The role of alcohol response phenotypes in the risk for alcohol use disorder

Andrea C. King, Dingcai Cao, Harriet deWit, Sean J. O’Connor and Deborah S. Hasin

Summary
Heavy alcohol use is pervasive and one of our most significant global health burdens. Early theories posited that certain alcohol response phenotypes, notably low sensitivity to alcohol (‘low-level response’) imparts risk for alcohol use disorder (AUD). However, other theories, and newer measures of subjective alcohol responses, have challenged that contention and argued that high sensitivity to some alcohol effects are equally important for AUD risk. This study presents results of a unique longitudinal study in 294 young adult non-dependent drinkers examined with alcohol and placebo testing in the laboratory at initial enrolment and repeated 5 years later, with regular follow-up intervals assessing AUD (trial registration: http://clinicaltrials.gov/ct2/show/NCT00961792). Findings showed that alcohol sedation was negatively correlated with stimulation across the breath alcohol curve and at initial and re-examination testing. A higher rather than lower alcohol response phenotype was predictive of future AUD. The findings underscore a new understanding of factors increasing vulnerability to AUD.

Declaration of interest
None.

Keywords
Alcohol; stimulation; sedation; differentiator model; low-level response theory.

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Method
Participants were healthy young non-alcohol-dependent drinkers (42% female; mean age 25.4, s.d. = 2.9) who were at high or low risk for AUD based on their alcohol consumption patterns. High-risk drinkers (n = 208) were defined as those who consumed ≥5 standard drinks (≥4 for women) per occasion 1–4 times/week, >14 units weekly and low-risk, light drinker (n = 86) were defined as those who consumed 1–6 drinks/weekly with no/rare heavy drinking. After providing informed consent, participants were individually tested in two 5 h afternoon laboratory sessions in which they consumed either 0.8 g/kg alcohol or placebo in random order under double-blind conditions. They were told the beverage could contain a stimulant, sedative, alcohol or placebo or a combination of two substances. Beverages were consumed in two 5 min intervals separated by a 5 min break and consisted of flavoured drink mix, sucralose-based sugar substitute, water and 16% volume 190-proof ethanol (1% taste mask for placebo), with an average beverage volume of 471 mL. Alcohol doses for women were 85% of those of men to adjust for striatal dopamine release, a better predictor of risk for AUD. In an attempt to resolve these discrepant results, an alternative theory, the differentiator model, posited that AUD risk is marked by both greater stimulatory alcohol effects during the ascending limb of the breath alcohol concentration (BrAC) and lower sedative responses during the descending limb. Our group subsequently refined this model by showing that these alcohol responses simply measured at peak BrAC were predictive of future increases in alcohol consumption and AUD symptoms. Resolving conflicting theories of addiction risk requires sensitive outcome measures, large sample sizes and longitudinal data. Since the time the low-level response theory was formulated, measures of acute subjective effects of alcohol have improved, making it possible to measure alcohol stimulation concurrently with sedation. In our prospective Chicago Social Drinking Project (trial registration: http://clinicaltrials.gov/ct2/show/NCT010961792), we used these measures to assess acute responses to alcohol (versus placebo) over a 5-year period in 294 drinkers varying in risk for AUD. The goal was to examine the long-term relationship between alcohol’s stimulant and sedative effects in non-dependent drinkers, and to determine whether higher or lower responses to alcohol predict AUD in early to middle adulthood.
Scores on the BAES sedation and stimulation scales were consistently inversely related at rising, peak and declining BrAC limbs (r ≥ −0.37, P < 0.001) in both light and heavy drinkers, and at initial and 5-year re-examinations (see Fig. 1(a) for peak BrAC; and supplementary Fig. 1 available at https://doi.org/10.1192/bjo.2019.18 for all BrAC limbs and study phases). Of participants meeting AUD+ during follow-up, at initial testing peak BrAC, very few were low-level alcohol responders (low stimulation and low sedation; 88%, n = 9/111; Fig. 1(b), quadrant III), in contrast to 46% who exhibited a high-level alcohol response (n = 51/111; Fig. 1(b), quadrant I). This difference in the frequency of low- and high-level responders was also evident during ascending and descending BrAC limbs and persisted through re-examination (2% low-level responders, n = 1/47 vs. 51% high-responders, n = 24/47). Thus, drinkers developing AUD were about five times more likely to be high rather than low alcohol responders (P < 0.001) and this did not change over time.

Discussion

Lower alcohol sedation was consistently inversely associated with higher stimulation across the BrAC, for the whole sample and drinker subgroups, and persisted for 5 years. In addition, higher-rather than lower-level responses to alcohol predicted the development of AUD, challenging the conventional notion of the exclusive role of low-level response to alcohol as the key alcohol risk response phenotype. Conflicting theories of the role of alcohol response in the risk for future AUD may have resulted from inconsistencies in examining alcohol effects relative to placebo, and lack of attention to the higher stimulation that is associated with AUD.

Our findings from the most extensive repeated alcohol challenge study to date warrant a new understanding of the risk for AUD. Sensitivity to both the stimulating and sedating effects of alcohol may underlie its reinforcing properties and foster heavy drinking.
drinking and development of AUD. Early identification of this alcohol response phenotype may provide information for interventions that could reduce the burden of heavy drinking and AUD in society.

Andrea C. King, PhD, Professor, Department of Psychiatry & Behavioral Neuroscience, University of Chicago, USA; Dingcai Cao, PhD, Associate Professor, Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago, USA; Harriet deWit, PhD, Professor, Department of Psychiatry & Behavioral Neuroscience, University of Chicago, USA; Sean J. O’Connor, MD, Professor, Departments of Psychiatry and Biomedical Engineering, Indiana University School of Medicine and Purdue University, USA; Deborah S. Hasin, PhD, Professor, Mailman School of Public Health, Columbia University; College of Physicians and Surgeons; and New York State Psychiatric Institute, USA

Correspondence: Andrea King, Department of Psychiatry & Behavioral Neuroscience, University of Chicago, 5841 S. Maryland Avenue (MC-3077), Chicago, IL 60637, USA. Email: aking@bsd.uchicago.edu

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Supplementary material
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