MALE AND FEMALE HEAVY DRINKERS SHOW SIMILAR AND INTACT BRAIN AND BEHAVIOURAL MARKERS OF INHIBITION

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Executive Summary

Introduction: The ability to exert control over inappropriate actions is central to everyday life, and is given increasing importance in new models of the development, maintenance, and relapse to substance use. Some previous evidence has suggested female heavy drinkers show greater deficits in inhibitory control, while male heavy drinkers are relatively spared, although not all studies report this effect. Here, we investigate inhibitory capacity using two different paradigms, which tap related but separate aspects of inhibitory control.

Methods: Heavy drinkers (24 female, 19 male) and light-drinking controls (28 female, 25 male) completed a stop-signal task, which assesses the urgent inhibition of a response that is already underway, and a cued-Go/NoGo task, which assesses response preparation, execution and inhibition. EEG was recorded and analyses focus on ERPs to the stop-signal, to cues and targets in the Go/NoGo task, and error-related activity in both tasks.

Results: No alcohol group or sex differences were observed in the cued-Go/NoGo task, but in the stop-signal task, a sex x alcohol group interaction was observed. However, follow-up analyses revealed that female controls and heavy drinkers showed similar inhibitory capacity, while male controls were worse than male heavy drinkers. Few alcohol group x sex interactions were observed in ERP measures.

Implications: The surprising results suggest little impairment among heavy drinkers, especially females, and that further questions arising from a purported deficit (e.g., do deficits predict treatment outcomes? Can inhibitory training help to reduce use?) should be investigated with reference only to people with a dependence.

1. INTRODUCTION

Problems with inhibitory control (the ability to delay, withhold or stop inappropriate overt behaviours) are implicated in recent models of development, maintenance, and relapse to substance abuse (Hester et al., 2010, Lubman et al., 2004). These processes can be assessed behaviourally in experimental paradigms such as the stop-signal task (Logan et al., 1984), Go/NoGo task (Donders, 1969), error awareness tasks (Hester et al., 2005) and flanker tasks (Eriksen and Eriksen, 1974). We and others have confirmed behavioural deficits in these tasks across a range of categories of substance use, including a small effect among heavy drinkers (Smith et al., 2014, Luijten et al., 2014).

For inhibitory processing in heavy drinkers in particular, there is mixed evidence for differences in dysfunction according to sex: some studies have reported that female heavy drinkers show greater inhibitory decrements than males (Kreusch et al., 2013, Nederkoorn et al., 2009, Smith et al., 2016, Townshend and Duka, 2005, Weafer et al., 2015, Weafer and de Wit, 2014). On the other hand, other studies report no sex differences (Czapla et al., 2015, Franken et al., 2017, Rossiter et al., 2012). Given the well-known sex differences in alcohol consumption and prevalence of alcohol-related disorders (see Erol and Karpyak, 2015, World Health Organization, 2011), it is important to establish whether cognitive correlates of heavy alcohol use indeed differ by sex, especially since these may suggest different prevention and/or treatment options for women and men.

In this study, we investigate using both behavioural and brain functional measures, the presence and extent of differences in inhibitory control and performance monitoring among young heavy drinkers and light drinkers, according to sex. We tested participants on both cued Go/NoGo and stop-signal tasks; both tasks require behavioural inhibition but the cued Go/NoGo task requires withholding a prepared response, while the stop-signal task requires interrupting a response that is already underway (e.g., Wright et al., 2014, Barkley, 1997). Brain functional measures such as the event-related potential (ERP: the brain's average electrical response to an event) can be more sensitive to group differences than behavioural measures (e.g., O'Halloran et al., 2019), and decades of work has established functional interpretations of the characteristic peaks and troughs of the ERP. In this study, we build on our prior work (e.g., Smith et al., 2016) investigating the P3, a positive component peaking around 300-600ms after stimulus onset, which is larger at frontocentral sites when a motor response is actively cancelled, compared to when a response is executed as planned, or when an attempt at inhibition fails (e.g., Groom and Cragg, 2015, Kok et al., 2004, Smith et al., 2008). Here, we also consider the N2 ERP component, a negative component peaking around 200-400ms post-stimulus and indicating conflict between the demanded behaviour (that is, inhibition of a response) and the likely behaviour (that is, execution of a response; Botvinick et al., 2001, Dimoska et al., 2006). We also investigate a component related to response preparation – specifically, the contingent negative variation (CNV; Walter et al., 1964) – and components related to performance monitoring – specifically, the error-related negativity (ERN) and the error positivity (Pe). The CNV is a complex of at least three slow waves occurring between the cue and target in a cued paradigm, namely, an early wave around 450-650ms post-cue, indexing orienting to the cue (Loveless, 1979, Rohrbaugh et al., 1976), and two separate late waves peaking just before the onset of the target, indexing anticipation of the target stimulus (a stimulus-preceding negativity; Brunia, 1988, Damen et al., 1996) and preparation of a response (the readiness potential; Kornhuber and Deecke, 1964, Vaughan et al., 1968). The late portion of the CNV is typically largest over central sites, contralateral to the responding hand. The error-related negativity (ERN), peaking around 50ms after an erroneous response, and indicating unconscious detection of the error, and the error positivity, a slow wave occurring around 400-600ms after an error, and indicating conscious detection of the error (e.g., Falkenstein et al., 1990, Falkenstein et al., 2000, Nieuwenhuis et al., 2001, Simons, 2010).

2. METHODS

2.1 Participants

Participants were 96 adults (mean age 22.4 years, SD = 3.8 years) recruited from a paid research participation webpage, and from an undergraduate psychology student research pool, at the University of New South Wales. Participants were recruited into four groups based on sex and drinking behaviour in the past year: heavy drinkers consumed more than four Australian standard drinks (one Australian standard drink = 10 g ethanol) on one occasion at least monthly (33% at least weekly, and 67% at least monthly but not as often as weekly), while controls drank heavily less often than this (66% at least once but not as often as monthly, 26% never consumed 4 standard drinks on one occasion, and 8% had not consumed any alcohol). This grouping criterion was based on alcohol consumption guidelines from the Australian National Health and Medical Research Council (NHMRC, 2009). Because these guidelines are the same for men and women, we used the same grouping criterion. Table 1 lists participant demographics. Participants were excluded from the study if they reported: ever suffering an epileptic seizure, head injury or period of unconsciousness; ever being diagnosed with a psychiatric illness; currently taking any psychotropic medication; had smoked more than 10 cigarettes/cigars/pipes in their lifetime; or regular (more than once a month in the past 12 months) use of e-cigarettes, illegal substances, or prescription medication for a purpose other than for which it was advised. They were recruited via an online research participation system, and received either a $20 voucher and $10 cash, or points towards undergraduate psychology course requirements, for their effort and time (2 hours total). An additional 3 participants completed the study but were excluded due to poor performance on the tasks (stop-signal: 2 participants with a flat inhibitory function below 50% success; cued-Go/NoGo: 1 participant with over 40% errors after Go cues). The research protocol was approved by the Human Research Ethics Committee of UNSW before data collection began, and all participants provided written informed consent.

