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Heritability of anterior and posterior visual N1

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Abstract

Previous studies have reported that individual variation in N1 amplitude is related to attentional problems and alcoholism. Using data from 651 twins and siblings from 292 families we examined whether variation in N1 amplitude and latency can be explained by genetic factors. In half of the subjects the age centered around 26 (young adult cohort), in the other half the age centered around 49 (middle-aged adult cohort). Two visual N1 components were identified by a spatial PCA — an early anterior component peaking from 88 to 168 ms after stimulus presentation and a posterior one peaking from 132 to 220 ms. Significant heritability was found for anterior N1 amplitude (22%) and posterior amplitude (50%), and for anterior latency (45%) and posterior latency (43%). We conclude that visual N1 amplitude and latency may serve as endophenotypes to detect genetic variation in susceptibility to psychiatric disorders.
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1. Introduction

The N1 is an early endogenous ERP component peaking in the time range of 75–250 ms after the evoking stimulus. In cognitive psychophysiology, the N1 is thought to reflect the allocation of processing capacity to sensory input (the orienting response), or the active filtering of information (Coles et al., 1990; Altenmüller and Gerloff, 1999). As early as 1964, Eason et al. (1964) reported that attended stimuli evoke larger, more negative N1s than unattended stimuli, a finding replicated many times in selective attention tasks. In the auditory domain the N1 peaks at the vertex (Cz), whereas in the visual domain two main negative peaks can be found: an early anterior N1, and a somewhat later posterior N1 (Vogel and Luck, 2000). The N1 peak amplitude and latency have been studied widely to investigate individual differences in disease susceptibility (e.g., Olbrich et al., 2000; Winsberg et al., 1997).

The N1 can be obtained from the same oddball paradigm that is used to invoke the well-known P3 (Almasy et al., 1999). In this paradigm, frequent nontarget stimuli are interspersed with target stimuli that are infrequent but task relevant, i.e. they require some response of the subject in contrast to the frequent nontargets. Unlike the P3 component, the occurrence of the N1 is independent of the task relevance of the stimuli. To optimize the signal-to-noise ratio, the N1 is therefore usually obtained by ensemble averaging the response to the frequent nontarget stimuli.

In contrast to the P3, which has received a lot of attention from geneticists (Anokhin et al., 2001; Carlson et al., 2002; Katsanis et al., 1997; O'Connor et al., 1994; Polich and Burns, 1987; van Baal et al., 1998; van Beijsterveldt et al., 2001; Wright et al., 2001), the earlier N1 component has only rarely been subjected to genetic analyses in twin samples. In the few studies available, the results have been mixed. In the auditory domain, significant heritability was found for the N1 amplitude by some (Polich and Burns, 1987; O'Connor et al., 1994) but not by others (Surwillo, 1980). In the visual modality, only two studies have been performed with contrasting results. In a first study (Almasy et al., 1999) small genetic effects on variation in nontarget N1 amplitude and latency were reported for frontal

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leads (heritability of amplitude 19% to 31%; heritability of latency 10% to 16%) whereas larger effects were found for occipito-temporal leads (amplitude 45% to 54%, latency 3% to 12%). In the second study (Katsanis et al., 1997) only small and nonsignificant genetic effects on variation in target N1 were reported for three parietal leads.

The current study aims to re-examine the contribution of genetic and environmental factors to variance in the N1 amplitude and latency in a visual oddball task. To this end, we used a large sample of adult MZ and DZ twins from the Dutch population with the addition of their non-twin brothers and sisters. Using this sample, we first established that two early endogenous components could be identified using a spatial PCA (Spencer et al., 1999), an anterior and a posterior one. For these components, we scored N1 amplitude and latency. Since variation stemming from measurement error and other unreliable trial-by-trial variation is generally of no interest in genetic analyses, we estimated the amount of variation due to such factors by analyzing the odd and even trials separately following van Baal et al. (2001). This allowed us (a) to estimate the reliability with which N1 amplitude and latency can be established, and (b) to estimate the genetic and environmental contributions to the reliable part of the N1. In addition, we investigated whether the genetic makeup of these early endogenous components is different for young versus middle-aged adults.

