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Genetic correlates of the development of theta event related oscillations in adolescents and young adults

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ABSTRACT

The developmental trajectories of theta band (4–7 Hz) event-related oscillations (EROs), a key neurophysiological constituent of the P3 response, were assessed in 2170 adolescents and young adults ages 12 to 25. The theta EROs occurring in the P3 response, important indicators of neurocognitive function, were elicited during the evaluation of task-relevant target stimuli in visual and auditory oddball tasks. Associations between the theta EROs and genotypic variants of 4 *KCNJ6* single nucleotide polymorphisms (SNPs) were found to vary with age, sex, scalp location, and task modality. Three of the four *KCNJ6* SNPs studied here were found to be significantly associated with the same theta EROs in adults in a previous family genome wide association study. Since measures of the P3 response have been found to be a useful endophenotypes for the study of a number of clinical and behavioral disorders, studies of genetic effects on its development in adolescents and young adults may illuminate neurophysiological factors contributing to the onset of these conditions.

1. Introduction

Studies of the age-variation of the effects of genotypic variants on the development of brain function will provide increasing insight into the processes of brain maturation and in particular the influences of neurophysiological factors during the transition from childhood through adolescence to adulthood. One important indicator of neurocognitive function is the P3 (or P300) response, evidenced by the production of a large positive waveform with a peak between 300 ms and 700 ms after the presentation of a target stimulus. The P3 response is elicited by infrequently presented target stimuli in a stream of more frequently occurring non-target stimuli in auditory or visual target detection (oddball) tasks, which call for the subject to respond to only the target stimulus. The P3 response has been proposed to index attentional and working memory resources (Polich, 2007). It has been associated with several anatomical loci including the supramarginal gyrus, hippocampus, locus coeruleus, anterior cingulate cortex (ACC), insula, and the right-lateralized frontal and temporoparietal regions of the ventral attention network which may be part of a distributed circuit (Menon et al., 1997; Brázdil et al., 1999; Ardekani et al., 2002; Polich and Criado, 2006; Mantini et al., 2009; Sara and Bouret, 2012; Walz et al., 2014). Studies of visual and auditory target detection tasks using functional magnetic resonance imaging (fMRI) suggest that common, supramodal functional systems are involved as well as modality-specific systems (Walz et al., 2013; Linden et al., 1999). Frequency domain analysis suggests that the theta band event related oscillation (ERO) is a major constituent of the P3 response (Karakas et al., 2000a,b; Yordanova et al., 2003; Jones et al., 2006a,b; Rangaswamy et al., 2007). Theta EROs are important for processes underlying frontal inhibitory control, conscious awareness, recognition memory and episodic retrieval, as shown in a number of experimental contexts (Gevins et al., 1998; Jacobs et al., 2006; Klimesch et al., 1994, 2001, 2008; Vertes, 2005; Babiloni et al., 2009; Crowley et al., 2014).

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There are many changes related to brain development during adolescence that may affect theta ERO power. On the neuronal level, there is a decrease in gray matter density and cortical thickness in adolescence, as well as increases in white matter, reflecting synaptic pruning and myelination (Sowell et al., 2004; Toga et al., 2006). On the structural/anatomical level, trajectories of brain volumes of different regions and tissue types, as well as other features of cortical anatomy, exhibit curvilinear properties which vary between regions (Lenroot et al., 2007; Shaw et al., 2008; Giedd et al., 2010; Raznahan et al., 2011a; Sullivan et al., 2011) and between sexes (Lenroot and Giedd, 2010; Lenroot et al., 2007; Peper et al., 2011; Koolschijn and Crone, 2013), as determined by magnetic resonance imaging (MRI) of subjects between the ages of 8 and 20. Sex differences are also present in functional MRI studies of the development of task-related brain activity in adolescents and young adults in a number of different tasks (Rubia et al., 2006; Christakou et al., 2009; Rubia et al., 2010, 2013; Rubia, 2013). Brain networks develop from a pattern of local connectivity to more global patterns of connectivity (Fair et al., 2008, 2009; Power et al., 2010; Supekar et al., 2009; Uddin et al., 2011; Vogel et al., 2010; Zielinski et al., 2010; Menon, 2013; Wu et al., 2013). Systematic changes of the electrophysiology of brain activity occur with age, both in the resting state and in a variety of task–related conditions (Segalowitz et al., 2010; Sturman and Moghaddam, 2011). Among the most prominent are decrease in power in oscillatory activity in both resting state and task–related activity (Yordanova and Kolev, 1997; Whitford et al., 2007). Sex differences in development have also been observed in task–related activity (Nanova et al., 2011, 2008). Previous studies have examined patterns of the development of visual and auditory P3 peak amplitude in adolescents (Katsanis et al., 1996; Hill et al., 1999a; Stige et al., 2007; Nanova et al., 2008; van Beijsterveldt et al., 1998, 2001; Carlson and Iacono, 2006; Sumich et al., 2012). A previous study from our laboratory of adolescents and young adults (ages 12 to 25) described the developmental trajectories of theta band EROs measured in both auditory and visual tasks at three scalp locations (Chorlian et al., 2015). That study found that the developmental trajectories of the theta EROs are characterized by a general decrease in power with age, with large differences in temporal pattern between males and females, and relatively small differences between task modality and scalp location within each sex.

