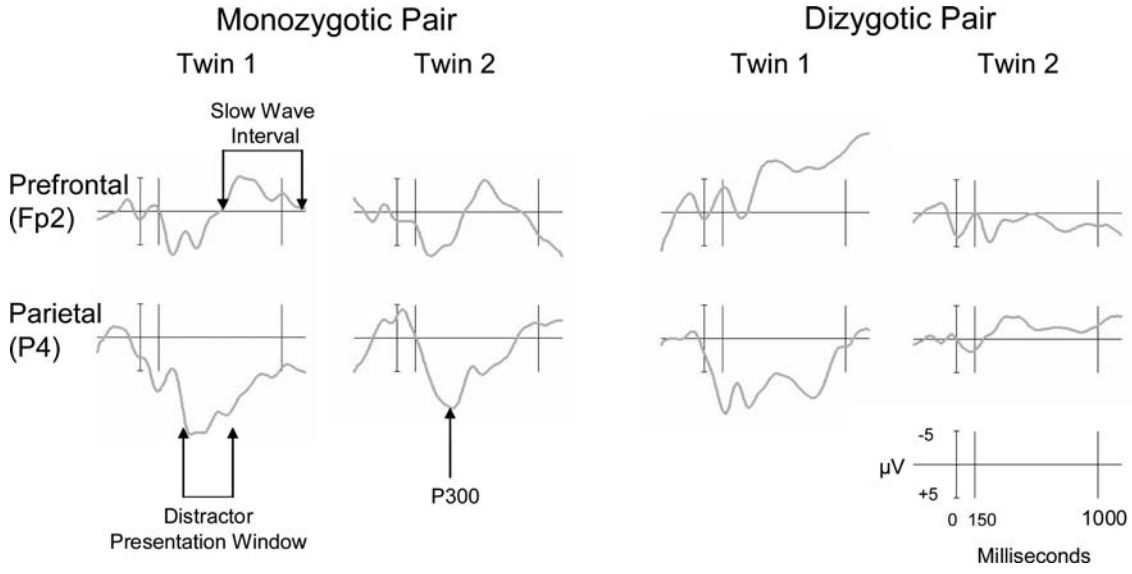

Fig. 1. Waveforms are shown for MZ and DZ co-twins. They were recorded at right-hemisphere prefrontal (Fp2) and parietal sites (P4) during 1 second delay trials of the delayed-response task in memory distractor trials. Vertical lines indicate target onset, target offset, and 1 second post-target onset. ERP components examined were P300 latency (i.e. time from target onset to peak maximum) and slow wave average amplitude (650–1150 ms interval). Distracting stimuli were presented randomly for 150 ms in the 300–700 ms window.

Table I. Means (Standard Deviations) and Maximum Likelihood Phenotypic Correlations Between Parietal (P4) and Prefrontal (Fp2) P300 Latency (P300 Lat) and Slow Wave Average Amplitude (SW Amp), IQ, Working-Memory Performance (WM Perf), Choice-reaction time (CRT), and Inspection Time (IT)

	Parietal		Prefrontal					
	P300 Lat (ms)	SW Amp (μV)	P300 Lat (ms)	SW Amp (μV)	IQ	WM Perf ($)	CRT (ms)	IT (†)
N (pairs)	418	479	439	479	518			
Mean	306	−2.9	299	0.4	111	26	297	86
(SD)	(64)	(6.3)	(54)	(8.1)	(13)	(5)	(31)	(45)
P4 SW Amp	0.20*							
Fp2 P300 Latency	0.41*	0.19*						
Fp2 SW Amp	0.07*	0.32*	0.24*					
IQ	−0.06	−0.06	−0.04	−0.11*				
WM Performance	−0.12*	−0.10*	−0.41*	−0.09*	0.25*			
CRT	0.16*	0.12*	0.14*	0.04	−0.27*	−0.26*		
Inspection Time	0.03	0.01	0.02	0.07	−0.37*	−0.12*	0.20*	

†Raw measure of the standard deviation of the IT curve.
*Correlation is significant based on 95% confidence intervals (calculated in Mx to account for non independence of observations).

that females had slightly faster parietal P300 latencies than males (301 ms versus 311 ms), while males had shorter inspection times (82.7 versus 89.9), and higher IQ (113.7 versus 109.4). In addition, variances were found to be slightly higher in males than females for parietal slow wave (43.3 versus 36.3) and inspection time (48.4 versus 42.3). A speed-accuracy trade-off effect was found for choice-reaction time and in subsequent analyses all choice-reaction time data were corrected for accuracy. Furthermore, to adjust for sex effects on the mean, a male deviation was included in the means model of further analyses.

