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Development and genetics of brain temporal stability related to attention problems in adolescent twins

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ABSTRACT

The brain continuously develops and reorganizes to support an expanding repertoire of behaviors and increasingly complex cognition. These processes may, however, also result in the appearance or disappearance of specific neurodevelopmental disorders such as attention problems. To investigate whether brain activity changed during adolescence, how genetics shape this change, and how these changes were related to attention problems, we measured EEG activity in 759 twins and siblings, assessed longitudinally in four waves (12, 14, 16, and 18 years of age). Attention problems were assessed with the SWAN at waves 12, 14, and 16. To characterize functional brain development, we used a measure of temporal stability (TS) of brain oscillations over the recording time of 5 min reflecting the tendency of a brain to maintain the same oscillatory state for longer or shorter periods. Increased TS may reflect the brain's tendency to maintain stability, achieve focused attention, and thus reduce "mind wandering" and attention problems. The results indicate that brain TS is increased across the scalp from 12 to 18. TS showed large individual differences that were heritable. Change in TS (alpha oscillations) was heritable between 12 and 14 and between 14 and 16 for the frontal brain areas. Absolute levels of brain TS at each wave were positively correlated with attention problems but not significantly. High and low attention problems subjects showed different developmental trajectories in TS, which was significant in a cluster of frontal leads. These results indicate that trajectories in brain TS development are a biomarker for the developing brain. TS in brain oscillations is highly heritable, and age-related change in TS is also heritable in selected brain areas. These results suggest that high and low attention problems subjects are at different stages of brain development.

1. Introduction

ADHD is a highly prevalent neurodevelopmental disorder that has been the target of many (neuro)biological investigations. One important feature of ADHD is that during adolescence and into young adulthood a decrease in prevalence is observed (Faraone et al., 2006; Hart et al., 1995). Persistence of ADHD symptoms is generally low (ranging 15–65%, depending on rater type and the threshold in the definition of persistence) (Faraone et al., 2006). At the same time, the brain shows evidence for large developmental changes, as revealed in anatomical (imaging) studies (Casey et al., 2000; Fornari et al., 2007; Giedd and Rapoport, 2010; Huttenlocher, 1979; Iglesias and Villa, 2006). Cortical thickness developmental trajectories suggested that ADHD subjects show a developmental delay compared to controls (Castellanos et al., 2002; Shaw et al., 2007). This may explain part of the relatively low persistence of ADHD symptoms, or the possible reduced experience of symptom severity (Faraone et al., 2006).

Symptoms of ADHD include cognitive elements, foremost attention deficits and executive function (Barkley, 1997). What brain processes underlie the brain tendency to lose focus has become the focus of recent investigations (e.g., (Christoff, 2012; Mason et al., 2007; Weissman et al., 2006). One specific line of research investigates spontaneous brain activity, including resting-state dynamics of brain activity. These investigations have revealed that an essential property of the human brain is to continuously fluctuate in activity level. Patterns of temporal covariation in brain activity have revealed spatially distributed networks (Resting State Networks (Damoiseaux et al., 2006; Raichle et al., 2001; Stevens et al., 2009)). These networks are surprisingly fixed and consistent spatially within and between individuals. However, brain activity shows surprising instability and fluctuation along the *temporal* dimension with fast switches in brain states and relatively stable periods in-between (Ville et al., 2010). It has been suggested that these continuous fluctuations are the source of mind wandering and inattention (van Leeuwen and Smit, 2012).

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Fluctuations in brain activity do not show a simple Gaussian distribution but show temporal correlations with random walk signature. Brain activity signals in EEG, MEG and fMRI have been shown to follow power-law spectra $P = 1/f^{\alpha}$ where α is the power-law exponent and reflects the speed of decay in autocorrelation (He, 2014; He et al., 2010; Linkenkaer-Hansen et al., 2007; Smit et al., 2011; Ville et al., 2010). This power-law is consistent with the brain being in a so-called critical state (Bak and Tang, 1987; Haldeman and Beggs, 2005; Poil et al., 2012). Other lines of research found evidence for criticality via avalanche dynamics with a similar scale-free properties (Haldeman and Beggs, 2005; Palva et al., 2013; Petermann et al., 2009; Shew et al., 2011, 2009). Complex systems like the brain that are at or near a critical state have been shown to possess favorable computational properties, including high dynamic range in representational capacity and flexibility (Kello et al., 2010; Kinouchi and Copelli, 2006; Poil et al., 2012). Interestingly, however, the exponent \alpha is not a fixed value, but shows strong interindividual differences that are heritable and stable (Linkenkaer-Hansen et al., 2007; Smit et al., 2011). Since \alpha reflects the speed of decay in autocorrelation—with high values reflecting stronger autocorrelation, longer propagation of brain states and thus stronger deviation from baseline—variability in \alpha may reflect the temporal stability (TS) of the brain, where high values may reflect increased wandering of brain states (Smit et al., 2013). Moreover, previous results have shown that individual variation in the exponent \alpha is able to predict temporal dynamics in simple cognitive and motor tasks (Palva et al., 2013; Smit et al., 2013).

For these reasons, we hypothesize that brain TS might be a valuable endophenotype for the tendency of the brain to wander, and thus attention problems. Due to the high temporal resolution of EEG, endophenotypes extracted from brain activity that reflect temporal dynamics may be particularly useful. In addition, many EEG based parameters are highly heritable (de Geus, 2010), fulfilling the one requirement to serve as endophenotype for heritable traits like attention problems. Variation in attention problems measured with self-report and mother rating questionnaires has been shown to be a highly genetic trait (Derks et al., 2007; Hudziak et al., 2005; Polderman et al., 2007). Brain TS has also been shown to be heritable at 16 to 19 years of age. Moreover, TS of oscillations in alpha and beta bands have been shown to have an inverted-U developmental curve across the lifespan (Smit et al., 2011). Late adolescence (age 16 to 18) showed a particularly strong development in TS in the alpha band.

Here, we will expand findings from the extant literature in several ways. First, we will establish whether the previously observed change in brain TS also shows heritability and change in earlier puberty by including ages 12 and 14). Next, we will establish whether change in TS is heritable. Next, we will investigate if brain TS is correlated with attention problems. Finally, we will investigate whether developmental trajectories in TS are related to attention problems, since evidence from MRI derived anatomy suggests that ADHD sufferers may show lagged brain development compared to normal controls (Castellanos et al., 2002). To achieve these aims, we will use a large longitudinal EEG twin dataset to investigate the genetics of brain TS development, and whether TS develops differentially in high and low attention problem subjects (Shaw et al., 2006). Although the present study investigates a population-based sample rather than an ascertained case-control sample, the results may indicate how subclinical variation in attention problem scales find its origin in variation in brain temporal dynamics.

2. Methods

2.1. Participants

Subjects were adolescent twins participating in a longitudinal study of Genetics, Neurocognition, and Adolescent Substance Abuse (GNASA). All participants were recruited from the local population using a database of state birth records, therefore, the sample is largely representative of the general population. Exclusion criteria were minimal and included a history of serious head trauma and health conditions precluding a laboratory visit or the ability to perform the experimental tasks (e.g. severe visual impairment or mental retardation). The first (baseline) assessment was conducted at age 12, and follow up assessments were conducted at ages 14 and 16. A substantial reduction of the sample size at age 16 was caused primarily by funding interruption, rather than participants' drop-out. SWAN questionnaire was introduced during the first (age 12) assessment wave and administered to 434, 592, and 369 subjects at ages 12, 14, and 16, respectively. Zygosity was determined using a set of >1000 DNA markers. The study was approved by Washington University Institutional Review Board, and written informed assent and consent were obtained from adolescent participants and their parents, respectively, after complete description of the study to the subjects and their parents.

