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Centrally-mediated sensory information processing is impacted with increased alcohol consumption in college-aged individuals

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ABSTRACT

Alcohol consumption can have an impact on a variety of centrally-mediated functions of the nervous system, and some aspects of sensory perception can be altered as a result of long-term alcohol use. In order to assess the potential impact of alcohol intake on sensory information processing, metrics of sensory perception (simple and choice reaction time; static and dynamic threshold detection; amplitude discrimination with and without pre-exposure to conditioning stimulation) were tested in college-aged subjects (18 to 26 years of age) across a broad range of levels of alcohol consumption. The analysis indicated no detectable associations between reaction time and threshold measures with alcohol consumption. However, measures of adaptation to short duration (0.5 s) conditioning stimuli were significantly associated with alcohol consumption: the impact of a confounding conditioning stimulus on amplitude discriminative capacity was comparable to values reported in previous studies on healthy controls (28.9 ± 8.6) for light drinkers while the same adaptation metric for heavy drinkers (consuming greater than 60 drinks per month) was significantly reduced (8.9 ± 7.1). The results suggest that while some of the sensory perceptual metrics which are normally impacted in chronic alcoholism (e.g., reaction time and threshold detection) were relatively insensitive to change with increased alcohol consumption in young non-alcoholic individuals, other metrics, which are influenced predominantly by centrally-mediated mechanisms, demonstrate a deviation from normative values with increased consumption. Results of this study suggest that higher levels of alcohol consumption may be associated with alterations in centrally-mediated neural mechanisms in this age group.

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Abbreviations: 2AFC, two-alternative forced-choice; AD, amplitude discrimination; AUDIT-C, alcohol use disorders identification test (consumption); DL, difference limen; DPM, drinks per month; GABA, γ-aminobutyric acid; NMDA, *N*-methyl-D-aspartate; RAPI, Rutgers alcohol problem index; RT, reaction time; SSA, single-site adaptation; TLFB, timeline follow back

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1. Introduction

Previously, we reported that the ability of an individual to perceive the difference between two simultaneously-delivered vibratory stimuli to the skin can be impacted significantly by relatively brief (0.2 to 2 s) periods of pre-exposure to conditioning stimuli (Folger et al., 2008; Francisco et al., 2011; Tannan et al., 2006, 2007, 2008; Tommerdahl et al., 2007a, 2007b, 2010a; Zhang et al., 2008, 2009, 2011a, 2011b). The measure that we currently use to describe the impact that conditioning stimuli have on some aspect of sensory discriminative capacity – but most often amplitude discriminative capacity – is the *adaptation metric*, a value which has been demonstrated to be relatively constant across a large age spectrum of healthy controls (Zhang et al., 2011b). However, the adaptation metric for a number of neurological conditions has been demonstrated to be reduced or below normative values. Observations from a number of studies have demonstrated substantial decreases in adaptation metrics: subjects with autism (Francisco et al., 2011; Tannan et al., 2008; Tommerdahl et al., 2007a), mild NMDA receptor block (Folger et al., 2008), a number of types of chronic pain (Tommerdahl et al., 2010b; Zhang et al., 2011a), and concussion (Tommerdahl et al., 2010b). These findings suggest that the method could be viewed as a potential indicator or marker of systemic cortical alterations, as adaptation, at this short duration time scale, is impacted by a number of factors. In particular, these factors include GABA and NMDA receptor-mediated neurotransmission, and neuron–glial interactions (for discussion, see (Folger et al., 2008; Francisco et al., 2008; Tannan et al., 2007, 2008; Tommerdahl et al., 2007a, 2010a, b; Zhang et al., 2009, 2011a, 2011b). A central theme of these observations – discussed in each of the aforementioned reports – is that the adaptation metric, at these relatively short durations (for review of dynamic mechanisms involved, see Tommerdahl et al., 2010a), is impacted by alterations that are predominantly centrally-mediated.

A number of studies have demonstrated that alcohol use can lead to peripheral sensory impairment and/or altered central processing of sensory information. Sensory assessments of individuals with alcoholism, in particular assessments of vibration thresholds, thermal sensitivities, and pain tests, have provided useful metrics in detecting and describing alcoholic peripheral neuropathy (Hilz et al., 1994, 1995; Jochum et al., 2010; Sosenko et al., 1991; Yarnitsky and Zaslansky, 1998). Additionally, impairment in central neural mechanisms in individuals with alcohol use disorders has been implicated by studies describing abnormal inhibition of sensory gating; reports have demonstrated that thalamocortical feed-forward interactions modulate sensory information processing (Wang et al., 2010), as well as disinhibition of sensory evoked potential recovery patterns (Marco et al., 2005; Mochizuki et al., 2004). These previous evaluations provided rationale for analyzing sensory percepts of college students, a population with high prevalence of moderate to heavy binge drinking (Grant et al., 2004; Wechsler et al., 2002; Wechsler and Nelson, 2001). Moderate-to-heavy alcohol consumption in this age group has been shown to impair a variety of centrally-mediated functions of the nervous system inclusive of, but not limited to, spatial memory judgment and decision-making, mood and behavior, motor performance, learning, executive functioning, and rate of information processing (Courtney and Polich, 2009). Taken together, the above-described studies would suggest that a centrally-mediated metric of sensory information processing, such as the adaptation metric, may be significantly impacted by heavy alcohol use by college-aged students.