Phenotypic Correlations

The strongest association found between an ERP and a non-ERP cognitive measure was −0.41, indicating that faster prefrontal P300 latency, or faster target evaluation, was associated with superior performance on the working-memory task (Table I). A similar, but weaker, significant association was found for *parietal* P300 latency (−0.12). Faster P300 latency was also associated with faster choice-reaction time (0.16 at parietal and 0.14 at prefrontal), but P300 latency had no significant association with inspection time or IQ. Larger (more negative) slow wave, or greater resource allocation during the delay period with its memory requirement, was associated to a small degree with higher IQ (−0.11 at prefrontal), and faster responses in the choice-reaction time task (0.12 at parietal). Other significant, but very weak, associations ranging from 0.09 to 0.10 (absolute values) are shown on Table I.

Among the ERP measures, parietal and prefrontal P300 latency were positively associated (0.41) and faster P300 latency was associated with larger (more negative) slow wave amplitude (0.20 at parietal, 0.24 at prefrontal). Parietal and prefrontal slow wave amplitudes were positively correlated (0.32). Correlations among the non-ERP measures ranged from 0.12 to 0.37 (absolute values).

Twin Correlations

Examination of the twin correlations (Table II) indicated additive genetic and unique environmental influences on all variables, as DZ correlations were approximately half the MZ correlations. Familial influence was greatest for IQ ($r_{MZ} = 0.84$) and of lower magnitude for the remaining variables (r_{MZ}'*s* ranged 0.40–0.49). Closer testing of the data indicated that the MZ and DZ correlations did not differ significantly for sex (i.e., $r_{MZF} = r_{MZM}$, $r_{DZF} = r_{DZM}$, and r_{DZO} (female first-born) $= r_{DZO}$ (male first-born), χ^2_3 ranged 0.7–7.3, critical value = 7.81). However, it should be noted that for inspection time, the twin correlation for MZ females (0.53) could not be set equal to that of MZ males (0.31) in a one degree of freedom test ($\chi^2_1 = 4.8$, critical value = 3.84). In view of the number of tests carried out, this was not explored further in these analyses. Correlations between opposite-sex pair co-twins did not differ

Table II. Maximum Likelihood Twin Correlations (and 95% Confidence Intervals) by Zygosity Group and Sex for Parietal (P4) and Prefrontal (Fp2) P300 Latency (P300 Lat) and Slow Wave Average Amplitude (SW Amp), IQ, Working-Memory Performance (WM Perf), Choice-reaction time (CRT), and Inspection Time (IT)

	MZ (195–241 Pairs)	DZ (223–282 Pairs)	MZF (106–132 Pairs)	MZM (89–109 Pairs)	DZF (61–72 Pairs)	DZM (54–67 Pairs)	DZO (108–144 Pairs)
P4							
P300 Lat	0.47 (0.35, 0.57)	0.22 (0.10, 0.34)	0.42 (0.23, 0.56)	0.52 (0.36, 0.64)	0.16 (−.04, 0.35)	0.34 (0.06, 0.54)	0.23 (0.04, 0.39)
SW Amp	0.46 (0.36, 0.56)	0.33 (0.22, 0.43)	0.40 (0.25, 0.53)	0.54 (0.39, 0.65)	0.25 (−.10, 0.49)	0.45 (0.25, 0.59)	0.29 (0.14, 0.43)
Fp2							
P300 Lat	0.46 (0.35, 0.55)	0.19 (0.07, 0.31)	0.45 (0.31, 0.57)	0.46 (0.29, 0.59)	0.21 (−.05, 0.43)	0.06 (−.20, 0.30)	0.24 (0.07, 0.40)
SW Amp	0.40 (0.27, 0.51)	0.15 (0.03, 0.26)	0.40 (0.23, 0.54)	0.40 (0.20, 0.55)	0.14 (−.14, 0.39)	0.11 (−.15, 0.34)	0.16 (0.02, 0.31)
IQ	0.84 (0.80, 0.87)	0.47 (0.37, 0.55)	0.85 (0.80, 0.88)	0.82 (0.76, 0.87)	0.54 (0.34, 0.67)	0.48 (0.30, 0.62)	0.43 (0.29, 0.54)
WM Perf	0.45 (0.34, 0.53)	0.19 (0.07, 0.30)	0.42 (0.27, 0.54)	0.47 (0.33, 0.59)	0.12 (−.14, 0.35)	0.05 (−.22, 0.32)	0.26 (0.11, 0.39)
CRT	0.49 (0.39, 0.58)	0.22 (0.10, 0.33)	0.46 (0.31, 0.57)	0.54 (0.39, 0.64)	0.11 (−.20, 0.38)	0.28 (0.03, 0.48)	0.23 (0.07, 0.36)
IT	0.41 (0.29, 0.51)	0.19 (0.07, 0.31)	0.53 (0.38. 0.64)	0.31 (0.14, 0.45)	0.41 (0.17, 0.57)	0.16 (−.09, 0.37)	0.10 (−.08, 0.28)

