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ORIGINAL ARTICLE

Environmental Factors Shape Sleep EEG Connectivity During Early Adolescence

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Abstract

Quantifying the degree to which genetic and environmental factors shape brain network connectivity is critical to furthering our understanding of the developing human brain. Sleep, a state of sensory disengagement, provides a unique opportunity to study brain network activity noninvasively by means of sleep electroencephalography (EEG) coherence. We conducted a high-density sleep EEG study in monozygotic (MZ; $n = 38$; mean age = 12.46; 20 females) and dizygotic (DZ; $n = 24$; mean age = 12.50; 12 females) twins to assess the heritability of sleep EEG coherence in early adolescence—a period of significant brain rewiring. Structural equation modeling was used to estimate three latent factors: genes, environmental factors shared between twins and environmental factors unique to each twin. We found a strong contribution of unique environmental factors (66% of the variance) and moderate genetic influence (19% of the variance) on sleep EEG coherence across frequencies and sleep states. An exception to this was sleep spindle activity, an index of the thalamocortical network, which showed on average a genetic contribution of 48% across connections. Furthermore, we observed high intraindividual stability of coherence across two consecutive nights suggesting that despite only a modest genetic contribution, sleep EEG coherence is like a trait. Our findings in adolescent humans are in line with earlier findings in animals that show the primordial cerebral map and its connections are plastic and it is through interaction with the environment that the pattern of brain network connectivity is shaped. Therefore, even in twins living together, small differences in the environment may cascade into meaningful differences in brain connectivity.

Key words: adolescence, coherence, connectivity, heritability, sleep spindles, sleep EEG

Introduction

The complexity of brain function is not only tied to isolated activity of specific brain regions, but also to the dynamic interactions between regions (Tononi et al. 1994; Tognoli and Kelso 2009). The integration of information across regions has been linked to cognitive function and behavior (e.g., Gray et al. 1989; Varela et al. 2001; Tarokh et al. 2014) and is altered in disease states (Henry and Cohen 2019). Identifying the degree to which genetic and environmental factors account for interindividual variability in brain network activity is necessary for laying the groundwork for future research. Only by knowing the degree to which environmental factors impact brain connectivity, can we measure the success of psychosocial interventions. Conversely, if connectivity is largely genetically determined, it may serve as a useful endophenotype.

Brain connectivity can be assessed noninvasively by means of the electroencephalography (EEG) due to the high temporal (in the millisecond range) resolution that EEG recordings provide. EEG coherence—a measure of connectivity based on correlation of EEG signals at a specific frequency—has been shown to reflect functional interactions between neural networks (e.g., Nunez and Srinivasan 2006). EEG coherence also tracks

the developmental rewiring of the brain critical to healthy development (Thatcher 1994). During adolescence, substantial reorganization of the brain takes place (e.g., Giedd et al. 1999; Paus et al. 1999; Sowell et al. 2003), wherein underutilized synapses are eliminated (Huttenlocher 1979; Goldman-Rakic 1987). Experimental work in carnivores and nonhuman primates shows a general pattern of overproduction of synapses early in life (Innocenti et al. 1977; Rakic et al. 1986; Bourgeois et al. 1994; Bressoud and Innocenti 1999) followed by a selective elimination during the adolescent period (Bourgeois et al. 1994). At the same time, highly used connections are strengthened through myelination (Benes 1989). In a study examining human brain specimens across seven decades of life, Benes et al. (1989) found an increase in myelination across several brain regions including prefrontal cortex, cingulate cortex, parahippocampal gyrus, subiculum, presubiculum, and the hippocampal formation during adolescence. These processes are thought to result in a more specialized and efficient brain, however, at the cost of plasticity (Giedd 2015). While the synaptic pruning that takes place during adolescence is believed to be reflected in a decline in sleep EEG power (Feinberg 1982; Campbell and Feinberg 2009; Feinberg and Campbell 2010; Buchmann et al. 2011; Goldstone et al. 2018), the increased myelination and rewiring of brain networks are likely reflected in an increase in sleep EEG coherence (Tarokh et al. 2010).

Studies using the sleep EEG to examine changes to coherence during adolescence have reported an increase in sleep EEG coherence across this period (Tarokh et al. 2010, 2014). The study by Tarokh et al. (2010) examined sleep EEG coherence in three age cohorts, children aged 9–10, teenagers aged 15–16, and adults aged 20–23 years and included a follow-up assessment 2–3 years later. The authors found a linear increase in intrahemispheric and diagonal coherence across all cohorts, sleep states and most frequency bands spanning the ages of 9–23 years, likely reflecting anatomical changes such as increases in white matter (Paus et al. 2001). Though this early study has established that developmental changes in sleep EEG coherence occur, it is based on a few EEG derivations (i.e., four); therefore, information about regional aspects of changes to coherence across development are lacking.

Recent evidence suggests that brain network organization rather than dysfunction of isolated regions is implicated in the etiology of numerous neurodevelopmental and psychiatric disorders (Henry and Cohen 2019). A recent systematic review of quantitative EEG biomarkers in child psychiatric disorders (McVoy et al. 2019) identified studies demonstrating reduced EEG coherence during waking in autism (Coben et al. 2008; Machado et al. 2015) and increased EEG coherence during waking in attention deficit disorder (Chabot et al. 1999). During sleep, reduced coherence has been associated with major depression disorder (Armitage et al. 1999), schizophrenia (Wamsley et al. 2012), and posttraumatic stress disorder (Modarres et al. 2019) in adults. Furthermore, in one study comparing children with autism to those without, increases in coherence associated with autism were only present in sleep and not in waking, suggesting that during sleep, we can measure unique network activity that may be of functional relevance (Buckley et al. 2015).