In this study, standard screening methods of alcohol consumption were paired with metrics of sensory perception in order to assess potential sensory information processing changes in college-aged individuals who consumed alcohol on a regular basis. The results of the study suggested that, although some of the sensory perceptual metrics (in particular, reaction times and detection thresholds) were relatively insensitive to change with increased alcohol consumption, adaptation metrics were significantly lower in the group of subjects who consumed higher quantities of alcohol.

2. Results

2.1. *Increased alcohol consumption does not have an impact on reaction time or threshold measures in 18–26 year olds.*

As Fig. 1 illustrates, both simple and choice reaction times demonstrated little variation across the range of alcohol consumption. The mean simple reaction times (247.6 ± 12.3 ms) across all levels of consumption were consistently faster than choice reaction times (405.9 ± 11.6 ms) ($n=87$; $*p \ll 0.01$).

Static and dynamic detection threshold assessments were also independent of consumption as shown in Fig. 2. The mean dynamic thresholds (10.0 ± 0.5 μm; $n=84$) were consistently higher than those of static thresholds (16.2 ± 0.5 μm; $n=87$) across all quantities of consumption ($*p \ll 0.01$).

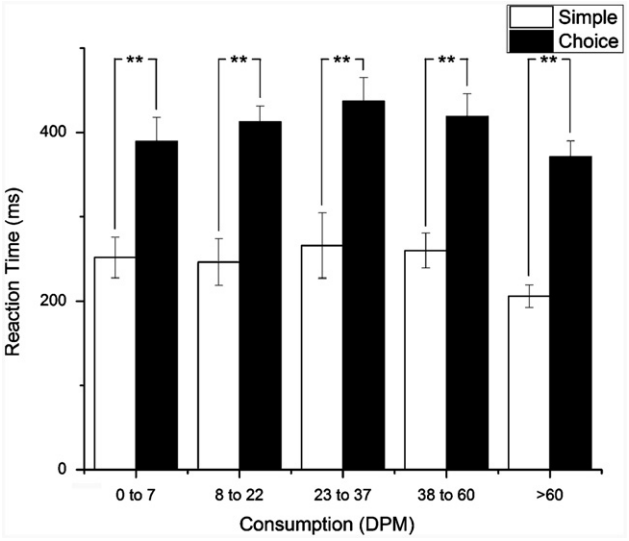

Fig. 1 – Impact of alcohol consumption on simple and choice reaction times. The reaction times (ms) are not affected over increases in alcohol consumption reported as drinks per month ($n=87$; $**p \ll 0.05$).

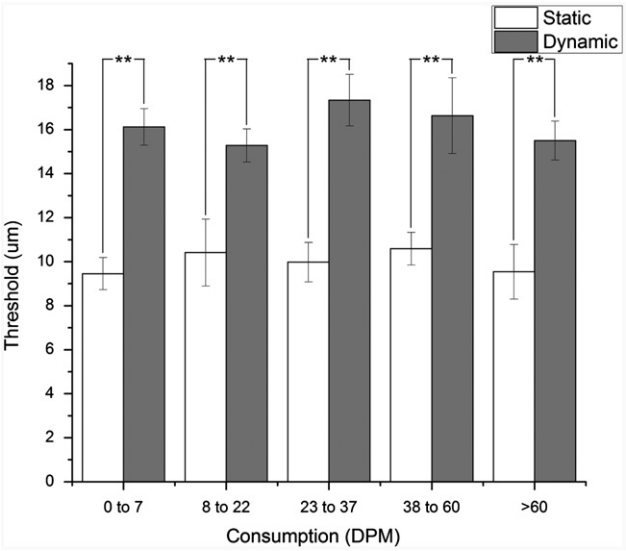

Fig. 2 – Impact of alcohol consumption on detection thresholds. The detection thresholds (μm) are not affected over increased reported alcohol consumption in drinks per month ($n=84$; $n=87$; $**p \ll 0.05$).

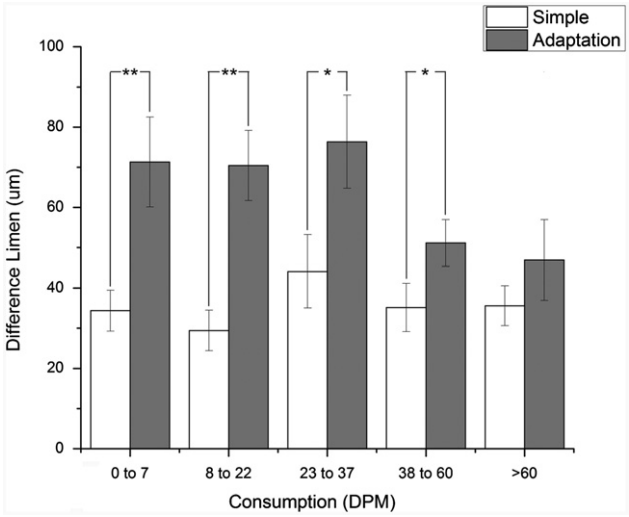

Fig. 3 – Impact of alcohol consumption on amplitude discrimination in the presence ("adaptation") and absence ("simple") of pre-exposure to a single-site conditioning stimulus. Amplitude discriminative capacity remained relatively unaffected by alcohol consumption. However, the impact of adaptation via single-site conditioning for the amplitude discrimination task across subjects was decreased with increased alcohol consumption reported as drinks per month ($n=67$; $**p<0.01$, $*p<0.05$).

