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Genetic influence demonstrated for MEG-recorded somatosensory evoked responses

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Abstract

We tested for a genetic influence on magnetoencephalogram (MEG)-recorded somatosensory evoked fields (SEFs) in 20 monozygotic (MZ) and 14 dizygotic (DZ) twin pairs. Previous electroencephalogram (EEG) studies that demonstrated a genetic contribution to evoked responses generally focused on characteristics of representative brain potentials. Here we demonstrate significantly smaller amplitude differences within MZ compared to DZ twin pairs for the complete SEF time series (across left and right hand SEFs: 0.37 vs. 0.60 pT^2 and 0.28 vs. 0.39 pT^2 for primary [SI] and secondary [SII] sensory cortex activation) and higher MZ than DZ wave shape correlations (.71 vs. .44 and .52 vs. .35 for SI and SII activation). Our findings indicate a genetic influence on MEG-recorded evoked brain activity and also confirm our recent conclusion (van 't Ent, van Soelen, Stam, De Geus, & Boomsma, 2009) that higher MZ resemblance for EEG amplitudes is not trivially reflecting greater MZ concordance in intervening biological tissues.

Descriptors: Somatosensory evoked response, Magnetoencephalogram, MEG, Similarities, Monozygotic twins, Dizygotic twins

Studies that compared similarities of electroencephalogram (EEG) characteristics between genetically identical, monozygotic (MZ) twins and nonidentical, dizygotic (DZ) twins have indicated a significant genetic contribution to individual differences in electrical brain activity. For example, with regard to power of EEG traces in the classical delta, theta, alpha, and beta frequency bands, high heritabilities (i.e., higher similarities for EEG power within MZ as compared to DZ twin pairs) have been found ranging from 55% up to 90% (Smit, Posthuma, Boomsma, & De Geus, 2005; Smit, Wright, Hansell, Geffen, & Martin, 2006; Van Baal, De Geus, & Boomsma, 1996; van Beijsterveldt, Molenaar, De Geus, & Boomsma, 1996; Zietsch et al., 2007). In addition to ongoing brain activity, there is also evidence from EEG studies for genetic control of primary sensory brain responses to visual, auditory, and somatosensory stimulation as well as brain potentials related to higher order cognitive processing such as the P300 component (van Beijsterveldt, Molenaar, De Geus, & Boomsma, 1998; van Beijsterveldt & Van Baal, 2002; Wright et al., 2001). Studies on heritabilities of evoked/event-related potentials generally compared similarities within MZ versus DZ twin pairs for peak amplitudes, peak latencies, or both of one or more characteristic components of the brain response waveform.

Instead of focusing on selected subsections, a more complete picture is obtained if within twin-pair similarities are assessed across the entire brain response time series. In fact, already in an early stage of EEG twin research, Lewis, Dustman, and Beck (1972) tested for a genetic influence on amplitude and wave shape of complete brain response waveforms and found that amplitudes of visual, auditory, and somatosensory evoked response waveforms were significantly more similar within MZ twin pairs compared to DZ twin pairs or pairs of unrelated individuals. The picture was less clear for wave shape, which showed significantly higher MZ correlations for visual- and auditory-evoked responses, but not for somatosensory-evoked responses (although there was a marginal trend toward higher MZ resemblance). Of note, the study was performed with a single EEG electrode over the somatosensory brain region, and therefore, as the authors also noted, the negative finding might have been because of within-twin-pair discrepancies in recording location.

In this study, we investigated genetic influences on waveform amplitude and morphology of the entire time series of somatosensory-evoked brain activity in a sample of MZ and DZ twins while controlling for a possible confounding effect of differences

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in sensor location. To achieve this, we measured brain activity using a magnetoencephalogram (MEG) scanner equipped with a 151-sensor array. The MEG sensors are arranged to cover the whole head, so that the most optimal recording location can be identified separately for each individual. Further, for heritabilities of EEG amplitudes, it has been suggested that MZ twin resemblance may be strongly inflated because of greater MZ similarity of biological tissues between the brain and EEG electrodes, primarily the skull, which are also under genetic control (Kohn, 1991). In a recent study (van 't Ent, van Soelen, Stam, De Geus, & Boomsma, 2009), we disproved this hypothesis for ongoing resting state brain activity by showing that large MZ twin correlations for power in the classic frequency bands remain if brain activity is recorded with MEG, which is virtually undisturbed by intervening tissues (Okada, Lahteenmaki, & Xu, 1999; Wolters et al., 2006). The use of MEG, rather than EEG, in the present study also allowed us to investigate if this finding applies equally to evoked brain response amplitudes.