2.2. Attention problems

Dimensional measures of Attention (ATT) and activity (ACT) were obtained using The Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Scale (SWAN-AP) (Polderman et al., 2007; Swanson et al., 2012). The SWAN-AP contains 18 items to assess attention (9 items) and activity/impulsivity (9 items) and is designed to capture the full range of variability in these traits, including both normal and symptomatic. Twins' mothers were asked to indicate on a 7-point Likert scale how each twin (rated separately) compared to "other children the same age" over the preceding month. Item scores were centered around zero with scores ranging from −3 to 3. The questions were framed such that it was beneficial to be "far above" average (e.g., "organize tasks and activities", "stay seated (when required by class rules/social conventions")). The nine items on each scale were summed to create a total score (possible range 9–63 for each subscale). To facilitate the comparison with clinical studies that used symptomatic measures, in the present analyses all items were reverse-coded, such that higher scores correspond to the dysfunctional end of the distribution (inattention and hyperactivity), while lower scores correspond to the adaptive end (high attentional skills and well-regulated behavior). The SWAN-AP has been found to have strong internal consistency (0.80 to 0.95), acceptable test-retest reliability (0.72–0.90), construct validity and a normal distribution in previous studies (Arnett et al., 2013; Lakes et al., 2012; Polderman et al., 2007; Reiersen and Todorov, 2013; Swanson et al., 2012). In a previous analysis of ATT and ACT scales in the present data, Crobach's alpha ranged from 0.93 to 0.96 for two subscales (Peng et al., 2015). Its two-factor structure was confirmed at all three age points (CFI ranged from 0.986 to 0.989, TLI ranged from 0.986 to 0.988) by conducting Confirmatory Factor Analysis (Peng et al., 2015).

ADHD symptoms and diagnoses were derived from Missouri Assessment of Genetics Interview - Adolescent Version (MAGIC-A) administered to participants in person during each lab visit. MAGIC is a validated semi-structured, glossary-based diagnostic interview based on the Diagnostic Interview for Children and Adolescents (DICA)(Todd et al., 2003). MAGIC allows the assessment of the structure of the diagnostic domains as DSM-IV categories, spectra of related diagnoses, or continuous variables.

2.3. EEG registration and cleaning

The EEG was recorded from 30 scalp locations according to the extended 10–20 system using an elastic cap with Ag/AgCl electrodes and a ground electrode on the forehead, with high- and low-pass filters set at 0.05 and 100 Hz, respectively. The left mastoid served as reference, and an averaged mastoid reference was digitally computed off-line using the right mastoid recording as a separate channel. Vertical electro-oculogram recording was used for eyeblink artifact correction using a regression-based procedure (Semlitsch et al., 1986).

2.4. Brain Temporal Stability (TS)

TS was assessed as the long-range temporal (auto)correlations in the modulation of oscillation amplitude of alpha (6–13 Hz), beta (15–25 Hz), and theta oscillations (3–5.6 Hz). A lower alpha bound than regularly was used to capture the slower oscillation frequency seen in younger subjects (Smit et al., 2012). By filtering brain EEG signals into the frequency of interest and using the Hilbert transform, the instantaneous amplitude of the oscillations (or envelope) can be determined. As Fig. 1A shows, the amplitude envelope of oscillations show continuous change, but also periods (bursts) of high amplitude with irregular interval and duration. These bursts cause the autocorrelations. A constant (power-law) decay in autocorrelation is present when power spectra show a linear relation between power and frequency in log-log space: $P(f) \propto 1/(f\hat{}\beta) = f\hat{}(-\beta)$. Beta is the power-law exponent and represents the slope of the regression line fitted to the power spectrum (Smit et al., 2013, 2011). Alternatively, Detrended Fluctuation Analysis (DFA) (Linkenkaer-Hansen et al., 2001; Peng et al., 1995) may be a more robust estimation method where the spectral power-law exponent β relates linearly to the DFA exponent α as $\beta = 2\alpha\text{-}1$. Subjects with high DFA exponents show longer stable periods of alpha oscillatory brain activity than subjects with low DFA exponents. An exponent of $\backslash alpha = 0.5$ has no autocorrelation as in white noise.

DFA calculates exponent α by first integrating the signal, dividing it into windows of a specified size in which the integrated signal is linearly detrended, and computing the root-mean-square (RMS) deviation. The window is moved along the signal and the RMS of adjacent windows is averaged. This process is repeated for logarithmically increasing window sizes. The current analysis of the amplitude modulation of oscillations used windows from 1 s to 20 s. The results did not critically depend on choice of the upper or lower limit (viz., windowing 1 s to 60 s correlated $r = 0.96$ with 1 s to 20 s). The lower edge was chosen so as to remove the effect of the lower frequency filter edge (at 8 Hz). Fig. 1B shows how this analysis works for the sample presented in Fig. 1A.

2.5. Genetic twin modeling

To handle the complex covariance structures present in twin-family datasets with missing data, we used structural equation modeling implemented in R as freely available package OpenMx (Boker et al., 2011) to estimate MZ and DZ correlations using full information maximum likelihood (FIML). The likelihood of a model-based *expected* covariances and means are compared with the *observed* data by applying the FIML function:

$$-2LL = \sum_{i=1}^{N} k_i \cdot log(2\pi) + log(\,det(\Sigma)) + (x_i - \mu_i)\Sigma^{-1}(x_i - \mu_i)^T$$

where –2LL is –2 times the log of the likelihood, i is the iterator over independent observations (families), k_i is the number of non-missing observations in each family, $det(\Sigma)$ is the determinant and Σ^{-1} the inverse of the model estimated covariance matrix Σ of order $(k_i \times k_i)$, and x_i and μ_i are the $(1 \times k_i)$ row vectors with observed data and expected means, respectively. SEM models are constructed so as to specify expected means and (co)variances from free parameters, which may include correlations, grand-average means, regression betas, or more complex algebraic formulae. Maximally likely parameter estimates are found by stepwise moving through parameter space and stopping at minimum −2LL.

We fitted univariate models to both attention problems scales across three measurement waves for which attention problems data was available (12, 14, and 16 years), and the same univariate model to average TS across the 30 leads of the brain, for each frequency band (theta, alpha, beta). These models were so-called saturated models which estimated a male MZ, female MZ, male DZ, female DZ, and opposite sex correlations, variances for males and females separately, a grand mean, an age fixed effect, and a sex fixed effect.

By fixing parameters to zero or equating estimated parameters, a nested simpler model is created with an increased −2LL. The difference in −2LL is asymptotically chi-square distributed with the number of constrained parameters as the degrees of freedom. When the model simplification does not yield a significant increase in −2LL, then the simpler model is retained by the rule of parsimony. Note that SEM using FIML is asymptotically equivalent to the least-squares model fitting in specific cases, but in general naturally handles missing data with uneven sample sizes, correlated observations, and can be used for confirmatory factor analysis.

To test whether differences existed in the genetic structure between males and females, we first equated the variances across males and females, next equated all DZ/sibling correlations (i.e., DZM, DZF, OS) as well as MZ correlations (MZF, DZF). The models were fitted to summary variables only, to reduce the number of tests (i.e., average TS across all ages and leads, and average attention problems across all ages).