Note: MZ = Monozygotic, DZ = Dizygotic, MZF = MZ Female, MZM = MZ Male, DZF = DZ Female, DZM = DZ Male, DZO = DZ Opposite Sex.

significantly from those between same-sex DZ cotwins (χ^2_1 ranged 0.0–3.3, critical value = 3.84). Data were therefore pooled across sex in the multivariate analyses.

Multivariate Genetic Modeling

Multivariate Cholesky modeling showed familial influence to be significant, as dropping both A and C influences from a fully saturated ACE model resulted in a highly significant worsening of model fit ($\Delta\chi^2_{72} = 722.8$, $p < 0.001$). Dropping A alone resulted in a significant worsening of fit ($\Delta\chi^2_{36} = 146.2$, $p < 0.001$), indicating that additive genes were a significant influence. However, C could be dropped without any worsening of fit ($\Delta\chi^2_{36} = 11.7$, $p > 0.05$).

Genetic and unique environmental correlations from the full AE model are shown in Table III. To simplify the genetic factor structure from that obtained through Cholesky decomposition, the matrix of genetic factor loadings was varimax rotated to simple structure. Three factors with eigenvalues greater than 1, and accounting for 68% of the variance, were identified (Table IV). The rotated factor pattern indicated a first factor influencing IQ, working-memory performance, choice-reaction time and inspection time; a second factor influencing prefrontal and parietal P300 latency, working-memory performance, and choice-reaction time; and a third factor influencing prefrontal and parietal slow wave.

This genetic factor structure was tested using an independent pathway modeling approach Neale, 1992 #161), which also allowed for specific genetic influences on each variable. For the purpose of model identification, common influences on prefrontal and parietal slow wave amplitudes were set to be equal

Table III. Genetic Correlations (lower triangle) and Unique Environmental Correlations (*upper triangle*) from the AE Cholesky Model for Parietal (P4) and Prefrontal (Fp2) P300 Latency (P300 Lat) and Slow Wave Average Amplitude (SW Amp), IQ, Working-Memory Performance (WM Perf), Choice-reaction time (CRT), and Inspection Time (IT)

	Parietal		Prefrontal					
	P300 Lat	SW Amp	P300 Lat	SW Amp	IQ	WM Perf	CRT	IT
P4 P300 Latency		*0.20*	*0.34*	*0.16*	−0.07	*−0.06*	*0.06*	*−0.08*
P4 SW Amp	0.20		*0.19*	*0.25*	*0.07*	*−0.08*	*0.07*	*−0.08*
Fp2 P300 Latency	0.50	0.18		*0.21*	*−0.04*	*−0.32*	*0.02*	*0.03*
Fp2 SW Amp	−0.04	0.38	0.28		*−0.03*	*−0.03*	*0.02*	*−0.04*
IQ	−0.06	−0.12	−0.04	−0.19		*−0.05*	*−0.11*	*−0.11*
WM Performance	−0.21	−0.12	−0.53	−0.17	0.45		*−0.06*	*0.07*
CRT	0.28	0.17	0.27	0.07	−0.41	−0.51		*0.07*
Inspection Time	0.16	0.13	0.01	0.22	−0.55	−0.38	0.40	

Table IV. Factor Output for Factor Analysis of Genetic Correlations from the AE Cholesky Model

	Factors		
	1	2	3
P4 P300 Latency	−0.06	**0.79**	−0.02
P4 Slow Wave Amp	−0.05	0.17	**0.76**
Fp2 P300 Latency	−0.03	**0.86**	0.25
Fp2 Slow Wave Amp	−0.14	−0.01	**0.86**
IQ	**0.84**	0.06	−0.11
WM Performance	**0.62**	**-0.51**	−0.08
Choice-reaction time	**-0.66**	**0.40**	−0.03
Inspection Time	**-0.81**	−0.04	0.14

Note: All loadings >0.3 are shown in **bold**.

