Magneetoencephalography in Twins Reveals a Strong Genetic Determination of the Peak Frequency of Visually Induced Gamma-Band Synchronization

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Many aspects of brain processing are intimately linked to brain rhythms. Essentially all classical brain rhythms, i.e., delta, theta, alpha, beta, and sleep waves, are highly heritable. This renders brain rhythms an interesting intermediate phenotype for cognitive and behavioral traits. One brain rhythm that has been particularly strongly linked to cognition is the gamma rhythm: it is involved in attention, short- and long-term memory, and conscious awareness. It has been described in sensory and motor cortices, association and control structures, and the hippocampus. In contrast to most other brain rhythms, the gamma frequency highly depends on stimulus and task conditions, suggesting a low heritability. However, the heritability of gamma has not been assessed. Here, we show that visually induced gamma-band synchronization in humans is strongly genetically determined. Eighty twin subjects (20 monozygotic and 20 dizygotic twin pairs) viewed a moving sinusoidal grating while their brain activity was recorded using magnetoencephalography. The stimulus induced spectrally confined gamma-band activity in sensors over visual cortex in all subjects, with individual peak frequencies ranging from 45 to 85 Hz. Gamma-band peak frequencies were highly correlated across monozygotic twins \( r = 0.88 \) but not across dizygotic twins \( r = 0.32 \) or unrelated subjects \( r = 0.02 \). This implies a heritability of the gamma-band frequency of 91%. This strong genetic determination suggests that gamma-related cognitive functions are under close genetic control.

Introduction

Many cognitive functions are related to brain rhythms (Buzsáki, 2006). Both brain rhythms and cognitive functions vary among individuals, and individuals also vary in their genetic makeup. It has been challenging to establish clear links between genetic and cognitive makeup (Green et al., 2008; Koten et al., 2009). Identifying the genetic basis of brain rhythms might help in the understanding of the genetic basis of associated cognitive and behavioral traits, with brain rhythms serving as an intermediate phenotype.

Many of the classical brain rhythms are highly heritable. In the 1970s, for example, Vogel (1970) and Young et al. (1972) investigated the heritabilities of the delta, theta, alpha, and beta rhythms in twins and showed heritabilities up to 0.9. Those early and subsequent related studies used resting-state or sleep recordings (Lykken, 1982; van Beijsterfeldt et al., 1996; Linkowski, 1999; Posthuma et al., 2001; Smit et al., 2006; Linkenkaer-Hansen et al., 2007) (for review, see van Beijsterfeldt and van Baal, 2002), because many of the classical brain rhythms are strongest under those conditions.

By contrast, the gamma-band rhythm (30–100 Hz) is strongly associated with active brain processing (Gray et al., 1989; Fries et al., 2001; Pesaran et al., 2002; Buschman and Miller, 2007; Colgin et al., 2009; Tallon-Baudry, 2009): gamma-band activity is induced by sensory stimulation in the visual (Hoogenboom et al., 2006; Muthukumaraswamy et al., 2009), auditory (Brosch et al., 2002), and somatosensory (Bauer et al., 2006) modality. It is enhanced among neurons driven by attended stimuli (Fries et al., 2001) and predicts corresponding behavioral benefits (Taylor et al., 2005; Womelsdorf et al., 2006). It reflects the content of working memory (Pesaran et al., 2002; Howard et al., 2003), predicts the quality of long-term memory encoding (Fell et al., 2001), and correlates with conscious awareness of a stimulus (Fries et al., 2002; Wyart and Tallon-Baudry, 2008). At the same time, the amplitude and peak frequency of gamma-band synchronization is highly variable across individual human (Hoogenboom et al., 2006; Muthukumaraswamy et al., 2009, 2010) and animal (Vinck et al., 2010) subjects, similar to cognitive functioning.

In contrast to most classical frequency bands, the peak frequency of gamma-band activity is highly variable within an individual subject: gamma frequency depends on stimulus and task parameters, such as stimulus contrast (Ray and Maunsell, 2010),
velocity (Swettenham et al., 2009), and size (Ray and Maunsell, 2011). This suggests that the heritability of gamma-band synchronization might be low. We therefore set out to test whether gamma-band activity is genetically determined and performed a classical twin study into the heritability of visually induced gamma-band activity by using MEG. We found that gamma-band synchronization is 91% heritable. This also suggests that cognitive functions related to gamma are under close genetic control.