After saturated model fit, we applied variance decomposition models to estimate the relative contribution of genetic (heritability) and environmental effects to the trait variance, retaining only significant differences between males and females (e.g., if variance of the trait differed, this was retained in the variance-decomposition

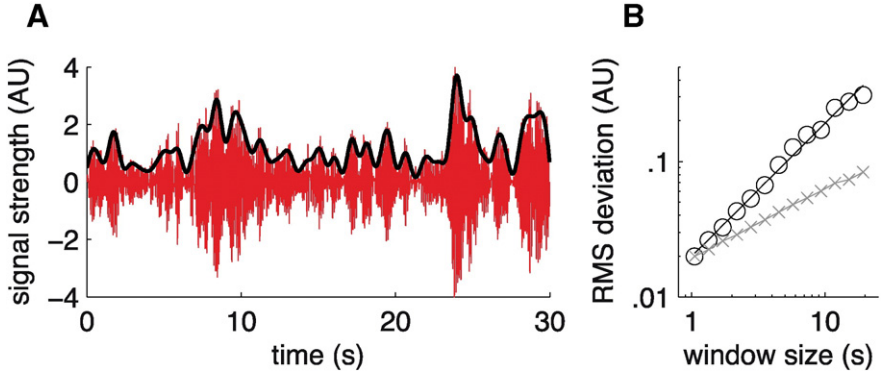

Fig. 1. Power-law scaling in brain oscillations. (A) A compressed view of an alpha (6–13 Hz) filtered EEG signal shows clustered bursts of high amplitude (red). The amplitude envelope (black) is determined using the Hilbert transform: $A(t) = |s(t) + iH(s)(t)|$ where $s(t)$ is the original (filtered) signal over time t, i is sqrt(−1), and $H(s)$ is the Hilbert transform of signal s. This signal was entered into detrended fluctuation analysis for estimating TS. The amplitude envelope shown here was smoothed for illustration purposes only. (B) DFA is calculated by integrating the amplitude envelope of the oscillations, chunking into windows of variable sizes, calculating RMS deviation to the local regression, averaging across all chunks, and plotting the resulting averaged RMS against the window size. The slope of the linear fit reflects the level of autocorrelation (black circles), which is higher than the slope of the fit of filtered white noise (gray x's).

modeling). Resemblance (covariance) in psychological and psychophysiological traits between twins derive either from genetic relatedness or common (shared) environmental influences (Boomsma et al., 2002). If the correlation between DZ twins, who share on average 50% of their segregating genetic make-up, is half the correlation between MZ twins, who are genetically identical, this is seen as evidence for additive genetic influences (A). If the correlation between DZ twins or siblings is less than half the correlation between MZ twins this is seen as evidence for dominant (non-additive) genetic influences (D). If the correlations between MZ and DZ twins/siblings are comparable and nonzero this is evidence for common (shared) environmental influences (C) such as the shared family rearing environment. If the correlation between MZ twins is less than unity, this is taken as evidence for nonshared, unique environmental effects (E).

Broad-sense heritability is defined as the proportional contribution of genetic effects (A + D) to the total variance (A + C + D + E). In a twin-sibling design, however, no information is available to estimate the effects of C and D simultaneously. The relative size of the DZ to the MZ correlation is then used to guide which is selected. If the DZ correlation is less than half the MZ correlation, then the A + D + E factors are modeled. If it is more than half the MZ correlation, A + C + E are modeled. The variance decomposition model is graphically depicted in Fig. 2. Since there has been evidence for nonadditive genetic effects for TS, we fitted an ADE model with additive genetic, dominant genetic, and unique environmental effects for TS. For SWAN-AP, evidence for common environmental effects has been reported (Peng et al., 2015). Therefore, these models were ACE models. The models were tetravariate models across the four measurement waves for TS and trivariate models across three measurement waves for attention problems.

We applied Benjamini & Hochberg FDR correction at $q = 0.05$ across the 90 frequency and/or lead combinations when applicable (Benjamini and Hochberg, 1995).

2.6. Fixed effect modeling

Fixed effects (such as the effect of age) predicting dependent scores that violate the assumption of independency of residuals can be modeled efficiently with Generalized Estimating Equations (GEE). In the current dataset, both longitudinal modeling and repeated measures (within subject) are sources of violation of the independency assumption. In GEE, regression weights are estimated as in regular (logistic) regression as these are unbiased. The standard errors (SEs) of regression weights, however, are underestimated. Sandwich-corrected robust SEs are larger than their non-robust counterparts depending on the residual correlation within predefined clusters where correlation between observations are to be expected, such as families and repeated measures. We used GEE with the exchangeable correlation matrix, which estimates a single correlation across residuals within clusters (viz., family number). Even though the residual correlation matrix is in fact more complex than the single estimated working correlation (for example, within-subject correlations and MZ twin correlations are expected to be higher than other within-family correlations), the robust SEs are not affected by this misspecification (Minică et al., 2014).

2.7. Cluster permutation

A Monte-Carlo cluster permutation (Maris and Oostenveld, 2007) was performed to examine the relation between attention problems and developmental trajectories of the DFA exponents across the ages of 12 to 18. For this, we split the subjects into the top 25% and bottom 25% on attention problems. Standardized residuals were used after regressing out the effect of measurement wave (ages 12, 14, and 16). Subjects' average across all available time-points were used. Top (P25) and bottom (P75) were chosen within sex by ethnicity crosstabs in order to keep subgroups equally represented within high and low attention problems. This ensured that low and high SWAN-AP groups were not dominated by a single group. Note that this step did not remove the requirement of correcting for sex and ethnicity in the linear modeling.

Next, we performed GEE to establish whether dichotomized attention problems moderated the linear effect of age on TS at all 30 scalp signals. Cluster permutation was performed by calculating the residuals for the DFA exponent (TS) using sex and ethnicity for each channel for each subject. At the initial step, a cluster was obtained without permutation. In the present case, 30 GEE models were fit with age, attention problems-group and the age-by-attention problems-group interaction. All effects below $p = 0.01$ were considered significant, and a cluster defined of all significant nearest neighbors. The GEE robust-z values of the age-by-attention problems-group interaction were summed within the largest cluster.

Next, the attention problems group values were permuted 2000 times. The permutations were performed across families rather than across observations, which keep the complex within-family/within-subject correlational structure intact (including correlations across scalp channels). At each permutation, the same steps of calculating GEE robust-z scores for the age-by-attention problems-group interaction were obtained, summed across the largest cluster of significant effects (significance held constant at $p < 0.01$). The 2000 summed-z values represented the null-distribution for the largest cluster with the specific within-family/within-subject correlational structure. The summed-z value obtained in the initial step was tested against this distribution. Note that the level of significance at $p < 0.01$ if not true significance, but rather an arbitrary chosen value that defines cluster sizes. The empirical p-value of the cluster is obtained by comparison of the summed-z to the null-distributions of summed-z scores.

3. Results

3.1. Swan correlates with ADHD diagnosis

We examined the relation between SWAN-AP with ADHD diagnosis by running a *t*-test within age group (with GEE corrected p-values) and calculating effect size r_t. For all waves we found highly significant effects (wave 12: $t(432) = -8.31$, robust-$z = -9.9$, $p = 3.09\ 10^{-23}$, $r_t = 0.37$; wave 14: $t(586) = -5.71$, robust-$z = -12.0$, $p = 2.03\ 10^{-33}$, $r_t = 0.23$; wave 16: $t(365) = -5.60$, robust-$z = -12.6$, $p = 3.56\ 10^{-36}$, $r_t = 0.28$). Effect sizes were moderate.

3.2. Brain TS and attention problems development

Brain TS changed with age. Figs. 3–5 shows the histograms of the TS scores (left), the scalp topography, and the stepwise difference between 12 and 14, 14–16, and 16–18 years of age. Fig. 3 shows theta, Fig. 4 alpha, and Fig. 5 TS in beta oscillations. The TS topography (middle column) showed a consistently higher level of TS in posterior brain areas for both alpha and beta oscillations, regardless of age. Change between the measurement waves (right column) was quite diffuse, although TS increase was less in the most frontal areas for beta oscillations. For theta oscillations, increases were largely confined to left and right frontal areas. A linear regression of brain TS on age corrected for sex was significant for all leads in the alpha and beta bands (GEE robust $z > 3.93$, FDR corrected-$p < 8.2^{-5}$). For theta oscillations, the increase in TS was significant mainly in a cluster of bilateral frontocentral leads.