Table V. Maximum Likelihood Path Coefficients for the Non-Shared Environmental Factors (E1–E8) from the Final Model (Additive Genetic Influences shown in Figure 2) for Parietal (P4) and Prefrontal (Fp2) P300 Latency and Slow Wave Average Amplitude (SW Amp), IQ, Working-Memory Performance (WM Performance), Choice-reaction time (CRT), and Inspection Time

	E1	E2	E3	E4	E5	E6	E7	E8
P4 P300 Latency	0.76							
P4 SW Amp	0.20	0.70						
Fp2 P300 Latency	0.26	0.14	0.73					
Fp2 SW Amp	0.10	0.28	0.19	0.74				
IQ	−0.05	0.01	−0.02	−0.04	0.41			
WM Performance	−0.01	−0.07	−0.26	0.04	−0.05	0.71		
CRT	0.09	0.08	−0.03	−0.01	−0.07	−0.04	0.73	
Inspection Time	0.00	−0.03	0.03	0.02	−0.09	0.06	0.06	0.75

(reflecting the similar factor loadings shown in Table IV). Unique environmental influences, which include measurement error, were left in Cholesky format (see Table V) in order to obtain the most conservative test of the genetic structure. This model (i.e., independent factor structure for A, Cholesky E) had a slightly worse fit to the data compared to the full AE Cholesky ($\Delta\chi^2_{18} = 34.5$, $p < 0.02$, critical value $= 28.87$), but was retained due to its economy and greater interpretability.

Estimates of the additive genetic path coefficients are shown in Figure 2, as are heritability estimates (h^2), which were obtained by squaring and adding all genetic components for a given observed variable. The heritability estimates indicated that, apart from IQ for which heritability was 0.82, genetic influences accounted for similar amounts of variance in the ERP and the behavioral non-ERP measures (ranging 0.33–0.47 for the ERP measures and 0.41–0.44 for the non-ERP measures excluding IQ). The additive genetic factor A1 (Figure 2) accounted for 38% of the variance in prefrontal P300 latency, 12% of the variance in parietal P300 latency, 12% of the variance in working-memory performance, and 4% of the variance in choice-reaction time. In addition, a group genetic factor (A2) accounted for 11% of the variance in prefrontal and parietal slow wave amplitudes. A final genetic factor (A3) accounted for 46% of the variance in IQ, 15% of the variance in working-memory performance, 13% of the variance in choice-reaction time, and 20% of the variance in inspection time.

Specific genetic factors influenced each variable with the exception of prefrontal P300 latency. They accounted for variance in parietal P300 latency (31% of total variance), parietal slow wave (36%), prefrontal slow wave (22%), IQ (36%), working-memory performance (14%), choice-reaction time (27%), and inspection time (21%).

DISCUSSION

This study was successful in identifying a common genetic source influencing both ERP and behavioral non-ERP measures of processing speed. This factor was also found to influence a non-ERP measure of working-memory performance. In contrast, ERP slow wave measures previously shown to vary with working memory load {e.g., \Geffen, 1997 #163} were found to be genetically independent of non-ERP working-memory performance and all processing speed measures. Furthermore, neither of the factors influencing ERP P300 and slow wave components was associated with variation in general cognitive ability (IQ).

The common genetic factor influencing both ERP and non-ERP measures of processing speed and working memory function (i.e., Factor A1) influenced measures of prefrontal and parietal P300 latency, choice-reaction time, and a general measure of working-memory performance. Faster P300 latency was associated with faster choice-reaction time and better working-memory performance. The primary influence of this factor was on prefrontal P300 latency, where it accounted for *all* of the genetic variance, thereby reflecting all of the genetic influences on mechanisms influencing variation in P300 latency (i.e., the duration of neural activity required to