2. Methods

2.1. Subjects

The study received prior approval by the institutional review body of the VU medical centre. Informed consent was obtained from each subject. Subjects were recruited from the Netherlands Twin Registry (Boomsma et al., 2002a) as part of a large project on the genetics of cognition and adult brain functioning (Posthuma et al., 2001). Adult twins and their non-twin siblings were invited to participate. Subjects were required to have normal or corrected-to-normal vision. Family members with previous head trauma (including concussion) or coma were not eligible.

A total of 760 family members from 309 twin families participated in the study and EEG data was available from 732 subjects from 305 families. Subjects were selected from two twin cohorts, one of about 26 years old, and one of about 49 years old. For this study, we restricted the age range to young and middle-aged adulthood: only subjects in the range of 20 to 65 years were included. This resulted in a final sample of 715 subjects from 303 families. After EEG data cleaning, 661 subjects from 292 families had sufficient error free data on at least one lead for genetic analyses, resulting in a younger cohort of 336 subjects (45.8% male, mean 26.5 years, SD 3.8) and a middle-aged cohort of 325 subjects (40.9% male, mean 48.7 years, SD 6.2). Age cohort inclusion was per family and based on the age of the twins on the day of measurement with the cut-off at 35 years. Two younger siblings under 35 were included in the middle-aged cohort on the basis of the twins being over 35, and 11 older siblings over 35 were included in the young adult cohort on the basis of the twins being under 35. Participating families consisted of one to seven siblings (including twins). On average, 2.3 participants per family participated.

2.2. Procedure

The subjects were asked to participate in a 4.5 hour testing protocol. During one part of the experimental protocol, psychometric intelligence, inspection time, and reaction times were assessed. During the other, the subjects performed, amongst others, a visual oddball task. The order of the two parts of the protocol was randomized across family members. Consequently, half of EEG registration sessions were during morning hours, and half were in the afternoon.

During EEG recording subjects were seated in a comfortable reclining chair in a dimly lit, sound attenuated and electromagnetically shielded room. They were instructed to relax, and to minimize blinking, eye and body movement. Subjects were instructed to silently count the number of targets (cats).

2.3. Stimuli

The oddball stimuli were white-on-black line drawings of cats and dogs by Snodgrass and Vanderwart (1980), balanced in the amount of physical stimulation. The dog stimuli were shown frequently (100/125) and were the nontargets. The cat stimuli were shown only infrequently (25/125) and were the targets. A stimulus set with an identical order of stimuli and intertrial intervals was presented to all subjects. In this set, dogs and cat stimuli were generated in an unpredictable order and trial duration was made to vary randomly from 1500 to 2000 ms. Stimulus duration was always 100 ms. Before the task, one example of each stimulus was presented. The computer screen was positioned 80 cm in front of the participants which was verified by use of a rod.

2.4. EEG registration

EEG was recorded with 19 Ag/AgCl electrodes mounted in an electrocap. Signal registration was conducted using an AD amplifier developed by Twente Medical Systems (TMS, Enschede, The Netherlands) for 612 subjects and Neuroscan SynAmps 5083 amplifier (Compumedics, El Paso, TX) for 103 subjects. Signals were continuously represented online on a Nec multisync 17 inch computer screen using Poly 5.0 software or Neuroscan Acquire 4.2 (Compumedics, El Paso, TX). Standard 10–20 positions were F7, F3, F1, Fz, F2, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1 and O2. For Neuroscan subjects Fp1, Fp2, and Oz were also included. The vertical electro-oculogram (EOG) was recorded bipolarly between two Ag/AgCl electrodes, affixed one cm below the right eye and one cm above the eyebrow of the right eye. The horizontal EOG was recorded bipolarly between two Ag/AgCl electrodes affixed one cm left from the left eye and one cm right from the right eye. An Ag/AgCl electrode placed on the forehead was used as a ground