Method

Participants

The sample consisted of 20 healthy right-handed MZ twin pairs (10 male: 18.8 ± 0.6 years; 10 female: 18.8 ± 0.4 years) and 14 healthy right-handed DZ twin pairs (6 male: 20.2 ± 0.4 years; 8 female: 19.9 ± 0.4 years) recruited from the Netherlands Twin Register (Boomsma et al., 2006). Zygosity was based on buccal cell DNA typing. All twins provided informed consent, and the study was approved by the medical ethics committee of the VU University Medical Center.

MEG Recordings

The twin and co-twin from a twin pair always visited the laboratory on the same day (morning or afternoon). Magnetic brain activity was recorded using a 151-sensor whole-head MEG scanner with axial gradiometers (VSM Medtech Ltd., Canada). Sampling rate was 625 Hz, with low-pass filtering at 265 Hz. Somatosensory-evoked responses were obtained separately for the left hand (left-hand SEF) and right hand (right-hand SEF), in two 2.5-min sessions, by electrically stimulating the median nerve at the wrist. Stimulation was provided by a constant current unit connected to a Grass S48 square-wave stimulator. The electric pulses were of 0.2-ms duration and delivered at 2 Hz. Particularly important factors that determine the sensitivity of the median nerve to the externally applied stimuli are the composition of the nerve and the location of the nerve relative to the ventral surface of the wrist, and it is conceivable that there is a higher anatomical resemblance of the upper limbs in MZ than in DZ twins. Therefore, to ensure that the median nerve was activated with similar strength in both MZ and DZ individuals, we adjusted the stimulus intensity for each individual to just below the threshold of thumb twitch. A post hoc analysis, in fact, did indicate that the applied strength of electrical stimulation tended to be more similar in MZ compared to DZ twins: mean within-twin-pair differences for left hand stimulation: 1.42 ± 0.99 mA (MZ) vs. 2.43 ± 2.28 mA (DZ); mean within-twin-pair differences for right hand stimulation: 1.08 ± 0.86 mA (MZ) vs. 2.34 ± 2.46 mA (DZ); main effect of twin pair type (MZ vs. DZ): $F(1,28) = 4.14$, $p = .051$, across left- and right-hand stimulation; data on stimulation strength were incomplete for 1 MZ twin pair and 3 DZ twin pairs.

Before and after each measurement, head position was determined and, to correct for the influence of head position on recorded amplitudes, MEG data for each individual were extrapolated onto new data sets with the same sensor locations corresponding to an average head position across all twins (de Munck, Verbunt, van 't Ent, & van Dijk, 2001).

Data Processing

MEG signals were processed using Fieldtrip software (F.C. Donders Centre for Cognitive Neuroimaging; http://www.ru.nl/fcdonders/fieldtrip). Raw MEG data were visually inspected for artifacts including eye movements and excessive muscle activity. Subsequently, artifact-free epochs subtending from 100 ms before to 500 ms after stimulation onset were selected and averaged using the first 100 ms as a prestimulus baseline. The resulting SEF waveforms consisted of a number of successive components originating from activity in the primary and secondary somatosensory cortexes.

For each individual, characteristic SEF waveform templates were obtained for two consecutive time windows (Figure 1). Time Window 1 covered the initial 90-ms phase of the SEF and Time Window 2 a subsequent, and final, 100-ms phase. To account for individual differences in arm length, the onset of Time Window 1 was set at the peak of the first SEF component. The templates (green colored traces in Figure 1) were obtained by averaging in each time window the SEF response at the sensor with maximum magnetic outflux and the amplitude inverse of the SEF at the sensor with maximum influx. The characteristic SEF in Time Window 1 (see small MEG field map insert in Figure 1) corresponds to a single region of SI activation contralateral to the side of stimulation. For this window, the sensor with maximum magnetic outflux (blue trace in Figure 1) was first selected from all MEG sensors covering the right temporal brain (sensors labeled MRT: $N = 21$) and right frontal brain (sensors MRF: $N = 16$) for left-hand SEFs and all sensors over the left temporal brain (MLT: $N = 21$) and left frontal brain (MLF: $N = 16$) for right-hand SEFs. The time point of maximum magnetic outflux was then determined from this sensor, and, subsequently, the sensor with maximum magnetic influx (red trace) at this time was selected from all remaining sensors. In Time Window 2, the characteristic field maps for left- and right-hand SEFs are similar and correspond to bilateral SII activation. For this window, for both left- and right-hand SEFs, the sensor with maximum magnetic outflux (blue trace in Figure 1) was selected from all sensors over the left temporal brain (MLT) and the sensor with maximum magnetic influx (red trace) from all sensors over the right temporal brain (MRT). Left temporal outflux and right temporal influx are associated with left and right SII activation, respectively; return flux for both sources partially overlap and cancel out over central brain regions.