Materials and Methods

Subjects. Subjects were 80 twins, consisting of 20 monozygotic (MZ) and 20 dizygotic (DZ) pairs, who were recruited through the Netherlands Twin Registry (Boomsma et al., 2006). All subjects gave written informed consent according to institutional guidelines of the local ethics committee (Commissie Mensgebonden Onderzoek Arnhem-Nijmegen, The Netherlands). None had previous experience with a similar experimental setup. Only same-sex pairs were tested (MZ, 15 female pairs; DZ, 10 female pairs), with average ages (±SD) of 21.0 ± 3.0 (MZ) and 21.7 ± 2.9 (DZ). Two MZ and four DZ twins were left-handed. Zygosity was determined based on blood group polymorphisms for five twin pairs and longitudinal assessment of parental report on physical resemblance for the other pairs.

Experimental paradigm and stimuli. The paradigm used was modified from Hoogenboom et al. (2006) and is known to induce strong gamma-band synchronization in visual cortex in human MEG. While seated in the MEG, subjects viewed a foveally presented, circular sine wave grating that was presented on a translucent screen 80 cm in front of their eyes by using an EIKI LCD projector. In each of a total of 180 trials, subjects had to press a response button with their right index fingers when the stimulus increased in velocity (step to 1.2°/s), which could occur at any unpredictable time. Gamma-band activity was subsequently defined as the frequency range of interest was 40 to 100 Hz, which was used as input for the genetic analysis. In this range, all subjects showed a single peak of activation. Some subjects showed a second band of activity at lower gamma frequencies (25–40 Hz). The subsequent analysis of the correlation in gamma peak frequencies required a single frequency value per subject. In subjects with two bands, we used the upper band, because it was clearly a gamma (rather than a higher beta) band, and it always showed a stronger increase versus baseline.

To compare the similarities in peak frequencies within twin pairs in both groups (MZ and DZ twins), the intraclass correlation (ICC) was computed between the gamma frequencies of the members of each twin pair (Falconer and Mackay, 1996). The corresponding regression slope was subsequently estimated by averaging the slopes of 10° regressions in which axis assignment of data points (as x or y value) was randomly permuted. To compare twin pairs to unrelated subject pairs, we computed the ICC for 20 pairs of randomly drawn unrelated subjects. This was done 100 times to estimate the average ICC for unrelated subjects.

Genetic analysis. The genetic influences to individual differences in gamma peak frequency were estimated by fitting a genetic structural equation model (SEM) to the peak frequency data in which the observed variance of the phenotype of interest is decomposed into genetic and environmental components (Falconer and Mackay, 1996). These components include variance caused by additive (A) and nonadditive (D); i.e., genetic dominance, possibly including epistasis) genetic factors and individual environmental factors including measurement error (E). The relative contribution of these latent factors is expressed by the path coefficients a, d, and e, which are estimated by maximum likelihood. Based on the pattern of MZ and DZ twin correlations, the influence of D was included in the model rather than a common environment factor (Falconer and Mackay, 1996). To estimate the values of a, d, and e, the gamma peak frequency data of the MZ and DZ twin pairs were analyzed by using the Mx software package for genetic linear structural equation modeling (Neale et al., 2003). Overall goodness of fit of the full (ADE) model was determined on the basis of the χ² statistic. Subsequently, the significance of factors A and D was assessed by means of likelihood ratio tests comparing the full model with a submodel from which these factors were constrained at zero. When the fit significantly worsened, the contribution of genetic factors was considered significant. The broad heritability (h²) of the gamma peak frequency was defined as the percentage of the total variance of the phenotype that could be explained by genetic factors (A + D).

Power. We explored the power of our experimental design to detect broad sense heritability for different values of h² based on the current sample size, by testing ADE versus E with a 2 df test and alpha of 5%. The power to detect an h² of 40, 60, or 80% was 39, 79, and 98%, respectively, when the contributions of additive (a²) and nonadditive (d²) effects were equal. For higher values of h², as suggested by this study, the power was 99% or higher.