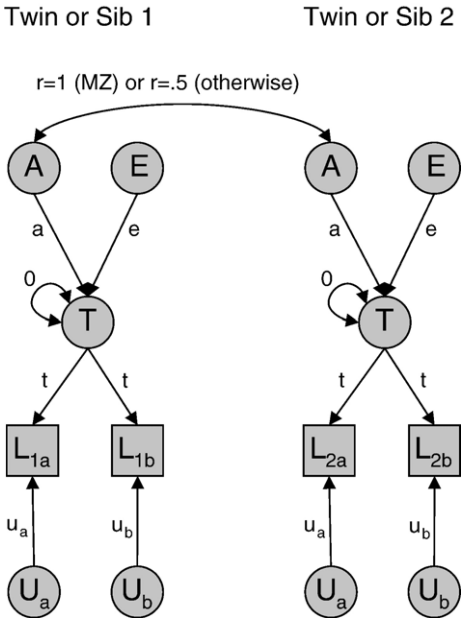

Fig. 1. Path model for the genetic modeling of repeated measures (a, b) of the N1 of lead L for twins (or siblings) 1 and 2. U_a and U_b represent the measurement error and is by definition zero correlated between measurement occasions (i.e., the split-halves.) The genetic modeling is performed on the factor T which represents the remaining, correlated variance which excludes the measurement error variance U. Unique environmental variance (E) has zero correlation between twins / siblings, whereas additive genetic variance (A) correlates 1 between MZ twins and .5 between fraternal twins and siblings. Note that the zero variance indicates that T is a mathematical construct which does not explain variance of the observed variables by itself but is decomposed further by factors A and E.

electrode. Impedances of all EEG electrodes were kept below 3 kΩ, and impedances of the EOG electrodes were kept below 10 kΩ. The EEG was amplified, digitized at 250 Hz and stored for offline processing. Amplifier filter settings for TMS were a single order FIR bandpass filter with cutoff frequencies of 0.05 Hz and 30.0 Hz. Neuroscan filter settings were a lowpass filter at 50.0 Hz and no high pass filtering. Strong DC shifts were manually reset before the start of the experiment.

2.5. Data processing

Only nontarget trials were used in the analyses. All signals were recalculated with averaged earlobes as reference and analyzed using Neuroscan Edit (Compumedics, El Paso, TX). Next, if the signals were absent or the signals were deemed extremely noisy upon visual inspection the subject was excluded from further analysis. This resulted in the removal of twenty-six subjects. Signals from all leads were then reviewed for artifactual episodes (swallowing, muscle artifacts, eye movements (not blinks), and technical problems such as clipping). These episodes were removed and excluded from the analyses. Next, blink artifact reduction was performed following the procedure introduced by Semlitsch et al. (1986). Epochs were created from 100 ms pre-stimulus up to 700 ms post-stimulus with baseline offset correction including only epochs that did not overlap with artifactual episodes.

We expected the anterior and posterior N1 in the time range of about 50 to 250 ms post-stimulus. Data from each subject and for each time-point in this window were concatenated and subjected to a spatial PCA with Promax rotation on the resulting covariance matrix (comparable to Spencer et al., 1999). This procedure aimed to find evidence for separate anterior and posterior N1 components as reported by Vogel and Luck (2000). From these data we identified those leads that best describe the components using the factor pattern matrix from the PCA. Next, we determined N1 scoring time windows based on grand average waves for the selected leads. Finally, individual N1 peak amplitude and latency were scored in these time windows.

To estimate the reliability of N1 amplitude and latency, we separated the nontarget trials of each individual into a set of odd and a set of even trials for each of the leads analyzed. For both sets an ERP was calculated and the N1 peak-to-baseline amplitudes and the corresponding latencies were scored. A minimum of 30 trials in each set was required.

2.6. Genetic analyses

Resemblance (covariance) in ERP traits between siblings derive from genetic relatedness or shared environmental influences (Falconer and Mackay, 1996). If the covariance between DZ twins or siblings, who share on average 50% of their genetic make-up, is half the covariance between MZ twins, who are genetically identical, this is seen as evidence for additive genetic influences (A). If the covariance between DZ twins or siblings is less than half the covariance between MZ twins this is seen as evidence for dominant (non-additive) genetic influences (D). If the covariances between MZ and DZ twins/siblings are comparable and non-zero this is evidence for shared environmental influences (C). If the covariance between MZ twins is not unity this is evidence for environmental effects unique to each individual (E).

By comparing MZ and DZ covariances using Structural Equation Modeling, we obtained maximum likelihood estimates of the relative contributions of each of these factors to the total trait variance. Heritability was defined as the proportional contribution of genetic effects (A + D) to the total variance (A + C + D + E). In a twin-sibling design, however, the effects of both C and D cannot be estimated in the same model. The size of the DZ correlation relative to the MZ correlation determines which component to include in the model. If the DZ correlation was less than half the MZ correlation, then D was modeled. If it was more than half the MZ correlation, C was modeled. For more information on the basis of genetic modeling we refer to Boomsma et al. (2002b) and Posthuma and Boomsma (2005).

