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Neural and genetic correlates of binge drinking among college women

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ABSTRACT

Ninety-seven female students were assigned to groups consisting of 55 infrequent and 42 frequent binge drinkers. The groups were compared on self-report measures of impulsivity, sensation seeking, and alexithymia, as well as several measures relevant to neural and genetic mechanisms, such as brain activation during a time estimation task and selected genotypes. Analyses of stimulus-locked brain activity revealed a slow cortical potential over the right parietal cortex during time estimation that was more negative among frequent binge drinkers. This group also showed a greater prevalence of a *CHRM2* genotype previously associated with substance dependence and Major Depressive Disorder as well as a modest elevation on a non-planning impulsiveness scale. We conclude that the enhanced brain activation shown by binge drinkers compensates for an underlying deficit. That deficit may be reflected in poor planning skills and a genetic difference indicating increased risk for problems in later life.

1. Introduction

An impaired ability to estimate the passage of time has been linked to substance use. For example, Smart (Smart, 1968) found that alcoholics performed less well than social drinkers on the Future Time Perspective (Wallace, 1956) task, which measures the ability to conceptualize the future in terms of the timing and ordering of future events. Manganiello (1978) described a similar finding from his comparison of 45 adult heroin addicts and 50 high school students. In addition, Petry, Bickel, and Arnett (1998) found that heroin addicts scored lower than a control group on both the Future Time Perspective task and the future orientation subscale of the Stanford Time Perception Inventory (TPI; Zimbardo, 1992). In all three studies, substance-abusing patients reported shorter time horizons than the control group. Petry and others have theorized that the shortened time horizons of substance abusers could contribute to delay discounting – a disadvantageous preference for immediate, smaller rewards versus delayed, larger rewards.

Other research suggests that altered time perception and delay discounting are not only demonstrable in patients. Laghi, Liga, Baumgartner, and Baiocco (2012) and Vuchinich and Simpson (1998) have demonstrated similar findings in a subset of college students whose heavy drinking patterns suggest increased risk for future problems (Jennison, 2004), including dependence. Laghi and colleagues surveyed a total 1350, 17–19 year old participants of whom 422 met the study definition for frequent binge drinking. On the Stanford TPI, frequent binge drinkers exhibited lower scores than the control group on the positive future orientation subscale. Vuchinich and Simpson similarly found that heavy drinking college students reported low future time orientation scores on the TPI, as well as greater delay discounting of a hypothetical reward.

The present study was designed to extend these studies of altered time perception in heavy drinking college students. It offered at least four specific innovations. First, it examined time perception ability with a simple task in which the students used a button press response to register their estimate of the passage of a fixed interval of time. Because of its relative simplicity, a button press response offers the advantage of being less dependent than time perception questionnaires upon individual differences in reading skill, verbal comprehension, and motivation. It can also be argued that it is a more valid estimate of time estimation ability for actual events than are perceptions of time within fictional scenarios.

The second innovation was the use of a slow electroencephalographic potential (SP) as an indicator of neural differences underlying time estimation. Normal subjects with poor time estimation ability have been shown to exhibit SPs of a more negative

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amplitude and slope than normal subjects with accurate time estimation ability (Ladanyi & Dubrovsky, 1985). We have previously demonstrated more negative SP amplitudes indicating premature response preparation among cocaine-dependent adults with Antisocial Personality Disorder (Bauer, 2001) and HIV/AIDS patients with an obese body mass (Bauer, 2008). In the present study of college students, we improved upon on our previous methods. More specifically, in the present study, we adopted a new method in which we were able to differentiate and separately localize the SP associated with the complex process of estimating time (see Bueti & Walsh, 2009 for a review) from the electroencephalographic change associated with executing a motor response, i.e., the motor potential.

The third innovative feature was the examination of covert genetic mechanisms that may contribute to binge drinking. Given the limited scope of this study, a short and a priori-specified list of candidate gene single nucleotide polymorphisms (SNPs) were tested. All of the candidates had previously been associated with risk for alcohol dependence in large cooperative studies, such as the Collaborative Study on the Genetics of Alcoholism. The genes studied presently were *GABRA2* (Edenberg et al., 2004), *CHRM2* (Wang et al., 2004), and *ANKK1* (Dick et al., 2007). Accompanying the genetic assessment was an assessment of stable personality features that may also predict binge drinking (Moreno et al., 2012; Shin, Hong, & Jeon, 2012). Personality was measured with three self-report instruments that captured different aspects of the impulsivity construct – the Toronto Alexithymia Scale (TAS; Taylor, Ryan, & Bagby, 1985), Barratt Impulsiveness Scale (BIS-11; Patton, Stanford, & Barratt, 1995) and the Sensation Seeking Scale (SSS; Zuckerman, Eysenck, & Eysenck, 1978).

The final and most intriguing aspect of the study was its exclusive focus on women. This focus was suggested by evidence (McCabe, 2002) showing that women experience their heaviest drinking during the early years of college whereas the peak occurs during the later years for men. Because this sex difference may indicate the presence of other differences (Balodis, Potenza, & Olmstead, 2009; Randolph, Torres, Gore-Felton, Lloyd, & McGarvey, 2009) between women and men in the causes, correlates, and consequences of heavy drinking over time, including both sexes in the present study was not defensible. Instead, we recruited enough members of one sex to provide a powerful test of our hypotheses, which were the following:

(1) In comparison to infrequent drinkers, binge drinkers will overestimate time passage (i.e., respond prematurely), exhibit a larger SP during the time estimation interval, and report higher scores on impulsivity scales (BIS-11, TAS, SSS).
(2) The frequency of *GABRA2*, *ANKK1*, and *CHRM2* SNP genotypes previously associated with substance dependence or impulsive personality features will be greater among binge drinkers in comparison to infrequent drinkers.

