Genetic Overlap between Evoked Frontocentral Theta-Band Phase Variability, Reaction Time Variability, and Attention-Deficit/Hyperactivity Disorder Symptoms in a Twin Study

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Background: Electrophysiological and hemodynamic activity is altered in attention-deficit/hyperactivity disorder (ADHD) during tasks requiring cognitive control. Frontal midline theta oscillations are a cortical correlate of cognitive control influencing behavioral outcomes including reaction times. Reaction time variability (RTV) is consistently increased in ADHD and is known to share genetic effects with the disorder. The etiological relationship between the cognitive control system, RTV, and ADHD is unknown. In a sample of twins selected for ADHD and matched control subjects, we aimed to quantify the strength of the phenotypic, genetic, and environmental relationships between event-related midline theta oscillations, RTV, and ADHD.

Methods: Our sample included 134 participants aged 12 to 15 years: 67 twin pairs (34 monozygotic; 33 dizygotic) with concordance or discordance for ADHD symptomatology assessed at 8, 10, and 12 years of age. Our main outcome measures were frontal midline theta activity, derived from both channel and source decomposed electroencephalographic data, and behavioral performance on a response-choice arrow flanker task known to elicit theta activity.

Results: Variability in stimulus event-related theta phase from frontal midline cortex is strongly related to both RTV and ADHD, both phenotypically and genetically.

Conclusions: This is the first finding to confirm the genetic link between the frontal midline cognitive control system and ADHD and the first to identify a genetically related neurophysiological marker of RTV in ADHD. Variability in the timing of the theta signal in ADHD may be part of a dysfunctional brain network that impairs regulation of task-relevant responses in the disorder.

Key Words: ADHD, biomarker, cognitive control, EEG, genetic, twin study

The ability to quickly adapt thinking and behavior to changing internal states and external circumstances is critical for maintaining efficient, goal-directed behavior. Abnormalities in such cognitive control are associated with numerous psychopathological disorders including attention-deficit/hyperactivity disorder (ADHD). Converging evidence indicates that electrophysiological and hemodynamic measures from medial prefrontal cortex (mPFC) and anterior cingulate cortex are altered in ADHD during action monitoring, conflict detection, error signaling, and reinforcement learning (1–6).

A growing body of work focuses on the relation of frontal midline theta band (5–8 Hz) electroencephalographic (EEG) activity to cognitive control (7). Frontal midline event-related potential (ERP) indices of cognitive control, including those abnormal in ADHD (1,2,6,8,9), have most energy in the theta band (7,10) and can be interpreted as brief bursts or complexes of theta-band activity partially time- and phase-locked to relevant stimulus presentations (11) or motor responses (12). The link between cognitive control and frontal midline theta is further supported by human and monkey reports that theta-band activity in mPFC increases with cognitive control demands, for example, those involved in task rule changes and stimulus feature task conflict (13–16). A number of studies indicate that trial-to-trial tuning of frontocentral theta activity may play a role in optimizing behavioral performance (17–19). Of particular interest to ADHD research, mPFC activation has been shown to influence reaction times (17,20). Monkey studies have also indicated that theta phase dynamics have a general role in response initiation and a specific role in conflict-modulated reactions (15,21).

Reaction time variability (RTV) in repetitive response tasks consistently discriminates between ADHD and control samples in a broad range of tasks and sensory modalities (22–26). Consistent with a relationship between frontal midline brain activity and reaction times, a number of investigations point toward a possible functional relationship between RTV and medial frontal blood oxygen level–dependent activation (27,28), and a functional magnetic resonance imaging report indicated that decreased activation in anterior cingulate, basal ganglia, and thalamus is correlated with the increase in RTV in ADHD (29). Despite the evident role of RTV in ADHD, there is little empirical research into its neurophysiological correlates (30).

Both RTV and cognitive control appear to share an etiological relationship with ADHD. The majority of familial, and genetic, influences on RTV are shared with ADHD (31–34). Similarly, two family studies indicate a shared familial relationship between cognitive control and ADHD (1,2). However, as family designs are unable to discriminate between genetic and environmental

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influences, the exact etiology of familial overlap between ADHD and cognitive control abnormalities is unknown. Twin studies provide a powerful way to delineate the etiological architecture of cognitive abnormalities associated with ADHD (35,36).

In the present study, we investigated the relative strengths of genetic and environmental relationships between ADHD, RTV, and an EEG marker of cognitive control, event-related frontal midline theta. We measured EEG activity during the well-defined Eriksen arrow flanker task (1,2) in 67 adolescent monozygotic (MZ) and dizygotic (DZ) twin pairs concordant or discordant for high and low ADHD symptom scores. The Eriksen flanker task is known to elicit a strong theta response, particularly in high-conflict trials (21). First, we identified measures that shared phenotypic variance with ADHD symptoms and reaction times and then we applied structural equation modeling to separate this phenotypic covariance into genetic and environmental components (37). In line with previous studies on cognitive control and ADHD (1,2,6), we predicted that the greatest phenotypic relationship between theta measures and ADHD symptoms would be in high-conflict trials. Specifically, we aimed to quantify the strength of the genetic and environmental relationships between stimulus-locked midline theta oscillations and 1) ADHD symptoms and 2) reaction times.