2.2 Procedure

On arrival to the laboratory, the experimenter showed participants the EEG recording equipment and explained the experimental protocol before the participant gave written informed consent. Participants completed a short demographics questionnaire, the DUDIT-E, and a modified version of the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993). In the modified version, question 3 was changed from “How often do you have six or more standard drinks on one occasion?” to “four or more standard drinks” to reflect Australian alcohol consumption guidelines (Council, 2009). Participants also completed the Depression Anxiety Stress Scale (Lovibond and Lovibond, 1995), due to prior research suggesting that alcohol-related differences in ERN amplitude may rather be due to differences in anxiety between groups (e.g., Karch et al., 2008, Hajcak et al., 2003), as well as their alcohol consumption over the past 7 days using a Timeline Followback (TLFB) method (Sobell and Sobell, 1992), and over their lifetime using the Lifetime Drinking History (Skinner, 1977). An Australian standard drinks guide was provided for easy reference while the participants completed the AUDIT, TLFB and LDH portions. The EEG recording electrodes were then fitted, and the participants completed, in counterbalanced order, the cued-Go/NoGo task and the stop-signal task. At the end of the session, all participants received sex-specific information on their drinking behaviour relative to Australian health guidelines and relative to others of the same age.

2.3 Stop-signal task

The Go stimuli were green arrows pointing to the left and right, which appeared above a grey central fixation cross on a black background. The fixation cross was continuously present throughout the experiment, while Go stimuli were presented for 1000 ms with a mean 1500 ms SOA (range 1200–1800 ms). Participants were required to press the ‘A’ button on a

Table 1. Demographic information, and selected performance and ERP summary statistics for each alcohol group and sex.

	Controls				Heavy drinkers			
	Females (n = 28)		Males (n = 25)		Females (n = 24)		Males (n = 19)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	22.4	3.6	23.1	4.5	22.5	4.0	21.3	2.6
% right-handed	100.0		80.0		95.8		94.7	
AUDIT score	3.2	2.7	3.2	2.4	9.6	4.0	9.3	3.2
Weekly consumption (95% CI)	1.6	(1.3-2.1)	1.5	(1.2-1.9)	10.7	(8.8-13.1)	3.3	(1.9-5.8)
Lifetime consumption (95% CI)	59.7	(30.3-117.6)	63.1	(26.7-149.1)	713.8	(454.8-1120.5)	543.1	(274.2-1075.9)
DASS depression	4.4	6.9	5.8	7.6	7.8	7.9	5.6	7.2
DASS anxiety	4.5	4.3	4.6	5.2	5.9	6.3	5.3	5.3
DASS stress	7.4	4.9	6.8	7.4	10.1	8.4	7.3	5.9
DUDIT-E score	0.4	1.0	0.2	0.6	1.1	2.3	0.5	0.8
Stop-signal task								
Go accuracy (%)	99.2	1.0	98.7	1.4	98.2	3.2	98.4	1.2
Go RT (ms)	566.8	96.9	550.2	107.1	562.0	81.8	606.2	122.0
SSRT (ms)	207.6	31.3	238.1	40.4	213.4	44.6	194.5	38.0
N2 failed inhibition amplitude (μV)	-13.8	6.6	-11.0	10.0	-10.8	6.2	-12.6	7.6
N2 successful inhibition amplitude (μV)	-7.0	5.6	-7.6	6.5	-6.2	6.0	-7.9	4.4
N2 failed inhibition latency (ms)	223.9	27.0	225.7	24.2	230.4	32.7	227.1	25.0
N2 successful inhibition latency (ms)	213.2	23.7	219.2	29.4	220.3	21.2	216.7	23.2
P3 failed inhibition amplitude (μV)	17.5	7.0	15.6	5.0	14.5	6.5	18.9	6.9
P3 successful inhibition amplitude (μV)	18.9	6.6	15.7	5.8	15.4	5.6	17.0	6.3
P3 failed inhibition latency (ms)	380.3	50.9	397.0	48.9	381.1	42.5	378.2	40.4
P3 successful inhibition latency (ms)	371.4	37.5	387.7	46.3	384.5	36.8	372.8	41.1
ERN amplitude (μV)	-5.8	4.0	-6.5	5.4	-5.0	3.1	-5.7	3.4
ERN latency (ms)	70.0	30.6	81.7	30.1	58.5	29.8	68.2	34.1
Pe amplitude (μV)	7.2	4.5	7.4	2.4	6.6	4.2	10.1	4.6
Go/NoGo task								
	n = 12		n = 14		n = 12		n = 14	
ERN amplitude (μV)	-8.1	11.8	-7.4	6.0	-6.0	3.6	-8.0	5.1
ERN latency (ms)	41.8	19.3	34.9	20.7	35.3	23.2	37.6	24.3
Pe amplitude (μV)	11.6	7.4	14.5	4.8	6.4	7.1	10.9	5.3

computer keyboard with their left index finger on presentation of the leftward arrow, and press the ‘L’ button with their right index finger to the right arrow. On a random 25% of trials a stop signal was presented indicating that the participants should attempt to inhibit their response. The stop-signal was a replacement of the green arrow with a red arrow in the same direction for 200ms. Participants completed 4 blocks of 120 trials each, as well as 50 practice trials.