Somatosensory-evoked responses were compared for waveform amplitude as well as wave shape similarity. Within-twin-pair amplitude similarity was quantified by computing the squared Euclidean distance between corresponding SEF template time series (vectors T_1 and T_2) for the twins of every pair: $(T_1 - T_2) \bullet (T_1 - T_2)'$, where $\bullet$ denotes the inner product and the transpose. Within-twin-pair wave shape similarity was assessed by means of Pearson's linear correlation coefficient between corresponding SEF templates:

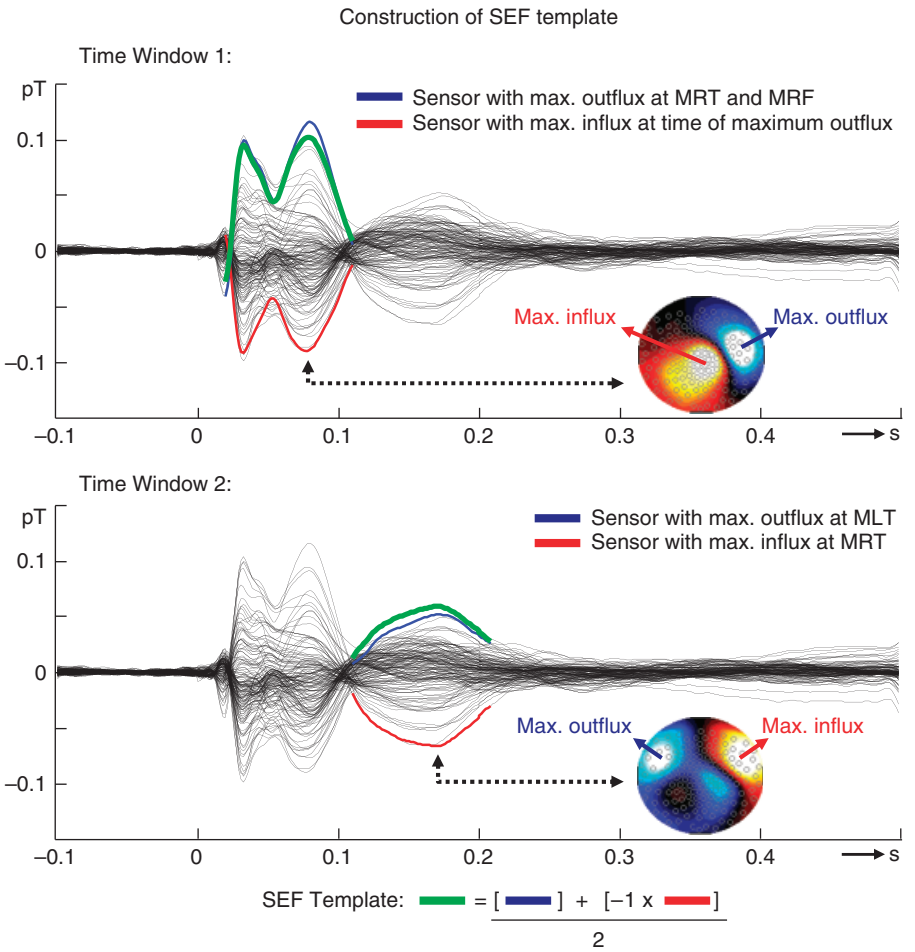

Figure 1. Construction of a SEF template (in green) for Time Window 1 (top panel) and Time Window 2 (bottom panel) illustrated for a left-hand SEF (grand average across all twins). In each panel, an overlay of the response at all MEG sensors is shown, with stimulation onset at 0 s.