Attention problems decreased from 12 to 16 years in the SWAN-AP. The linear regression was highly significant (GEE robust $z = -5.11$, $p = 3.2^{-7}$). Fig. 6A shows the results. Attrition was assessed by checking for initial SWAN scores for dropout subjects compared to non-dropout with an unequal-variances paired *t*-test. The effect was not significant for 12–14 dropout ($t(104.5) = 0.37$)

but significant for 14–16 ($t(288.5) = 3.82$, $p = 0.0002$). However, the change between the ages were still significant when considering only subjects with data available at both waves (12–14: GEE robust-$z = -4.44$, $p = 0.000009$; 14–16: GEE robust-$z = -3.68$ $p = 0.0002$).

3.3. Genetic modeling and equality of correlations across sex

Table 1 shows the male and female variances and the test for equality of these. In no situation, sex variances were unequal after FDR correction. Correlations were not different for TS or SWAN-AP. The resulting

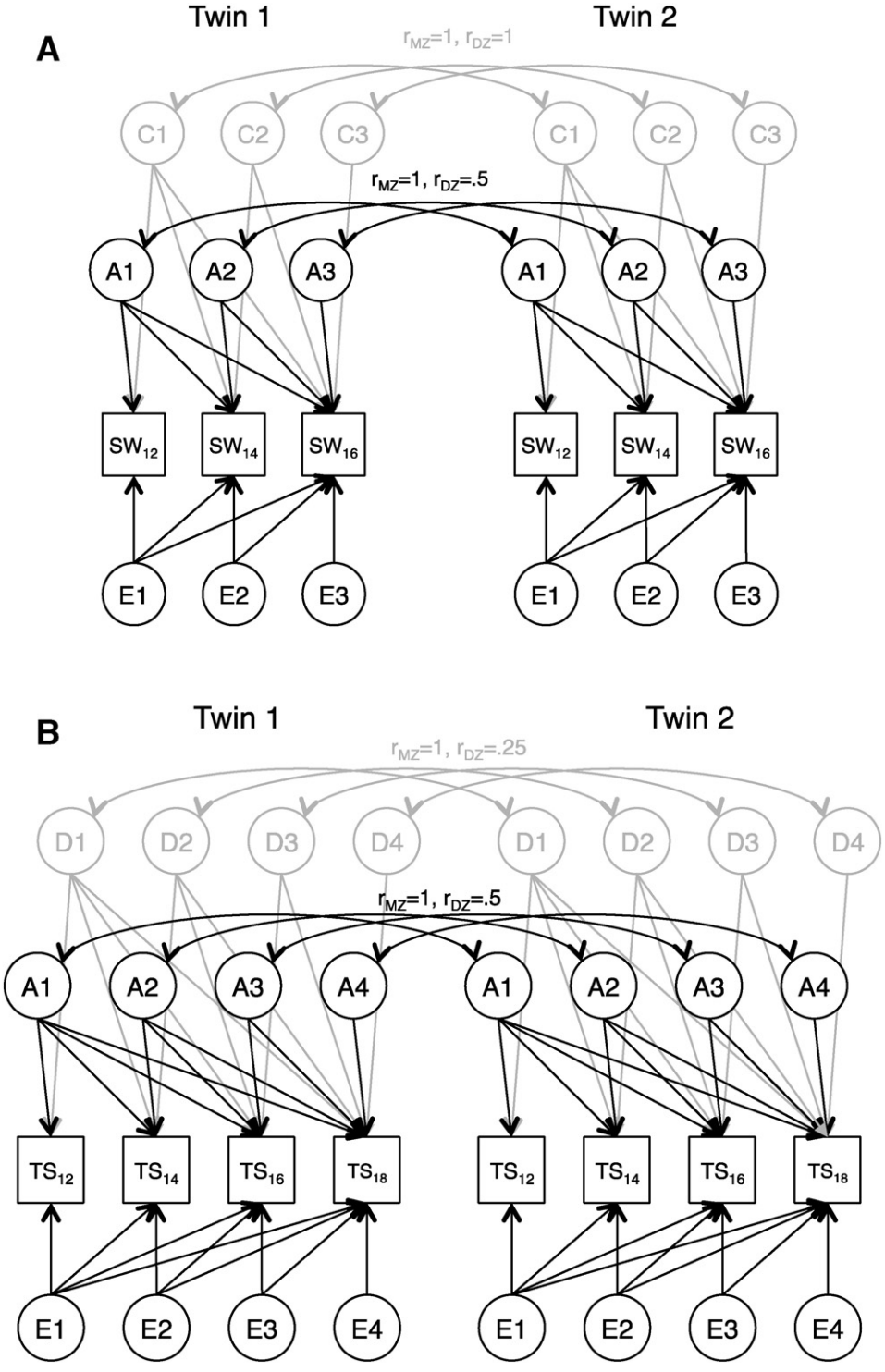

Fig. 2. Longitudinal ACE (for attention problems) and ADE (for brain TS) path models. A. Longitudinal ACE models were applied to the attention problems scale SWAN-AP using a so-called Cholesky decomposition. Additive genetic effects (A) correlate 1.0 between MZ and 0.5 between DZ twins. Unique environmental effects (E) are uncorrelated between all individuals. Common environment (C) are correlated 1.0 between all sibling types regardless of their genetic resemblance. B. ADE models were applied to brain TS for average values across the scalp as well as channel-by-channel. DFA exponents describing temporal stability in oscillation amplitude was analyzed per frequency (Theta: 3–5.5 Hz; Alpha: 6–13 Hz; Beta: 15–25 Hz). Additive genetic effects (A) correlate 1.0 between MZ and 0.5 between DZ twins. Nonadditive genetic effects (D) correlate 1.0 between MZ and 0.25 between DZ twin pairs. Unique environmental effects (E) are uncorrelated between all individuals. Broad-sense heritability is the combined effect of nonadditve and additive genetic effects (A plus D) relative to total trait variance.