The genetic analyses were performed on N1 peak amplitude and latency from individual ERPs from all trials. However, the standard twin model does not allow the separation of unreliable effects such as measurement error from unique environmental effects. ERP measures generally consist of multiple registration events in the form of multiple trials that can be used to estimate measurement inaccuracy, which can in turn be used to separate out the effect from other unique environmental effects. The

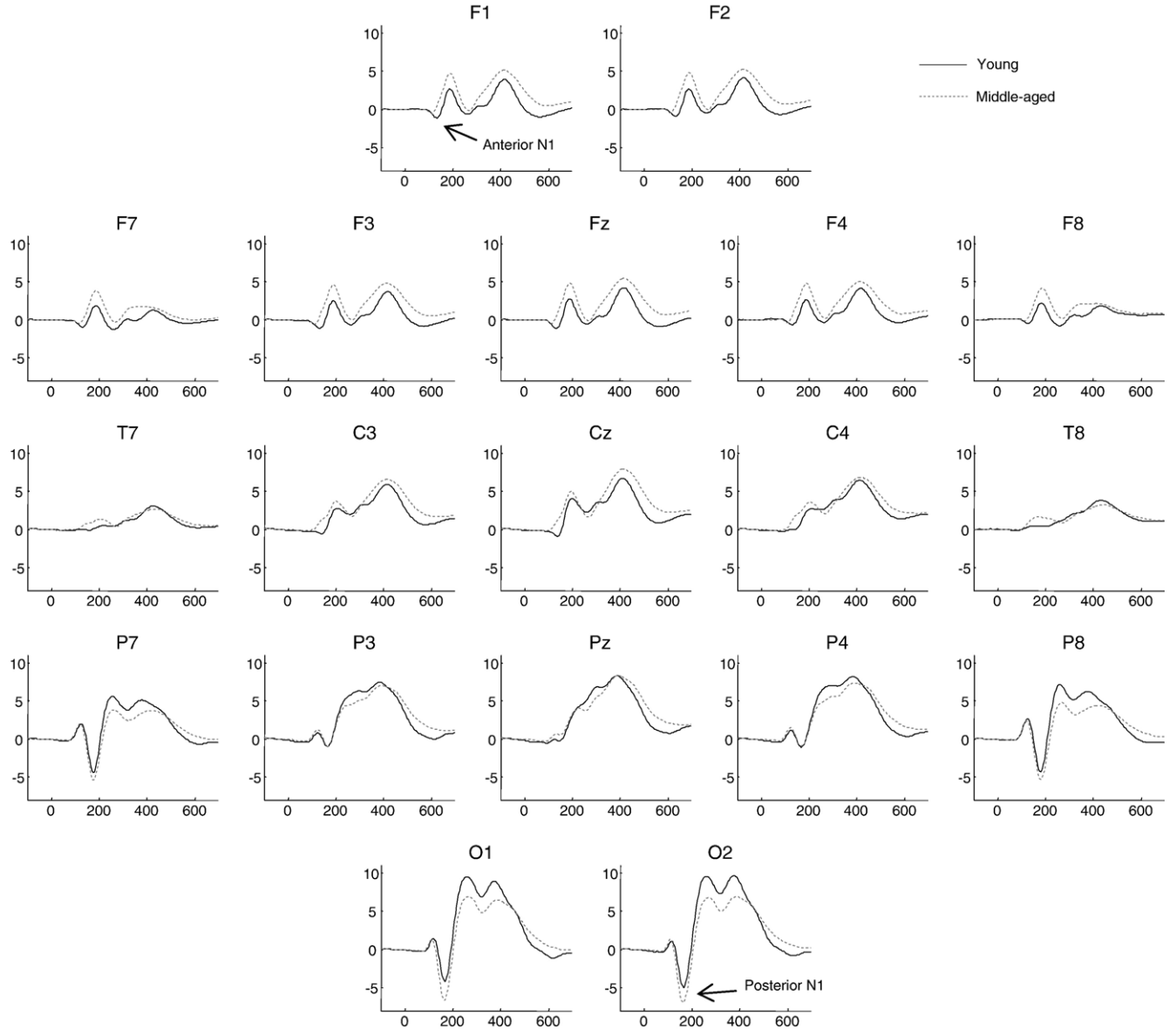

Fig. 2. Grand average waveforms.