2.2. *Increased alcohol consumption does not affect amplitude discriminative capacity but does impact adaptation metrics.*

The amplitude discrimination task was assessed in the absence and presence of conditioning stimulation to compare the impact of sensory conditioning in subjects with varying levels of alcohol consumption. The data represented means defined by an average of 13.4 ± 0.5 (ranging from 12 to 15) subjects per bin ($n=67$; see Fig. 3). The simple amplitude discrimination task showed no significant difference with increased alcohol consumption with an average DL of 35.9 ± 2.9 μm, which was comparable to metrics of healthy controls (35.0 ± 1.61 μm; $p \gg 0.05$). However, the DLs for the same task in the presence of conditioning stimulation demonstrated a decrease in the impact of the conditioning stimulus – or a decrease in the adaptation metric – with increased reported consumption. In order to more clearly observe the impact of conditioning stimulation on the simple amplitude discrimination task, a normalized percentage value corresponding to this ratio within subjects was plotted against the number of drinks the subjects reported consuming per month (DPM; Fig. 4). The same trend of decreased adaptation metric with increased alcohol consumption was observed ($28.9\pm8.6\%$ for between 0 and 7 DPM compared to $8.9\pm7.1\%$ for greater than 60 DPM).

In similar fashion, the impact of conditioning stimuli on amplitude discriminative capacity was evaluated in terms of the AUDIT and RAPI assessments (Fig. 5). The calculated values for the AUDIT scale for these subjects ranged from 0 to 28, for an average of 13.4 ± 0.9 (ranging from 12 to 16) subjects per bin. The effect of conditioning stimulation on amplitude discriminative capacity decreased with increasing AUDIT scores (Fig. 5, left panel). In order to further evaluate the relationship between alcohol consumption and

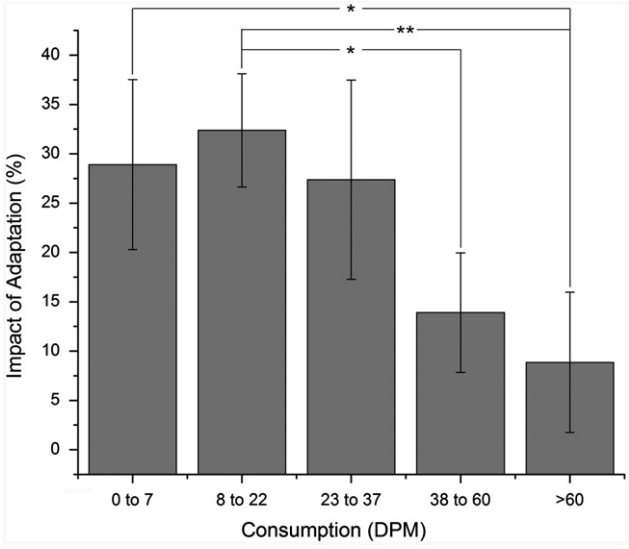

Fig. 4 – Impact of alcohol consumption on adaptation. The adaptation metric, or the difference between the two conditions of amplitude discriminative capacity (see Fig. 5), decreases with increased alcohol consumption reported as drinks per month ($n=67$; $**p<0.01$, $*p<0.05$).

adaptation metrics, the AUDIT-C (consumption) screen for hazardous alcohol use was more closely analyzed from the AUDIT questionnaire. Subjects responded by indicating how often they drank alcohol, how many standard drinks they consumed on a typical drinking day, and how often they consumed at least six drinks on one occasion. The adaptation metric was statistically significantly higher for subjects who

