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Research report

Gender modulates the development of theta event related oscillations in adolescents and young adults

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HIGHLIGHTS

- There are large differences in developmental rates between males and females.
- Locational and modality differences are small compared to gender differences.
- Development diverges between auditory and visual systems during ages 16 to 21.

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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. These tasks call upon attentional and working memory resources. Large differences in developmental rates between males and females were found; scalp location and task modality (visual or auditory) differences within males and females were small compared to gender differences. Trajectories of interregional and intermodal correlations between ERO power values exhibited increases with age in both genders, but showed a divergence in development between auditory and visual systems during ages 16 to 21. These results are consistent with previous electrophysiological and imaging studies and provide additional temporal detail about the development of neurophysiological indices of cognitive activity. Since measures of the P3 response has been found to be a useful endophenotypes for the study of a number of clinical and behavioral disorders, studies of its development in adolescents and young adults may illuminate neurophysiological factors contributing to the onset of these conditions.

1. Introduction

Brain development in adolescents and young adults occurs on neuronal, structural, and functional levels. 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 nontarget stimuli in auditory and 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 [1]. It has been associated with several anatomical loci (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 [2–5]. 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 [6,7].

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Frequency domain analysis suggests that the theta band event related oscillation (ERO) is a major constituent of the P3 response [8–13]. 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 [14–19].

There are many changes related to brain development during adolescence that may effect theta ERO power. On the neuronal level, there is a decrease in gray matter density and cortical thickness in adolescence, probably reflecting synaptic pruning and myelination, and an increase in white matter [20,21]. 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 [22–26] and between genders [22,27–29], as determined by magnetic resonance imaging (MRI) of subjects between the ages of 8 and 20. Gender 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 [30–34]. Brain networks develop from a pattern of local connectivity to more global patterns of connectivity [35–43]. Systematic changes of the electrophysiology of brain activity occur with age, both in the resting state and in a variety of task related conditions [44,45]. Among the most prominent are decrease in power in oscillatory activity in both resting state and task related activity [46,47]. Gender differences in development have also been observed in task related activity [48,49]. These factors suggest that a general decrease in power should be found in both genders and modalities, that trajectories may have non-linear characteristics, and that strong gender differences and increased correlation with age between locations will be found.

The theta ERO occurring in the P3 response to target stimuli in the visual oddball experiment has been shown to have significant genetic associations with genetic variants of several different genes encoding neurophysiologically significant factors [12,50–52]. No other neurophysiological measure has been found to have this span of genetic association. This suggests that a developmental study of the theta ERO would be a useful preliminary to any study of the genetics of the development of neurophysiological function. The development of theta band EROs during adolescence have not previously been studied, although previous studies have examined the pattern of the development of visual and auditory P3 peak amplitude in adolescents [48,53–59]. No developmental studies of neurophysiological function have attempted to characterize trajectories of any measure of task-related activity in the temporal detail provided here.

The primary goal of this study was to determine the developmental trajectories of the measures of the power of theta EROs obtained in the visual and auditory target detection tasks, and the trajectories of the correlations between them. The study focuses on elucidating gender, modality, and regional differences in these developmental trajectories. The trajectory of the correlations of power values provide a measure of the supraregional and supramodal characteristics of brain development of factors affecting theta ERO generation. In preliminary analyses, theta and delta band EROs in both total and evoked measures were examined. No significant differences in trajectories were found among these measures, so the analysis was restricted to the total power in the theta band in the three midline electrodes the interest of the simplicity of interpretation and consistency with prior studies [11,12,48,55]. In subsequent studies, the developmental trajectories of the associations between genetic variants (SNPs) from a number of genes associated with neurophysiological factors and the measures of the power of theta EROs employed in this study will be determined using the same data set and similar methodologies.

2. Methods and materials

2.1. Subjects

The sample comprised 2170 adolescents and young adults from the Prospective Study of the Collaborative Study on the Genetics of Alcoholism (COGA), a multisite collaboration designed to study the genetics of alcoholism [60], examined within the age range of 12 to 25 years. The Prospective Study began in 2004 as a prospective study of adolescents and young adults from pedigrees ascertained in previous phases of COGA, which contained members from alcoholic families (recruited through a proband in treatment) and a set of community (comparison) families, randomly ascertained to be representative of the general population. These families were recruited during the years 1990 to 2000. Although over 80% of the subjects are from families originally recruited through an alcoholic proband, fewer than 25% of the sample are first degree relatives of the probands, and many 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 [61–63], and are also available at this website: https://zork5.wustl.edu/niaaa/coga_instruments/resources.html. The experimental protocols were approved by each site's institutional review board, and informed consent (for those over eighteen years of age) or assent (for those under eighteen years of age) was obtained from all participants.

2.2. Electrophysiology

Two oddball tasks, one visual, the other auditory, which have been used in the COGA neurophysiology battery from the inception of the project [64,65] were used for this study. In each task, subjects were verbally instructed to suppress their eye blinks and to sit as still as possible. They were asked to respond to the target with a button press as quickly as possible, but not at the expense of accuracy, and not to respond to other stimuli.

2.2.1. Visual oddball task

A three-stimulus visual oddball task was employed with 280 visual stimuli of three different types: 35 targets (rarely occurring letter 'X') to which the subjects responded quickly and accurately with a button press, 210 non-targets (frequently occurring white squares) and 35 novels (rarely occurring random colored geometric figures) (probabilities of occurrence of 0.125, 0.750 and 0.125 respectively). Stimuli subtended a visual angle of 2.5 *degrees* with stimulus durations of 60 ms and inter-stimulus intervals of 1625 ms The stimuli were presented pseudo-randomly with the only constraint that a target or novel stimulus never preceded a target or novel stimulus.