In the practice block, stop-signals were set to occur at delays of 100 ms, 200 ms, 300 ms, 400 ms, and 500 ms after the Go stimulus, with one presentation at each delay for both left and right arrows. In the experimental blocks, the stop-signal delay varied according to the participant’s mean reaction time (MRT) to Go stimuli in the preceding block, to counteract strategic slowing (Logan et al., 1984, Logan and Cowan, 1984). MRT was calculated from correct no-stop-signal trials only, and stop-signals were presented at fixed intervals prior to MRT (here, around 570 ms), at either (MRT – 450) ms (i.e., shortly after the Go stimulus, so that inhibition is easy), (MRT – 350) ms, (MRT – 250) ms, (MRT – 150) ms, and (MRT – 50) ms (i.e., a long time after the Go stimulus and relatively close to the expected response time, so that inhibition is difficult). Where the above formula would result in stop-signals being presented before the Go stimulus, stop-signal onset was instead simultaneous with Go stimulus onset (Dimoska and Johnstone, 2007, Dimoska et al., 2006). There were three presentations of each delay for each (left and right) Go signal per block.

To further counteract strategic slowing, participants were instructed not to wait for the stop-signal as they would be unable to stop their response on every trial, and the experimenter noted changes in mean RT displayed at the end of the block and notified participants if this was variable or indicated slowing. Furthermore, if participants did not respond within 1000 ms, the Go stimulus was replaced with the words ‘TOO SLOW’ for 500 ms, and participants were advised to avoid this.

2.4 Cued-Go/NoGo task

Participants completed two short practice blocks and then 5 blocks of 120 trials each of a visual cued-Go/NoGo task, previously developed in Randall and Smith (2011). Trial types and contingencies are presented in Table 2. The first stimulus in a pair was green (either a filled square or arrows), and the second was white (either a circle or an arrow), each presented for 200ms in the middle of a black screen with a fixed cue-target stimulus onset asynchrony (SOA) of 1000ms, and a target-cue interval varying between 1500 and 2500ms. A grey central fixation cross was present whenever task stimuli were not presented. Participants were instructed to respond only to the white stimuli, with a left or right button press response according to the direction of the arrow (Go Left and Go Right targets), or withhold a response if the circle (NoGo target) was presented. Each cue was equiprobable, but predicted the different targets with varying probabilities: the NoGo, Go Left and Go Right cues were followed on 80% of trials by the corresponding target, but on the other trials, the other two targets were also possible (10% each). Participants were instructed that the cue usually, but not always, gave the correct information about the target to follow and the response that would be required, and to make fast and accurate responses to the target stimuli only.

This experimental design creates, in addition to analyses for the three types of cue, five target conditions (collapsed across response side): NoGo targets presented after NoGo cues, NoGo targets presented after Go cues, Go targets preceded by a Valid Cue, Go targets preceded by an Invalid cue, and Go targets preceded by a NoGo cue. For NoGo targets, conflict and inhibition are expected only after Go cues, and not after NoGo cues; for Go targets, conflict is expected after Invalid and NoGo cues, while inhibition is required only after Invalid cues (Smith, 2011, Randall and Smith, 2011).

2.5 Data recording and analysis

Continuous monopolar EEG was recorded from 32 scalp sites using an elasticised cap with tin electrodes, referenced to the tip of the nose. Additional electrodes recorded activity from the left and right mastoids, as well as vertical and horizontal EOG. Electrodes were grounded

Table 2. Cue-target pairs, their probabilities, and the stimuli used for each trial type.

Cue type (green symbol)	P(cue)	Target type (white symbol)	P(target|cue)	Condition name (collapsed by response side)
NoGo cue (■)	0.33	NoGo target (●)	0.80	NoGo after NoGo
		Go Left target (←)	0.10	Go after NoGo
		Go Right target (→)	0.10	Go after NoGo
Go Left cue (<<)	0.33	NoGo target (●)	0.10	NoGo after Go
		Go Left target (←)	0.80	Go after Valid
		Go Right target (→)	0.10	Go after Invalid
Go Right cue (>>)	0.33	NoGo target (●)	0.10	NoGo after Go
		Go Left target (←)	0.10	Go after Invalid
		Go Right target (→)	0.80	Go after Valid

midway between Fpz and Fz, and impedances were below 5 kΩ. Signals were recorded 0.1Hz to 200Hz, amplified 10 times, and sampled at 1000Hz using Neuroscan recording software and hardware (SynAmps 2).

The EEG was re-referenced to the mastoids and then filtered with a lowpass filter below 30 Hz (down 48 dB/oct, zero phase shift). Next, it was corrected for eye movements using Neuroscan's in-built procedure (Semlitsch et al., 1986). For stop-signal ERPs, epochs began 100 ms before the stimulus and lasted 700 ms (with a 100 ms pre-stimulus baseline), while for the ERN, epochs began 200ms before the overt response and lasted 700ms, with a 200 ms pre-response baseline. Epochs with amplitudes exceeding ±100μV were rejected. Averages were created to stop-signals on which inhibition was successful (mean epochs accepted: 65) and those on which it failed (mean epochs accepted: 40), and N2 was measured as the minimum amplitude in the window 150-300ms at FCz, while P3 was measured as the maximum amplitude in the window 280–450 ms at FCz. For the ERN, averages were created to correct responses (that is, responses to Go stimuli where no stop-signal had been presented) and error responses (that is, responses to Go stimuli where a stop-signal had been presented), and the difference waveform (incorrect minus correct responses) was calculated. The average number of epochs included for correct responses was 406, and for incorrect responses 40. The ERN was measured as the peak negativity at FCz in the window 0–120 ms after the response, while the Pe was measured as the mean amplitude between 300-500 ms at CPz.

For the cued-Go/NoGo task, a random sample of 20 correct trials each for left and right responses was selected (using the random sample function in SPSS) for the higher probability pairs (NoGo after NoGo and Go after Valid) to maintain a relatively equal signal-to-noise ratio between conditions. The cue ERP epoch lasted 1100 ms with a 100 ms pre-cue baseline, while the target ERP epoch lasted 7000 ms with a 100 ms pre-target baseline. Errors and trials with amplitudes exceeding ±100 μV in any scalp channel were rejected before averaging. The mean number of epochs accepted for averaging was ~190 for all cue averages, and ~38 for target epochs. The CNV was measured at C3 and C4 as the mean amplitude in the last 100 ms before the onset of the target. Peaks were detected at FCz as the maximum (P2 and P3) or minimum (N2) voltage within a specified latency range (P2: 150–250 ms; N2: 220–300 ms; P3: 270–470 ms). Due to variations in P2 as a potential explanation for variations in N2, we report P2–N2 peak-to-peak amplitude, rather than N2 peak-to-baseline measurements, after Randall and Smith (2011). Error-related activity was calculated and measured as above, except that a random sample of 30 correct responses was selected to maintain a relatively equal signal-to-noise ratio with incorrect trials. Participants were required to have a minimum 6 accepted error trials to be included in these analyses (Olvet and Hajcak, 2009); the mean was considerably higher at 17 epochs accepted. Therefore, the sample size for each group was (Female control: n = 12; Male control: n = 14; Female drinker: n = 12; Male drinker: n = 14).

