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Gender differences in reactivity to alcohol cues in binge drinkers: A preliminary assessment of event-related potentials

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ABSTRACT

Binge drinking is associated with functional brain abnormalities similar to those observed in alcoholics and can be viewed as a first step towards alcohol dependence. Adult men are twice as likely as women to develop alcoholism. This study investigates (1) the presence of alcohol cue reactivity in bingers, a feature that has been proposed to underlie the emergence of alcohol dependence; and (2) a possible higher alcohol cue reactivity in men binge drinkers which could explain their higher risk for alcohol use disorders in adulthood.The P3 component of the event-related potentials (ERPs) was recorded during a visual oddball task in which controls (n=27: 10 men and 17 women) and binge drinkers (n=29: 15 men and 14 women) had to detect infrequent deviant stimuli (related to alcohol or not) among frequent neutral stimuli. Results showed that binge drinkers, compared to light drinkers, displayed increased P3 reactivity to alcohol related cues with a greater effect among men. Our results suggest the phenomenon of alcohol cue reactivity to be a possible avenue by which a higher risk population, binge drinkers, and men in particular, are prone to develop problematic alcohol use.

1. Introduction

Binge drinking, the consumption of large amounts of alcohol in a short time, followed by a period of abstinence, is particularly evident in university students, with almost half of college students reporting binge drinking in epidemiological studies (Marczinski et al., 2009). There is considerable evidence indicating that the heaviest drinking pattern (including binge drinking) peaks during late adolescence (between 18–22 years) (Kuperman et al., 2005). It is often a normative (Wechsler et al., 1998) but developmentally limited feature of early young adulthood (Gotham et al., 1997) which declines with the increased responsibility due to life transitions such as employment, marriage or parenthood (*e.g.* Muthén and Muthén, 2000). However, in the meantime, young drinkers tend to ignore what damage they may actually be doing to their health in general and to their brain in particular. Indeed, besides the numerous negative short-term consequences associated with binge drinking (*e.g.* Marczinski et al., 2009), the increasing literature on cerebral consequences of binge drinking is quite alarming. Neuroimaging studies using event-related potentials (ERPs) and functional magnetic resonance imaging (fMRI) recordings during diverse cognitive tasks showed that binge drinking is associated with neurophysiological impairments (Ehlers et al., 2007; Crego et al., 2009; Maurage et al., 2009; Crego et al., 2010; Maurage et al., 2012; Petit et al., 2012a, 2012b; López-Caneda et al., 2012) and with abnormal activities in occipital, hippocampal, frontal and prefrontal areas (Schweinsburg et al., 2010, 2011; Squeglia et al., 2011; Xiao et al., in press). More importantly, these studies consistently have shown that, even if they may stay unexpressed at the behavioral level, or are less serious than those provoked by chronic alcoholism, binge drinking does provoke considerable cerebral dysfunctions which mirror those observed in chronic alcohol dependence.

These observations have a huge importance, as binge drinking and chronic alcoholism may correspond to two stages of the same phenomenon (*e.g.* Enoch, 2006; Li et al., 2007). Indeed, epidemiological studies have suggested that binge drinking in youths is associated with an increased risk of alcohol abuse/dependence in adulthood (*e.g.* Chassin et al., 2002; McCarty et al., 2004; Viner and Taylor, 2007) or, in other words, that binge drinking pattern may be considered as a precursor of chronic alcoholism. It is indeed reasonable to assume that some deficits and/or neurobiological changes due to binge drinking could play a role in the maintenance of alcohol use and abuse, and could cause difficulties to stop consumption and develop into long-term problem-use. Given this, and knowing that the highest risk period to develop alcohol use disorders is set at the beginning of the third decade of life

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(King et al., 2006), the period of heavy drinking in late adolescence/early adulthood constitutes a key time to elucidate the possible role of the emerging brain abnormalities as risk factors to chronic alcoholism. The way to achieve this goal is to further investigate the similarities that exist between the neurocognitive deficits and/or abnormalities detectable in binge drinkers and those observed in adult chronic alcoholics by focusing specifically on the ones that have been showed to play a role in the emergence and/or the maintenance of persistent drinking habits in chronic alcoholics.