Taken together, sleep EEG coherence has the potential to provide valuable information about functional organization of the brain in health and disease. Therefore, it is important to understand the degree to which sleep EEG coherence is heritable. Previous studies in both adults (Ambrosius et al. 2008; De Gennaro et al. 2008; Adamczyk et al. 2015) and adolescents (Rusterholz et al. 2018) have found high (<80%) heritability for sleep EEG power. Despite the abundance of studies showing the utility of sleep EEG coherence in measuring developmental changes to the brain (Tarokh et al. 2010, 2014; Kurth et al. 2013), and altered sleep EEG coherence in neurodevelopmental and psychiatric disorders (Armitage et al. 1999; Wamsley et al. 2012; Buckley et al. 2015; Modarres et al. 2019), we are unaware of a study to date examining the heritability of sleep EEG coherence.

Therefore, the current study uses a twin design to examine genetic and environmental influences on high-density sleep EEG coherence in early adolescence. Based on findings with regards to waking EEG coherence, which find moderate heritability (Baal et al. 1998; Beijsterveldt et al. 1998; Chorlian et al. 2007), we hypothesize a moderate genetic contribution and a somewhat weaker influence of unique environmental factors across frequencies. Furthermore, we assess the stability of sleep EEG coherence across two consecutive nights and hypothesize high stability as previously shown in waking across several months (Corsi-Cabrera et al. 1997, 2007).

Materials and Methods

Participants

Overnight sleep EEG was recorded in 19 MZ ($n = 38$; mean age = 12.46; SD = 1.22; 20 females) and 12 DZ ($n = 24$; mean age = 12.50; SD = 1.53; 12 females) same-sex twin pairs. The MZ and DZ groups did not differ with regards to the distribution of gender (χ^2 (1.62) = 0.04; $P = 0.84$), pubertal status (assessed using Petersen et al. 1988; χ^2 (4.62) = 2.46; $P = 0.65$) or age ($t(60) = -0.11$; $P = 0.90$). A set of triplets that included an MZ and a DZ twin pair was part of both MZ and DZ analyses. Zygosity was determined by means of a questionnaire administered to the parents shown to be 95% accurate (Goldsmith 1991). Participants were healthy and born after the 30th week of pregnancy. Written assent was obtained from all participants and written consent was obtained from their parents. Study procedures were approved by the local ethics committee of the Canton of Zurich and performed according to the Declaration of Helsinki.

Procedures

Sleep EEG recordings were conducted at participants' home during two consecutive nights (adaptation followed by a baseline night). Only data from the second night (baseline) were included in the heritability analysis apart from three subjects for which recordings from the adaptation night were used due to insufficient signal quality during the baseline. Prior to EEG recordings, participants spent at least 5 days on a stabilization schedule ensuring time in bed between 9.5 and 10 h. The sleep schedule was tailored according to the needs of the participants and actigraphy and sleep diaries verified adherence to this schedule.

Sleep EEG Analysis

Sleep EEG, electrooculogram (2 channels), electromyogram (2 channels), and electrocardiogram (2 channels) were recorded via a Geodesics system (GSN300; Electrical Geodesic Inc.) with 64 channels resulting in 58 EEG channels. The data were acquired at a sampling rate of 1000 Hz and downsampled to 250 Hz for analysis. The signal at each derivation was recalculated relative to the average of all derivations (average reference) after excluding bad channels based on visual inspection of spectrograms. All sleep recordings were scored in 30-s epochs according to the

criteria of Rechtschaffen and Kales (1968). Epochs with artifacts were detected and excluded using a semiautomated procedure whenever power in the low (0.8–4.6 Hz) and high (20–40 Hz) frequencies exceeded a threshold (Buckelmüller et al. 2006).

We examined sleep EEG coherence between all possible channel pairs, with coherence defined as $\frac{|P_{xy}(f)|^2}{P_{xx}(f)P_{yy}(f)}$ where $P_{xy}(f)$ is the cross-spectral density and $P_{xx}(f)$ and $P_{yy}(f)$ are the autospectral density functions of the two signals x and y at frequency f (Bendat and Piersol 2010). Coherence values range from 0 to 1 and are not normally distributed. Therefore, we applied a Fisher's z-transform to the square root of the data before statistical analyses. Electrode pairs with very small (<10 cm) or very large (>20 cm) separations, as reflected through their arc length, were excluded from analyses, to reduce volume conduction effects (Srinivasan et al. 2007), resulting in 559 connections. Of these 559 connections, 291 were classified as interhemispheric because they crossed the hemispheres and 268 were classified as intrahemispheric.

Coherence was calculated for 30-s epochs using Welch's method (average of six 5-s windows; Hanning window; no overlap; frequency resolution 0.2 Hz) in MATLAB (Mathworks) for the two states, rapid eye movement (REM) and nonrapid eye movement (NREM) sleep, and the following frequency bands: delta (1–4.6 Hz), theta (4.8–7.8 Hz), alpha (8–10.8 Hz), sigma (11–16 Hz), beta 1 (16.2–20 Hz), beta 2 (20.2–24 Hz), gamma 1 (24.2–34 Hz), and gamma 2 (34.2–44 Hz). Because the duration of sleep has an impact on the calculation of sleep EEG coherence, as the distribution of sleep stages as well as the abundance of specific oscillations change with the dissipation of sleep pressure (Achermann and Borbély 2011), we used the maximal common length of NREM and REM sleep epochs for each twin pair.

In addition to band coherence, we quantified the sigma peak in the coherence spectrum, which corresponds to sleep spindles—bursts of sleep EEG activity in the sigma frequency range generated by thalamocortical loops (Krosigk et al. 1993; Fuentealba and Steriade 2005). By subtracting background EEG activity and only examining the relative sigma peak, we obtain a measure of spindle coherence (modified from Gottselig et al. 2002). This procedure is illustrated in Supplementary Material, Figure S1.

Statistical Analysis

Structural equation modeling (SEM) was used to estimate genetic and environmental influences on coherence with OpenMx in R (Boker et al. 2011). SEM estimates the contribution of latent factors (i.e., genes [A], environmental effects shared between twins [C], and environmental effects unique to each twin and measurement error [E]) to observed data under the assumption that the genetic concordance between MZ twins is 1, while it is 0.5 in DZ twins. On the other hand, both MZ and DZ twins share a familial and school environment leading to a shared environmental (C) concordance of 1 for both MZ and DZ twins. Unique environmental factors and measurement error (E) are uncorrelated among both MZ and DZ twins. Each factor, A, C, and E can vary between 0 and 1 and all factors sum to 1 indicating the amount of variance explained by each of the factors. Model fit was assessed using the Akaike information criterion (AIC), as is standard in twin studies using SEM analysis (Lessov-Schlaggar et al. 2012; Shan et al. 2016; Vandenbosch et al. 2019). When the model fit, as determined by the AIC, was better for a reduced model (AE or CE) as compared to the full model (ACE), then we used the reduced model and set the value for the unused factor to zero (Rijsdijk and Sham 2002).