$$\frac{(T_1 - \overline{T_1}) \bullet (T_2 - \overline{T_2})'}{\sqrt{(T_1 - \overline{T_1}) \bullet (T_1 - \overline{T_1})'}\sqrt{(T_2 - \overline{T_2}) \bullet (T_2 - \overline{T_2})'}}$$

with

$$\bar{T}_1 = \frac{1}{N}\sum_j T_{1j} \text{ and } \bar{T}_2 = \frac{1}{N}\sum_j T_{2j}, \text{and } N = \text{number of samples.}$$

To additionally compare MZ and DZ groups with regard to characteristics of the sources in the brain underlying the SEFs, we also performed a dipole source analysis. Dipole modeling was performed on the peak of the P35m SEF component that occurs at about 35 ms after onset of median nerve stimulation and corresponds to contralateral SI activation. We focused on this component because it was generally the most prominent and could be identified in every subject. In addition, we generally obtained the most reliable single dipole fit solution for this component. Dipole analysis was performed using the DipoleFit software tool provided by the MEG system manufacturer. A single sphere was used as a head model (sphere center at $x = 0$ cm, $y = 0$ cm, $z = 5$ cm in the nasion-ear coordinate frame [de Munck et al., 2001]; sphere radius = 7.5 cm). Similarities of source characteristics were quantified by computed differences in dipole location (Euclidean distance), orientation (vector difference angle), and strength.

Statistical Analysis

SEF amplitude differences and wave shape correlations and differences in P35m source characteristics were computed for all MZ twin pairs and DZ twin pairs. In addition, but for qualitative comparison only, we computed amplitude differences and wave shape correlations for all possible couplings of twins from different pairs that could be constructed from our total sample of 68 MZ and DZ twins ($N = 2240$ unique pairs of unrelated twins, without consideration of MZ or DZ status). Amplitude differences and wave shape correlations for these pairs were, however, not included in the statistical analyses, because they are not completely independent from the values computed for MZ and DZ pairs (as the pairs are constructed from twins of our MZ and DZ samples). Prior to statistical analysis, wave shape correlations were converted to Fisher Z scores to ensure a normal sampling distribution. Pearson correlation coefficients, rather than Z scores, are reported, however, to facilitate interpretation. SEF amplitude and wave shape similarities were evaluated using a general linear model with Stimulated Hand (within-twin-pair similarity for left-hand SEFs versus within-twin-pair similarity for right-hand SEFs) and Time Window (within-twin-pair SEF similarity for Time Window 1 vs, within-twin-pair SEF similarity for Time Window 2) as within-twin-pair factors and Twin Pair Type (MZ vs. DZ) as the between-twin-pair factor. To check for an influence of differences in absolute somatosensory response

Table 1. *Means (and Standard Deviations) of SEF Amplitude Differences and Wave Shape Correlations within Twin Pairs*

Measure	Stimulated hand	Time window 1				Time window 2			
		MZ	DZ	Unrelated	MZ vs. DZ	MZ	DZ	Unrelated	MZ vs. DZ
Amplitude differences	Left	.39 (.17)	.55 (.23)	.66 (.26)	.025	0.29 (0.10)	0.34 (0.20)	0.39 (0.18)	.349
	Right	.35 (.15)	.64 (.24)	.72 (.28)	.001	0.26 (0.13)	0.43 (0.15)	0.45 (0.20)	.001
Wave shape correlations	Left	.64 (.41)	.49 (.33)	.30 (.39)	.102	0.43 (0.50)	0.32 (0.47)	0.11 (0.54)	.572
	Right	.78 (.18)	.38 (.34)	.27 (.39)	.000	0.61 (0.37)	0.37 (0.56)	0.18 (0.54)	.216

Note: Means and standard deviations of amplitude differences (top rows, and in pT^2) and wave shape correlations (bottom rows) for left- and hand right-hand SEFs (column Stimulated hand) in Time Window 1 and Time Window 2; within MZ twin pairs (column MZ), DZ twin pairs (DZ) and within pairs of randomly coupled, unrelated, twins (Unrelated). See also Figure 2 for a graphical display of the data. Columns MZ vs. DZ show results of statistical comparisons (p values) between SEF similarities within MZ and DZ twin pairs.