An important feature that has been proposed to underlie alcohol dependence is the processing bias for drug related stimuli (for reviews see Franken, 2003; Field et al., 2006; Field and Miles, 2008). It has been largely evidenced that alcohol dependent adults exhibit increased physiological reactivity in response to alcohol cues in the form of changes such as heart rate elevations or salivation to alcohol-related words, pictures, scents, tactile cues, or imaginal stimuli (*e.g.* Rohsenow et al., 1992; Monti et al., 2000). Cognitive reactions are also obvious elements of cue reactivity. Alcoholics display slower reactions to alcohol-related stimuli (*e.g.* Sayette et al., 1994) and difficulty shifting attention away from them (*e.g.* Stormark et al., 1997). Brain imaging studies using functional magnetic resonance imaging (fMRI) and event-related potentials (ERP) enable to reveal the neural underpinnings of the cognitive configuration and processing response to stimuli linked to substance use (Tiffany and Conklin, 2000). The use of the ERP technique has objectified that the cerebral activity recorded during processing of alcohol-related pictures is heightened in alcoholics patients compared to controls (Herrmann et al., 2000; Namkoong et al., 2004). Theoretical accounts underlying such cue reactivity rely deeply on the incentive sensitization theory of Robinson and Berridge (1993). The theory assumes that drugs of abuse can induce neuroadaptations in incentive motivation and reward systems, causing these systems to become hypersensitive to both drugs and drug-related stimuli. fMRI studies have objectified that alcohol dependent individuals show greater BOLD response to alcohol-related stimuli than controls in brain regions that have been conditioned with positive, rewarding aspects of alcohol use as the subcallosal cortex anterior cingulated, the left prefrontal cortex and bilateral insula (*e.g.* Maas et al., 1998; Garavan et al., 2000; Kilts et al., 2001; Tapert et al., 2004). In individuals with heavy drug use history, the exposure to substance-related stimuli that have regularly been associated with drug intake, its ensuing incentive-motivational and rewarding effects become conditioned stimuli which elicit conditioned responses such as drug craving and consumption (*e.g.* Everitt and Robbins, 2005). As such, the phenomenon of cue reactivity is believed to play a central role in the emergence and the maintenance of drugs consumption disorders (Goldstein and Volkow, 2002; Lubman et al., 2004) and relapse (Robbins and Everitt, 1999). Because the P3 component of the ERP is stated to reflect motivational engagement, motivated attention, and the activation of arousal systems in the brain (Cuthbert et al., 2000; Lang et al., 1997), authors of the electrophysiological studies on alcoholics cited above (Herrmann et al., 2000; Namkoong et al., 2004), by specifically reporting an enhancement of the P3 component in response to alcohol related stimuli (as compared to neutral ones), objectified the allocation of attentional resources to these stimuli, depicting alcoholics' motivational states. Interestingly, ERP studies have evidenced that higher reactivity to alcohol cues is not a phenomenon limited to pathological alcoholic population, but that adult heavy drinkers (Herrmann et al., 2001) and young heavy social drinkers (Petit et al., 2012a), respectively exhibit heightened alcohol related P3 and signs of altered inhibitory processes when confronted with an alcohol-related context. Moreover, studies have also indicated that enhanced P3 cue-reactivity, instead of being a consequence of alcohol use, may be one of its predictor and serve as a risk marker for substance use and dependence (Bartholow et al., 2007, 2010). These observations call up for further research as far as the objective that we pursue is concerned. The first aim of this study will therefore be to deepen the knowledge about the cue reactivity phenomenon in a non-clinical young drinker's population as the binge drinkers' one. The idea is that the cue reactivity phenomenon could be an important factor that could explain epidemiological studies' results linking binge drinking in youths and problem drinking in adulthood.

Secondly, we will especially focus on sex influence. Gender difference in episodic heavy drinking among late adolescents and university students is very small (*e.g.* Windle and Windle, 2005; Dawson et al., 2004) and even tends to become nonexistent in Europe (Currie et al., 2000). However, a discrepancy in prevalence rates for alcohol involvement is observed when youth enter into young adulthood: boys become increasingly more at risk for problematic drinking and alcohol use disorders (Young et al., 2005). Men are consistently more than twice as likely as women to report chronic heavy drinking (*e.g.* Meyer et al., 2000), recurrent alcohol intoxication (*e.g.* Rehm et al., 2001) and to develop alcoholism. Until now, the underlying biology contributing to this difference in vulnerability still remains largely unexplained. It has been stated for a long time that alcohol abuse disturbs the normal circuitry of rewarding and adaptive behaviors by enhancing the effect of midbrain dopamine (DA) function, particularly at the level of their terminals in the nucleus accumbens (NAc) (Di Chiara and Imperato, 1988). Recent research moreover showed that that not only alcohol, but alcohol's conditioned cues themselves, can elicit DA activity in the NAc (Katner et al., 1996; Katner and Weiss, 1999; Melendez et al., 2002; Doyon et al., 2003, 2005). Interesting recent findings indicating gender differences in the ability of alcohol to stimulate DA release could help explain the sex difference in alcoholism. Indeed, a positron emission tomography (PET) scan study (Urban et al., 2012) showed that when exposed to similar levels of alcohol, young heavy and binge drinkers' males showed greater DA release than women in the ventral striatum. They also demonstrated that alcohol stimulates DA release throughout the human striatum but most noteworthy in striatal regions involved in reward and motivation. This increased DA release also had a stronger association with subjective positive effects of alcohol intoxication and the authors concluded that this may contribute to the initial reinforcing properties of alcohol. We could therefore assume that, as it is the case for alcohol intake itself, males and females binge drinkers may have a differential sensitivity to cue reactivity mediated by neurochemical changes in the sense of a greater male vulnerability to cue reactivity. And this heightened cue reactivity could constitute a risk factor which could explain the gap in consumption between genders which emerges in late adolescence and persists into adulthood.

To test our two hypotheses, namely that binge drinking is associated with enhanced cue reactivity compared to controls and that cue reactivity is more pronounced in male bingers than female bingers, we will use in the present ERP study a variant of the classical oddball paradigm, in which university students, including binge drinkers and controls will have to detect (as quickly as possible, by clicking on a button) infrequent deviant stimuli among a series of frequent standard stimuli (*e.g.*, Petit et al., 2012b). University students is a particularly suitable population for our interest as binge drinking characterizes the drinking's style of adolescents and young adults (13–24 years of age) and is particularly evident in university students compared to the general population (*e.g.*, Marczinski et al., 2009). Deviant stimuli will consist of pictures that will either be related to alcohol or not. This task will help us investigate the presence of an electrophysiological and/or behavioral specific response to alcohol related stimuli in the binge