Because the latent factor E captures unique environmental factors in addition to measurement error, we sought to quantify the stability of sleep EEG coherence across consecutive recordings. To this end, we calculated intraclass correlation coefficients (ICCs) (Shrout and Fleiss 1979) for the two consecutive nights (adaptation and baseline). ICCs were defined as the between-subjects mean square minus the residual sum of squares divided by the between-subjects mean square. A large between-subject variance combined with a high within-subject similarity across the two recordings will result in large ICCs. Furthermore, previous studies (Ambrosius et al. 2008; De Gennaro et al. 2008; Adamczyk et al. 2015; Rusterholz et al. 2018; Gorgoni et al. 2019) have used ICC analysis to quantify heritability by subtracting ICC values of DZ twins from MZ twins with the assumption that due to the greater proportion of shared genetic material in MZ twins ICC values will be higher in MZ as compared with DZ twins. Therefore, to compare the between-night variance to heritability, we calculated ICC values for MZ and DZ twins separately and use the difference between MZ and DZ twins as a further index of heritability. Finally, a Wilcoxon rank sum test was conducted on sleep stage variables to assess whether the two groups of twins were comparable with regards to their sleep.

Results

The MZ and DZ twins in our sample showed no significant differences with regards to sleep stage variables and showed sleep architecture typical for this age group with a sleep efficiency >90% (Table 1).

Coherence Values

Figure 1 (first row) depicts the distribution of coherence values across the 559 connections for all frequency bands and sleep states and shows that the median value lies between 0.21 and 0.27 for NREM sleep and between 0.22 and 0.27 for REM sleep. These values are in accordance with a previous study of sleep EEG coherence in adolescence (Tarokh et al. 2010) and show a consistent decline across frequencies in REM sleep, while in NREM sleep, the decline is limited to the higher frequency range (beta 1 to gamma 2 bands). Supplementary Material, Figure S2 shows maps of coherence values during NREM sleep grouped in 14 regions averaged across subjects. These maps suggest that coherence values are high between central, parietal, and temporal regions for band coherence and central and frontal regions for sigma peak coherence. We observed similar patterns for REM sleep (Supplementary Material, Fig. S3).

ICC values were categorized as moderate (0.41–0.60), substantial (0.61–0.80), and almost perfect (0.81–1.00) by Landis and Koch (1977), a nomenclature that we use in the current report. Based on ICC analysis, coherence values across two consecutive nights showed intrasubject stability, with ICC values mainly in the substantial range across frequency bands and sleep states with median values between 0.60 and 0.82 (Fig. 1).

Heritability of Coherence

The SEM results are depicted in Figure 2 for the frequency bands delta to sigma and the sigma peak, and in Figure 3 for the

Table 1 Mean and standard deviation (in parentheses) of sleep parameters for monozygotic (MZ; $n = 36$) and dizygotic (DZ; $n = 24$) twins in our sample. The percent values were calculated with respect to total sleep time. Sleep latency is defined as the first occurrence of stage 2 sleep following lights out. Results from a Wilcoxon rank sum test comparing the two groups with regards to sleep parameters are also reported (z-values; *P*-values in parentheses)

Sleep parameter	MZ	DZ	z-statistic
Total sleep time (min)	522.61 (±51.16)	546.12 (±37.71)	−1.84 ($P = 0.07$)
Wake after sleep onset (min)	28.71 (±29.03)	23.29 (±25.94)	0.45 ($P = 0.65$)
Sleep latency (min)	22.01 (±17.85)	18.44 (±9.71)	0.27 ($P = 0.79$)
Sleep efficiency (%)	91.03 (±5.45)	92.69 (±4.33)	−0.92 ($P = 0.36$)
REM latency (min)	112.39 (±44.95)	93.06 (±40.12)	1.91 ($P = 0.06$)
Stage 2 (%)	44.26 (±10.08)	45.10 (±8.62)	−0.24 ($P = 0.81$)
Slow wave sleep (%)	29.36 (±9.56)	27.00 (±7.81)	0.86 ($P = 0.39$)
Stage REM (%)	25.98 (±5.01)	26.95 (±6.54)	−0.39 ($P = 0.69$)

frequency bands beta 1 to gamma 2 in NREM sleep. Generally speaking, we found a strong contribution of unique environmental factors (latent factor E) across bands for interhemispheric as well as intrahemispheric coherence in both NREM and REM sleep (median value range: $0.45 \leq E \leq 0.75$), with minimal contribution by shared environmental factors. The strongest impact of genetic factors (A) on both inter- and intrahemispheric coherence was found for NREM sleep sigma band (median value: $A = 0.38$) and sigma peak (median value: $A = 0.48$) coherence (Fig. 4). We performed an ANOVA comparing heritability values (latent factor A) across bands (i.e., 559 values corresponding to 559 connections per band) and found that NREM sleep sigma coherence significantly differed from all other frequency bands except for beta 1 as revealed by post-hoc *t*-tests ($P < 0.0001$; Tukey-corrected).

Furthermore, we used a χ^2 test to determine whether the total number of connections where more than half the variance was explained by a given factor (A, C, or E) differed for intra- versus interhemispheric coherence. We found that a larger number of intrahemispheric connections were explained by genetic factors as compared with interhemispheric coherence for NREM sleep sigma to gamma 2 bands, NREM sigma peak coherence and REM sleep alpha to sigma bands. In other words, despite an overall trend toward unique environmental factors explaining the most variance, in some frequency bands intrahemispheric coherence manifested a greater number of connections with a large genetic contribution as compared with interhemispheric coherence.