result is a heritability estimate that represents genetic and environmental effects while excluding all unreliable variance. We therefore repeated the genetic analyses on N1 amplitude and latency scores from odd and even trial ERPs. A repeated measures model as depicted in Fig. 1 was used. In this model, measurement error is assumed to be uncorrelated across occasions, in this case N1 amplitude and latency from the odd and even trial ERPs. Measurement error is thus defined as the unreliable variation between two sets of trials that are in close proximity in time. Genetic analysis was then performed on the remaining variance, that is, the reliable, correlated variance between the odd and even trials (factor T). This variance was further decomposed into the variance components (A, C, D, and E) described above. Although this procedure halves the number of observations for each ERP, if the error is random between trials the point estimates for A, C, and D are unchanged. Heritability is still defined as the relative contribution of genetic effects (A+D) over the total variance (A+D+C+E), however, the total variance has decreased since uncorrelated variance U has been partialled out from E.

All genetic modeling was performed with Mx (Neale, 2004).

3. Results

3.1. Preliminary analyses

Fig. 2 shows the ERP grand average waves to nontargets for each of the age cohorts separately. The frontal leads show a small N1 at around 135 ms, most clearly seen in the young adult cohort. Occipital and temporal leads show a clear N1 peak at about 180 ms. The spatial PCA resulted in two components with eigenvalues larger than 1.0, explaining 58.3% and 28.5% of variance (other components explained under 5% of variance). The component loadings after Promax rotation are shown Table

Table 1
Loadings of the two main spatial N1 components

	Component	
Lead	1	2
F7	0.90	−0.30
F3	0.97	−0.18
F1	0.98	−0.19
Fz	0.98	−0.19
F2	0.98	−0.19
F4	0.97	−0.18
F8	0.91	−0.29
T7	0.77	0.21
C3	0.92	0.25
Cz	0.94	0.15
C4	0.90	0.28
T8	0.74	0.19
P7	−0.26	0.86
P3	0.44	0.82
Pz	0.70	0.59
P4	0.35	0.86
P8	−0.31	0.83
O1	−0.13	0.91
O2	−0.16	0.90

1. Fig. 3 shows the topographic plot for both components. The components correlated slightly at $r = .05$. The first component loads mainly on central and frontal leads. We chose four leads (F3, F1, F2 and F4) to represent the anterior N1. The second component loaded mainly on occipital (O1 and O2) and lateral posterior leads (P7, P3, P4, and P8). Since P3 and P4 also loaded positively on the first component, we chose channels P7, O1, O2, and P8 to represent the posterior N1.

On the basis of the grand average waveforms peak picking windows were defined. Anterior peaks were picked in a window from 88 to 168 ms post stimulus on the selected anterior leads (F3, F1, F2, and F4); and posterior peaks between 132 and 220 ms post-stimulus on selected leads P7, O1, O2, and P8. For each peak a latency and an amplitude was scored. Both anterior and posterior amplitude scores were quite normally distributed. Since we have no reason to conclude that these data points were rogue, we excluded none from the data. Latency scores were all within the limited range of the peak picking window, disallowing outliers to be identified.

3.2. Effects of age and sex on N1 amplitude and latency

Table 2 shows the amplitude and latency means averaged over the anterior and posterior leads as a function of sex and age cohort. The last columns specify the significance of sex and cohort effects on the means. The middle-aged cohort showed reduced (less negative) anterior N1 and increased (more negative) posterior N1 amplitude. Posterior N1 latency showed no significant differences between the cohorts, anterior N1 latency is shorter in the middle-aged cohort compared to the young adults. Males showed reduced (less negative) anterior N1 amplitude and longer posterior N1 latencies compared to females.

3.3. Split-half reliability

Table 3 shows the reliabilities defined as the proportion reliable variance to the total variance as determined with the N1 scores obtained from the odd and even trials. These results suggest that the posterior N1 can be measured reliably ($r > .9$), but that the anterior N1 has only modest reliability in both amplitude and latency ($r \approx .6$).