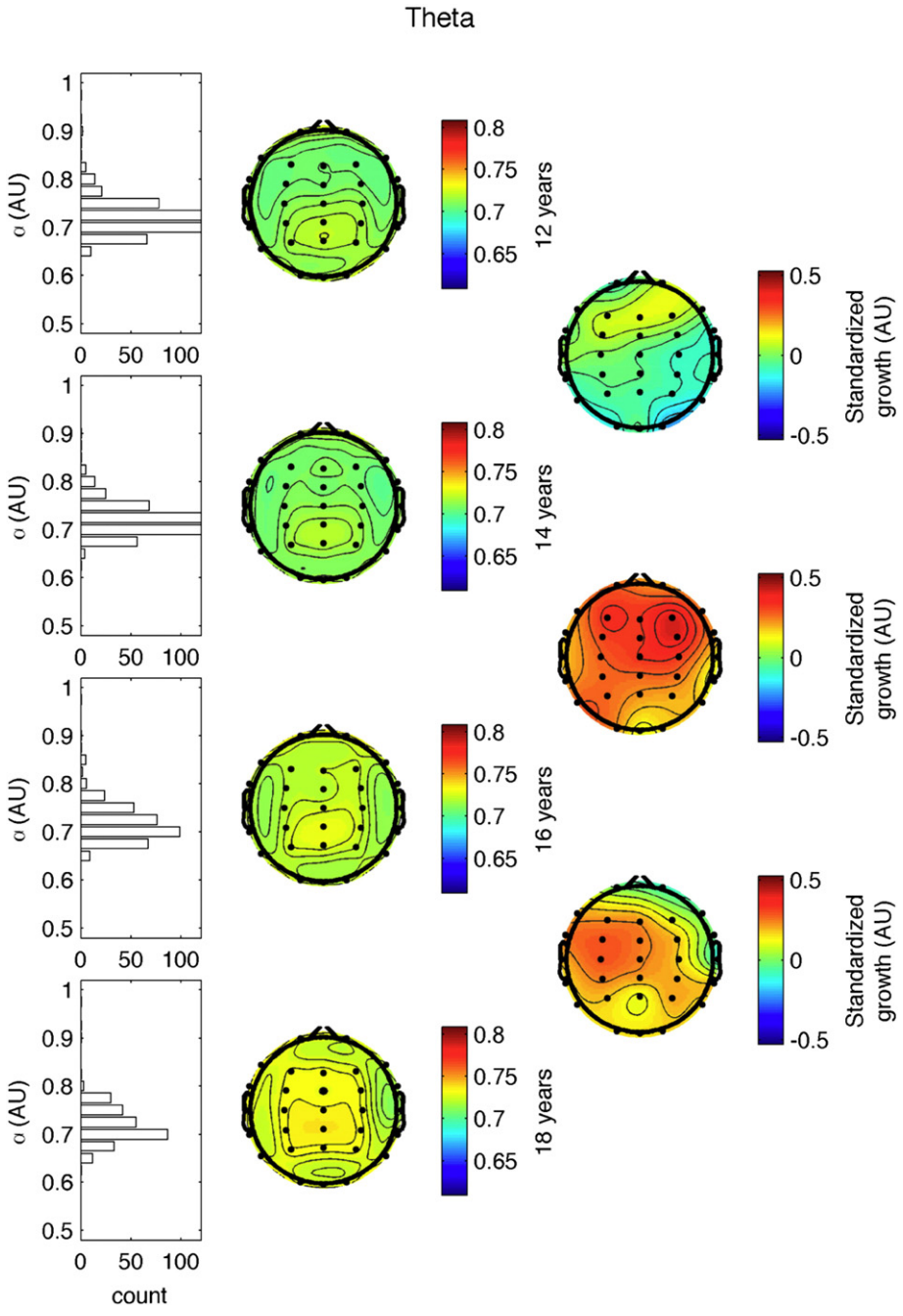

Fig. 3. Development of TS in theta oscillations. Each row represents the DFA exponents for a measurement wave (12, 14, 16, and 18 from top to bottom). Left are the histograms of TS (scalp wide average). Middle column are the scalp topographies. Right column are scalp topographies of the increase between measurement waves 12 to 14, 14 to 16, and 16 to 18, expressed as Cohen's d. Theta oscillation TS have a parietal maximum and show maximal increase between 14 and 16 (mostly frontal).

MZ and DZ twin correlations are shown in Table 1. Subsequent variance decomposition models assumed equality across the sexes. These correlations corroborate earlier findings in showing strong heritability for TS in alpha oscillations and – in many instances – DZ correlations that are lower than half the MZ correlations, indicating a presence of nonadditive genetic effects. These results in concordant with the extant literature (Derks et al., 2007; Hudziak et al., 2005; Linkenkaer-Hansen et al., 2007; Polderman et al., 2007).

3.4. Brain TS variability and heritability

Twin modeling proceeded with a tetravariate variance decomposition model with additive genetic, nonadditive genetic, and unique environmental effects (ADE model). These models showed that there is evidence for nonadditive genetic effects for TS for many leads and oscillation frequencies (Table 2) as tested by the omnibus effect of D. For alpha oscillation TS, D was significant for 22 of the 30 leads after FDR correction. For Beta oscillations, D was significant for 17 of the 30 leads. For theta oscillations, although D seemed present for almost all leads, it was not significant. Broad-sense heritability was significant for all leads in alpha oscillations, for 29 out of 30 leads for beta oscillations, but only 5 out of 30 leads for theta oscillations.

3.5. Attention problems heritability

There was no evidence for sex differences in attention problems. Heritability was estimated in trivariate longitudinal models (Table 1). SWAN-AP scores were highly heritable (Table 3) at all ages (12, 14,

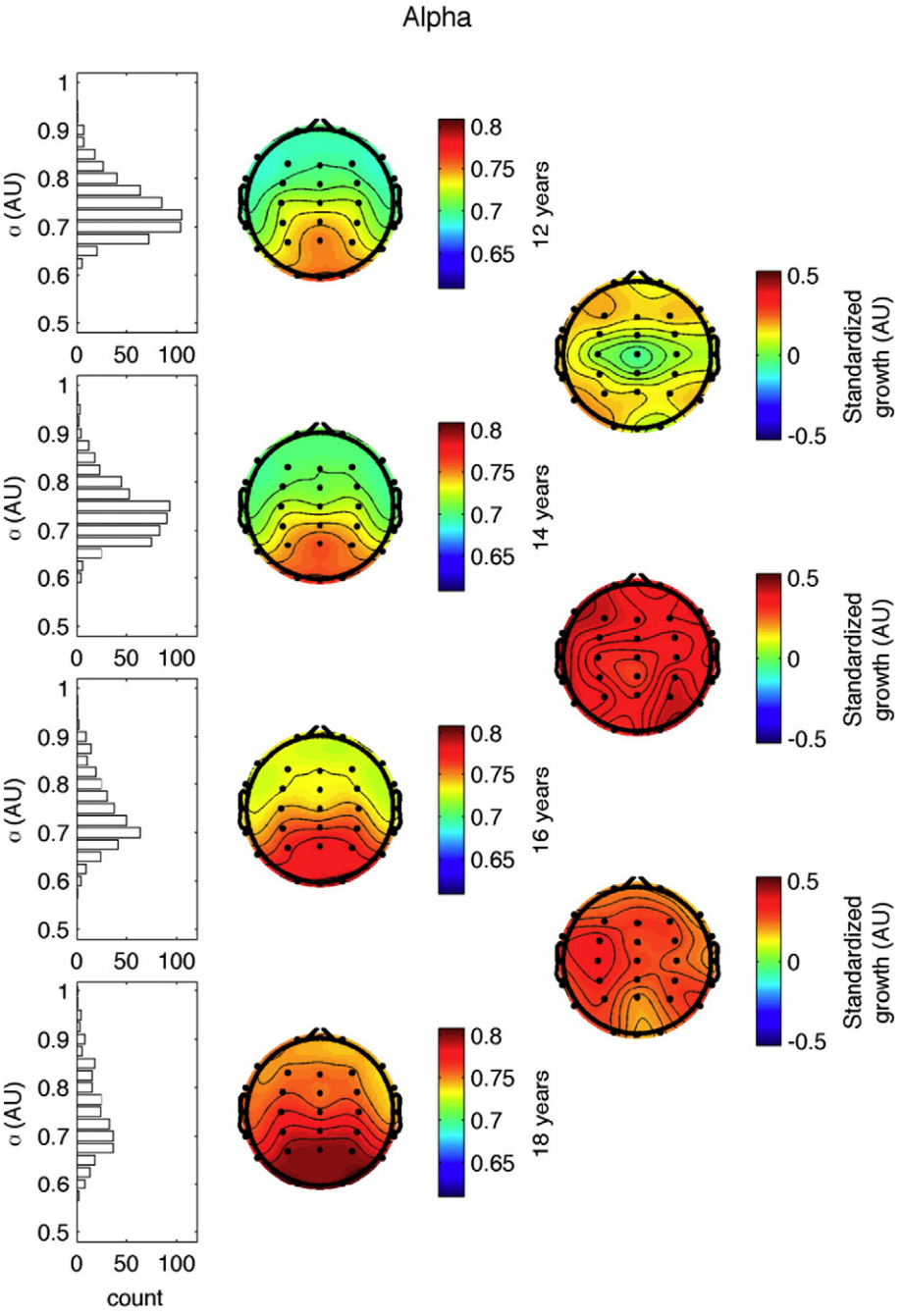

Fig. 4. Development of TS in alpha oscillations. See Fig. 4. Alpha oscillation TS have a clear occipital parietal maximum and show large increases with large effect sizes between 14 and 16. The increases are visible at all scalp locations. The scalp topography suggests a developmental lag for frontal areas.