Using ICC analysis to calculate heritability confirmed findings from SEM and revealed low heritability (third row in Fig. 1) as reflected in small differences in ICC values for MZ and DZ twins across states and frequencies (median value range: 0–0.43).

Discussion

The current study takes a behavioral genetics approach in adolescents to estimate the heritability of connectivity in the sleeping brain as indexed by sleep EEG coherence. Across frequencies and sleep states, we consistently observed that unique environmental factors had a large influence on sleep EEG coherence, while environmental factors shared among twins (latent factor C) had the weakest influence. Some frequency bands, such as the sigma band in NREM sleep as well as sigma peak coherence, showed modest genetic control. Our findings are in line with a large body of literature in animals showing that while the initial formation of brain structures relies on genetic regulation, the patterns of interaction between regions and the efficiency of such interactions are tuned through experience and external input (Rakic et al. 2009). According to one prominent hypothesis, the protomap hypothesis, a map of future cortical areas and their identity is established at the time of the last division of neural progenitor cells in the ventricular zone (Rakic 1988). However, the size of these areas and their synaptic features are influenced by afferent input (Rakic 1988; Rakic et al. 1991). Further reflecting the plasticity of network activity, a study in cat fetuses showed that by blocking action potentials through injections of a sodium channel antagonist, thalamocortical projections can be altered and manipulated (Catalano and Shatz 1998). Such plasticity of the cortex, thus, may be crucial to evolutionary development and adaptation (Rakic et al. 2009).

Our findings of low heritability and high unique environmental influences are partially in contrast to wake EEG studies, where heritability estimates are often higher (range: 0.22–0.71; Baal et al. 1998; Beijsterveldt et al. 1998; Chorlian et al. 2007) than those observed in the current study (mean range: 0.19–0.33). Direct comparison with waking studies is difficult due to the varied methodologies used to calculate heritability such as variance component models (Chorlian et al. 2007), or report on average heritability values rather than specific connections. Despite this, we note the wide range of heritability values observed in the current study, with estimates of heritability for some connections >0.5 (Figs 4 and 5). Indeed, when we directly compare our findings to those of previous wake EEG studies (Table 2) in 16-year olds (Beijsterveldt et al. 1998), we find similar values. As far as we are aware, this is the first high-density sleep EEG study of the heritability of coherence and thus, the lower overall estimate observed in our study may in part be due to the large number of connections studied, which may include weak connections which are not biologically meaningful (e.g., connections running diagonally from the left occipital to the right frontal cortex). On the other hand, only by examining a large number of connections is it possible to envisage the overall patterns of genetic and environmental influences on coherence. For these reasons, the use of high-density EEG provides a more thorough overview of this phenomenon and may explain why our findings are congruous with studies in animals and human magnetic resonance imaging (MRI) studies as compared with previous studies of wake EEG coherence.