3.4. Genetic analyses

Table 4 shows the twin correlations for N1 peak amplitude and latency from the analysis on all trials and from the analysis on odd and even trials with adjustment for measurement error. Since there was no clear difference in the pattern of male and female correlations, these were collapsed across the sexes. Overall there appear to be some differences in the correlations between the cohorts, but an omnibus test on MZ and DZ correlations showed no significance for any lead or variable (amplitude or latency). Variances differed significantly between the cohorts for anterior N1 amplitude. Subsequent genetic models were fit allowing for this difference by using a so-called scalar model. These models estimate a single heritability across both age cohorts, while allowing the total amount of variance to differ.

No significant effect of common environment or dominance were found for any of the leads/variables (all $\chi^2(1) < .74$,

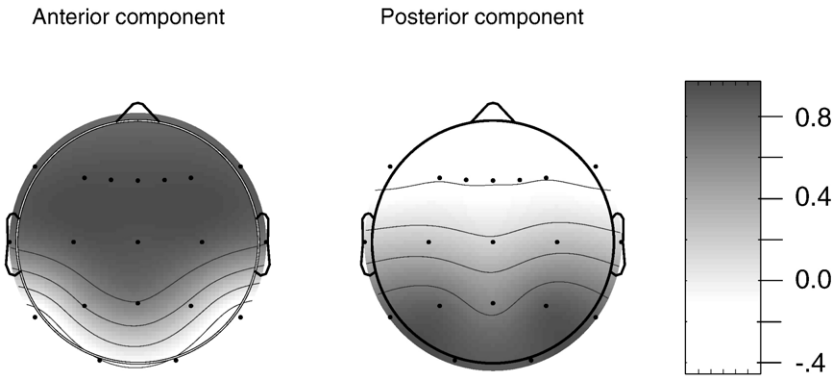

Fig. 3. Component loadings topographic plots.

Table 2
Anterior and posterior N1 descriptives

Region	Cohort												Group main effects [a]	
	Young						Middle-aged							
	Female			Male			Female			Male				
	N	M	SD	N	M	SD	N	M	SD	N	M	SD	Sex [b]	Age cohort [c]
Anterior														
Amplitude (μV)	180	−2.07	1.66	151	−1.54	1.33	187	−1.32	1.36	131	−1.13	1.30	0.33	0.58**
Latency (ms)	180	130.0	20.5	151	127.8	21.6	187	115.7	21.8	131	117.2	20.5	0.18	−12.67**
Posterior														
Amplitude (μV)	180	−5.78	3.97	152	−6.36	3.63	188	−7.67	4.20	132	−6.97	3.77	0.10	−1.33**
Latency (ms)	180	167.9	11.4	152	174.2	11.0	188	168.0	11.3	132	176.2	10.6	7.20***	0.58

[a] Sex group effects are collapsed across cohort, and cohort group effects are collapsed across sex groups. Significance is derived by structural equation modeling comparing the fit of models with and without cohort and sex specific means.
[b] males compared to females.
[c] middle-aged compared to young adult.
** $p<.001$.
*** $p<.01$.

$p>.39$). The most parsimonious models consisted of genetic and unique environmental influences to explain all of the variance in the N1. Table 5 lists the relative contribution of these factors to the N1 for the analysis of the full set of trials and the odd/even trial analysis.

4. Discussion

The spatial PCA of data in the early endogenous time frame of 50 ms to 250 ms post-stimulus confirmed that in a visual oddball task two components can be identified: an anterior and a posterior waveform (Vogel and Luck, 2000). The posterior waveform showed a large and clear N1 at ca. 170 ms of which amplitude and latency could be reliably measured in 30–50 trials. The anterior N1 at ca. 120 ms was much less reliably measured. Nevertheless, both the anterior and posterior N1 showed significant heritability. Posterior N1 showed 50% heritability for amplitude and 43% for latency . Adjusting for unreliable variance increased these estimates to 54% and 44% respectively. Anterior N1 showed lower heritability for amplitude (22%) but not for latency (45%). Adjusting for the unreliable variance increased these estimates to 35% and 56% respectively.

Two studies have previously reported on the heritability of the N1 in the visual domain. In contrast to our findings, Katsanis et al. (1997) found only nonsignificant or very low twin correlations for both latency and amplitude. Apart from the difference in oddball paradigm, the study by Katsanis et al. (1997) differed from the current study in several major ways which may have caused the difference in results. First, as the main topic of their article was the parietal P3, they chose to analyze the N1 on leads P3, Pz, and P4. These leads, however, do not generally show very clear visual N1 in the grand average waves, which is confirmed by inspection of the waveforms (their Fig. 1). Second, they reported on N1 data from the less frequent target trials rather than more frequent nontarget trials — the latter providing more reliable ensemble averages.