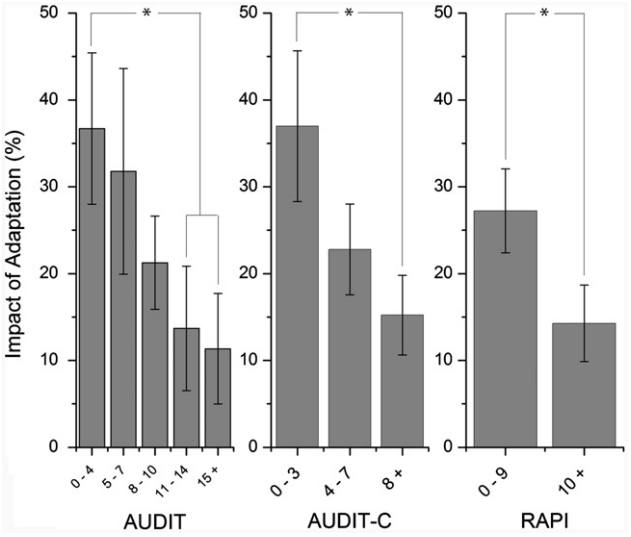

Fig. 5 – Adaptation metric decreases with increases in AUDIT, AUDIT-C and RAPI. The impact of single-site conditioning stimulation (%) on the amplitude discrimination task decreases with increased values on the AUDIT scale (left panel). The data support a relatively linear negative relationship ($n=67$). The effect of adaptation for the lowest (0 to 4) and the highest (15 to 28) AUDIT values are statistically significant ($*p<0.05$). The adaptation metric (%) is statistically significantly higher for subjects who scored lower on the AUDIT-C than for those who scored highest for identifying hazardous drinking behavior or active alcohol use disorders (AUDIT-C; center panel; $n=66$; $*p<0.05$). The adaptation metric (%) also decreases with increased risk of adolescent problems in correspondence with alcohol consumption (RAPI; right panel; $n=67$; $*p=0.05$).

never or rarely consumed alcohol (AUDIT-C score from 0 to 3; $n=13$) than for those who drank at least twice a week, at least five drinks per drinking day, and who had at least monthly binging episodes (AUDIT-C score at least 8; $n=18$; $p<0.04$). The RAPI was used to assess alcohol-related problems. The reported values ranged from 0 to 35 with 44 subjects who had indices less than 10 and 23 subjects who scored at least 10 on the RAPI scale. The impact of conditioning on amplitude discrimination was almost statistically significant ($p=0.05$) where the adaptation metric was higher for lower risk subjects (27.2±4.8%) than those who were at higher risk for alcohol-related problems (14.3±4.4%).

3. Discussion

In this study, sensory perceptual metrics were obtained on 87 college students. Six assessments were performed to evaluate reaction times (simple and choice), sensory detection thresholds (static and dynamic), and amplitude discrimination capacity with and without pre-exposure to conditioning stimulation. To our knowledge, previous studies have not analyzed similar sensory tasks as conducted in these experiments. The observations from this study indicated that there were no significant changes in reaction times and detection thresholds across the spectrum of levels of alcohol consumption in this study. However, the adaptation metric revealed that higher alcohol consumption was associated with a significantly reduced impact of conditioning on amplitude discriminative capacity. One interesting aspect of these observations is that subjects who consumed more alcohol performed better on the amplitude discrimination task in the presence of illusory conditioning than healthy control subjects. In other words, abnormal processing of the conditioning stimulus allows better task performance, and these results, along with prior reports, imply that this performance is a result of decreased CNS function in subjects who consume higher amounts of alcohol.

The reduction of the adaptation metric with increased alcohol consumption of alcohol in the college-aged population has not been previously reported, although such reductions in other subject populations have been observed previously, and the neurobiological basis of short-term adaptation has been discussed extensively (Folger et al., 2008; Francisco et al., 2008; Tannan et al., 2005, 2007, 2008; Tommerdahl et al., 2007, 2010a; Zhang et al., 2009, 2011a, 2011b). Although the neural mechanisms that underlie these effects of a pre-exposure to vibrotactile stimulation on perception remain to be established with absolute certainty, multiple animal studies have demonstrated that such a pre-exposure is reliably accompanied by reductions in neuronal responsivity at both peripheral and central levels of the somatosensory nervous system (Tommerdahl et al., 2010a). Neurophysiological studies have demonstrated that repetitive stimulation results in temporal changes in cortical activity, the most prominent of which is a reduction in cortical response with extended stimulus duration. At the single-cell level, somatosensory cortical pyramidal neurons undergo prominent stimulus-dependent modifications of their receptive fields and response properties with repetitive stimulation. These alterations can develop within tens of milliseconds of stimulus onset and can disappear within seconds after termination of the stimulus (Kohn and Whitsel, 2002; Tommerdahl et al., 1996, 1998, 2005a, 2005b). At the neural population level, optical imaging studies have also characterized the short-term dynamics of the contralateral primary somatosensory (SI) cortical response of squirrel monkey using different amplitudes and durations of vibrotactile stimulation (Chiu et al., 2005; Simons et al., 2005, 2007).

Sensory adaptation is an important fundamental neural mechanism involved in information processing (Cloninger, 1987; Hollins et al., 1990; Tommerdahl et al., 2007a, 2007b). Previous studies using this adaptation metric demonstrated that a conditioning stimulus delivered to one of the two sites prior to the amplitude discrimination task significantly altered a subject's ability to determine the actual difference between the two stimuli (; Tannan et al., 2007, 2008) by introducing a confound. In other words, the conditioning stimulus makes the subsequent stimulus, at the conditioned site, feel weaker and consequently, amplitude discriminative capacity is reduced. Neurophysiological studies have demonstrated that the effects of reduced intensity due to adapting stimulation are possibly attributable to a reduction in the

responsivity of central neurons after prolonged or repetitive stimulation. More specifically, Lee and Whitsel (1992) and Lee et al. (1992) found that the majority (58%) of the SI neurons sampled showed a decreased response to repetitive stimulation (3 to 5 Hz) of their receptive fields. In that report, it was proposed that the glutamate-mediated excitatory effects on NMDA receptors are, to a large extent, responsible for the appreciable capacities of cortical neurons to modify their physiological properties with repetitive sensory experience.