amplitudes on computed Euclidean amplitude differences, we also repeated the statistical evaluation on amplitude similarities after first separately normalizing the somatosensory response amplitudes in both time windows (to a maximum of 1 for the twin with the largest SEF amplitude). Finally, a bivariate Pearson correlation-based analysis was performed, again limited to SEF similarity values within MZ and DZ twin pairs, to test for a possible relation between SEF amplitude similarities and SEF wave shape similarities across left- and right-hand SEFs and both time windows ($N = 34$ twin pairs $\times$ 2 stimulation sides $\times$ 2 time windows = 136). Similarities of P35m dipole characteristics were evaluated using a general linear model with variable Stimulated Hand as within-twin-pair factors and variable Twin Pair Type as thebetween-twin-pair factor.

There were no indications for sex differences; therefore all statistics were computed for male and female twins, combined.

Results

SEF Amplitude Differences and Wave Shape Correlations

Means and standard deviations of computed amplitude differences and wave shape correlations are shown in Table 1 and Figure 2. For SEF amplitude differences within MZ and DZ pairs, there was no significant main effect for variable Stimulated Hand, $F(1,32) = 1.15$, $p = .292$, or a Stimulated Hand $\times$ Time Window interaction, $F(1,32) = 0.06$, $p = .804$. However, we did find an interaction between Stimulated Hand and Twin Pair Type, $F(1,32) = 6.29$, $p = .017$, which was explained by the fact that evoked response amplitude differences tended to be smaller for right- compared to left-hand SEFs within MZ twin pairs, but smaller for left- compared to right-hand SEFs within DZ twin pairs. There was also a significant main effect for variable Time Window, $F(1,32) = 48.61$, $p < .001$, which indicated that within-pair differences in SEF amplitude were relatively reduced in Time Window 2 compared to Time Window 1, in particular for DZ twin pairs: Time Window $\times$ Twin Pair Type interaction, $F(1,32) = 7.59$, $p = .010$. This finding disappeared, however, when statistical evaluation was repeated after separately normalizing the somatosensory response amplitudes in both time windows, indicating that it reflected a systematic difference of SEF amplitudes within the first and second time windows.

For wave shape correlations within MZ and DZ twin pairs, there were no differences for SEFs after left- versus right-hand stimulation or for SEFs in Time Window 1 versus Time Window 2: Stimulated Hand, $F(1,32) = 0.94$, $p = .340$; Time Window, $F(1,32) = 2.45$, $p = .127$; Stimulated Hand $\times$ Time window, $F(1,32) = 1.98$, $p = .169$; Stimulated Hand $\times$ Twin Pair Type, $F(1,32) = 1.39$, $p = .247$; Time Window $\times$ Twin Pair Type, $F(1,32) = 1.56$, $p = .220$.

Significant main effects of variable Twin Pair Type for both the analysis on amplitude differences, $F(1,32) = 17.31$, $p < .001$, and wave shape correlations, $F(1,32) = 11.96$, $p = .002$, indicated