2.6 Statistical analysis

For the stop-signal task, continuous demographic variables, Go RT and accuracy, SSRT, Pe amplitude and ERN amplitude and latency were entered into separate Sex (Female/Male) x Group (Control/Heavy Drinker) between-subjects ANOVAs. Probability of inhibition at different stop-signal delays were entered into a mixed design ANOVA with factors Delay (MRT-450, MRT-350, MRT-250, MRT-150, MRT-50), Sex and Group; polynomial contrasts were run on the Delay factor but only the linear change over trials is reported. N2 and P3 amplitude and latency to failed and successful inhibition trials were entered into separate mixed-design ANOVAs with factors Trial Type (failed/successful), Sex and Group.

For the cued-Go/NoGo task, reaction time for correct responses, error rates, and P2-N2 and P3 amplitude to Go stimuli were entered into separate 3 x 2 x 2 mixed design ANOVA with factors Cue type (Valid/Invalid/NoGo), Sex (Male/Female) and Alcohol Group (Control/Heavy Drinker). Planned contrasts on the Cue type factor compared the mean for Valid trials with Invalid and NoGo trials separately. Because these contrasts are non-orthogonal, to control for the family-wise error rate we report main effects and interactions involving Cue Type only if $p < 0.025$. For error rates, P2-N2 and P3 amplitude to NoGo stimuli, a 2 x 2 x 2 mixed design ANOVA was performed, with factors Cue type (Go/NoGo), Sex and Group. CNV amplitude to cues was entered into a 3 x 2 x 2 x 2 mixed design ANOVA with factors Cue type (NoGo/Go Left/Go Right) x Site (C3/C4) x Sex x Group; planned contrasts on the cue type factor compared Go Left with Go Right cues, and their mean with NoGo cues. When sex x alcohol group interactions were significant, we explored further with planned simple effects analyses of alcohol group within each sex. All reported contrasts have 1, 92 degrees of freedom, unless reported otherwise. ANOVA output and means are provided in online Supplementary Material. We provide (partial) eta squared as an indicator of effect size throughout.

3. RESULTS

3.1 Demographics

Summary statistics for each alcohol group and sex are presented in Table 1. Heavy drinkers and controls were well matched for age (all $F \leq 1.350$, $p \geq 0.248$) and handedness (no significant difference in handedness between light and heavy drinkers for females: $\chi^2 = 1.190$, $df = 1$, $p = 0.275$, or males: $\chi^2 = 1.991$, $df = 1$, $p = 0.158$). As expected, given recruitment criteria, AUDIT scores were significantly greater for heavy drinkers ($F = 97.129$, $p < 0.001$, $\eta_p^2 = 0.514$) but did not differ by sex ($F = 0.081$, $p = 0.776$, $\eta_p^2 = 0.001$) or interact ($F = 0.040$, $p = 0.842$, $\eta_p^2 = 0.000$). For total weekly consumption, analyses were performed on log transformed scores (after adding one to all scores, to avoid taking the log of zero); females consumed more than males ($F = 15.415$, $p < 0.001$, $\eta_p^2 = 0.144$), heavy drinkers more than controls ($F = 69.533$, $p < 0.001$, $\eta_p^2 = 0.430$), and the interaction was significant ($F = 11.017$, $p = 0.001$, $\eta_p^2 = 0.107$). Simple effect analysis revealed that the increase for heavy drinkers relative to controls was greater for females ($F = 26.455$, $p < 0.001$, $\eta_p^2 = 0.223$) than males ($F = 16.643$, $p < 0.001$, $\eta_p^2 = 0.153$). Log lifetime consumption was also greater for heavy drinkers than controls ($F = 42.008$, $p < 0.001$, $\eta_p^2 = 0.313$), but did not differ by sex ($F = 0.094$, $p = 0.760$, $\eta_p^2 = 0.001$) or interact ($F = 0.210$, $p = 0.648$, $\eta_p^2 = 0.002$). Scores did not differ by sex or alcohol group for DASS Depression (all $F \leq 1.376$, all $p \geq 0.244$), Anxiety (all $F \leq 0.942$, all $p \geq 0.334$) or Stress (all $F \leq 1.468$, all $p \geq 0.229$). DUDIT scores did not differ by sex ($F = 2.044$, $p = 0.156$, $\eta_p^2 = 0.022$) or interact ($F = 0.534$, $p = 0.467$, $\eta_p^2 = 0.006$) but were marginally higher in heavy drinkers compared to controls ($F = 3.395$, $p = 0.069$, $\eta_p^2 = 0.036$).

3.2 Stop-signal task

Neither sex nor alcohol group affected Go accuracy (all $F \leq 2.286$, all $p \geq 0.134$; see Table 1 for means) or Go RT (all $F \leq 2.109$, all $p \geq 0.150$). For SSRT, the effect of sex was not significant ($F = 0.532$, $p = 0.468$, $\eta_p^2 = 0.006$), but SSRT was shorter for heavy drinkers than controls ($F = 5.652$, $p = 0.020$, $\eta_p^2 = 0.058$), unexpectedly indicating better response inhibition