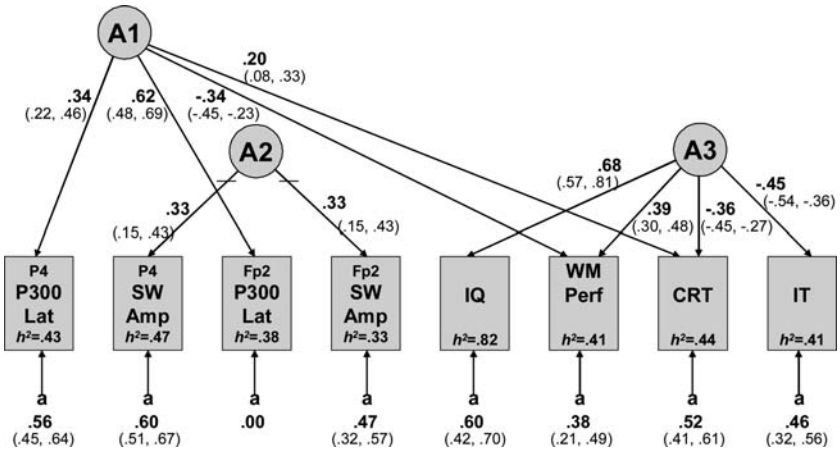

Fig. 2. Path diagram of additive genetic influences on parietal (P4) and prefrontal (Fp2) P300 latency (P300 Lat) and slow wave average amplitude (SW Amp), IQ, working-memory performance (WM Perf), choice-reaction time (CRT) and inspection time (IT). Estimates were standardized such that, when squared, they indicate the percentage of variance accounted for. Common factors (A1, A2, A3) and specific influences (a) are shown. For each parameter estimate, 95% confidence intervals are shown. Parameter estimates for pathways from A2 to parietal and prefrontal slow wave were set equal for model identification. Heritabilities (h^2) are shown. Each variable was also influenced by non-shared environmental factors, which are shown in Table V.

evaluate the target stimulus). More specifically, the measure reflected the duration of neural processing in the prefrontal brain regions. The prefrontal cortex is considered to function at the highest level in the executive hierarchy of brain functions, with its functions including focusing and maintaining attention, integrating actions with perceptions, and cooperating with other areas of the neocortex and with subcortical structures (Fuster, 2000). Thus, the A1 factor may reflect genetic influence on the efficiency of attentional processes and intrabrain connections that would aid in the faster evaluation of the target stimulus. Furthermore, the factor indicates that these processes have a moderate influence on P300 latency recorded over parietal brain regions (where it accounted for 28% of the genetic variation), on working-memory performance (where it accounted for 29% of the genetic variation), and a small influence on choice-reaction time (where it accounted for 10% of the genetic variation).

The neural speed factor (A1) is consistent with a phenotypic study by McGarry-Roberts *et al.* (1992) that reported a positive association between concurrently recorded measures of P300 latency and choice-reaction time. They also reported significant correlations between full-scale IQ and P300 latencies recorded during paired-stimuli tasks, but not P300 latencies recorded during reaction time tasks. Thus, the relationship between P300 latency and IQ may be task specific. Furthermore, their results suggest that a significant relationship with IQ may be more likely when P300 latency is recorded in more cognitively demanding tasks. The delayed-response task used may not have been sufficiently demanding for a P300 latency/IQ relationship to emerge.

A further factor influenced both working memory and speed of processing measures, but influenced only behavioral non-ERP measures (i.e., Factor A3). This factor is consistent with previous studies showing similar associations (Luciano *et al.*, 2004b; Posthuma *et al.*, 2003). Better working-memory performance and higher IQ were associated with faster choice-reaction time and faster inspection time. The factor had greatest influence on IQ and inspection time (where it accounted for 56% and 49% of the genetic variance respectively) and moderate influence on working-memory performance (37% of genetic variance) and choice-reaction time (30% of genetic variance). The factor appears to reflect genetic influence on mechanisms associated not only with individual variation in general cognitive function, but also with variation in speed of information processing and working memory function, which are considered to be components of general cognitive ability (Deary, 2001).

Thus, two independent genetic factors (A1 and A3) showed evidence of an association between working memory function and speed of processing, suggesting that multiple speed- and efficiency-related processes influence their covariation. One source of covariation appears related to the efficiency of neural processing in evaluating target information,

particularly in the prefrontal brain regions. A further source appears related to mechanisms, including perceptual discrimination and reaction time, which influence general cognitive ability. However, in addition to the influence of common speed- and efficiency-related factors, working-memory performance was influenced by notable specific genetic influences. Approximately 36% of the genetic variance for working-memory performance was due to genetic influences specific to the measure, suggesting that variation in working-memory performance is not solely due to factors related to processing speed and efficiency.