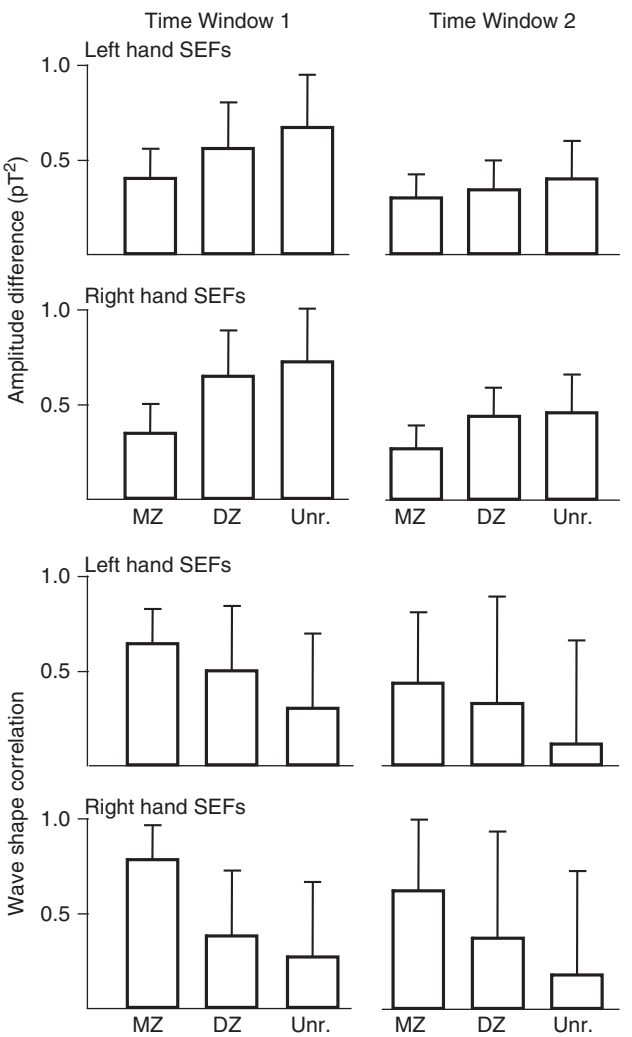

Figure 2. Mean amplitude differences (top) and wave shape correlations (bottom) for left- and right-hand SEFs in Time Window 1 (left bars) and Time Window 2 (right bars) within MZ twin pairs (MZ), DZ twin pairs (DZ), and pairs of unrelated twins (Unr). Error bars indicate standard deviations.

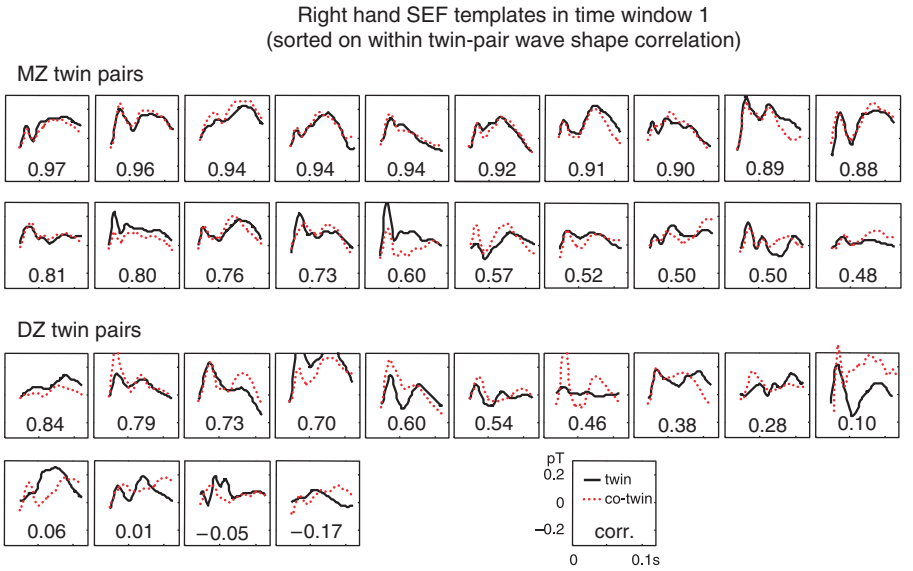

Figure 3. Templates for the initial part of the SEF, after right-hand stimulation, in Time Window 1. SEF data for the twin and co-twin (black vs. red colored traces) of MZ twin pairs (boxes displayed at the top) and DZ twin pairs (bottom boxes) are displayed, from left to right, according to a sort in descending order of within-twin-pair SEF wave shape correlations (indicated by the number in each box). Sorting was performed separately for MZ and DZ pairs.

that somatosensory-evoked brain responses showed higher resemblance (smaller amplitude differences and higher wave shape correlations) within MZ twin pairs as compared to DZ twin pairs. Qualitative comparison of amplitude difference and wave shape correlation values in Table 1 and Figure 2 suggests only a marginal tendency for higher SEF resemblance within DZ twin pairs compared to pairs of unrelated twins. Post hoc evaluation of every individual SEF comparison within MZ and DZ twin pairs (see Table 1, columns MZ vs. DZ) indicated that amplitude differences were significantly smaller within MZ twin pairs compared to DZ twin pairs for left- and right-hand SEFs in Time Window 1 and right-hand SEFs in Time Window 2 and that wave shape correlations were significantly higher within MZ compared to DZ twin pairs for right-hand SEFs in Time Window 1 (see also Figure 3).