The second study (Almasy et al., 1999) reported N1 data from multiple scalp locations, thus allowing the separation of anterior and posterior N1. Significantly heritable N1 amplitude was found for three frontal leads (F3, Fz, and F4). Although their heritability estimates for anterior N1 amplitude (23% to 31%) are slightly higher than our unadjusted heritability estimates (22%), they remain within the 95% confidence range (see Table 4). Likewise, our heritability of posterior N1 amplitude (50%) was very comparable to posterior heritabilities reported by Almasy et al. (1999): 37% to 53%. For anterior and posterior N1 latency, however, our estimates (45 and 43% respectively) were much higher than theirs (anterior: 10% to 16%; posterior: 3% to 12%). A possible explanation for this discrepancy lies in the difference in study population.: Almasy et al. (1999) studied families with a background of alcoholism, whereas the current results are from a population based, non-clinical sample. Alternatively, Almasy et al. (1999) may have used a suboptimal peak picking window for the posterior N1: They used a window of 75 to 180 ms post-stimulus irrespective of scalp location. This was adequate for the anterior N1, but, in our view, not so for the posterior leads. We consider it likely that most subjects' posterior N1 latency scores in their study were located at the upper bound of the peak picking window, causing a reduction of the variance of N1 latency and, to a lesser extent, N1 amplitude.

Table 3
N1 split-half reliabilities with 95% confidence intervals

Region	Estimate	95% CI
Anterior		
Amplitude	0.53	(0.50, 0.56)
Latency	0.64	(0.62, 0.67)
Posterior		
Amplitude	0.94	(0.93, 0.95)
Latency	0.91	(0.90, 0.92)

Note. Trials were split by trial number (odd, even). A minimum of 30 artifact-free trials for each set were required.

Table 4
Twin correlations with confidence intervals of average anterior and posterior N1 amplitude and latency for two age cohorts

			Cohort							
			Young adult				Middle-aged			
			MZ (95% CI)		DZ (95% CI)		MZ (95% CI)		DZ (95% CI)	
Anterior	Amplitude	Total variance	0.35	(0.07, 0.55)	0.13	(−0.02, 0.29)	0.14	(−0.09, 0.35)	0.07	(−0.07, 0.23)
		Reliable variance	0.48	(0.11, 0.76)	0.21	(−0.01, 0.44)	0.26	(−0.07, 0.54)	0.16	(−0.05, 0.38)
	Latency	Total variance	0.44	(0.17, 0.62)	0.22	(0.06, 0.37)	0.44	(0.22, 0.61)	0.20	(0.05, 0.35)
		Reliable variance	0.60	(0.29, 0.81)	0.28	(0.08, 0.47)	0.55	(0.28, 0.75)	0.20	(−0.02, 0.41)
Posterior	Amplitude	Total variance	0.36	(0.09, 0.56)	0.27	(0.11, 0.42)	0.60	(0.43, 0.71)	0.26	(0.10, 0.40)
		Reliable variance	0.40	(0.14, 0.60)	0.28	(0.12, 0.44)	0.63	(0.46, 0.75)	0.29	(0.13, 0.44)
	Latency	Total variance	0.45	(0.20, 0.62)	0.23	(0.08, 0.38)	0.37	(0.11, 0.55)	0.23	(0.07, 0.38)
		Reliable variance	0.49	(0.22, 0.66)	0.26	(0.10, 0.42)	0.40	(0.13, 0.58)	0.26	(0.09, 0.41)

Note. All correlations were estimated using Mx after removal of age and sex effects on the means. DZ correlations include all fraternal (non-identical) siblings pairs, including opposite sex pairs.

The N1 topography appears to be very sensitive to stimulus modality (Altenmüller and Gerloff, 1999). In the auditory domain there is no anterior or posterior N1, but instead a component with comparable timing and morphology is found at the central leads. O'Connor et al. (1994) reported a heritability of 60% for the amplitude of this auditory N1 at lead Cz, and 56% for its latency. It is unclear whether the auditory N1 compares better to the anterior or to the posterior visual N1. A powerful way to address this would be to examine auditory and visual N1 in the same set of twins using a bivariate genetic model.