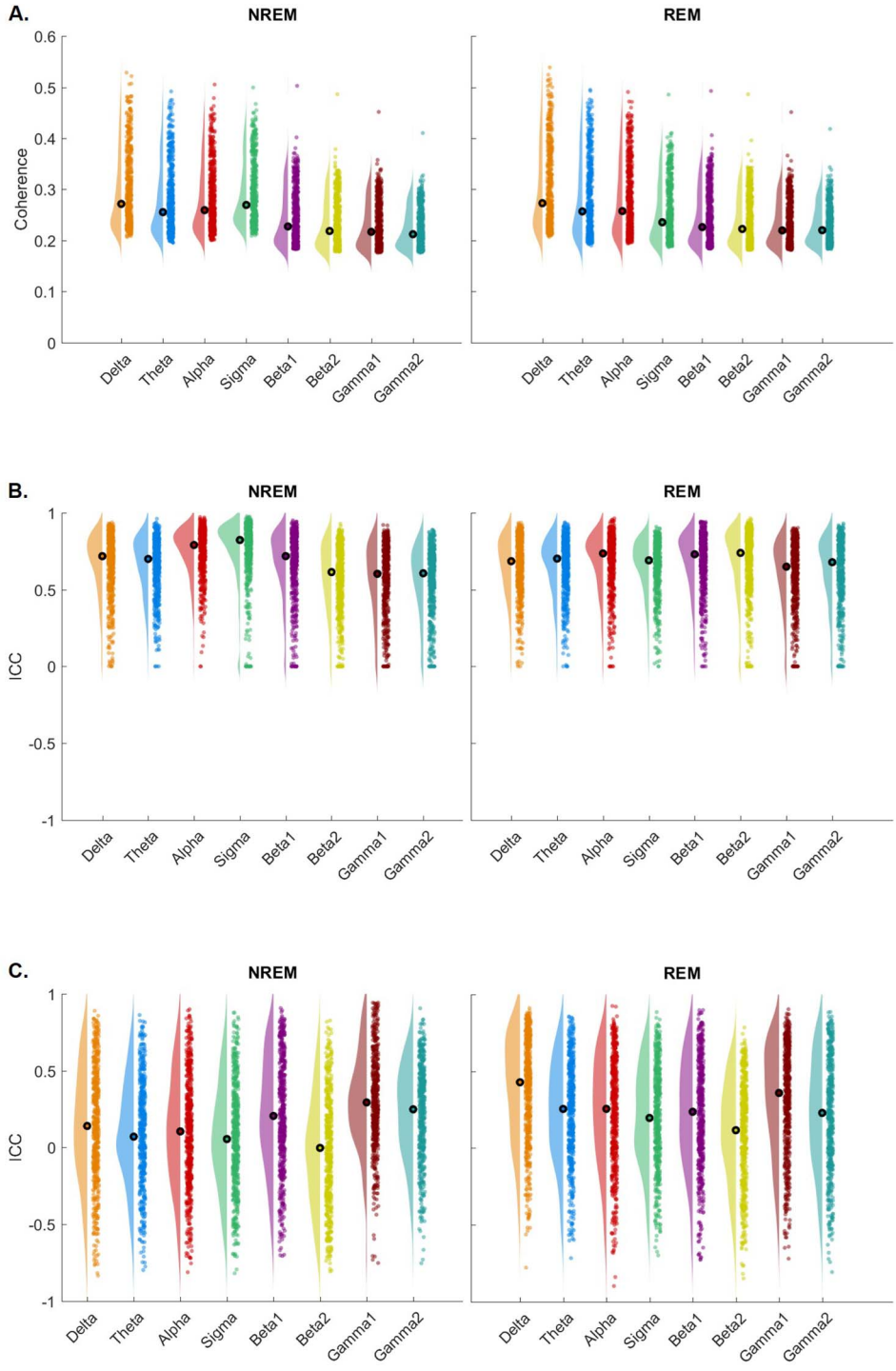

Figure 1. (*A*) Raincloud plots (Allen et al. 2019) showing the distribution of coherence values across all 559 connections for all frequency bands and both sleep states averaged across subjects. (*B*) Distribution of ICC values calculated between two consecutive nights of assessment across all 559 connections for all frequency bands and both sleep states. (*C*) Distribution of differences in ICC values between monozygotic (MZ) and dizygotic (DZ) twins (MZ-DZ) across all 559 connections for all frequency bands and both sleep states. In these plots, the scattered dots represent the values for individual connections, while the circle in the middle depicts the median value.

Nonetheless, our finding suggests that the brain's functional connectivity during sleep is largely shaped by individual experiences, not shared among twins, and, therefore, possibly one of the features making each individual unique. An EEG study of source connectivity showed that dynamic functional connectivity of temporal lobe regions, the posterior cingulate, and the superior parietal region is correlated with personality traits such as neuroticism, agreeableness, and extraversion (Kabbara

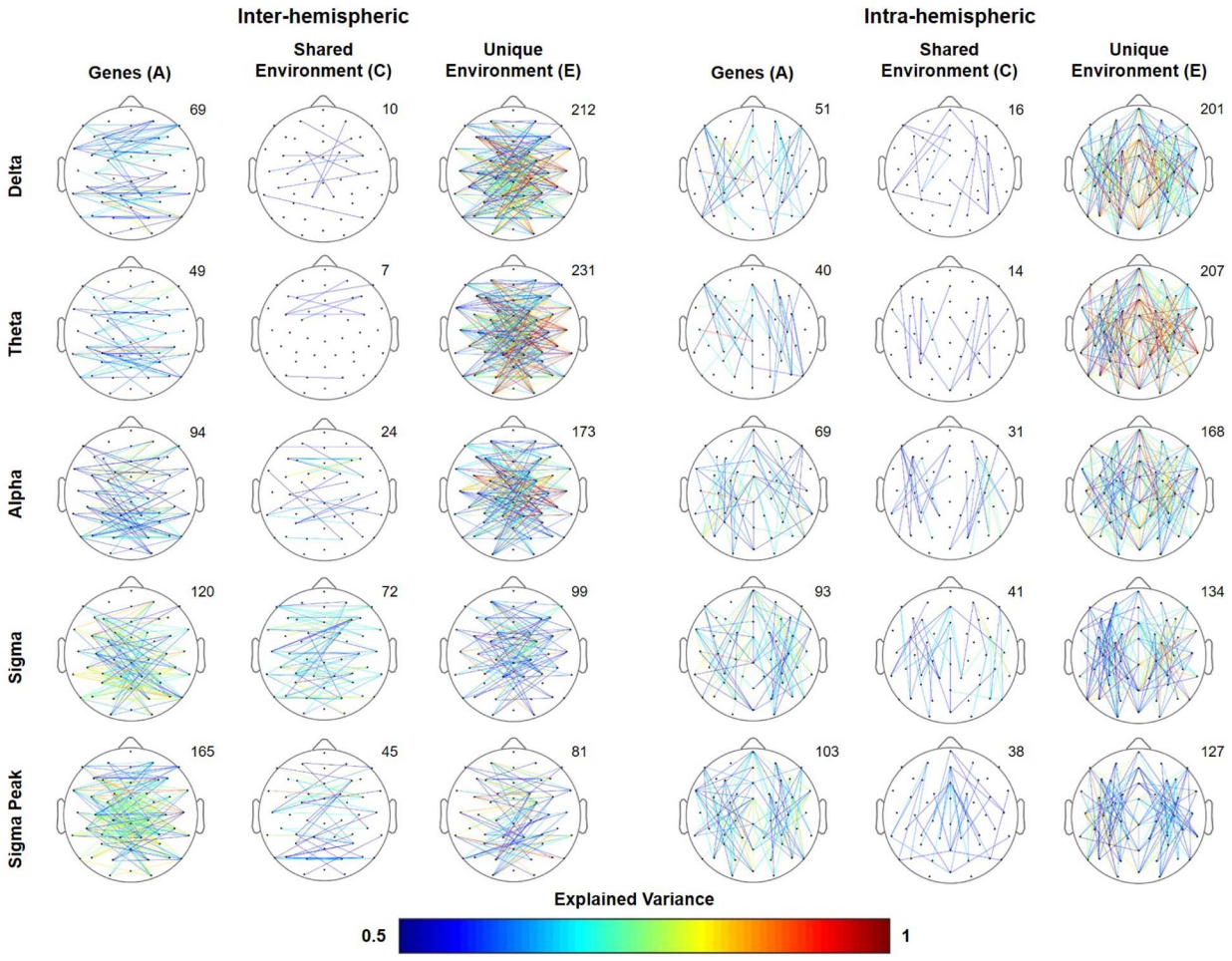

Figure 2. Topographic distribution of the results from structural equation modeling (SEM) shown for interhemispheric (left panel) and intrahemispheric (right panel) connections separately, and delta to sigma bands (first to fourth row) during NREM sleep as well as sigma peak (fifth row). The first column shows the contribution of genetic factors (latent factor A), the second column shows the contribution of environmental factors shared among twins (C), and the third column shows the contribution of environmental factors unique to each twin (E). The color corresponds to the magnitude of the contribution with warm tones representing large values (close to 1) and cool tones representing lower values (close to 0.5). Only connections with coherence values >0.2 and a contribution >0.5 for the shown factor are depicted (the number of connections with more than half the variance explained by that factor shown next to each map).