Results

Figure 1A shows the visually induced oscillatory activity from occipital cortex of one example subject as a function of time after stimulus onset and frequency. The visual stimulus resulted in gamma-band activity that lasted for the entire stimulus duration and was confined to a frequency band from approximately 50–65 Hz. Similar gamma-band activity patterns have been described before in human subjects (Hoogenboom et al., 2006; Muthukumaraswamy et al., 2010). As also found typically, the gamma frequency was slightly higher just after stimulus onset and then settled onto a sustained level (Hoogenboom et al., 2006; Swettenham et al., 2009; Muthukumaraswamy et al., 2010). The respective data for this subject’s MZ cotwin are shown in Figure 1B and reveal a strikingly similar pattern. The two subjects have
Figure 1. Visually induced gamma-band activity in a MZ and a DZ twin pair. A, B, Time-frequency representations (TFRs) of activity in the gamma range relative to prestimulus baseline levels in two twins of a MZ pair, averaged across 74 parieto-occipital MEG sensors. Time = 0 s denotes stimulus onset. C, Spectra of average magnetic field strength during baseline (green) and stimulation (red) epochs in the same subjects. D, Percentage signal change caused by visual stimulation, superimposed for both twins (black line, twin 1; blue line, twin 2). Signal change spectra correlate significantly in this twin pair ($r = 0.98; p < 0.001$). E–H, Same analyses as in A–D applied to a DZ twin pair. TFRs (E, F) and signal change spectra (G, H) show strong dissimilarities.

Figure 2. TFRs of visually induced gamma-band activities in all 80 recorded subjects. A, MZ twins. B, DZ twins. Adjacent TFRs represent twin and cotwin of a single pair, with the upper left twins being pair 1, and the lower right twins pair 20. Color scales are normalized to each subject's maximum signal change. Horizontal black lines indicate each subject's peak frequency of gamma-band activation during the sustained activation epoch. TFRs of MZ pair 15 and DZ pair 2 are the example subjects from Figure 1.
spectral bands of activation that have the same temporal evolution and width and are centered on the same frequencies. For the same subjects, Figure 1C shows the raw power spectra averaged across the prestimulus baseline and the sustained activation epoch (0.8-1.8 s), and Figure 1D shows the corresponding power changes as a function of frequency. The cross-correlation of power changes across frequencies, between MZ twins, was 0.98 (95% CI, 0.97-0.98). Figure 1E-H shows the same analysis for a DZ twin pair. Figure 1, E and F, shows that visually induced oscillatory activity is dissimilar, which is confirmed by a much lower cross-correlation of 0.25 (95% CI, 0.18-0.31).

The similarity illustrated for the example MZ twin pair was consistent across the population of 20 MZ twin pairs studied (Fig. 2A). One MZ twin pair showed very weak gamma-band activation, which was again concordant for the two respective twins. Also the dissimilarity found in the example DZ twin pair was found repeatedly across the population of 20 DZ twin pairs (Fig. 2B). Both the similarity among MZ twins and the dissimilarity among DZ twins applied to several aspects of gamma-band activity, like strength, peak frequency, and width of the frequency band. For a quantitative test of gamma heritability, we focused on the peak frequency, because it is least affected by measurement conditions like the distance between the brain and the MEG sensors. Figure 3A shows the gamma peak frequencies of the MZ twin pairs, with each dot representing one twin on the x-axis and the cotwin on the y-axis (arbitrary axis assignment, see Materials and Methods). Peak frequencies ranged approximately 45-90 Hz, and there was a strong intraclass correlation (ICC) across MZ twin pairs (slope, 1.01; SD, 0.13; ICC, 0.88; 95% CI, 0.72-0.95; p < 0.001), whereas DZ twin pairs (Fig. 3B) showed low resemblance (ICC, 0.32; 95% CI, −0.13-0.66; p = 0.17). Unrelated subjects (Fig. 3C) had an even lower correlation of their peak frequencies (ICC, 0.02; p = 0.40), which was significantly lower than the DZ twin ICC (p < 0.001).