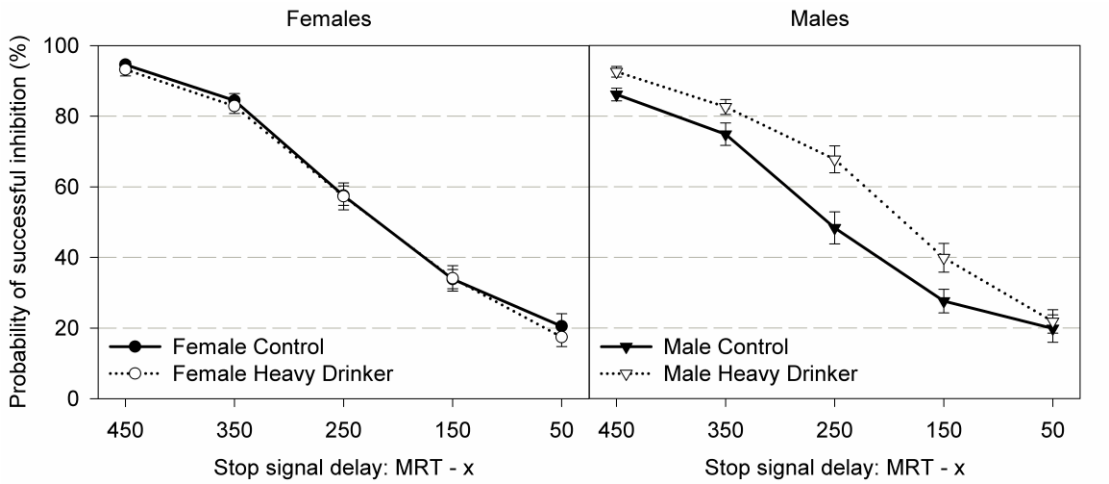

Figure 1. Probability of successful inhibition given a stop signal at different delays for female (left) and male (right) controls (black filled) and heavy drinkers (white filled). Error bars represent the standard error of the mean. The probability of inhibition is reduced at longer stop signal delays (i.e., closer to MRT).

among heavy drinkers. The interaction was also significant ($F = 9.599$, $p = 0.003$, $\eta_p^2 = 0.094$). Planned follow-up simple effects analyses of differences between alcohol groups within each sex indicated that male heavy drinkers showed a significantly shorter SSRT than male controls ($F = 13.757$, $p < 0.001$, $\eta_p^2 = 0.130$), while no difference was observed for female heavy drinkers vs. female controls ($F = 0.285$, $p = 0.595$, $\eta_p^2 = 0.003$). Probability of inhibition decreased linearly with increasing stop-signal delay ($F = 1649.383$, $p < 0.001$, $\eta_p^2 = 0.947$, see Figure 1), and did not differ by sex ($F = 0.526$, $p = 0.470$, $\eta_p^2 = 0.006$), but was greater among heavy drinkers ($F = 4.399$, $p = 0.039$, $\eta_p^2 = 0.046$). However, a group x sex interaction ($F = 7.347$, $p = 0.008$, $\eta_p^2 = 0.074$) was significant. Planned follow-up simple effects analyses revealed differences between control and heavy drinker groups for males ($F = 10.606$, $p = 0.002$, $\eta_p^2 = 0.103$) but not females ($F = 0.207$, $p = 0.651$, $\eta_p^2 = 0.002$).

Because the results for both SSRT and probability of inhibition were unexpected, we delved deeper with additional tests of the effect of sex within the control and heavy drinker groups separately, with alpha set at 0.025 for these post hoc contrasts. For SSRT, no difference was apparent between male and female heavy drinkers ($F(1,41) = 2.159$, $p = 0.149$, $\eta_p^2 = 0.050$), but female controls had much shorter SSRT than male controls ($F(1,51) = 9.542$, $p = 0.003$, $\eta_p^2 = 0.158$). Similarly, for probability of inhibition, male and female heavy drinkers displayed no significant differences ($F(1,41) = 1.820$, $p = 0.185$, $\eta_p^2 = 0.043$), but the probability of successful inhibition was significantly lower among male controls than female controls ($F(1,51) = 6.500$, $p = 0.014$, $\eta_p^2 = 0.113$).

Grand average ERP waveforms for the stop-signal task are presented in Figure 2. N2 amplitude, indicative of response conflict, showed the expected increase for failed compared to successful inhibition trials ($F = 81.065$, $p < 0.001$, $\eta_p^2 = 0.468$, see Table 1 for means); no other main effects or interactions reached significance (all $F \leq 2.662$, all $p \geq 0.106$). N2 latency was earlier for successful than failed inhibition trials ($F = 14.672$, $p < 0.001$, $\eta_p^2 = 0.138$) but no other effects were significant (all $F \leq 0.594$, all $p \geq 0.443$).

P3 amplitude, indicating active cancellation of the motor response, did not show the expected successful > failed inhibition effect ($F = 0.062$, $p = 0.804$, $\eta_p^2 = 0.001$). However, a sex x alcohol group interaction reached significance ($F = 5.613$, $p = 0.020$, $\eta_p^2 = 0.058$); further investigation of simple effects revealed that P3 was larger among female controls than female heavy drinkers ($F = 4.133$, $p = 0.045$, $\eta_p^2 = 0.043$), but (non-significantly) larger among male heavy drinkers than controls ($F = 1.827$, $p = 0.180$, $\eta_p^2 = 0.019$). For P3 latency, no effects were significant (all $F \leq 2.377$, all $p \geq 0.127$).