et al. 2019) and a wealth of studies examining the heritability of such traits show a significant contribution of unique environmental factors to personality traits (Plomin et al. 2008). One possible hypothesis is that functional brain connectivity, shaped by unique environmental influences, is unique to an individual and a potential substrate of personality. However, what these environmental influences might be remains largely unknown. Several environmental factors including stress and child–parent interactions have been shown to affect brain development (Marshall et al. 2008; McEwen 2011). Marshall et al. (2008) found that previously institutionalized children placed into foster homes at an earlier age had increased EEG alpha power and decreased short-distance alpha and beta EEG coherence during waking as compared with children with an older age at placement. Furthermore, they report that this effect was more robust for EEG coherence than for EEG power. However, it is not only highly adverse and dramatic life events that may impact brain development, but also subtle influences during sensitive periods can have long-term effects detectable later in life. This was demonstrated by a study showing that the level of caregiver support provided during a stressful task measured in early childhood is significantly associated with hippocampal volume growth across school age and early adolescence (Luby et al. 2016).

Our findings are in line with results from resting-state MRI studies which typically show a high impact of unique environmental factors and a low to moderate genetic influence on functional connectivity (Fu et al. 2015; Reineberg et al. 2018). In the study by Fu et al. (2015), which examines a sample of adolescents between 12 and 19 years of age, the genetic contribution, however, varies between the examined brain networks and reaches its highest values for sensory networks, which develop early in life (Antonini and Stryker 1993). The authors, thus, argue that such networks are more crucial to survival and, therefore, might have a stronger genetic control (Fu et al. 2015). Networks involved in cognition, on the other hand, mature later in life and are, therefore, exposed to environmental influences to a greater extent (Fu et al. 2015). In our analysis of sleep EEG

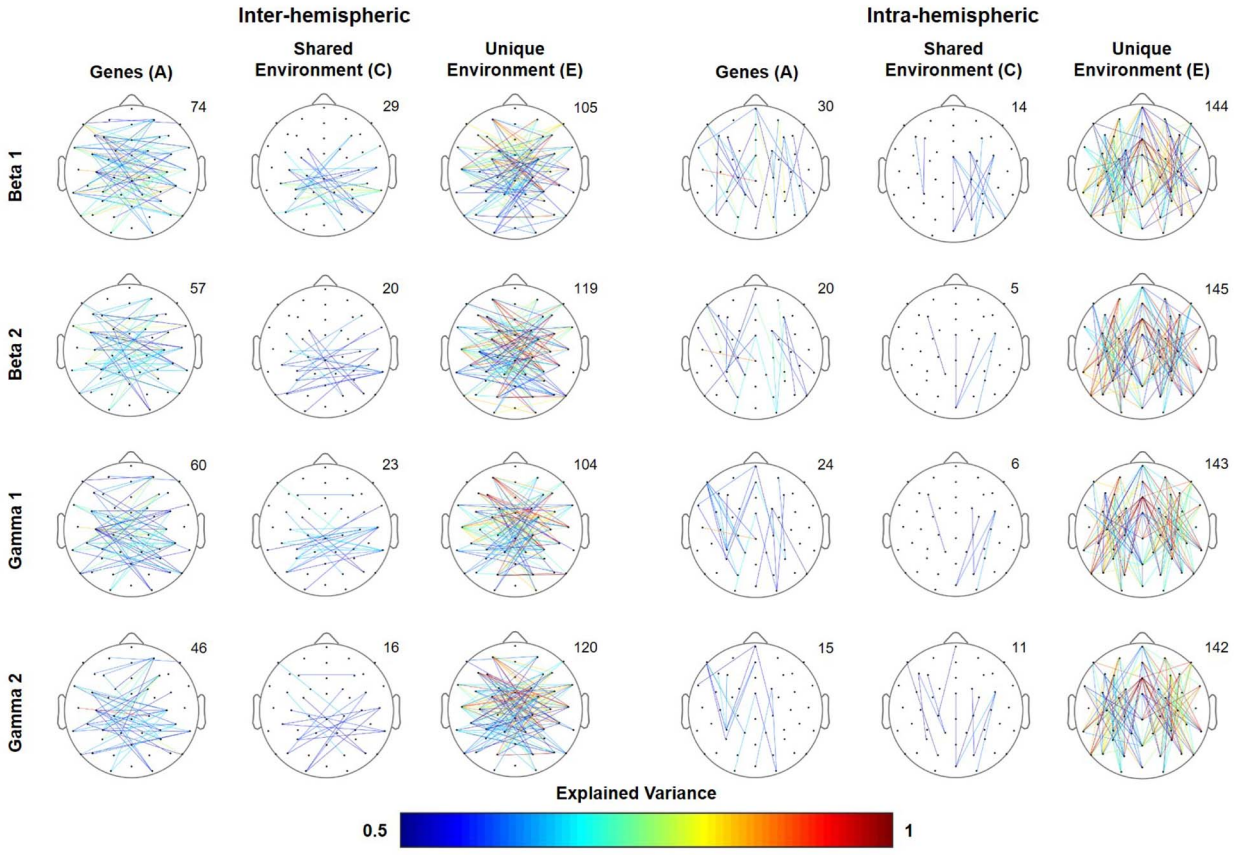

Figure 3. Topographic distribution of the results from SEM shown for interhemispheric (left panel) and intrahemispheric (right panel) connections separately, and beta 1 to gamma 2 bands (first to fourth row) during NREM sleep. The first column shows the contribution of genetic factors (latent factor A), the second column shows the contribution of environmental factors shared among twins (C), and the third column shows the contribution of environmental factors unique to each twin (E). The color corresponds to the magnitude of the contribution with warm tones representing large values (close to 1) and cool tones representing lower values (close to 0.5). Only connections with coherence values >0.2 and a contribution >0.5 for the shown factor are depicted (the number of connections with more than half the variance explained by that factor shown next to each map).

coherence, the genetic contribution reaches its highest values in the sigma band as well as for sigma peak coherence, possibly suggesting a moderate genetic control of the thalamocortical network, which relays sensory information to the cortex, but at the same time serves as an integrative hub for information processing across networks (Hwang et al. 2017). Nonetheless, what is clear from our study, experimental studies in animals (e.g., Rakic 1988; Rakic et al. 1991; Catalano and Shatz 1998) and brain imaging studies (e.g., Fu et al. 2015; Reineberg et al. 2018) is that brain plasticity allows for the brain to be shaped in response to environmental influences.