It is an important scientific objective to characterize the genetic basis of the large neurophysiological and neuroanatomical changes occurring in adolescence, which influence the cognitive and affective processes underlying behavioral changes. Twin studies suggest that there are genetic effects on P3 electrophysiological measures obtained in target detection tasks during adolescent development (Katsanis et al., 1997; van Beijsterveldt et al., 1998, 2001; Carlson and Iacono, 2006). A considerable number of studies have found high degrees of heritability for structural brain features measured in adolescents (see Douet et al. (2014) for a review) which exhibit a variety of developmental patterns as described above. Gene expression studies suggest large variations in gene expression during adolescence, both in humans and in rodents (Colantuoni et al., 2011; Kang et al., 2011; Naumova et al., 2013; Stead et al., 2006). Thus it might be expected that there would be considerable age variation in association between SNPs and neurophysiological measures during adolescence. To this end, genetic variants which have been shown to have a considerable association with neurophysiological measures in adults and in which the genetic factors are known to be related to cognitive function are attractive candidates for analysis.

The Collaborative Study on the Genetics of Alcoholism (COGA) previously reported an association with genome wide significance between the power of theta band (4–7 Hz) EROs in a visual oddball task and *KCNJ6* single nucleotide polymorphisms (SNPs) in a predominantly adult sample (Kang et al., 2012). The protein encoded by *KCNJ6* is known as GIRK2, which is widely distributed in the brain and is an important functional element in dopaminergic, cholinergic, GABAergic and glutamatergic synapses and hence regulation of neuronal excitability (Saenz del Burgo et al., 2008). To examine the age variation in the association between theta EROs and *KCNJ6* SNPs during adolescence and young adulthood, the current study followed the methodology of a recent study of developmental trajectories of theta EROs (Chorlian et al., 2015), using the same sample of adolescents and young adults. Consideration of the results in that study (Chorlian et al., 2015), as described in Section 3.1, informed the analysis employed in the present study. The developmental trajectories (time-series) of the association between *KCNJ6* gene variants and theta band EROs during the P3 response to targets in adolescents and young adults are measured by the effect size of the genetic variants in a non-parametric regression model of the theta band EROs. These associations are described as a function of age, sex, task modality, and scalp location. The current study is not designed as a replication of the adult study; 19% of the subjects included in this study were subjects in Kang et al. (2012). This is the first developmental study of neurophysiological function that characterizes trajectories of the genetic association of task-related electrophysiological activity with specific SNPs.

2. Methods and materials

2.1. Subjects

The sample comprised 2170 adolescents and young adults (1060 males and 1110 females) from the Prospective Study of the Collaborative Study on the Genetics of Alcoholism (COGA), examined within the age range of 12 to 25 years. COGA is a multisite collaboration designed to study the genetics of alcoholism (Begleiter et al., 1995) that has investigated members from multiplex alcoholic families (recruited through a proband in treatment) and a set of community (comparison) families, ascertained to be representative of the general population. These families were recruited during the years 1990 to 2000. The Prospective Study began in 2004 as a continuing study of adolescents and young adults from pedigrees ascertained in previous phases of COGA, and contained members from both the multiplex alcoholic families and the community (comparison) families. These families were recruited during the years 1990 to 2000. Over 80% of the subjects are from families originally recruited through an alcoholic proband, but fewer than 25% of the sample are first degree relatives of the probands, and many of the subjects from alcoholic families are only distantly related to the probands.

Participants in the study were reassessed at approximately two year intervals. Subjects were excluded from neurophysiological assessment if they had any of the following: (1) recent substance or alcohol use (i.e., positive breath-analyzer test and/or urine screen), (2) hepatic encephalopathy/cirrhosis of the liver, (3) history of head injury, seizures or neurosurgery, (4) uncorrected sensory deficits, (5) use of medication known to influence brain functioning, (6) history/symptoms of psychoses, (7) positive test for human immunodeficiency virus, (8) other acute/chronic medical illnesses that affects brain function and (9) and a score of less than 25 on the Mini Mental State Examination. This sample comprised subjects with one or more neurophysiological assessments: 475 had 1 assessment, 583 had 2, 576 had 3, 494 had 4, and 42 had 5 assessments. Data from six collection sites have been included in this study: SUNY Downstate Medical Center; University of Connecticut Health Science Center; Washington University School of Medicine in St. Louis; University of California at San Diego; University of Iowa, and Indiana University School of Medicine. Recruitment and assessment procedures have been described elsewhere (Reich, 1996; Begleiter et al., 1998; Edenberg et al., 2005), and are also available at this website: https://zork5.wustl.edu/niaaa/coga_instruments/resources.