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Genetic influences on composite neural activations supporting visual target identification

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ABSTRACT

Behavior genetic studies of brain activity associated with complex cognitive operations may further elucidate the genetic and physiological underpinnings of basic and complex neural processing. In the present project, monozygotic (N = 51 pairs) and dizygotic (N = 48 pairs) twins performed a visual oddball task with dense-array EEG. Using spatial PCA, two principal components each were retained for targets and standards; wavelets were used to obtain time-frequency maps of eigenvalue-weighted event-related oscillations for each individual. Distribution of inter-trial phase coherence (ITC) and single trial power (STP) over time indicated that the early principal component was primarily associated with ITC while the later component was associated with a mixture of ITC and STP. Spatial PCA on point-by-point broad sense heritability matrices revealed data-derived frequency bands similar to those well established in EEG literature. Biometric models of eigenvalue-weighted time-frequency data suggest a link between physiology of oscillatory brain activity and patterns of genetic influence.

1. Introduction

Comprehensive evaluation of genetic influences on neural activity in normal cognitive neuroscience studies is important for many reasons. First, brain activity measures are closer to the primary gene products than are molar-level behaviors (Iacono and Clementz, 1993), so they may have simpler genetic profiles. Second, activity in particular brain regions and of particular types may provide more specific information than molar-level behaviors about genetic variance in specific neural circuitries supporting complex cognitive operations. Third, studying genetic variation at the level of neural activity may provide useful information about the genetics of cognitive control that is independent of particular task demands. Most studies of genetic influence on human behavior focus on personality and/or characteristics associated with psychopathologies (Frederick and Iacono, 2006; Lykken, 2006). Neuroimaging studies (fMRI and EEG/MEG) investigating genetic variance of neural activations supporting cognition in normal twins are uncommon, with many imaging genetic studies focusing on twins discordant for certain pathologies (Gottesman and Gould, 2003).

The present study used a classical twin design to evaluate genetic influences on spectral components of brain responses that are associated with both simple and complex cognitive operations elicited by a visual oddball task (Katsanis et al., 1997; Steinhauer et al., 1987; Simson et al., 1977). Multiple brain regions are activated during such tasks, including visual, parietal, inferior temporal, anterior cingulate, and prefrontal cortices (Linden, 2005). A prominent brain response, called the P300, has been the focus of most twin studies using similar target detection tasks (e.g., van Baal et al., 1998; van Beijsterveldt et al., 1998; van Beijsterveldt et al., 2001; Begleiter et al., 1998; Almasy et al., 1999; Anokhin et al., 2001; Carlson and Iacono, 2006). The P300 is generally associated with context updating in working memory and target evaluation (Linden, 2005). Meta-analytic studies show that about 60% of the variance in P300 amplitude and 50% of the variance in latency is attributable to genes (van Beijsterveldt and van Baal, 2002). These analyses, however, were mostly limited to evaluations of voltage at single sensors (Pz) so they may have incompletely described the genetic and environmental variance constituents of this neurophysiologically complex trait.

Considerable effort has been devoted to studying genetic influences on P300, including its endophenotype characteristics (e.g., Bestelmeyer et al., 2009; Hall et al., 2009; Schulze et al., 2008; Yoon et al., 2006; Bramon et al., 2005; Carlson et al., 2004), but other brain responses elicited during the same tasks have received considerably less attention. Indeed, the degree of genetic influence on other brain responses in visual oddball paradigms is, at best, uncertain (e.g., Katsanis et al., 1997; Almasy et al., 1999; Smit et al., 2007). The standard N100 appears to be moderately heritable (Almasy et al., 1999; Smit et al., 2007), while, surprisingly, the target N100 seems to possess limited genetic variance (Katsanis et al., 1997). Katsanis

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and colleagues (1997) also reported significant genetic variance for P200 and N200 neural responses. Like most P300 investigations, these studies also used few sensors, and measured neural activity at a small number of time points, limiting their ability to completely describe genetic contributions to these complex neural responses.

Brain processes can be measured in many ways. Investigations of genetic influences on amplitude and latency of individual ERP peaks (at a limited set of individual time points) have been useful. Such ERP peak measurements in the time domain, even for brain responses to simple stimuli, however, incompletely describe the complexity of neural responding that is evident in time-frequency representations (Kilmesch et al., 2007). Indeed, quantifying oscillatory phenomena captures an important aspect of neural processing that is a predominant characteristic of brain function (e.g. Privman et al., 2011; Samar et al., 1995; Gray and Singer, 1989).

