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Genetic determinants of target and novelty-related event-related potentials in the auditory oddball response

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ABSTRACT

Processing of novel and target stimuli in the auditory target detection or 'oddball' task encompasses the chronometry of perception, attention and working memory and is reflected in scalp recorded event-related potentials (ERPs). A variety of ERP components related to target and novelty processing have been described and extensively studied, and linked to deficits of cognitive processing. However, little is known about associations of genotypes with ERP endophenotypes. Here we sought to elucidate the genetic underpinnings of auditory oddball ERP components using a novel data analysis technique. A parallel independent component analysis of the electrophysiology and single nucleotide polymorphism (SNP) data was used to extract relations between patterns of ERP components and SNP associations purely based on an analysis incorporating higher order statistics. The method allows for broader associations of genotypes with phenotypes than traditional hypothesis-driven univariate correlational analyses. We show that target detection and processing of novel stimuli are both associated with a shared cluster of genes linked to the adrenergic and dopaminergic pathways. These results provide evidence of genetic influences on normal patterns of ERP generation during auditory target detection and novelty processing at the SNP association level.

Introduction

The scalp recorded event-related potential (ERP) samples a sequence of cerebral processes leading to discrimination of a target or novel stimulus in an oddball experiment. The waveform comprises a number of ERP components, such as the early negative peak, N1, which peaks around 100 ms post-stimulus, N2 at about 200 ms and a P3 between 300 and 500 ms (Polich, 2003; Polich and Kok, 1995).The P3 has been most widely studied to investigate cognitive processes such as attention, memory and decision making processes (Donchin and Coles, 1988; Hansenne, 2000; Kugler et al., 1993; Picton, 1992; Polich, 2007) in healthy controls as well as in a wide range of mental illnesses, such as schizophrenia and Alzheimer disease, where P3 responses are abnormal (Antal et al., 2000; Blackwood, 2000; O'Donnell et al., 2004; Polich and Corey-Bloom, 2005; Turetsky et al., 2000). ERPs elicited by deviant stimuli interspersed with repetitive standard elements demonstrate two subcomponents of P3, a earlier positive peak (~250–270 ms) with frontocentral distribution elicited by task-irrelevant distracters (P3a) or novel stimuli (Novelty P3), indicating an automatic/bottom-up shift of attention, and a later (~300–350 ms) parietal P3b that is elicited by task-relevant stimuli, which is particularly sensitive to probability, stimulus sequence, and target-to-target interval (Croft et al., 2003; Squires et al., 1976; Sutton et al., 1965).

The generating mechanisms of ERPs, in particular those of P3, are of great interest (Polich and Criado, 2006). Generator sites of P3 potentials are widespread across the brain and involve multiple regions in the frontal, temporal and parietal lobes (Eichele et al., 2005; Kiehl et al., 2005). Javitt and colleagues recently reviewed the underlying pathophysiological mechanisms for schizophrenia, and P3 abnormality was associated with abnormal dopaminergic function, as well as GABA-ergic and cholinergic functions (Javitt et al., 2008). To date, the locus coeruleus noradrenergic system and the ventral tegmental area and substantia nigra dopaminergic pathways have been proposed as dominant transmitter systems for P3 responses (Nieuwenhuis et al., 2005a, Polich, 2007). This is (indirectly) supported by fMRI activations in these areas elicited by novelty

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processing and predictive coding, functions known to drive the P3 (Bunzeck and Duzel, 2006; D'Ardenne et al., 2008).

In twin and family studies, ERP measures show high degrees of heritability (van Beijsterveldt and van Baal, 2002). The P3a and P3b show similar high heritability ranges from 0.6 to 0.8 (Frangou et al., 1997; van Beijsterveldt and Boomsma, 1994). These findings suggest that ERPs can provide reliable endophenotype information for the pursuit of a genetic basis of brain functions and their generation mechanism. However, little is known about the genetic underpinnings of ERPs, the knowledge so far is derived from very limited studies on the P3 (Begleiter et al., 1998; Hammond et al., 1987; Hansenne, 2000; Mulert et al., 2006). Somewhat divergent results show that the P3 is connected with a set of scattered dopamine-related (Mulert et al., 2006), adrenergic related and cholinergic-related genes (loci), and also mapping to additional loci on chromosomes 2 and 6 (Begleiter et al., 1998). In the majority of studies of genetic influences to normal or disordered brain processes performed so far, a small set of genes were preselected based on prior information, and then investigated using a hypothesis-driven approach (Cedazo-Minguez, 2007; Mulert et al., 2006; Vawter et al., 2004b). To avoid problems associated with gene pre-selection biases, here we developed a data-driven method for larger, unbiased, gene pools.