Finally, we found a significant negative correlation between SEF amplitude differences and SEF wave shape correlations within twin pairs ($r = -.28$, $p = .001$), which demonstrates that SEF amplitudes tended to be more similar between twins (smaller amplitude differences) if SEF wave shapes were more similar (higher wave shape correlations).

Differences in Dipole Source Characteristics

Table 2 shows means and standard deviations of within-twin-pair differences in position, orientation, and strength of equivalent current dipole (ECD) sources fitted to the P35m SEF component. Statistical analysis indicated a significant main effect for variable Stimulated Hand only for dipole position: position, $F(1,32) = 5.07$, $p = .031$; orientation, $F(1,32) = 0.09$, $p = .767$; strength, $F(1,32) = 0.88$, $p = .356$, which was explained by the fact that within twin-pair differences in dipole location were smaller for left- compared to right-hand SEFs. There were no significant interactions between variables Stimulated Hand and Twin Pair Type for any of the dipole characteristics: position, $F(1,32) = 1.01$, $p = .323$; orientation, $F(1,32) = 0.79$, $p = .381$; strength, $F(1,32) = 0.80$, $p = .378$. Significant main effects of variable Twin Pair Type, indicating higher similarity within MZ relative to DZ twin pairs, were found for dipole position, $F(1,32) = 9.44$, $p = .004$, and strength, $F(1,32) = 4.68$, $p = .038$, but not for dipole orientation, $F(1,32) = 0.31$, $p = .583$. Post hoc evaluation of every individual comparison within MZ and DZ twin pairs (Table 2, column MZ vs. DZ) indicated that smaller differences in MZ twin pairs were evident in particular for po-

Table 2. *Means (and Standard Deviations) of Within-Twin-Pair Differences in Characteristics of the Dipole Fitted to the P35m SEF Component*

Measure	Stimulated hand	MZ	DZ	MZ vs. DZ
Position difference	Left	1.24 (0.67)	1.65 (0.73)	.104
	Right	1.44 (0.42)	2.18 (1.00)	.006
Orientation difference	Left	19.31 (22.68)	28.88 (38.89)	.372
	Right	23.20 (29.02)	21.04 (9.34)	.791
Strength difference	Left	8.38 (6.28)	11.52 (11.62)	.316
	Right	8.47 (7.76)	15.38 (10.88)	.038

Note: Means and standard deviations of differences in position (in centimeters), orientation (°), and strength (nanoAmpere meters) of the dipoles fitted to the P35m component of the SEF after left- and hand-right hand stimulation (column Stimulated hand), within MZ twin pairs (column MZ) and DZ twin pairs (DZ). Column MZ vs. DZ shows results of statistical comparisons (p values) between dipole parameter similarities within MZ and DZ twin pairs.