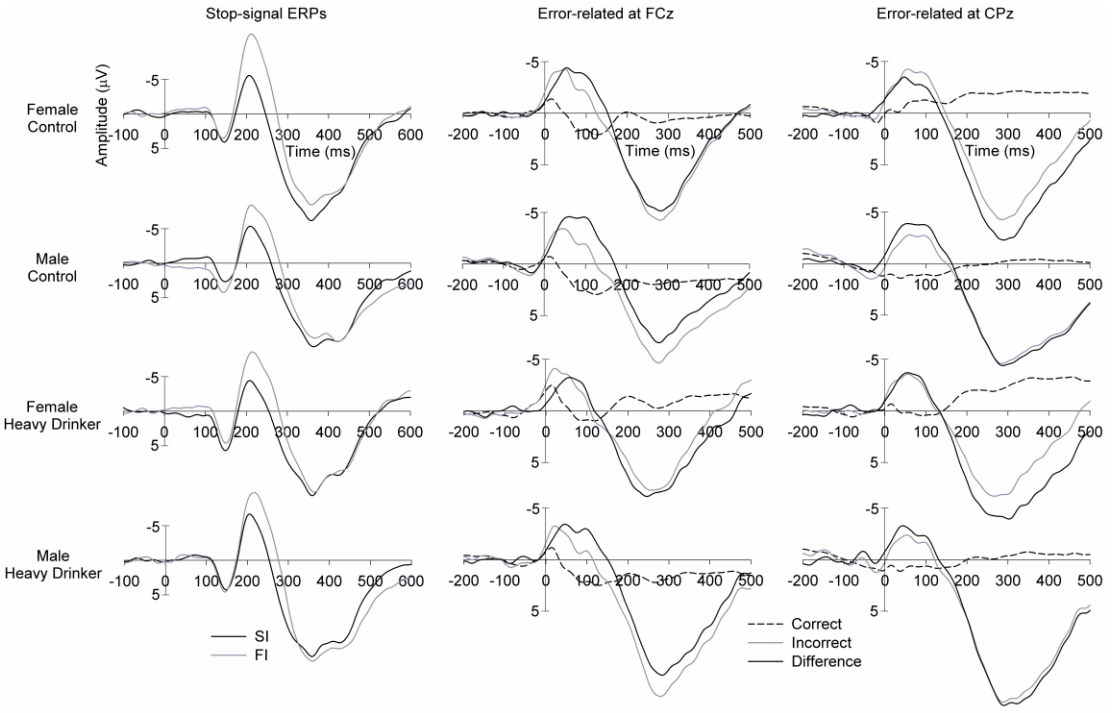

Figure 2. Left: Grand mean waveforms at FCz to stop signals on trials for which inhibition succeeded (SI) vs. failed (FI). Time zero marks the onset of the stop signal. Middle and right: Grand mean waveforms at FCz (middle) and CPz (right) for responses when the response was correct or incorrect, and the difference waveform. Time zero marks the button press response. In this and subsequent figures, negativity is plotted up and amplitude is in microvolts.

When examining components related to performance monitoring, no significant effects were observed for ERN amplitude (all $F \leq 1.146$, all $p \geq 0.287$; see Figure 2 and Table 1). For ERN latency, heavy drinkers peaked marginally earlier than controls ($F = 3.795$, $p = 0.054$, $\eta_p^2 = 0.040$). Pe amplitude was greater for males than females ($F = 4.993$, $p = 0.028$, $\eta_p^2 = 0.051$), but a sex x alcohol group interaction was significant ($F = 4.037$, $p = 0.047$, $\eta_p^2 = 0.042$): further simple effects analyses revealed that male heavy drinkers showed a larger Pe than male controls ($F = 5.221$, $p = 0.025$, $\eta_p^2 = 0.054$), with no significant difference between alcohol groups for females ($F = 0.229$, $p = 0.634$, $\eta_p^2 = 0.002$).

3.3 Cued-Go/NoGo task

Grand mean ERP waveforms to cues are presented in Figure 3. CNV amplitude (related to response preparation) was greater for Go than NoGo cues ($F = 199.628$, $p < 0.001$, $\eta_p^2 = 0.685$, see Figure 4), and was larger at C3 than C4 for Go Right cues, and larger at C4 than C3 for Go Left cues ($F = 13.393$, $p < 0.001$, $\eta_p^2 = 0.127$). Females showed a greater increase in amplitude for Go relative to NoGo cues, than did males (interaction: $F = 4.636$, $p = 0.034$, $\eta_p^2 = 0.048$). No other effects reached significance (all $F \leq 2.725$, all $p \geq 0.102$).

Error and reaction time means are presented in Figure 4 for each group. As expected, when preceded by a Go cue, more errors were made to NoGo targets ($F = 28.377$, $p < 0.001$, $\eta_p^2 = 0.236$). No other effects were significant (all $F \leq 0.345$, all $p \geq 0.558$). Similarly, error rates to Go targets were also increased after Invalid compared to Valid cues ($F = 41.968$, $p < 0.001$, $\eta_p^2 = 0.313$), and error rates were greater among males than females ($F = 3.995$, $p = 0.049$, $\eta_p^2 = 0.042$), but no other effects were significant (all $F \leq 2.326$, all $p \geq 0.131$).