Our analysis also identified a common source of genetic influence on prefrontal and parietal slow wave amplitude (Factor A2). However, substantial specific genetic influences on each of these measures indicated that they were largely independent, consistent with previous findings (Hansell *et al*., 2001). ERP slow wave measures (recorded while individuals retained target information), were weakly associated at best with working-memory performance and general cognitive ability. Thus genetic factors influencing fundamental neural processes as expressed in slow wave amplitude appear to have little or no influence on more complex measures of working memory and cognitive function. In other words, while the activation of neural resources may vary with memory load (Barcelo *et al*., 1997; Geffen *et al*., 1997; Rama *et al*., 1995; Ruchkin *et al*., 1995; Ruchkin *et al*., 1990; Ruchkin *et al*., 1992), the level of activation itself was not, in this instance, directly related to performance outcome.

In addition, neither ERP measures of neural efficiency (P300 latency) nor behavioral non-ERP measures of processing speed (choice-reaction time, inspection time) correlated strongly with the slow wave measures. However, small associations between P300 latency and slow wave amplitudes were observed, such that faster P300 latency was associated with larger (more negative) slow wave amplitude. This finding may reflect slow wave interval selection rather than an effect of increased processing speed on slow wave amplitude. The slow wave interval was fixed, and consequently, an earlier P300 would allow for the earlier emergence of the slow wave and thus the probability of higher amplitude in the selected interval.

Non-shared environmental influence was quite substantial for all measures except IQ. It covaried between many of the ERP and performance measures that were obtained from the delayed-response task (and similarly, has previously been shown to covary between different measures from the same choice-reaction time task (Luciano *et al*., 2001a)). However, as is typically found in genetic studies examining cognitive measures from different tasks (e.g., Posthuma *et al*., 2001; Rietveld *et al*., 2000), virtually no non-shared environmental covariation was found between the delayed response task, speed of processing, and IQ measures. This suggests that non-shared environmental influence may be task specific, whereas the same genetic factors can, and do, influence performance on a broad range of cognitive tasks. Previous analyses have suggested that approximately 25% of slow wave and CRT variance, and 10% of IQ variance is due to measurement error (Hansell *et al*., 2001; Luciano *et al*., 2001b), thus measurement error accounts for a substantial portion of the non-shared environmental influences on these measures.

Future studies will seek to gain further insights into the processes underlying cognitive function by employing molecular genetic methods (i.e., linkage and association analyses) which aim to determine which genes are influential. Univariate linkage analyses of slow wave amplitude measures have identified suggestive regions of influence on Chromosome 10 (Hansell *et al*., in press). However, a multivariate approach combining measures of fundamental electrophysiological processes and more complex outcome or performance measures is yet to be explored. Such an approach appears promising, as the first multivariate genome-wide scan for QTLs linked to a complex trait (developmental dyslexia) showed advantages in power and in clarification of the pattern of QTL influence compared to analyzing correlated measures separately (Marlow *et al*., 2003). Genetic covariants identified in the present study (i.e., P300 latency and working-memory performance) will be examined using multivariate linkage and association methods and these analyses may provide new insights into the fundamental processes underlying cognitive function.

ACKNOWLEDGMENTS

This study was supported by the Australian Research Council (Grant Numbers: A79600334, A79906588, A79801419, DP0212016, DP0343921) and the Human Frontier Science Program (Grant Number: RG0154.1998-B). We thank Ann Eldridge, Marlene Grace, and Kathleen Moore for twin recruitment and data collection and the twins and their families for their participation.

REFERENCES

Ando, J., Ono, Y., and Wright, M. J. (2001). Genetic structure of spatial and verbal working memory. *Behav. Genet*. **31**:615–624.

Baddeley, A. (1986). *Working Memory*. New York: Oxford University Press.

Baker, L. A., Vernon, P. A., and Ho, H. (1991). The genetic correlation between intelligence and speed of information processing. *Behav. Genet*. **21**:351–367.

Barcelo, F., Martin-Loeches, M., and Rubia, F. J. (1997). Event-related potentials during memorization of spatial locations in the auditory and visual modalities. *Electroencephalogr. Clin. Neurophysiol*. **103**:257–267.