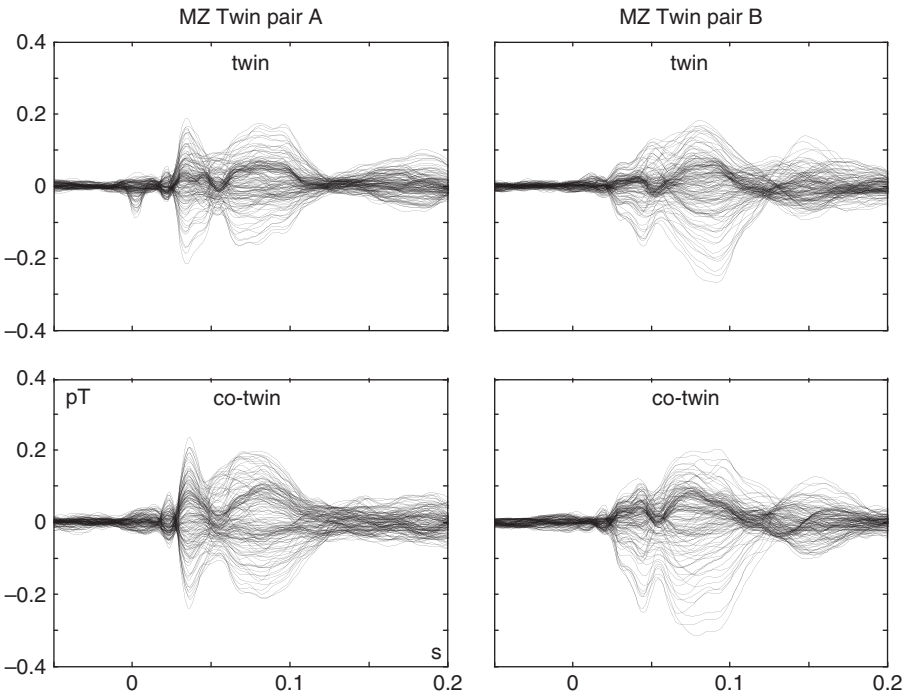

Figure 4. Somatosensory-evoked fields of two selected MZ twin pairs (overlay of all MEG sensors); the SEFs exhibit high within-twin-pair (columns) but lower between-twin-pair (rows) resemblance.

sition and strength of dipoles fitted to the P35m of SEFs after right-hand stimulation.

Discussion

This is, to our knowledge, the first study to test for a genetic influence on sensory-evoked brain activity recorded with MEG. In line with previous EEG findings (Lewis et al., 1972), the results demonstrate that somatosensory-evoked responses show a high degree of correspondence between genetically identical MZ twins (e.g., Figure 4). We show this for the complete evoked response, as opposed to focusing on selected characteristics of representative brain potentials, which has been common practice in most previous EEG studies (for an overview, see van Beijsterveldt & Van Baal, 2002). Our findings thus indicate a substantial genetic influence on the complete time course of evoked brain activity. In combination with evidence for more similar dipole source characteristics of the SEF in MZ compared to DZ twins, our results are in line with previously reported evidence for strong genetic control of brain anatomy, including the sensory cortex (Lenroot et al., 2009; Peper, Brouwer, Boomsma, Kahn, & Hulshoff Pol, 2007; Peper et al., 2009).

Although we tested a large number of individuals for a MEG study ($N = 68$ in total), the sample size is still relatively limited for a MZ versus DZ twin-pairs comparison of resemblance. Nevertheless, the present finding of a genetic influence on amplitudes of evoked brain activity measured with MEG is in agreement with our recent findings for power of ongoing brain activity during rest (van 't Ent et al., 2009) and with previous EEG studies on larger twin samples (van Beijsterveldt & Van Baal, 2002). The present results therefore substantiate that our previous conclusion that higher MZ resemblance for amplitudes of ongoing brain activity in EEG traces is not just reflecting greater MZ concordance in intervening biological tissues (van 't Ent et al., 2009) can also be extended to amplitudes of evoked brain responses.

We also found that SEF amplitudes tended to be more similar between twins if SEF wave shapes were more similar. SEF wave shapes obviously are more alike if the constituent SEF components have more similar amplitudes. However, wave shape and amplitude are not necessarily strictly coupled. SEFs with highly similar wave shapes might, for example, differ in amplitude across the entire response or an extended section of the response. This can occur because of systematic differences in the physiology of the brain, such as individual differences in depth location, orientation, or strength of SEF sources. In particular for later SEF components, top-down processes may also play a role, such as differences in the amount of attention paid to the electrical stimulation (Eimer & Forster, 2003). The finding of a significant correlation between SEF morphology and amplitude therefore provides an indication that such systematic differences did not play a significant role in this study.

The present data inform us that genetic factors influence SEF variation but do not allow us to draw definite conclusions on the exact mechanisms that underlie this influence. There might be a direct genetic effect, but it is also conceivable that genetic effects are indirect (e.g., through personality) through an influence on the environments that people expose themselves to. In either case, MEG appears to be useful as an endophenotype for individual differences in brain structure and function. Endophenotypes represent biological markers intermediate in the pathway between genetic variation and final individual differences of behavior and are a key construct of imaging genetics (de Geus, Goldberg, Boomsma, & Posthuma, 2008; Green et al., 2008). Measurements closer to the level of neural circuits underlying specific behaviors or behavior disorders are likely more tightly

associated with the effect of a single gene or a limited set of genes, which increases the power of genetic association testing. A number of genomic loci have already been linked to individual differences in cortical oscillations and event-related potentials measured with EEG (Begleiter & Porjesz, 2006; Bodenmann et al., 2009; Espeseth, Rootwelt, & Reinvang, 2009; Liu et al., 2009). The present evidence suggest that MEG endophenotypes may prove similarly useful in genetic research.

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