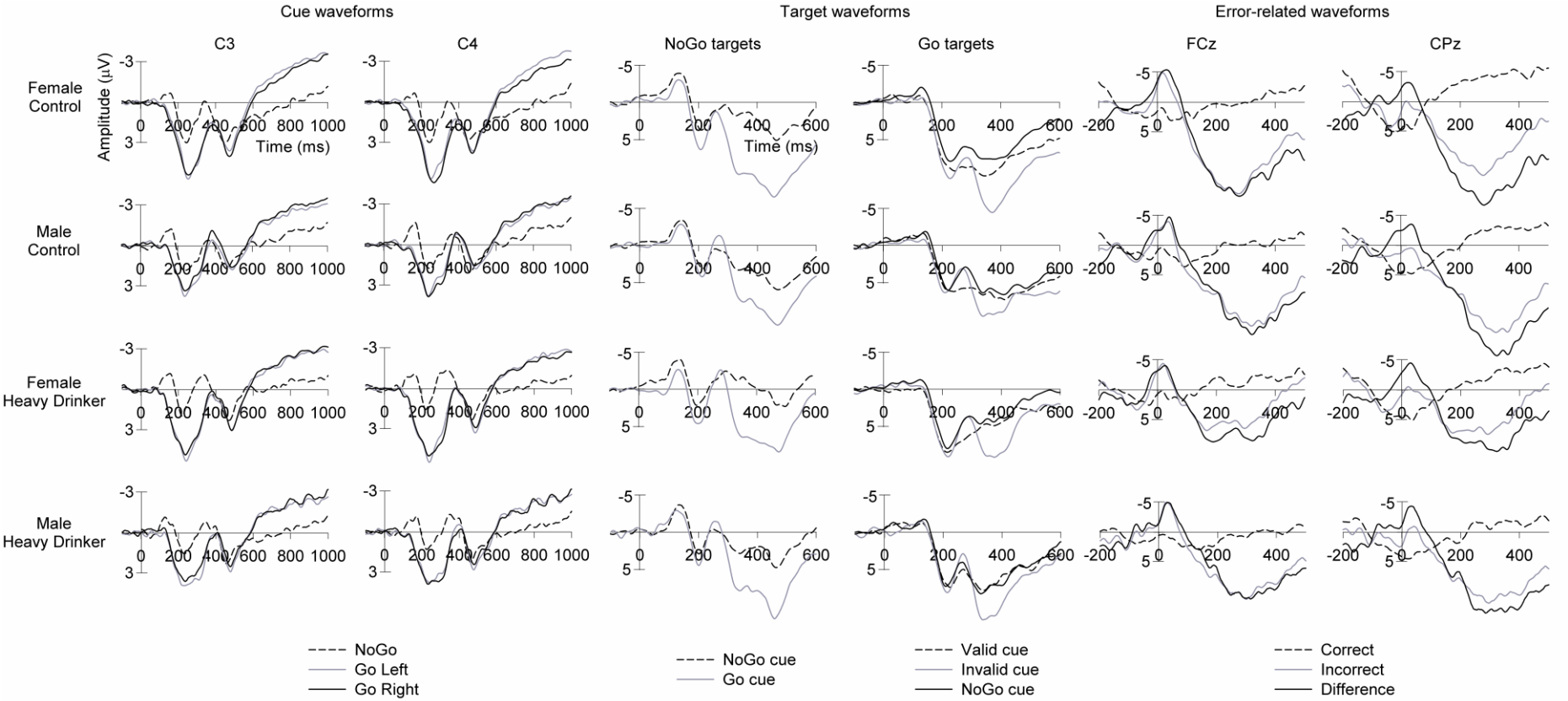

Figure 3. Left: Grand mean ERPs at C3 and C4 to cue stimuli. Time zero marks the onset of the cue stimulus; target stimulus occurs at 1000ms. The CNV was measured over the last 100ms of the epoch. Middle: Grand mean ERPs at FCz to NoGo targets and Go targets preceded by different cue types. Time zero marks the onset of the target stimulus. The N2 peak can be seen around 300ms, followed by the P3. Right: Grand mean waveforms at FCz and CPz for responses when the response was correct or incorrect, and the difference waveform. Time zero marks the button press response. The ERN is visible as a negative peak in the first 50ms, followed by the long slow Pe wave.

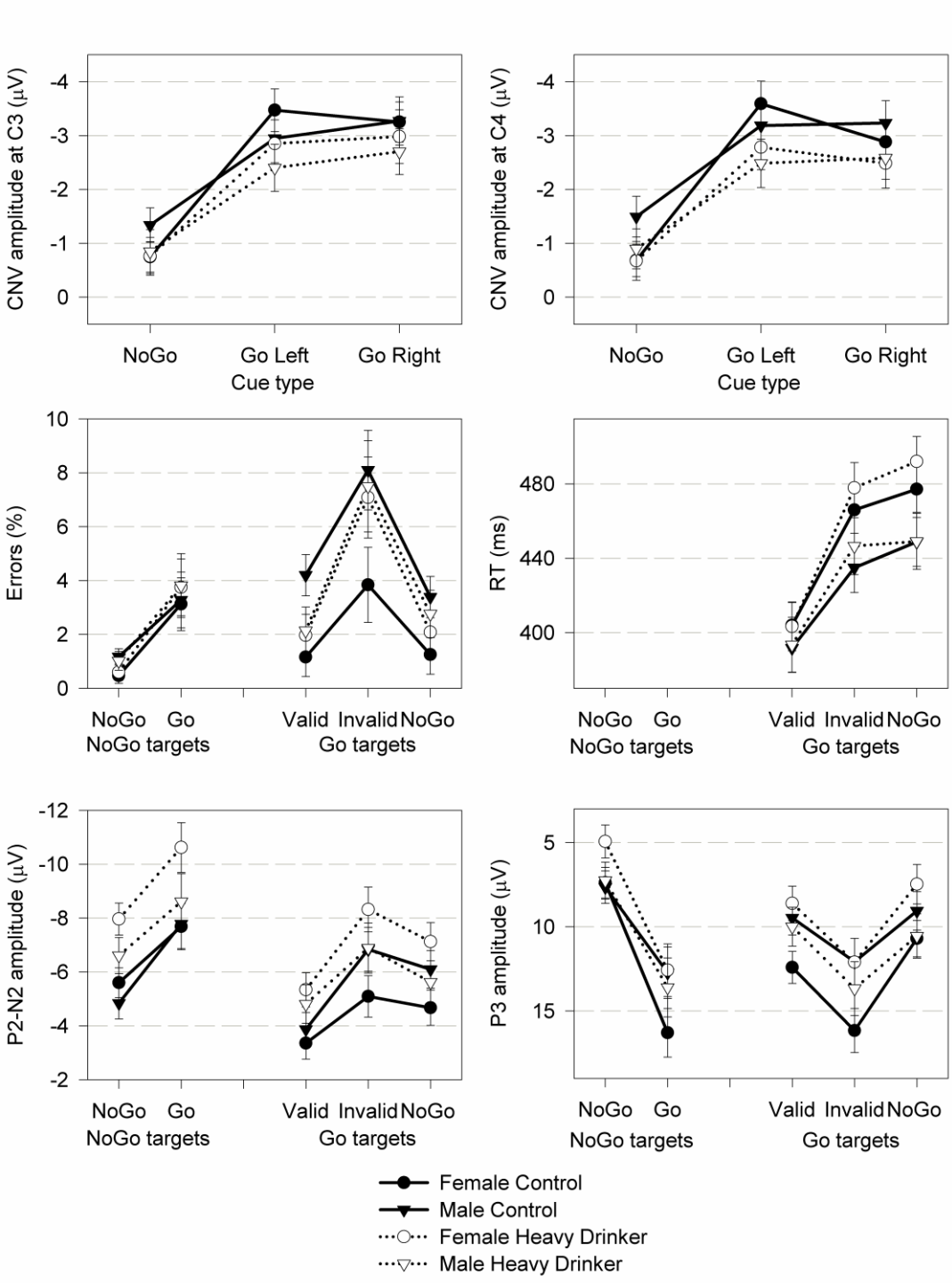

Figure 4. Top: Mean CNV amplitude at C3 (left) and C4 (right) for each group and cue type. Negativity is plotted up. Middle: Mean error rates (left) and reaction time for correct responses (right) for NoGo and Go targets, preceded by different cue types. Bottom: Mean P2-N2 (left) and P3 (right) amplitudes at FCz for NoGo and Go targets, preceded by different cue types. Negativity is plotted up. For all panels, error bars represent the standard error of the mean.

In line with the error data, participants responded faster to Go targets after Valid cues than Invalid cues ($F = 217.151$, $p < 0.001$, $\eta_p^2 = 0.702$) and NoGo cues ($F = 170.277$, $p < 0.001$, $\eta_p^2 = 0.649$, see Figure 4). Females responded significantly slower than males ($F = 4.261$, $p = 0.042$, $\eta_p^2 = 0.044$). Relative to males, females also showed greater slowing for Go targets

after Invalid compared to Valid cues (interaction: $F = 6.471$, $p = 0.013$, $\eta_p^2 = 0.066$), and after NoGo compared to Valid cues (interaction: $F = 5.456$, $p = 0.022$, $\eta_p^2 = 0.056$). No effects of alcohol group were significant.