16). C was significant for SWAN-AP in the omnibus test ($\chi^2(6) = 48.5$, $p < 0.001$). C was also significant for ages 14 and 16, but not for age 12. These findings have been reported earlier (Peng et al., 2015). The AE model as best fitting model at age 12 is consistent with earlier findings in large twin samples from other countries (Polderman et al., 2007). Due to the appearance of C at 14, heritability scores reduced for ages 14 and 16.

3.6. No significant correlation between attention problems and TS

To assess a direct effect of brain TS on attention problems, we fitted longitudinal common factor models. These models fitted a single factor for brain TS (across four waves) and a single factor for attention problems (across three waves), and subsequently estimated the correlation between the two factors. No significant correlation was found for any of the frequency bands. Although some correlations were significant at $p < 0.05$, these were not significant after FDR correction across the 30 leads. Correlations were at best modest ($r < 0.26$). Genetic and environmental correlations were also not significant for any of the genetic common factor models. Fig. 6B–C shows the topoplots for the phenotypic correlations.

3.7. Change in brain TS is heritable in specific regions

Change in TS from 12 to 14, 14 to 16, and 16 to 18 was available for 427, 291, and 119 subjects respectively. Change scores showed no evidence for effects of D or C (all $p > 0.12$, unadjusted), therefore, we continued with AE models. Brain TS for theta and beta oscillations showed

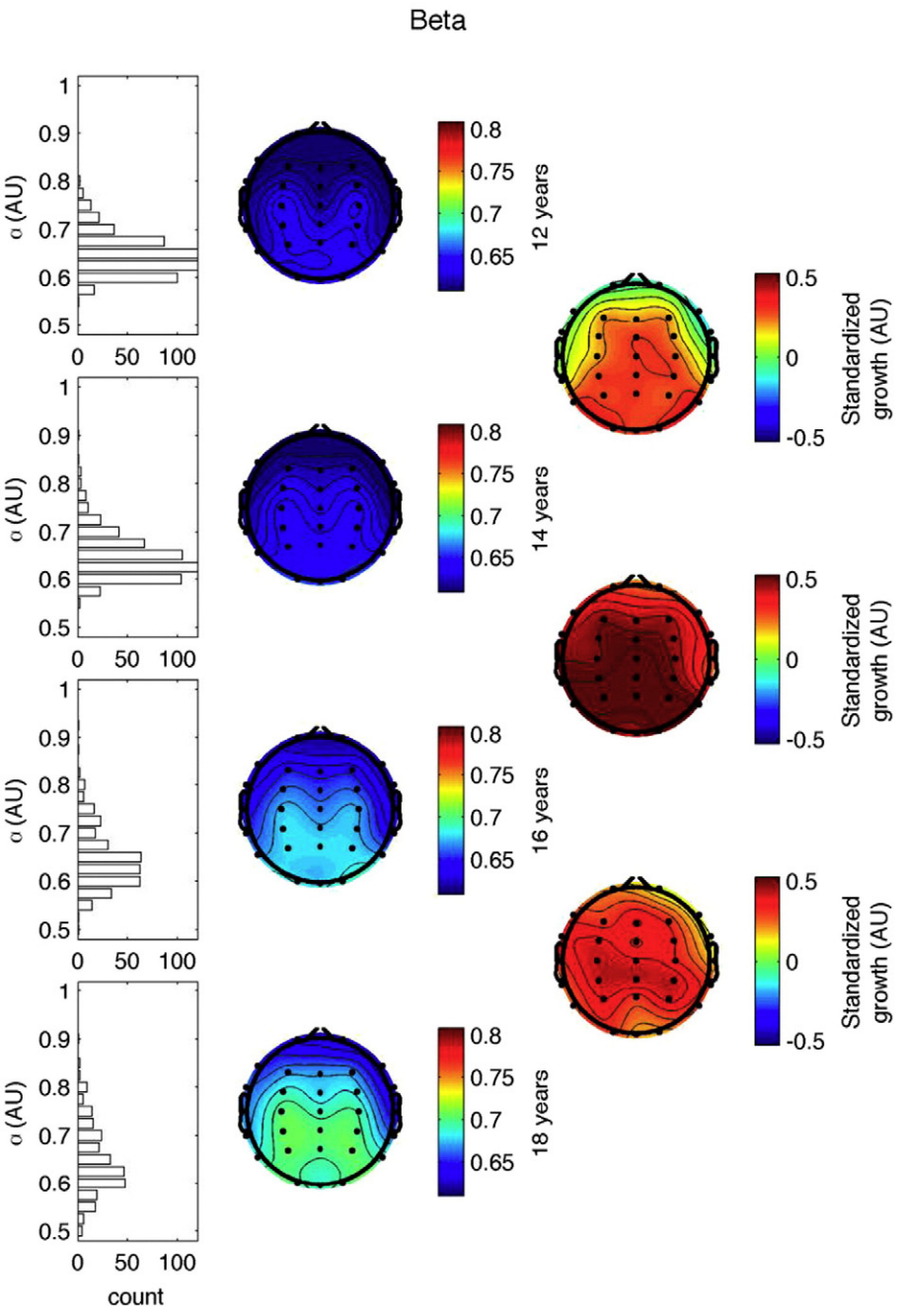

Fig. 5. Development of TS in beta oscillations. Beta oscillation TS are in absolute terms lower. They have a midline oriented central/posterior maximum and show very large effect sizes between 14 and 16. Frontal beta TS does not increase as much as other scalp locations.

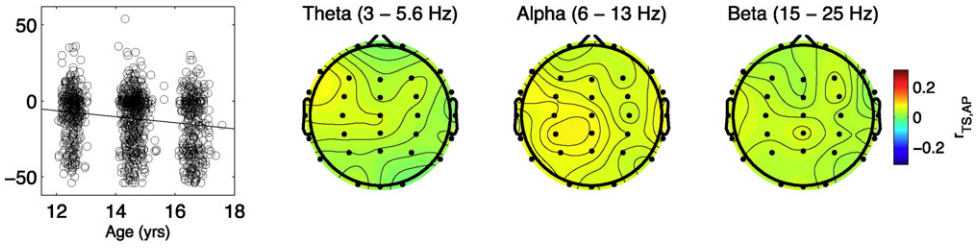

Fig. 6. (A) Development of SWAN-AP strongly decreased from 12 to 16 years of age. B-C Topographic plots of the correlation of SWAN-AP with brain TS in the theta, alpha and beta frequency bands are consistently positive, but not significant. Correlations shown are calculated as partial correlations across all available measurements corrected for age and sex.

Table 1
Twin correlations, variance per sex, and significance testing for equating correlations and variances across sexes.

		MZ		DZ		Testing equality of variances				Testing equality of correlations	
Variable	Age group	R	p	R	p	s^2_{male}	s^2_{female}	p	FDR	p	FDR
TS Theta	12	0.29	0.010	0.11	0.165	0.029	0.034	0.011	0.543	0.350	0.780
	14	0.40	0.000	0.18	0.025	0.033	0.031	0.214	0.577	0.988	0.988
	16	0.45	0.000	0.14	0.272	0.037	0.037	0.738	0.865	0.253	0.780
	18	0.48	0.000	0.13	0.305	0.034	0.035	0.865	0.865	0.487	0.780
TS Alpha	12	0.60	0.000	0.27	0.002	0.053	0.057	0.159	0.577	0.048	0.259
	14	0.65	0.000	0.28	0.001	0.059	0.064	0.347	0.577	0.419	0.780
	16	0.49	0.000	0.13	0.253	0.067	0.074	0.055	0.577	0.041	0.259
	18	0.51	0.000	0.30	0.015	0.079	0.084	0.410	0.577	0.049	0.259
TS Beta	12	0.49	0.000	0.11	0.210	0.040	0.041	0.481	0.577	0.211	0.780
	14	0.61	0.000	0.38	0.000	0.047	0.051	0.207	0.577	0.741	0.808
	16	0.53	0.000	0.01	0.963	0.058	0.063	0.137	0.577	0.446	0.780
	18	0.49	0.001	0.23	0.064	0.067	0.074	0.341	0.577	0.420	0.780
SWAN-AP	12	0.81	0.000	0.21	0.066	0.940	0.762	0.040	0.120	0.032	0.096
	14	0.82	0.000	0.61	0.000	1.045	0.970	0.165	0.247	0.473	0.473
	16	0.86	0.000	0.62	0.000	1.088	1.097	0.519	0.519	0.187	0.280

Note. Correlations for brain TS were estimated for average DFA exponents across the whole scalp (removing any missing data). FDR corrected p-values for unequal variances between males and females were corrected across waves and frequencies for TS, and across measurement waves for attention problems.