2. Methods

2.1. Participants

One-hundred-and-four female students, aged 18–20 years, were recruited from 4 private and 2 public universities in Connecticut. They were examined during their freshman or sophomore years. Students were contacted through a variety of methods, including newspaper and radio ads and posters. Interested parties were asked to call the study office for information and eligibility screening. Those who appeared eligible were invited to visit the Health Center on a subsequent day for further screening and evaluations. Students who reported no past year pregnancy, psychosis, or major medical disorders that would complicate their general health (HIV, thyroid disease) or evoked electroencephalographic responses (head injury, seizure disorder, heart disease, neurological disorders) were included. To ensure consistency of outside influence, they were also required to have full-time status, live on campus, and participate in the school's food service meal plan. Ineligible volunteers were paid $30 for time and effort and dismissed. The students who completed the full evaluation were paid $150 each.

2.2. Laboratory evaluation

At the time of their in-person visit to the laboratory, students reviewed and signed an IRB-approved informed consent and HIPAA agreements. They were then asked to complete questionnaires assessing alcohol (Saunders & Lee, 2000) and drug (McCabe, Boyd, Cranford, Morales, & Slayden, 2006) use. They provided medical history information by self-report and records obtained from the primary care physician. Sensation-seeking and alexithymic traits were assessed with the Sensation Seeking (Zuckerman et al., 1978) and Toronto Alexithymia Scales (Taylor, Bagby, Ryan, & Parker, 1990), respectively. In addition, self-ratings of impulsivity in the attention, motor, and non-planning categories were obtained from the BIS-11 (Patton et al., 1995) scale. A saliva sample was collected for DNA analysis.

To assess time estimation, we recorded electroencephalographic activity and response latency while the students performed a simple task consisting of 50 trials. Before the task, they were instructed to focus attention on a computer monitor which would display the letter "X" (retinal angle = 2.8°) once every 4 s. They were asked to estimate the passage of 1.5 s after the onset of this stimulus and indicate their estimate by pressing a response key with the left index finger. Two seconds after each button press, the phrase "too slow", "too fast", or "on-target" was presented indicating that the estimate was slow, fast, or on-target (1.5 ± 0.25 s).

During the task, electroencephalographic activity was recorded from a cap (Electro-Cap International, Eaton, OH) containing 64 Ag/AgCl electrodes. The cap electrodes were referenced to linked ear electrodes. Similar electrodes placed above and below the right eye were used for eye movement and eyeblink detection. All signals were digitized at 500 Hz, amplified to a gain of 10 K, and processed with a Synamps^2 system (Compumedics Neuroscan, Charlotte, NC) running SCAN 4.4 software.

2.3. Data reduction

2.3.1. Slow potentials, motor potentials, and task performance

Slow potentials (SP) were derived from filtered (bandpass = 0.5–12.0 Hz, 24 db/octave) epochs spanning a period from 100 ms preceding to 1500 ms following the onset of the time estimation cue, "X". Each epoch was mathematically corrected for eye movement artifact (Semlitsch, Anderer, Schuster, & Presslich, 1986) and the average voltage of the pre-stimulus period. All epochs without A/D converter overflow or large voltage deviations (>20 μV) were formed into time-point averages. In keeping with the recommendations of Mordkoff and Gianaros (2000), the mean voltage of the SP was measured during a likely pre-onset period (502–1000 ms) and during a period within which it was likely to peak (1002–1500 ms). The amplitude change across these periods was then computed. It was the difference in voltage between the peak minus pre-onset periods at each of 4 electrode sites in the vicinity of pre-motor (FC3, FC4) and post-motor cortex (CP3, CP4).

Motor potentials (MP) were similarly derived from filtered and artifact-corrected EEG epochs. In contrast to SPs which were derived from epochs aligned by stimulus onset, MPs were computed from epochs aligned by button press onset. Each epoch spanned a period from 1000 ms preceding to 500 ms following button press onset. All artifact-free epochs were formed into a time-point average. The amplitude of the large negative peak at response onset was measured at FC3, FC4, CP3, and CP4 sites relative to the average voltage within a pre-onset period (−1000 ms to −500 ms).

Behavioral estimates of time passage were also calculated. The principal estimate was button press latency measured to the nearest 2 ms. In addition, within-subject variability in time estimation was measured by the standard deviation of button press latency across all trials.

2.3.2. DNA

Genomic DNA was purified from saliva samples by the University of Connecticut's Clinical Research Center core lab. DNA samples were placed in 96-well plates and genotyped using PCR based TaqMan 5′-nuclease allelic discrimination assay methods. Representative single nucleotide polymorphisms (SNP) were assayed within *CHRM2* (rs12673281 and rs324650) and *GABRA2* (rs279871) chromosomal regions. Within the *ANKK1* region, the SNP at rs1800497 (also known as the Taq1a polymorphism) as well as a downstream SNP at rs17115439 (Dick et al., 2007) were assayed.

2.3.3. Group assignment and data analysis plan

In the analysis, the 55 students reporting infrequent (n = 30 never plus n = 25 less than monthly) episodes with ≥6 alcohol drinks consumed on the AUDIT were compared to the 42 students reporting frequent (n = 28 monthly plus n = 14 weekly) episodes on this scale.

Analyses of variance (ANOVAs) were used to compare these groups on background variables such as age, alcohol and drug use, BIS-11, sensation seeking, and alexithymia scale scores. For the analysis of electrophysiological data, separate ANOVAs were performed on SP amplitude change and MP peak amplitude across the 4 representative electrode sites. The ANOVAs tested binge drinking frequency as a grouping factor as well scalp distribution differences by region (anterior/posterior)