This marked difference between MZ and DZ pairs suggests a strong genetic determination of the gamma peak frequency. The relative contributions of additive genetic (A), nonadditive genetic (D), and environmental factors (E) were estimated through genetic SEM (see Materials and Methods for details). The standardized A, D, and E variance components were 0.225 and 0.681, corresponding to a broad heritability of 91% (CI, 80–96%). The standardized environmental variance component was estimated at 9% (95% CI, 4.8%–20%). Removing the influence of A and D factors from the model gave a significant worsening of the goodness of fit (χ² = 32; df = 2; p < 0.001).

The heritability found here applies strictly only to visually induced gamma. Yet, visual gamma shares central features with gamma-band activities in other areas or under different conditions (Bragin et al., 1995; Pesaran et al., 2002; Bauer et al., 2006). It is positively correlated to processing and functioning, is sustained along the corresponding process or function, and is of limited band width for a given subject and condition (for review, see Fries, 2009). Thus, gamma-band activities in different areas and conditions might well be similar in their underlying mechanisms and potentially reflect a fundamental process subserving several cognitive functions (Fries, 2009; Tiesinga and Sejnowski, 2009).

Previous twin studies on the heritability of brain rhythms focused on the classical EEG rhythms, delta, theta, alpha, and beta, and sleep rhythms (Vogel, 1970; Young et al., 1972; Lykken, 1982; van Beijsterveldt et al., 1996; Linkowski, 1999; Posthuma et al., 2001; Smit et al., 2006; Linkenkaer-Hansen et al., 2007). These were studied mainly during rest, when they are particularly pronounced (for review, see van Beijsterveldt and van Baal, 2002). By contrast, gamma-band activity in our study was induced by the visual stimulus and was most likely involved in stimulus processing and task performance (Fries, 2009). In agreement with this, the gamma peak frequency is modulated substantially by stimulus features such as contrast (Ray and Maunsell, 2010), size (Ray and Maunsell, 2011), or velocity (Swettenham et al., 2009). Such stimulus dependence might suggest a lower heritability of gamma than alpha peak frequency, because the latter is essentially fixed for a given individual (Steriade et al., 1990; Klimesch et al., 1996). By contrast, alpha frequency heritability has been found to be smaller (71–83%) than the gamma-frequency heritability observed here (≥91%) (Posthuma et al., 2001; Smit et al., 2006).

The gamma rhythm has consistently been linked positively to cognitive functions (Gray et al., 1989; Fries et al., 2001; Pesaran et al., 2002; Buschman and Miller, 2007; Tallon-Baudry, 2009) and the fMRI BOLD signal in both animals (Logothetis et al., 2001) and humans (Scheeringa et al., 2011). This has prompted particular interest in this rhythm. The strong heritability that we found for visually induced gamma-band activity warrants an investigation of the underlying genetic mechanisms, which might elucidate the causal role of gamma for cognition. Mechanisms behind gamma-band activity have so far been derived primarily from in vitro studies in combination with theoretical work (Traub et al., 2003; Kopell and Ermentrout, 2004; Bartos et al., 2007; Tiesinga and Sejnowski, 2009). Those studies highlighted the role of GABAergic inhibition. GABAergic inhibition is affected in schizophrenia (Lewis et al., 2005), which in turn is related to reduced gamma-band activity (Kwon

Discussion
In this study, we focused on the frequency of visually induced gamma-band activity for several reasons. The estimation of heritability of a particular quantitative trait requires that this trait be quantified in each twin individually. If the individual estimate was noisy, it would lead to an underestimation of the similarity among monozygotes and thereby to an underestimation of the actual heritability. Such noise appears particularly weak in the case of gamma-band activity in the visual system (Hoogenboom et al., 2006; Muthukumaraswamy et al., 2009, 2010). For a related reason, we focused on the gamma-band peak frequency. This parameter is immune to several factors like distance between brain and sensors, skull shape, or instrumentation noise.
et al., 1999). The current findings mandate future studies that will investigate in detail the interplay between GABAergic inhibition, gamma-band synchronization, and the vulnerability for conditions like schizophrenia.

References