Table 2
Broad-sense heritability and standardized estimates of genetic and environmental effects on the scalp-wide average of the DFA exponent, with significance testing using the likelihood-ratio test in Structural Equation Modeling.

Variable	Age	A	D	E	Broad-sense h^2	p_D in 10 df test	p_{h2} in 20 df test
TS Theta	12	0.07	0.16	0.77	0.23	0.999	0.042
	14	0.22	0.06	0.72	0.28		
	16	0.07	0.32	0.61	0.39		
	18	0.10	0.07	0.83	0.17		
TS Alpha	12	0.39	0.12	0.49	0.51	1.000	<0.001
	14	0.47	0.08	0.45	0.55		
	16	0.35	0.21	0.44	0.56		
	18	0.32	0.18	0.50	0.50		
TS Beta	12	0.20	0.17	0.63	0.37	1.000	<0.001
	14	0.23	0.01	0.76	0.24		
	16	0.05	0.30	0.64	0.36		
	18	0.05	0.17	0.78	0.22		

Note. TS = Temporal stability. A = additive genetic, D = nonadditive genetic, E = unique environment. Variance components A, D and E effects were estimated in tetravariate longitudinal models for TS, and trivariate models for attention problems (SWAN, CBCL). D and broad-sense heritability (h^2) were tested for significance in an omnibus test for all D or A + D effects within and between time points, resulting in a 10df test for D and a 20df test for h^2 (see Fig. 2).

no significant effect. Fig. 7 shows the results for alpha oscillation TS. Changes between waves 12 and 14 showed scalp-wide significant heritability. From 14 to 16 a large frontal heritable cluster was seen. Interestingly, the heritability topographic patterns were quite dissimilar to the developmental pattern as shown in Fig. 5. For example, scalp-wide heritability of change from 12 to 14 with maximal increase in (right) central area did not match the pattern of reduced increase in the central areas from Fig. 5. In addition, the moderate to strong development over the whole scalp from 14 to 16 with effects sizes around Cohen's d 0.5 were only heritable for frontal areas, and reflect unique environmental effects for central, temporal, and posterior areas. Therefore, the heritability was clearly not an issue of signal-to-noise, where absence of change could have reflected absence of signal and zero heritability by definition.

Table 3
Variance decomposition into genetic and environmental effects for the SWAN.

Age	A	C	E	h^2	p_C	p_A
12	0.77	0.02	0.21	0.77	$9.8 \cdot 10^{-6}$	$1.8 \cdot 10^{-12}$
14	0.46	0.36	0.17	0.46		
16	0.55	0.28	0.16	0.55		

Note. A = additive genetic, C = common environment, E = unique environment. Variance components A, C, and E effects were estimated in trivariate models for SWAN-AP. A and C were tested using SEM in an omnibus test removing all A or C effects within and between time points, resulting in p-values p_A and p_C respectively.

3.8. Brain developmental trajectories differ between high and low attention problems

We investigated whether brain developmental trajectories were different for the 25% highest and lowest scoring attention problems subjects. Because of the stratified selection the number of females was n = 87 for both high and low SWAN-AP, n = 82 for males. Ethnicity was n = 143 for Caucasian and n = 22 for other in both groups. Pearson chi-square tests showed that self-reported ethnicity and sex did not interact between low and high attention problems groups ($\chi^2(2) < 4.5$, $p > 0.13$). The actual proportion of subjects selected was slightly lower than 25% at 24.8%. Since subjects were selected without regard for data availability at specific waves, we assessed the ages for which brain TS data was available. The ages did not differ between the two groups ($M_{lo} = 15.1$, $M_{hi} = 15.0$, GEE robust-z = 0.55). Low and high SWAN-AP groups differed strongly in ADHD diagnosis (0.8% vs 15.1% respectively).

Fig. 8 shows the results of the age-by-attention-problem interaction effect. Frontal leads showed developmental differences in alpha band brain TS (Fp2 is shown in Fig. 8A). Low-attention problems groups showed greater change in brain TS. The significance of the interaction

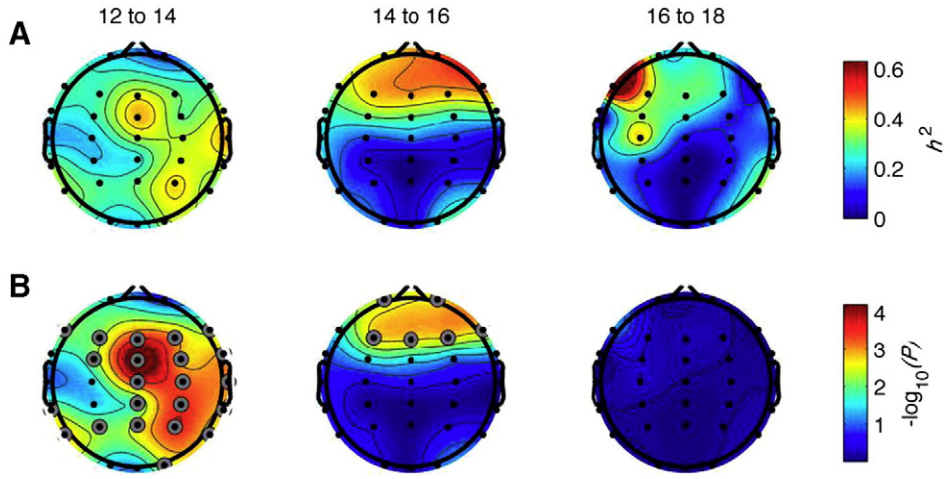

Fig. 7. Heritability topographies for change in TS between waves 12–14, 14–16, and 16–18, for 6–13 Hz alpha oscillation modulation. Top row are heritability estimates from models estimating the relative contribution of additive genetic and unique environmental factors (AE). Bottom row are the FDR corrected p-values (correction across 30 channels only). 12–14 showed moderate heritability in change scores, which was significant across a widespread area. Change from 14 to 16 was visible (and significant) in the frontal areas only.

effect while taking into account multiple comparisons was established using the cluster permutation test, revealing a significant frontal cluster of 5 channels (empirical $p = 0.031$). However, the effect was somewhat dependent on the proportion selected (e.g., using 15% or 20% top and bottom attention-problem selections yielded $p = 0.026$ for a 7-channel cluster and $p = 0.049$ for a 5-channel cluster, respectively). FDR corrected effects of single channels were not significant. Therefore, the results indicate that the effect was noisy, necessitating clustering across channels to obtain more robust effects.