The purpose of the present study was to explore the genetic influences on the ERP using a set of 384 single nucleotide polymorphisms (SNPs) located in 222 genes. This array was initially designed for metabolism studies and includes genes from different physiological systems. We used a three-stimulus auditory oddball discrimination task to elicit target and novelty-related responses, yielding the N1, N2b, P3a and P3b component peaks in the ERP waveforms. To identify the underlying relationship between SNP patterns and ERP patterns, where the SNP patterns present associations encoding different physiological processes and ERP patterns reveal independent event-related brain processes, we assumed that multiple associations exist in the SNP pool, and multiple brain functions are represented in the ERP such that the potential connections between them are inherently multivariate. In other words, we proposed that SNP associations may contribute to biological/cognitive functions and that the functions may affect portions of the ERP waveform. This idea is supported by recent findings revealing the associations of multiple SNPs with complex cognitive processes (Roffman et al., 2006; Seshadri et al., 2007). Following this assumption, we adapted a blind source separation method that affords a parallel multivariate decomposition of data from different modalities, based on independent component analysis (ICA). Parallel ICA provides a way to extract the overall strongest connections between two modalities from a multivariate perspective. It has been previously applied to combine functional magnetic resonant imaging and genetic data collected from schizophrenia patients and controls (Liu et al., 2008; Liu et al., 2009), and was able to extract a set of genes linked to schizophrenia.

In this paper, parallel ICA of ERPs and SNPs is employed to extract relationships between patterns of ERP components and SNP associations. We show that novelty and target processing are associated with a common cluster of genes linked to the adrenergic and dopaminergic pathways. These genetic influences on ERP generation during auditory novelty and target processing help to understand the signal generation mechanisms underlying these brain responses, and may ultimately help identify multimodal diagnostic markers of mental illnesses.

Materials and methods

Subjects

We selected data from 41 healthy Caucasian participants (24 female, age 39 ± 19; 17 male, age 38 ± 14) who were recruited for several related studies at the Olin Neuropsychiatry Research Center at the Institute of Living in Hartford (CT). All participants were free from any history of DSMIV Axis I or Axis II psychopathology as assessed with the SCID (structured clinical interview for diagnosis). All participants provided written, informed, IRB-approved consent at Hartford Hospital.

Experiment design

The auditory oddball discrimination task consisted of responding to an infrequent target sound within a series of frequent standard sounds and infrequently presented task-irrelevant novel sounds, as used in our prior studies (Kiehl et al., 2005). The standard stimulus was a 500 Hz tone, the target stimulus a 1000 Hz tone, and the novel stimuli consisted of non-repeating meaningless sounds (*e.g.*, tone sweeps, whistles). The target and novel stimuli occurred with a probability of 0.10 each; the standard stimuli occurred with a probability of 0.80. Each stimulus was presented to participants by a computer-controlled sound system that delivered the auditory stimuli with a 200 ms duration and a 2000 ms stimulus onset asynchrony. Participants were instructed to respond as quickly and accurately as possible with their right index finger every time they heard a target stimulus and not to respond to standards or novels.

Data acquisition

EEG/ERP

Electroencephalograms (EEG) were acquired continuously while participants were performing the auditory oddball task. Data were collected using an SA bioelectric amplifier system capable of amplifying electrical activity from 64 separate single-ended channels. Scalp potentials were recorded from tin electrodes (ElectroCap International) placed over 62 electrode sites according to standard placement guidelines of the International 10–20 System and some additional sites. (EOG) was recorded from electrodes located on the lateral and supra-orbital ridges of the right eye. All electrodes were referenced to the nose. Electrical impedances were maintained below 10 kΩ throughout the experiment. The EEG channels (SA instruments) were amplified (20,000 gain) with a band pass filter of 0.01 to 100 Hz, digitized on-line at a rate of 500 samples per second, and recorded on computer hard disk.

Continuous EEG recordings were filtered by a high pass 0.05 Hz filter, pre-processed using independent component analysis (ICA) to remove eye blink artifacts. The ICA utility built in the EEGLAB software (Delorme and Makeig, 2004) was used to decompose EEG recordings to independent components, and then an in-house template matching algorithm (Jung et al., 2000) was used to identify eye blinks (see supplement Fig. 1 for the eye blink template). Then, EEG signals were segmented from 210 ms pre-stimulus to 1050 ms post-stimulus. ERPs were constructed for trials in which participants correctly responded, and those trials were baseline corrected, artifacts rejected with a 100 μV maximum amplitude safeguard, averaged and filtered with a 30 Hz low pass filter. The averaged epoch was 1250 ms long with a 200 ms pre-stimulus baseline.

SNP data

A blood or saliva sample was obtained for each subject and DNA was extracted. Genotyping was performed using the Illumina BeadArray™ platform and the GoldenGate™ assay (Fan et al., 2003; Oliphant et al., 2002). The PG Array of Genomas Inc. (Hartford, CT, USA) was used, which contains a SNP array consisting of 384 SNPs from 222 genes from 6 physiological systems: neurobiology, cardiovascular system, inflammation, metabolism, cholesterol biochemistry, and cell proliferation (Liu et al., 2009). The following pathways were represented: neurotransmitter axes (serotonin, dopamine cholinergic, histamine and glutamate), apolipoproteins and receptors, insulin