A deficit in the ability to adapt to conditioning stimulation may be due to a disruption in the balance of excitation and inhibition (Heiss et al., 2008; Higley and Contreras, 2006), which can lead to inefficient neural coding (Reinagel, 2001). When metrics of adaptation are examined across a number of subject populations with compromised CNS – as may be the case with a neurodevelopmental disorder (autism; Tannan et al., 2008; Tommerdahl et al., 2007a), acute pharmacological block (Folger et al., 2008) or chronic pain conditions (Hollins and Sigurdsson, 1998; Zhang et al., 2011a) – metrics of adaptation are significantly diminished from that of the control population. These findings suggest that the method could be viewed as a potential indicator or marker of systemic cortical alterations, as adaptation, at this short duration time scale, is impacted by a number of factors. In particular, these factors include GABA and NMDA receptor-mediated neurotransmission, and neuron–glial interactions (for discussion, see (Folger et al., 2008; Francisco et al., 2008; Tannan et al., 2007, 2008; Tommerdahl et al., 2007a, 2010a, 2010b; Zhang et al., 2009, 2011a, 2011b) which play significant roles in the way in which cortical information processing capacities of a number of clinically-identified subject populations are impacted by their respective disorders.

While specific cortical regions may be associated with the impulsion and/or motivational factors leading to alcohol use and abuse, alcohol consumption induces a systemic effect on the entire CNS which impacts both cortical and subcortical regions. We view that the adaptation metrics in this study, although they primarily targeted interactions within somatosensory cortex, are good indicators of systemic cortical alterations. Neural mechanisms involved in the process of adaptation are suspected to be impacted in alcoholism, or with significant alcohol consumption, because chronic exposure to ethanol has been shown to affect GABAergic neurotransmission as well as NMDA receptor densities. Previous animal and human studies have demonstrated that at the level of inhibitory neurotransmission, chronic exposure to ethanol alters pre- and post-synaptic GABA function (Fleming et al., 2009; Valenzuela, 1997; Vengeliene et al., 2009). Furthermore, there is a redistribution and increase in excitatory NMDA receptor concentration and density by upregulation mechanisms with chronic ethanol exposure (Clapp et al., 2009). These adaptive mechanisms balancing excitatory and inhibitory neurotransmission are still under research and involve consideration of factors not limited to acute versus chronic exposure as well as ethanol tolerance, dependence, withdrawal hyperexcitability, etc. (for reviews, see Kumar et al., 2004, 2009). Imaging and neurobiological research has shown that chronic alcohol consumption can lead to white matter degradation, disrupt neurocircuitry, and impact neural plasticity which can alter neurotransmission, particularly by increasing tonic inhibition (Cardenas et al., 2005; Crews et al., 2005; Herting et al., 2010; McBurney and Balaban, 2009; Oscar-Berman and Marinkovic, 2007; Pfefferbaum et al., 2010; Santhakumar et al., 2007; Sullivan and Pfefferbaum, 2005). Particularly relevant to the college-aged population, high doses of adolescent ethanol exposure has been shown to produce lasting changes in functional brain activity (for review, see Ehlers and Criado, 2010). These changes are likely to reflect the neuroadaptational response to alcohol involving alterations in the healthy functional balance between inhibitory and excitatory mechanisms (Clapp et al., 2009; Fleming et al., 2009; Heiss et al., 2008; Higley and Contreras, 2006).

Perhaps one of the more significant findings of this report is what was *not* observed: although a larger quantity of consumption clearly had an impact on the centrally-mediated adaptation metrics of this subject population, it did not have an impact on sensory thresholds and reaction times even though studies have indicated that there are altered reaction times and sensory threshold measures in chronic alcoholics (Criado and Thies, 1994; Gabernet et al., 2005; Schweizer and Vogel-Sprott, 2008; Tzambazis and Stough, 2000). While not all participants consumed large amounts of alcohol, the screening tools revealed that a portion of students ranked higher for alcohol consumption and higher risk of alcohol-related problems. Considering these data, certain segments of the subject population could be characterized as binge drinkers. However, in comparison with other reports, most alcohol studies categorize chronic alcoholism by analyzing subjects who consume approximately twice or three times more than the highest-consuming subjects in this study, and separating populations according to chronic consumption or substance abuse is difficult. The level of alcohol consumption is important to consider due to the impact of the length of exposure to high doses of alcohol and the subsequent neurobiological and physiological alterations which can develop (Valenzuela, 1997; Kumar et al., 2004, 2009). Therefore, metrics within this college-aged population may differ from those in adult populations due to the duration of alcohol use (or abuse) as well as other factors such as nutrition.