There are few investigations of event related oscillations (EROs) in twins (Gilmore et al., 2010a; Gilmore et al., 2010b). Most studies reporting heritability statistics on the spectral characteristics of EEG and ERP activity come from resting state paradigms with no external stimulus. In the resting state, heritability has been established for delta, theta, alpha, and beta bands (Lykken et al., 1982; Smit et al., 2005; Smit et al., 2010; Posthuma et al., 2001; van Baal et al., 1996; van Beijsterveldt et al., 1998; Zietsch et al., 2007). Genetic influences on oscillations occurring in response to an external stimulus or task have been useful in studies of twin pairs discordant for specific pathologies (Hall et al., 2011; Smit et al., 2009), but are infrequent in the normal cognitive neuroscience literature. Reports on oddball task EROs often focus entirely on the P300, and many use ERP-related methods for quantification, such as grand-averaging and/or restricted time ranges (Basar-Eroglu et al., 2001; Devrim et al., 1999; Ergen et al., 2008; Gilmore et al., 2010a; Ucles et al., 2009; but see Demiralp et al., 1999), despite evidence that alternative approaches may be useful (Andrew and Fein, 2010). For instance, single trial analyses, a method increasingly used in ERP studies can parse neural contributions to multiple ERP components (Mouraux and Iannetti, 2008; Hu et al., 2010). Because neural oscillatory activity changes over the course of stimulus processing, quantifying heritability changes in frequency space during stimulus processing could be useful. This paper quantifies genetic influences on neural oscillatory activity during cognitive processing over time using point-by-point broad spectrum heritability of whole head neural activity.

The purpose of the present investigation was to investigate the utility of a novel approach for studying genetic variance on brain activations during complex cognitive processing. Two specific modifications to the typical approach used in twin studies were implemented here. First, spatial principal components analysis (PCA) was used to reduce whole head EEG data to components that efficiently captured neural activation variance in response to task stimuli. These components were then subjected to frequency decomposition over time using Morlet wavelets. Significant time-frequency regions of heritable neural activity were submitted to Cholesky decomposition to evaluate sources of genetic and environmental variance for brain oscillatory behavior during cognitive processing. This approach (i) used minimal data processing adjustments to impose the fewest restrictions possible on data analyses, (ii) integrated information across a large number (61) of EEG sensors, allowing for maximal use of available data, (iii) rather than arbitrarily selecting sensors for analyses, used spatial PCA to empirically derive a multi-sensor neural response that could be quantified with enhanced signal-to-noise ratio and improved reliability of measurement (Braboszcz and Delorme, 2011), (iv) used broad sense heritability information to derive frequency bands with similar heritability patterns, and (v) evaluated neural responses over the entire time range of stimulus processing to provide a closer approximation to the actual functional characteristics of brain activations supporting cognitive operations during visual target detection.

2. Materials and Methods

2.1. Participants

The Minnesota Twin Family Study, begun in 1990, is an epidemiological study of same sex twin pairs born in the state of Minnesota during selected birth years. For the present study, 51 MZ (24 female) and 48 DZ (22 female) twin pairs from this project were used, all 29 yrs of age (see Iacono et al., 1999 for a description). The total cohort included 457 twin pairs (259 female). Twin pairs were randomly selected as every 5th pair in chronological order from a subgroup of subjects with relatively artifact-free EEG data and no significant neurological history. No exclusions were made for psychopathology in order to preserve the representativeness of the sample. Twenty-two subjects (12.6%), 13 of them females, met DSM IV criteria for major depressive disorder for the 5-year interval since their last assessment, 18 subjects (10.3%, 6 of them female) were nicotine dependent for this interval, while 8 (5.0%, 1 of them female) met DSM-IV criteria for alcohol dependence in this interval. Five subjects met DSM-IV criteria for a diagnosis of cannabis (all males) or psychostimulant (4 males) dependence in the 5-6 years since their last assessment.

2.2. Procedure

In the EEG environment, participants performed the rotated heads task developed by Begleiter and colleagues (1984; see also Carlson and Iacono, 2006). Subjects viewed a sequence of 240 stimuli. The stimuli were presented for 100 ms with an interstimulus interval of 3-4 sec (rectangular distribution). One third of the stimuli (targets) showed a top-down view of a schematic head, with nose and one ear depicted by a triangle and a small oval, respectively. The remaining 160 trials (standards) showed a simple oval with no corresponding head features. Participants were asked to respond to targets and indicate whether they saw a left or right ear by pressing a corresponding left or right response button. For half of the targets, the nose pointed upward and the task was relatively straightforward. For the other half of the targets, the head was rotated 180 degrees to make the nose point downward, making the task of indicating left or right more difficult. There was no required response for standard trials. Target stimuli to which subjects failed to respond were immediately re-presented, preceded by two standards to maintain the ratio of target to standard responses (Gilmore et al., 2009).

2.3. ERP Recording

EEG was continuously recorded and digitized at 1024 Hz, with a 5th-order Bessel anti-aliasing filter at 205 Hz, using a 61-channel BioSemi system with sensors placed according to the International 10/10 system (Chatrian et al., 1985). Recording included two earlobe sensors, two sensors on the outer canthus of each eye, and one sensor each above and below the right eye to record eye movements. All sensors were referenced to a monopolar reference feedback loop (connecting a driven right leg passive sensor and common mode sense active sensor, both located on posterior scalp).

2.4. EEG Data Analysis

Raw data were visually inspected offline for bad sensor recordings. Bad sensors were interpolated using a spherical spline interpolation method as implemented in BESA 5.1 (MEGIS Software, Gräfelfing, Germany). Trials with sensor amplitudes