As we are interested in brain activity that may influence reaction times, we measured stimulus-locked theta phase and amplitude in a poststimulus, preresponse window. We measured theta activity both at frontal midline scalp electrodes and also at the source level using independent component analysis (ICA). Independent component analysis is a statistical blind source separation technique that has been found to be useful for separating out independent EEG signals from many cortical and noncortical sources (38–43). Interpretation of ERP indices of cognitive control is limited by the fact that conventional ERPs represent only trial averages, neglecting consideration of the temporally dynamic brain activations that support the adjustments and behaviors across many trials (21,44). The improved signal-to-noise ratio achieved with ICA facilitates identification of single-trial EEG activity that can be more tightly linked to behavior and cognition than scalp channel-based measures (45,46) and may be particularly useful for characterizing trial-to-trial theta-band dynamics in ADHD.

We also compared ADHD and control children on behavior and EEG variables in high-conflict trials (high cognitive control) and low-conflict trials (lower cognitive control), which enabled the examination of increased demand of cognitive control on all measures.

Methods and Materials

Sample

The sample was selected from the Twins' Early Development Study, a birth cohort study of all twins born in England and Wales between 1994 and 1996 (47) (Supplement 1). The Neurophysiological Study of Activity and Attention in Twins subset used in this study consisted of 67 male twin pairs in groups of 22 pairs concordant for high levels of ADHD symptoms (corresponding to a clinical diagnosis; MZ: 11; DZ: 11), 8 pairs discordant for ADHD symptoms (MZ: 2; DZ: 6), and 37 control pairs concordant for low levels of ADHD symptoms (MZ: 21; DZ: 16). For further information on selection of twins, see Supplement 1. Demographic characteristics are given in Tye *et al.* (35). No children were taking medication at the time of the study. The study was approved by King's College London Psychiatry, Nursing and Midwifery Research Ethics Subcommittee. Participating families gave their written informed consent.

Task

The task is identical to the version of the Eriksen arrow flanker paradigm used by us and colleagues in previous studies (2,48,49) and consisted of 10 blocks of 40 trials. Two flankers (black arrowheads above and below the position of a fixation mark) were presented for 100 milliseconds before the central target black arrowhead appeared for an additional 150 milliseconds. Participants had to press a response button with the index finger of the hand (left or right) corresponding to the direction indicated by the target arrow (left or right). On congruent trials, flanker and target arrowheads pointed in the same direction; on incongruent trials, they pointed in opposite directions. Further task details are available in Supplement 1. Performance measures were target reaction time ([MRT]; mean response latency in msec after target onset) and intraindividual variability in reaction time ([RTV]; standard deviation of response latency) in the congruent and incongruent correct trials separately.

IQ

General cognitive ability was assessed at age 14 as part of ongoing Twins' Early Development Study web-based data collection (50). The twins were tested on the Wechsler Intelligence Scale for Children as a Process Instrument vocabulary multiple choice subtests (51) and Raven's standard and advanced progressive matrices (52). Further information on the calculation of IQ is in Supplement 1.

EEG Recording and Processing

Electroencephalographic data were recorded using a 64-channel (BrainAmp DC; Brain Products, GmbH, Munich, Germany) extended 10–20 system montage (reference at FCz). Vertical and horizontal electro-oculogram data were simultaneously recorded from electrodes placed above and below the left eye and at the outer canthi. The EEG and electro-oculogram signals were digitized at a 500-Hz sampling rate. Data processing was performed offline using the EEGLAB toolbox (v11.0.3.1b) (53) for MATLAB (R2012a; The Mathworks, Inc., Natick, Massachusetts). Before processing, the channel signals were re-referenced to average reference. We then applied a 1-Hz high-pass filter. Time points with any channel value larger than 100 μV in absolute value were rejected from the data and excluded from further analysis. We further rejected the .8% of trials in which the button press occurred later than 1200 milliseconds after target presentation.

EEG Analyses

We used adaptive mixture ICA (46,54) to separate the channel data into maximally instantaneous independent component (IC) processes (Supplement 1). We computed equivalent dipole models for each IC scalp topography using a template four-layer adult boundary element method head model implemented in the DIPFIT toolbox for MATLAB (55). Independent components with less than 15% residual variance between estimated dipole projection and IC scalp topography were clustered based on dipole location and spectral and ERP features, yielding (among other clusters) a prominent central midline cluster (Supplement 1). Channel-based measures were calculated at the channel (Cz) where theta activity was maximal, after first removing projections to this channel from ICs accounting for eye movement and blink

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