One question that may be posed by the study results is whether or not the decrease in the adaptation metric is indicative of cause or effect of drinking behavior. To address this question, we look at the broader picture addressing first what the adaptation metric indicates. Adaptation entails several cortical mechanisms that are involved in sensory information processing, and when any of these mechanisms is dysfunctional or operating at lower than normal functionality, then the adaptation metric is lower than normal. The metric itself was designed on observations obtained from in vivo experimentation that demonstrated that the SI cortical responses to repetitive stimulation were altered significantly with changes in both GABAergic and NMDA receptor-mediated mechanisms (for review, see Tommerdahl et al., 2010a). To date, the adaptation metric described in this report has been collected from over 800 individuals, and the metric itself is relatively constant across all age groups of healthy controls (Zhang et al., 2011b). Significant deviations from normative values do occur, but thus far we have only

observed this in cases of neurodevelopmental, neurodegenerative, traumatic or pharmacological compromise. For example, individuals with autism who are suspected of being GABA deficient (see Tommerdahl et al., 2006 for discussion) have lower-than-normal adaptation metrics (Tannan et al., 2008; Francisco et al., 2011). The below normal adaptation metric in autism was recently duplicated in another lab (McGonigle et al., 2012), and it was found that sensory information processing changes do change in proportion to GABA levels (McGonigle et al., 2012; Puts et al., 2011). Patients with acute pain do not demonstrate lower than normal adaptation metrics, but patients with a history of chronic pain do (Zhang et al., 2011a). Altering NMDA receptor functionality via mild NMDA receptor block also has an impact on the adaptation metric, but the metric goes back to normative values after the drug follows its time course (Folger et al., 2008). On longer time scales of recovery, we have recently made observations in which trauma (concussion) temporarily lowers the metric for 3–10 days post-trauma (and returns to baseline when the subject becomes asymptomatic), and in the case of alcoholics returning to sobriety, the metric, which is initially well below normative values, returns to normative values within 12 weeks (Tommerdahl et al., 2010b). Based on the cross-sectional studies that we have done to date, it would be difficult to hypothesize that a longitudinal study of the cohort of subjects in this report would yield results implicating below normative sensory information processing leading to drinking behavior rather than drinking behavior leading to below normal information processing capacity.

Previous sensory studies assessing a large number of healthy subjects demonstrated that the ability to discriminate between two simultaneously-delivered vibrotactile stimuli, differing only in amplitude and location, was very robust and repeatable but also very sensitive to different types of single-site conditioning stimuli such as altering the duration of adaptation stimulation (Zhang et al., 2011b). This modification significantly altered the ability of a subject to perceive the actual difference among the two stimuli in a predictable and quantifiable fashion. As a result, these methods could be viewed as a reliable indicator of the influence of adapting stimuli on the central nervous system response, as changes in the peripheral response are not significantly changed at these short stimulus durations (for discussion see Francisco et al., 2008, 2011; Tannan et al., 2007, 2008; Tommerdahl et al., 2007a, 2007b, 2008; Zhang et al., 2011a, 2011b). These findings may have value as a method of assessing cortical dysfunction in relation to unhealthy alcohol use across the spectrum from low-level risk drinking to overt alcohol dependence.

4. Experimental procedure

4.1. Subjects

One-hundred sixty-two college students (79 males, 83 females; 12 non-drinkers, 8 former drinkers, 142 drinkers) ranging from 18 to 26 years of age were recruited via electronic mail announcement from the office of the Vice Chancellor of Student Affairs at the University of North Carolina at Chapel Hill. College-aged students were analyzed for the study because they are a population with high prevalence of moderate to heavy binge drinking (Grant et al., 2004; Wechsler et al., 2002; Wechsler and Nelson, 2001). Subjects completed a survey on current medications and medical history before the experimental tests to exclude participants with any history of neurological impairment. The study design was structured to ensure that approximately 50% of the population had an AUDIT score of $\geq$8. The study was performed in accordance with the Declaration of Helsinki and was approved by the Committee for the Protection of the Rights of Human Subjects at the University of North Carolina at Chapel Hill. Subjects completed a written informed consent form after a complete description of the study was explained, and the experimental procedures were reviewed and approved in advance by an Institutional Review Board.

As the intent of the original study was to obtain information on personality measures and sweet-liking, the sensory testing was only performed on a subset of subjects. Of the 162 students who participated in the screening assessments, 87 subjects (46 males, 41 females) completed the simple and choice reaction time tasks as well as the dynamic threshold task, 84 subjects (45 males, 39 females) completed the static threshold task, and 67 subjects (40 males, 27 females) completed the simple and single-site adaptation amplitude discrimination tasks. Furthermore, within this pool of subjects who completed at least one sensory assessment, there were 7 non-drinkers, 5 former drinkers who abstained from alcohol consumption for at least 28 days (55.7$\pm$18.2 days), and 75 light to heavy drinkers.

4.2. Screening assessments

4.2.1. Alcohol consumption

The three screening tools used to assess alcohol consumption and alcohol-related problems were utilized to estimate the pattern of drinking considering the amount of alcohol consumed as well as the frequency of consumption over defined time periods. These screening methods are utilized in previous alcohol studies and are provide more quantitative information than DSM-IV diagnoses. The timeline follow back (TLFB) method (Sobell et al., 1988) was administered to estimate the quantity of alcohol consumption in a timeframe of one month. Alcohol consumption was defined by the product of the number of episodes in which subjects consumed alcohol per month and the drinks that they consumed per drinking day. This metric was subsequently defined as drinks per month (DPM). The Alcohol Use Disorders Identification Test (AUDIT) (Schmidt et al., 1995) was a screening tool used to categorize the subjects according to risk of alcohol-related problems. Typically scores below 8 are considered low risk for alcohol problems while scores of at least 8 indicate a higher risk for alcohol problems. Within the AUDIT, the AUDIT-C evaluation was also used for analyzing consumption behavior, particularly in understanding hazardous drinking or active alcohol use disorders. AUDIT-C scores of above 3 or 4 (for females and for males, respectively) are considered optimal for identifying these risk factors (Bush et al., 1998).