What has been unambiguously shown thus far is that sleep mirrors neurodevelopmental processes (e.g., Feinberg et al. 1990; Buchmann et al. 2011; Tarokh et al. 2014). Our study adds to this knowledge and provides support for the neurodevelopmental studies described above. Taken together, this study shows that, in the critical period of human adolescence encompassing turbulent changes in behavior and function, sleep EEG power, a measure reflecting the number of neurons in neuronal populations firing in synchrony (Nunez and Srinivasan 2006), is largely genetically determined (Rusterholz et al. 2018), whereas coherence, a measure reflecting the interaction between neuronal networks (Nunez and Srinivasan 2006), is shaped through interaction with environment.

Limitations

Several limitations are associated with the current study. First, the latent factor E is a measure of both unique environmental contribution to a phenotype combined with measurement error. Therefore, we cannot rule out the possibility that it is signal noise rather than unique environmental factors that account for the large E values that we observe. However, we believe that our results are not subject to significant measurement noise for three reasons: (1) we went through great effort to ensure that the analyzed data are artifact-free (2) previous analyses of this data set show high heritability of sleep EEG power (Rusterholz et al. 2018) and (3) coherence values are stable across two consecutive nights as reflected in high ICC values. A further limitation is that we were not able to examine differences in heritability between genders due to the small sample size. However, data from Beijsterveldt et al. (1998) show no evidence for gender differences in heritability of wake EEG coherence. Finally, a highly polemized issue associated with EEG coherence is the

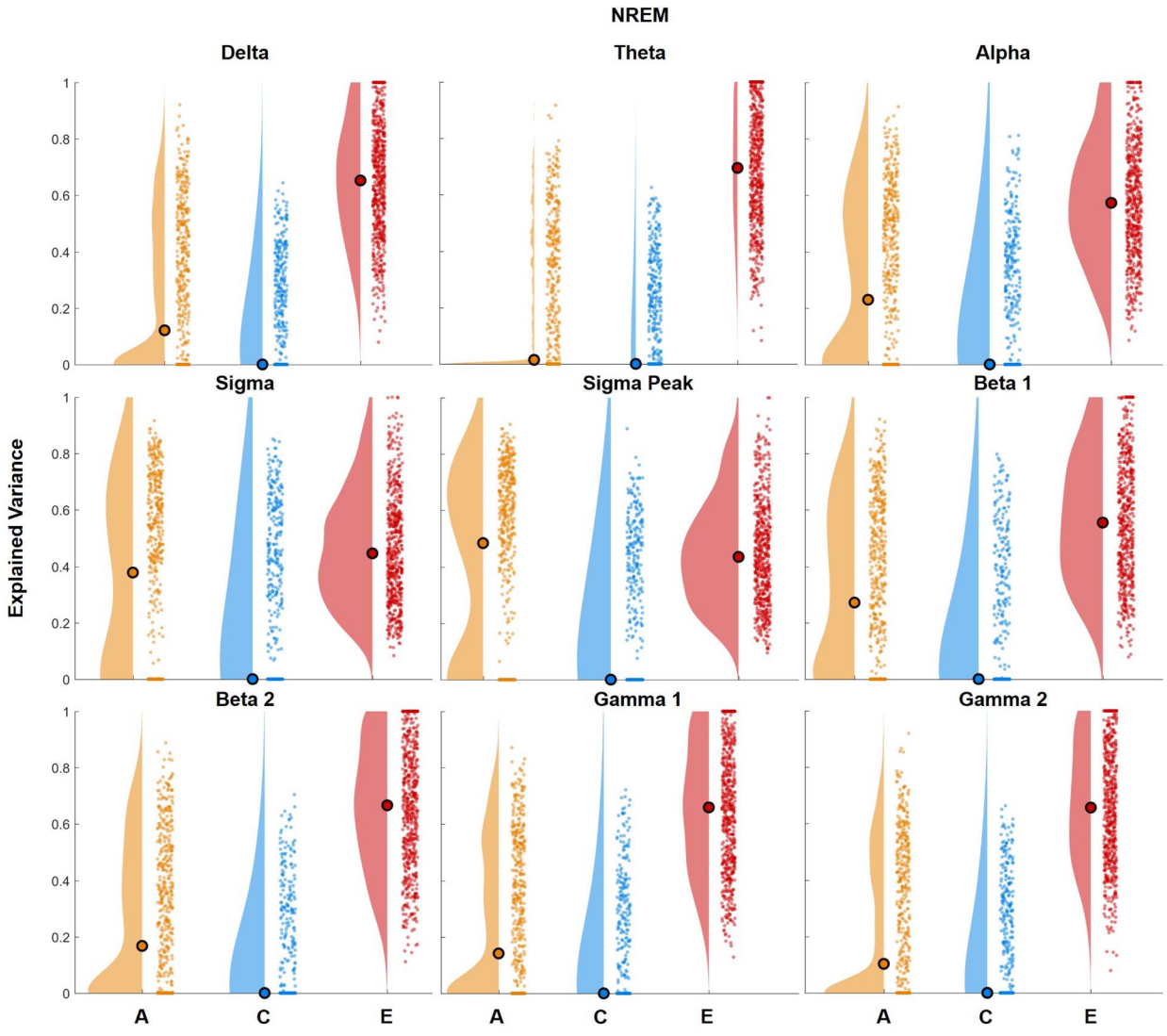

Figure 4. Raincloud plots (Allen et al. 2019) showing the distribution of the results from SEM across all 559 connections for all frequency bands during NREM sleep and sigma peak coherence including contributions from genetic factors (latent factor A), environmental factors shared among twins (C), and environmental factors unique to each twin (E). In each plot, the distribution of the data is shown in a split-half violin. The scattered dots represent the values for individual connections and the circle in the middle depicts the median value.