Batuev, A. S., Shaffer, V. I., and Orlov, A. A. (1985). Comparative characteristics of unit activity in the prefrontal and parietal areas during delayed performance in monkeys. *Behav. Brain Res*. **16**:57–70.

Conway, A. R., Kane, M. J., and Engle, R. W. (2003). Working memory capacity and its relation to general intelligence. *Trends Cog. Sci*. **7**:547–552.

Deary, I. J. (2001). Human intelligence differences: a recent history. *Trends Cog. Sci*. **5**:127–130.

Engle, R. W., Tuholski, S. W., Laughlin, J. E., and Conway, A. R. A. (1999). Working memory, short-term memory, and general fluid intelligence: a latent-variable approach. *J. Exp. Psychol. Gen*. **128**:309–331.

Fry, A. F., and Hale, S. (2000). Relationships among processing speed, working memory, and fluid intelligence in children. *Biol. Psychol*. **54**:1–34.

Fuster, J. M. (2000). Executive frontal functions. *Exp. Brain Res*. **133**:66–70.

Fuster, J. M. (2001). The prefrontal cortex—an update: time is of the essence. *Neuron* **30**:319–333.

Geffen, G. M., Wright, M. J., Green, H. J., Gillespie, N. A., Smyth, D. C., Evans, D. M., and Geffen, L. B. (1997). Effects of memory load and distraction on performance and event-related slow potentials in a visuospatial working memory task. *J. Cogn. Neurosci*. **9**:743–757.

Goldman-Rakic, P. S. (1992). Working memory and the mind. *Sci. Am*. **3**:111–117.

Hansell, N. K., Medland, S. E., Ferreira, M. A. R., Geffen, G. M., Zhu, G., Montgomery, G. W., Duffy, D. L., Wright, M. J., and Martin, N. G. (in press). Linkage analyses of event-related potential slow wave phenotypes recorded in a working memory task. *Behav. Genet*.

Hansell, N. K., Wright, M. J., Geffen, G. M., Geffen, L. B., and Martin, N. G. (2004). Genetic influence on cognitive processes of distraction: An event-related potential study of the slow wave. *Aust. J. Psychol*. **56**:89–98.

Hansell, N. K., Wright, M. J., Geffen, G. M., Geffen, L. B., Smith, G. A., and Martin, N. G. (2001). Genetic influence on ERP slow wave measures of working memory. *Behav. Genet*. **31**:603–614.

Jackson, D. N. (1984). MAB: multidimensional aptitude battery manual. Port Huron, Michigan: Research Psychologists Press Inc.

Jensen, A. R. (1993). Why is reaction time correlated with psychometric g. *Curr. Dir. Psychol. Sci*. **2**:53–56.

Kim, S. H., and Lee, Y.-H. (2004). Correlation between cognitive capacity screening examination and cognitive evoked potential in alcohol-dependent patients. *Yonsei Med. J*. **45**:796–802.

Luciano, M., Smith, G. A., Wright, M. J., Geffen, G. M., Geffen, L. B., and Martin, N. G. (2001a). On the heritability of inspection time and its covariance with IQ: a twin study. *Intelligence* **29**:443–457.

Luciano, M., Wright, M. J., Geffen, G. M., Geffen, L. B., Smith, G. A., and Martin, N. G (2004a). A genetic investigation of the covariation among Inspection Time, Choice Reaction Time and IQ subtest scores. *Behav. Genet*. **34**:41–50.

Luciano, M., Wright, M. J., Geffen, G. M., Geffen, L. B., Smith, G. A., and Martin, N. G. (2004b). Multivariate genetic analysis of cognitive abilities in an adolescent twin sample. *Aust. J. Psychol*. **56**:79–88.

Luciano, M., Wright, M. J., Smith, G. A., Geffen, G. M., Geffen, L. B., and Martin, N. G. (2001). Genetic covariance among measures of information processing speed, working memory, and IQ. *Behav. Genet*. **31**:581–592.

Marlow, A. J., Fisher, S. E., Francks, C., MacPhie, L., Cherny, S. S., Richardson, A. J., Talcott, J. B., Stein, J. F., Monaco, A. P., and Cardon, L. R. (2003). Use of multivariate linkage analysis for dissection of a complex cognitive trait. *Am. J. Hum. Genet*. **72**:561–570.