The Rutgers Alcohol Problem Index (RAPI) (Neal et al., 2006) was used to assess alcohol-related problems in this young adult population. Indices less than 10 are generally considered low levels of problems within this age range while those of at least 10 may indicate higher levels of alcohol problems (White and Labouvie, 2000).

4.2.2. *Metrics of sensory information processing*

During the experimental session, the subjects were seated comfortably in a chair with the right arm situated on an armrest attached to the head unit of a portable four-site vibrotactile stimulator (Fig. 6). The independent, computer-controlled probe tips were capable of delivering a wide range of vibrotactile stimulation of varying amplitudes (sinusoidal peak-to-peak displacements in μm) and frequencies (Hz). Vibrotactile flutter stimulation (25 Hz) occurred via 5 mm Delrin probes on the glabrous tips of either or both the second (index, D2) and the third (middle, D3) digits of the right hand. These digits were chosen as the test sites not only for convenience and comfort but also for the wealth of neurophysiological data which supports the evaluation of these somatotopic regions of the primate cerebral cortex. The left hand was placed on a two-button response device, and during testing, subjects were instructed to press the left or right button when the correct stimulus was perceived on the index or middle finger, respectively.

Visual cueing was provided through a computer monitor during each of the experimental runs. The cues indicated when the experimental stimuli were being delivered and when subjects were to respond. Training trials were conducted prior to each task allowing for the subjects to become familiar with the test, and correct responses on three consecutive training trials were required before the commencement of each assessment. Subjects were not given performance feedback or knowledge of the results during data acquisition. Stimulus parameters were specified by test algorithms based on specific protocols and the responses of the subjects during those protocols.

Fig. 6 – Four site vibrotactile stimulator. Each of the four probe tips was positioned by rotating the four independently-positioned drums to maximize contact between finger pads and the stimulator tips. During an experimental session, the subjects were seated comfortably in a chair with their arm resting on the arm rest attached to the head unit of the device. Digits D2 through D5 were then positioned for vibrotactile stimulation.

A series of sensory perceptual measures were employed to assess tactile information processing ability. These tests, from start to finish, lasted approximately twenty minutes and consisted of evaluations of reaction time (RT), vibrotactile threshold, and amplitude discrimination (AD) protocols. The individual tests – all described in previous reports (Folger et al., 2008; Francisco et al., 2008; Tannan et al., 2005, 2007, 2008; Tommerdahl et al., 2007a, 2007b; Zhang et al., 2009, 2011a, 2011b) – are described below.

4.2.2.1. Reaction time. For the simple reaction time (RT) task, the device delivered a single tap (300 μm, 40 ms) to D2, and the subject was asked to subsequently respond by clicking on the response device as soon as the tap was perceived. A randomized delay ranging from 2 to 7 s occurred between each of the trials. Response times were recorded for each of 14 trials.

The choice RT protocol was conducted by delivering the stimulus to one of the two digits (D2 or D3) and asking the subject to indicate as quickly as possible the digit (left or right) that had been tapped on the response device. The stimulus location was randomly selected on a trial-by-trial basis in order to minimize distractions, and response accuracy was also recorded for each trial. Each task consisted of 14 trials.

4.2.2.2. Detection thresholds. Two types of detection thresholds were collected and have been previously defined as "static" and "dynamic" (most recently described in Zhang et al., 2011a, 2011b). "Static" thresholds are thresholds obtained using stimuli that do not change in amplitude during an individual trial and "dynamic" thresholds are thresholds obtained using stimuli that are constantly amplitude-modulated during an individual trial.

For static threshold detection, the device delivered a vibromechanical stimulus (initial stimulus parameters: 15 μm, 1000 ms, 25 Hz) to either D2 or D3 over 20 trials using a two-alternative forced-choice (2AFC) modified von Békésy tracking protocol. The stimulus location was randomized on a trial-by-trial basis. Following each stimulus, subjects were prompted to select the digit where the stimulation felt perceptually larger. After a 5 s delay, based on the previous response of the subjects, the stimulus amplitude was modified until completion of the 20 trials. During the initial 10 trials, a 1-up/1-down algorithm was implemented for the purposes of amplitude modification. Correct responses resulted in the lowering of the magnitude of the stimulus while incorrect response raised the amplitude of the stimulus. After the initial 10 trials, the amplitude was varied using a 2-up/1-down algorithm. The rationale for implementing these algorithms was to initially expedite determination of vibrotactile discriminative range and then account for response bias.