choice of the EEG reference, as this will impact the volume conduction contamination and the measured coherence values (Nunez and Srinivasan 2006). Volume conduction effects arise from the different electrical properties of the brain tissues and can artificially inflate coherence between electrodes with very small (<10 cm) (Nunez et al. 1997, 1999) or very large (>20 cm) separations (Srinivasan et al. 2007). To minimize volume conduction effects on our results, we only included those electrode pairs with a distance between 10 and 20 cm and we make use of the average reference, which has been shown to approximate absolute potentials if the number of electrodes is large enough (Srinivasan et al. 1998), and might, therefore, be the best choice for high-density EEG data. Although there are numerous alternative measures of functional brain connectivity (e.g., phase synchronization; summarized in Sakkalis 2011), the majority of EEG studies apply coherence. Therefore, in order for our findings to be comparable to previous work and applicable, we use coherence as our measure of connectivity.

Conclusions

We add to the existing literature by showing that the genetic contribution to sleep EEG coherence in adolescence is low for band coherence, but moderate for sigma peak coherence. Given the implication of sleep EEG coherence in psychiatric disorders and its direct relation to brain connectivity, understanding the factors contributing to sleep EEG coherence and its maturation are of great importance. That environmental influences can regulate gene expression in neurons has been known for a long time, and complex disorders such as schizophrenia have been associated with both genetic risk as well as environmental experiences (Wiesel 1994). Numerous studies have supported the notion that the structural aspects of brain networks are shaped

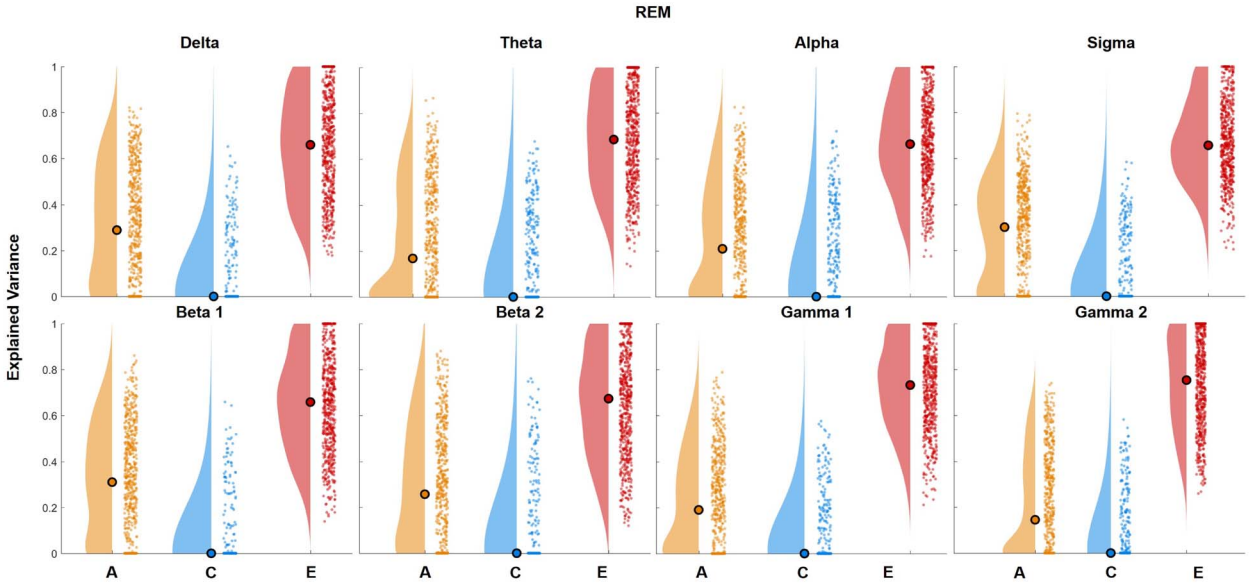

Figure 5. Raincloud plots (Allen et al. 2019) showing the distribution of the results from SEM across all 559 connections for all frequency bands during REM sleep including contributions from genetic factors (latent factor A), environmental factors shared among twins (C), and environmental factors unique to each twin (E). In each plot, the distribution of the data is shown in a split-half violin. The scattered dots represent the values for individual connections and the circle in the middle depicts the median value.

Table 2 Heritability estimates for the NREM sleep delta band from our study contrasted to heritability estimates for the delta band from Beijsterveldt et al. (1998), a previous study investigating heritability of 3 min of eyes closed wake EEG coherence in 16-year-old twins (213 adolescent twins; mean age = 16.8 years; SD = 0.55). We note the use of average reference in our study compared with linked earlobes in the Beijsterveldt et al. study. The estimates are shown only for those connections examined by Beijsterveldt et al. (1998) and we note the use of the full ACE model in the values that we report for our study as opposed to using the model with the best fit to make our results comparable to Beijsterveldt et al. (1998)

	Heritability estimate			Heritability estimate	
Left-hemispheric connection	Markovic et al.	Beijsterveldt et al.	Right-hemispheric connection	Markovic et al.	Beijsterveldt et al.
Fp1-F3	0.30	0.52	Fp2-F4	0.18	0.54
Fp1-C3	0.71	0.52	Fp2-C4	0.86	0.43
Fp1-P3	0.51	0.30	Fp2-P4	0.73	0.41
F3-O1	0.36	0.44	F4-O2	0.68	0.43
C3-O1	0.75	0.55	C4-O2	0.00	0.56
P3-O1	0.08	0.52	P4-O2	0.06	0.36

by our genes (e.g., Rakic 1988), whereas the fine modulations of connectivity patterns happen through the interaction with the environment (e.g., Rakic 1988; Rakic et al. 1991; Catalano and Shatz 1998). This interaction not only undergoes critical periods during brain development creating windows of susceptibility to diseases, but also opportunities and targets for early intervention and prevention.

Supplementary Material

Supplementary material is available at *Cerebral Cortex* online.

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