McGarry-Roberts, P. A., Stelmack, R. M., and Campbell, K. B. (1992). Intelligence, reaction time, and event-related potentials. *Intelligence* **16**:289–313.

Neale, M., and Cardon, L. (1992). *Methodology for Genetic Studies of Twins and Families*. Dordrecht: Kluwer Academic Publishers.

Neale, M. C., Boker, S. M., Xi, G., and Maes, H. H. (2003). *Mx: Statistical Modeling*. Richmond, VA: Dept of Psychiatry.

Neubauer, A. C., Bauer, C., and Holler, G. (1992). Intelligence, attention, motivation and speed-accuracy trade-off in the Hick Paradigm. *Person. Individ. Diff*. **13**:1325–1332.

Polich, J., and Kok, A. (1995). Cognitive and biological determinants of P300: an integrative review. *Biol. Psychol*. **41**:103–146.

Posthuma, D., Baare, W. F. C., Hulshoff Pol, H. E., Kahn, R. S., and Boomsma, D. I. (2003). Genetic correlations between brain volumes and wthe WAIS-III dimensions of verbal comprehension, working memory, perceptual organization, and processing speed. *Twin Res*. **6**:131–139.

Posthuma, D., de Geus, E. J. C., and Boomsma, D. I. (2001). Perceptual speed and IQ are associated through common genetic factors. *Behav. Genet*. **31**:593–602.

Purcell, S. (2001). Behavioral Genetics. In R. Plomin, J. DeFries, G. E. McClearn and P. McGuffin (eds.), *Statistical Methods in Behavioral Genetics*. New York: Worth Publishers, pp. 4.

Rama, P., Carlson, S., Kekoni, J., and Hamalainen, H. (1995). A spatial oculomotor memory task perfomance produces a task-related slow shift in human electroencephalography. *Electroencephalogr. Clin. Neurophysiol*. **94**:371–380.

Rietveld, M. J. H., van Baal, G. C. M., Dolan, C. V., and Boomsma, D. I. (2000). Genetic factor analyses of specific cognitive abilities in 5-year-old Dutch children. *Behav. Genet*. **30**:29–40.

Rijsdijk, F. V., Vernon, P. A., and Boomsma, D. I. (1998). The genetic basis of the relation between speed-of-information-processing and and IQ. *Behav. Brain Res*. **95**:77–84.

Ruchkin, D. S., Canoune, H. L., Johnson, R. J., and Ritter, W. (1995). Working memory and preparation elicit different patterns of slow wave event-related brain potentials. *Psychophysiology* **32**:399–410.

Ruchkin, D. S., Johnson, R. J., Canoune, H., and Ritter, W. (1990). Short-term memory storage and retention: an event-related brain potential study. *Electroencephalogr. Clin. Neurophysiol*. **76**:419–439.

Ruchkin, D. S., Johnson, R. J., Grafman, J., Canoune, H., and Ritter, W. (1992). Distinctions and similarities among working memory processes: an event-related potential study. *Cog. Brain Res*. **1**:53–66.

Ruchkin, D. S., Johnson, R. J., Grafman, J., Canoune, H., and Ritter, W. (1997). Multiple visuospatial working memory buffers: evidence from spatiotemporal patterns of brain activity. *Neuropsychologia* **35**:195–209.

Sachs, G., Anderer, P., Margreiter, N., Semlitsch, H., Saletu, B., and Katschnig, H. (2004). P300 event-related potentials and cognitive function in social phobia. *Psychiatry Res*. **131**:249–261.

Tabachnick, B. G., and Fidell, L. S. (1989). *Using Multivariate Statistics*. New York: Harper Collins.

Vernon, P. A., and Weese, S. E. (1993). Predicting intelligence with multiple speed of information-processing tests. *Pers. Individ. Diff.* **14**:413–419.

Wright, M., de Geus, E., Ando, J., Luciano, M., Posthuma, D., Ono, Y., Hansell, N., Van Baal, C., Hiraishi, K., Hasegawa, T., Smith, G., Geffen, G., Geffen, L., and Kanba, S. (2001). Genetics of cognition: Outline of a collaborative twin study. *Twin Res.* **4**:48–56.

Wright, M. J., Luciano, M., Hansell, N. K., Geffen, G. M., Geffen, L. B., and Martin, N. G. (2002). Genetic sources of covariation among P3(00) and online performance in a delayed response working memory task. *Behav. Genet.* **61**:183–202.

Edited by Stacey Cherny