For the dynamic threshold task, after a delay period without stimulation, the device delivered a continuous stimulus

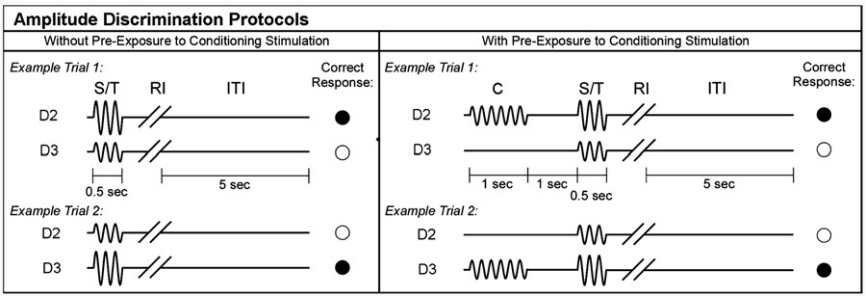

Fig. 7 – Schematics of amplitude discrimination protocols. The simple amplitude discrimination protocol (left panel) consisted of a 200 μm test and 100 μm standard amplitude stimulation at 25 Hz. The vibrotactile conditioning stimulus (200 μm, 25 Hz, 1 s) was delivered 1 s prior to the presentation of the pair of test and standard stimuli (right panel).

beginning at 0 μm (25 Hz) to either D2 or D3, and the stimulus location was randomly selected on a trial-by-trial basis. Four conditions of delay (seconds) were employed in separate trials: 0, 1.5, 2, and 3 s. The stimulus increased by 2 μm/s, and subjects responded with the appropriate digit when they just perceived the stimulus. The dynamic threshold task consisted of 7 trials, and the stimulus amplitude at the time of the response was recorded. Only accurate responses were used to calculate the dynamic threshold.

4.2.2.3. *Amplitude discrimination*. Amplitude discriminative capacity is defined as the minimal difference in amplitudes of two mechanical sinusoidal vibratory stimuli in which an individual can successfully identify the stimulus of larger magnitude (i.e., the subject can tell which stimulus is larger). For the amplitude discrimination (AD) task (Fig. 7, left panel), the device delivered simultaneous stimuli (initial stimulus parameters: 200 μm test, 100 μm standard, 25 Hz, 500 ms, 10 μm step size) to D2 and D3 over 20 trials. Discrimination capacity was assessed using a 2AFC tracking protocol that has been described and implemented in a number of previous studies (Folger et al., 2008; Francisco et al., 2008; Tannan et al., 2006, 2007, 2008; Tommerdahl et al., 2007a, 2007b; Zhang et al., 2009, 2011a, 2011b). The magnitude of the test stimulus was always greater than that of the standard stimulus, but the loci of the stimuli were randomly selected on a trial-by-trial basis. The subjects were then asked to determine which of the two digits felt the most intense stimulus. The difference between the amplitudes of the test and standard amplitudes was adjusted on the basis of the previous response such that correct responses resulted in the lowering of the test amplitude towards the standard amplitude while incorrect responses raised the test amplitude away from the standard amplitude. The same tracking algorithm previously described for static threshold detection was employed to track the discriminative capabilities of the subjects.

4.2.2.4. *Single-site adaptation*. The measure of the impact that conditioning stimuli have on some aspect of amplitude determined by measuring the impact that short duration conditioning stimuli have on amplitude discriminative capacity (described above). The effect of conditioning stimulation on subsequent test stimuli was analyzed by the addition of single-site adaptation (SSA), or pre-exposure to a conditioning stimulus delivered prior to the simple AD task (Fig. 7, right panel). Specifically, a vibrotactile conditioning stimulus (constant stimulus parameter: 200 μm, 25 Hz, 1 s) was delivered 1 s prior to the presentation of the pair of test and standard stimuli. The result of such a protocol modification is that the discriminative threshold, or difference limen (DL), is typically significantly elevated after pre-exposure to a single-site conditioning stimulation (Folger et al., 2008; Tannan et al., 2007, 2008; Zhang et al., 2009, 2011a, 2011b). When the conditioning stimulus is delivered at the same site as the test stimulus, the gain effect of adaptation, or reduction of the perceived intensity of the stimulus, can be quantified by comparison of the DL obtained in the adapted versus non-adapted conditions. The same amplitude discrimination tracking algorithm described previously was also employed to track the discriminative capabilities of the subjects. Each task consisted of 20 trials.

4.3. *Data analysis and normalization*

The reaction times, tactile thresholds, and discriminative thresholds (DLs), were calculated by averaging the amplitudes of the last five trials recorded in the tasks. For the DLs, the standard amplitude was subtracted from the mean of the last five trials. In order to normalize the results by each subject and analyze the effect of conditioning stimulation on amplitude discrimination, the ratios of the DLs were calculated: the discriminative thresholds in the presence (DL_{SSA}) to those in the absence (DL_{Simple}) of single-site adaptive stimulation (Eq. 1). These calculations were arbitrarily converted to percentages where larger values implied that sensory adaptation inhibited amplitude discrimination while smaller values suggested that adaptive stimulation contributed little to the discriminative task.

$$\text{Impact of adaptation (\%)} = \left(\left(DL_{SSA}/DL_{Simple}\right) - 1\right) \times 100 \quad (1)$$

Statistical analytical techniques, specifically two-sample t-tests, were used to evaluate the difference in the performance of each of the subjects across different groups. Data are presented as means and standard errors of the mean. A probability (p-value) of less than 0.05 was considered statistically significant.

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