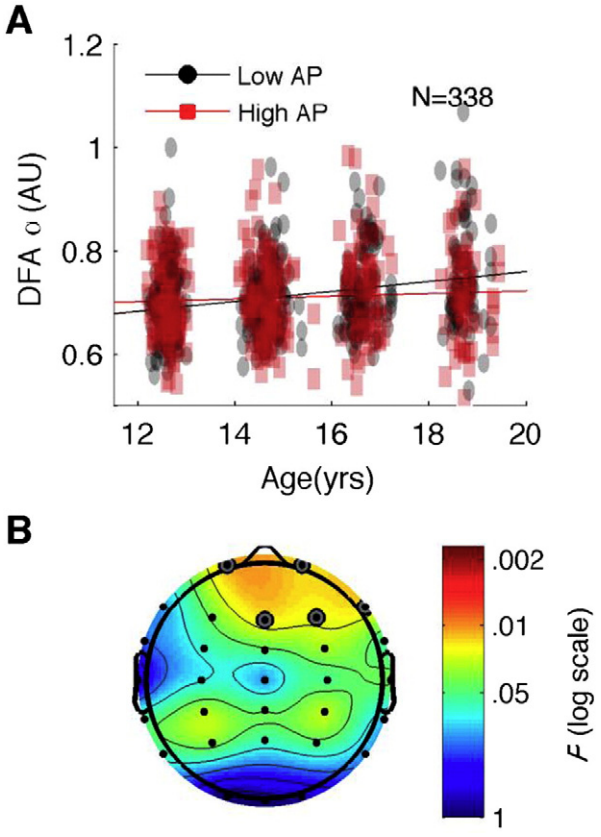

Fig. 8. High and low attention problems show different trajectories in brain TS development. Top and bottom 25% in attention problems were selected stratified within the ethnicity by sex. (A) Low attention problems showed stronger development than high attention problems in brain TS. The effect is shown for frontal lead Fp2. (B) Scalp topography with results of the cluster permutation effect shows a significant 5-lead cluster in the medial/right-frontal area. The cluster's empirical-p was 0.031.

4. Discussion

The current data confirmed familial influences on attention problems scale of SWAN-AP. Using a different model than the one presented earlier on these data, we confirmed the existence of effects of common environment (Peng et al., 2015). The data also confirmed the heritability of brain TS (Linkenkaer-Hansen et al., 2007). Moreover, the longitudinal modeling indicated that nonadditive genetic effects were significant—a novel finding when comparing to previous results in a Dutch twin family sample (Linkenkaer-Hansen et al., 2007).

Both attention problems and brain TS developed within the age range investigated within adolescence (12 to 16 and 12 to 18 years respectively). Attention problems showed a consistent decline, which is partly consistent with results from the extant literature. For example, the review by Costello et al. (2011) reports consistent decrease in attention problems from childhood to adolescence, which continues into young adulthood. Bongers et al. report a curvilinear effect, with peak levels of CBCL attention problems around age 11 and subsequent decline consistent with the current results (Bongers et al., 2003). Kan et al. (2013) showed relatively stable levels of Youth Self Report attention problems during adolescence and a decline only in later adolescence and young adulthood, but importantly, strong rater effects (mother vs self-report). Likewise, the mixed modeling approach by Robbers et al. (2011) categorizing the developmental trajectories of CBCL attention problems revealed that most subjects could be categorized as systematically low scoring, whereas an almost equal proportion in an upward or downward developmental path. The age range for Robbers et al. (2011) was however 6–12 years. These studies have made clear that methodology (instrument as well as rater bias) can severely influence the reported trajectories in attention problems.

Brain TS reflected in the DFA exponent showed a substantial and highly significant increase that was visible over the whole scalp for alpha and beta oscillations. This finding is consistent with findings in a Dutch sample that showed a large increased in brain TS from childhood to adolescence (about 7 to 16 years of age) and within adolescence (16 to 18 years) (Smit et al., 2011). This change was heritable depending on age, frequency, and scalp location. For alpha oscillations, from waves 12 to 14 the DFA exponent was moderately heritable widespread over the scalp. From 14 to 16, it was heritable for frontal areas. For beta oscillations, only left parietal change between 12 and 14 was significant after FDR correction. This suggests that change in brain TS does not reflect

the homogenous expression of genetic and environmental effects, but rather a complex mixture of genetic unfolding and unique environment. This pluriformity provides insight into how unique environmental effects in the developing brain may form a separate set of factors affecting brain activity at a particular (cross-sectional) wave. If timing of brain maturation is of such a complex nature, then this may obscure or confound cross-sectional observations of correlations between brain activity and behavior.

We argued that assessing the temporal decay in autocorrelation in brain activity measured by EEG could reflect the tendency of the brain to show random walk patterns. High levels of autocorrelations, we hypothesized, may be related to a greater level of mind wandering, and thus serve as an endophenotype for attention problems. Previous results had shown that individual variation in the exponent \alpha was able to predict performance in simple cognitive and motor tasks (Palva et al., 2013; Smit et al., 2013). However, we found no significant correlations, or correlations that failed to reach significance after adjusting for FDR. Therefore, we must conclude that brain TS is not a useful endophenotype for attention problems as measured with the SWAN-AP, in spite of both traits' high heritability.

The developmental trajectories differed significantly between the 25% highest and lowest SWAN-AP scores. Low-attention problems subjects showed stronger development of frontal brain TS (i.e., larger change) than high attention problems. This may indicate that high attention problems subjects differ in their developmental phase. Previously it has been reported that ADHD-patients have a developmental lag (Shaw et al., 2007), however, the current EEG data cannot indicate whether high-attention problems have lagged development compared to low-attention problems or vice versa. The frontal location of the effect is consistent with effect of delayed cortical thinning observed in the prefrontal cortex in (Shaw et al., 2007). Note, however, that these developmental delays in the prefrontal cortex occurred at a much earlier age (up to age 12.5) than in the current sample.

The significant frontal cluster of leads where brain TS trajectories differed between high and low-attention problems subjects may highlight the involvement of the prefrontal cortex. This finding is consistent with neuroscientific findings in attention problems and ADHD research. Attention problems and ADHD are marked by executive dysfunction (Willcutt et al., 2005), resulting in deviant ability to suppress inappropriate responses (response inhibition) with prolonged reaction times. These processes are consistently localized in the prefrontal cortex (Ridderinkhof et al., 2004). Also error monitoring and reward evaluation are suboptimal in attention problems and ADHD, and have been localized in the prefrontal cortex (Castellanos and Tannock, 2002; Oosterlaan et al., 1998; Ridderinkhof et al., 2004). Differential developmental trajectories, however, could indicate that the relative immaturity of frontal brain areas (Shaw et al., 2007) may underlie some of the symptomatology in attention problems. Immature frontal brains could result in insufficient control, and thus, induce age-inappropriate behavior and symptoms.

Genome-wide studies of ADHD have not yet pinpointed to specific genetic variants (Neale et al., 2010), possibly due to the phenotypic complexity of the trait (van der Sluis et al., 2010). As with most complex (psychiatric) traits, the lack of significant hits lies in the fact that the effect sizes for specific genetic variants are low, resulting in loss of power for detecting such effects. One solution to ameliorate the power loss due to phenotypic complexity may be to look for endophenotypes that are related to symptoms of ADHD (Castellanos and Tannock, 2002; de Geus, 2010, 2002; Gottesman and Gould, 2003; Rommelse et al., 2011). These endophenotypes may have a simpler genetic structure by tagging a single genetic expression pathway rather than the full complex phenotype by tagging brain-based subcomponents of the complex disease. The current results indicate that TS developmental trajectories may act as an endophenotype.

In sum, we confirm earlier reports of high heritability of brain TS, and showed a significant nonadditive genetic contribution. SWAN-AP also was heritable, but also showed significant effects of common environment, as previously shown in the current sample (Peng et al., 2015). TS generally increased from 12 to 18 years of age, but the strength of increase depended strongly on scalp location and frequency band. This increase was only significant for alpha band TS between 12 and 14, and between 14 and 16 for selected frontal leads. Brain TS did not significantly correlate with SWAN-AP. However, high and low attention problems subjects' frontal brain area seemed to develop with different trajectories, suggesting that brain TS is a biomarker for brain development rather than a direct endophenotype reflecting the (in)ability to show focused attention. Future research is needed to establish whether the findings reflect a developmental lag for high attention problems subjects.

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