Because age effects have been reported on other ERP components other than the N1 (Curran et al., 2001; Fabiani and Friedman, 1995; Fjell and Walhovd, 2004; Polich, 1997a,b) we explicitly tested for the effect of age cohort on N1 amplitude and latency. For the entire anterior waveforms, an upward shift was seen in the middle-aged compared to the young adult cohort beginning at about 100 ms and lasting for the length of the ERP interval (>650 ms). This caused the shortening of the latency in the middle-aged cohort while slightly decreasing the anterior N1 amplitude. The posterior waveforms showed a downward shift beginning at about 100 ms and lasting for about 500 ms into the ERP interval. This had no effect on the posterior N1 latency which was scored in a window later than the anterior N1, but caused increased posterior N1 amplitude in the middle-aged cohort. The faster anterior N1 latency is contrary to the findings in previous reports in auditory domain, where either no latency effect was found (Polich, 1997b; Beck et al., 1980), or evidence for a slower N1 response in older subjects (Curran et al., 2001). In spite of the cohort differences in amplitude and latency, the MZ and DZ correlations for all N1 measures were not significantly different across the young and middle-aged groups. We found no evidence, therefore, of age effects on the genetic architecture of the N1.

The heritability of the N1 makes it a candidate endophenotype for related psychopathology. In the extant literature it has been reported that individual differences in N1 amplitude are related to attentional problems. Satterfield et al. (1984) reported reduced N1 amplitude for hyperactive children aged 7–9 and 10–12. For ADD with combined attentive and hyperactive symptoms, Johnstone et al. (2001) reported reduced N1 amplitude at ages 8–10, 12–14, and 16–18 years, but not at 10–12 and 14–16 years. Smith et al. (2004) also reported reduced N1 amplitude in ADHD using a go/no-go task. By contrast, several other studies reported no significant group differences for amplitude in the N1 time range (Rothenberger et al., 2000; Winsberg et al., 1997). It is possible that more consistent effects may be found in the 'processing negativity', which is the negative shift seen in a selective attention task by comparing ERPs of stimuli from the attended to those of the unattended channel, appearing in a time range covering the N1, P1 and N2 (Altenmüller and Gerloff, 1999). Recently, it has indeed been reported that ADHD patients have a reduced processing negativity in an auditory selective attention task (Jonkman et al., 1997; Kenemans et al., 2005).

Reduced visual N1s have also been reported in alcoholics. Cohen et al. (2002) reported the effect in the parietal region. Olbrich et al. (2000) reported reduced N1 amplitude at lead Cz. In the auditory domain, some authors reported enhanced auditory N1 in abstinent alcoholics (Ahveninen et al., 2000), whereas no such effect was reported by most (Cohen et al., 1996, 2002; Olbrich et al., 2000; Patterson et al., 1987; Pfefferbaum et al., 1979). Overall, these findings suggest a modality specificity of the effect of alcoholism on the N1. It must be noted, however, that reduced N1 amplitude may not reflect the liability to develop alcoholism: People with a family

Table 5
Heritabilities with confidence intervals of anterior and posterior N1

Region	Total variance		Reliable variance	
	h^2	95% CI	h^2	95% CI
Anterior				
Amplitude	0.22	(.08, .35)	0.35	(.16, .53)
Latency	0.45	(.31, .57)	0.56	(.40, .71)
Posterior				
Amplitude	0.50	(.37, .61)	0.54	(.42, .64)
Latency	0.43	(.30, .55)	0.44	(.30, .56)

Note. The models included additive genetic (A) and unique environmental (E) factors.
"Total variance" shows heritabilities from individual peak picking on the average of all trials, while "reliable variance" shows heritabilities from the reliable variance between peaks from odd and even trials.
h^2 = heritability.

history of alcoholism did not show affected N1 amplitude (Cohen et al., 1996), and normal N1 amplitudes were obtained before alcohol ingestion (Porjesz and Begleiter, 1990; Porjesz et al., 2005). Strong trends towards reduced amplitude in people with a family history of alcoholism were found for visual and auditory N1 by Patterson et al. (1987). Future family or twin studies may elucidate the nature of the relation between the visual N1 and alcohol use. With the correct definition of the eliciting tasks, topography, and latency, the N1 may perhaps repeat the success of the P3 as an endophenotype for alcoholism (Williams et al., 1999; Dick et al., 2006).

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