Grand mean ERP waveforms to targets are presented in Figure 3, and means for each alcohol group in Figure 4. Indicating greater response conflict, P2-N2 amplitude was greater to NoGo targets after Go than NoGo cues ($F = 33.085$, $p < 0.001$, $\eta_p^2 = 0.264$), and was larger overall for heavy drinkers than controls ($F = 8.851$, $p = 0.004$, $\eta_p^2 = 0.088$). No other effects were significant (all $F \leq 2.301$, all $p \geq 0.133$). For Go targets, P2-N2 was greater after Invalid cues ($F = 28.103$, $p < 0.001$, $\eta_p^2 = 0.234$) and NoGo cues ($F = 23.084$, $p < 0.001$, $\eta_p^2 = 0.201$) compared to Valid cues. P2-N2 was larger for heavy drinkers than controls ($F = 5.365$, $p = 0.023$, $\eta_p^2 = 0.055$), and a sex x alcohol group interaction reached significance ($F = 4.099$, $p = 0.046$, $\eta_p^2 = 0.043$). Further simple effects analyses revealed that P2-N2 was larger for heavy drinkers than controls among females ($F = 10.349$, $p = 0.002$, $\eta_p^2 = 0.101$), but no significant difference was observed among males ($F = 0.039$, $p = 0.844$, $\eta_p^2 = 0.000$). No other effects reached significance (all $F \leq 2.170$, all $p \geq 0.144$).

The P3 component to NoGo targets (indicating active cancellation of the motor response) was greater after Go than NoGo cues ($F = 118.083$, $p < 0.001$, $\eta_p^2 = 0.562$, see Figure 4), with larger effects for women than men (interaction: $F = 3.975$, $p = 0.049$, $\eta_p^2 = 0.041$). For Go targets, P3 was larger after Invalid cues than Valid cues ($F = 48.788$, $p < 0.001$, $\eta_p^2 = 0.347$). A sex x alcohol group interaction was significant ($F = 4.860$, $p = 0.030$, $\eta_p^2 = 0.050$). Further simple effects analyses indicated smaller P3 amplitudes for heavy drinkers than controls among females ($F = 6.086$, $p = 0.015$, $\eta_p^2 = 0.062$), but no significant difference was observed for males ($F = 0.536$, $p = 0.466$, $\eta_p^2 = 0.006$). No significant interactions of sex or alcohol group with cue type were observed.

Error-related waveforms can be seen in Figure 3, and ERN and Pe means (related to performance monitoring) can be seen in Table 1. Degrees of freedom for effects reported here are (1, 48). No effects of group or sex were observed for ERN amplitude (all $F \leq 0.452$, all $p \geq 0.505$) or latency (all $F \leq 0.556$, all $p \geq 0.459$). However, Pe amplitude was significantly greater for men than women ($F = 4.683$, $p = 0.035$, $\eta_p^2 = 0.089$), for controls compared to heavy drinkers ($F = 6.656$, $p = 0.013$, $\eta_p^2 = 0.122$), with no interaction ($F = 0.239$, $p = 0.627$, $\eta_p^2 = 0.005$).

4. DISCUSSION

In this study, we aimed to assess behavioural and psychophysiological indices of inhibition, conflict detection, and performance monitoring in young heavy drinkers compared to light drinking controls, and additionally, whether sex differences were apparent in this relationship. The sample we recruited was fit for the purpose: our heavy drinkers scored an average 9 on the AUDIT, above the threshold to indicate hazardous and harmful drinking (Saunders et al., 1993), and had consumed substantially more alcohol in their lifetime and in the week prior to the study. Although the DUDIT score, as an index of involvement with other drugs, was significantly greater among the heavy drinkers, we point out that the scores were low overall, and indicated only experimentation with other substances, and that regular use of other drugs (defined as more than once a month) was an exclusion criterion.

The cued-Go/NoGo task used here was based on that used in our previous study (Randall and Smith, 2011) and replicated those results entirely: CNV amplitude at lateral central sites C3 and C4 was larger following Go than NoGo cues (i.e., when the cue indicated a response would likely be required, compared to likely not required). CNV was also larger contralateral to the cued side for Go Left and Go Right cues, indicating specific preparation for the responding hand. Reaction time and error data also indicated preparation according to the cue, with fastest RT and few errors for validly cued targets (that is, when the cue indicated correctly the response required), and slower RT and more errors for invalidly cued targets (when the prepared response had to be changed to a different response). For Go targets after a NoGo cue (when no response had been prepared), responses were slow but accurate,

consistent with the need to activate a new response plan, but without the bias to an inaccurate response occurring on Invalidly cued trials. Some sex differences were apparent, such that females were slower and more accurate than males, particularly for Invalidly cued and Uncued Go trials, suggesting a speed-accuracy trade-off. P2-N2 amplitude increases were observed whenever the cued/planned response was different from that demanded by the target (i.e., for NoGo targets after Go cues, for invalidly cued Go targets, and for Go targets after NoGo cues), while P3 amplitude was increased whenever a planned response had to be inhibited (i.e., NoGo targets after Go cues, and invalidly cued Go targets). Here, we also newly considered response-related activity, and observed a frontocentral midline error-related negativity (ERN), and centroparietal midline error positivity (Pe) as expected after erroneous responses (Falkenstein et al., 1990, Falkenstein et al., 2000, Nieuwenhuis et al., 2001, Simons, 2010).

However, we observed little evidence of differences in these processes among controls and heavy drinkers: there were no alcohol group effects for CNV amplitude, errors, reaction time, P3 amplitude to NoGo targets, or ERN amplitude or latency. Further, while there were some alcohol group main effects for P2-N2 to Go and NoGo targets, and group x sex interactions for P2-N2 and P3 to Go targets, none of these showed significant three-way interactions dependent on trial/cue type. That is, even though there were absolute differences in amplitude, controls and heavy drinkers show similar *changes* in amplitude according to conflict and inhibition for almost all measures included here, indicating intact response preparation, execution and inhibition processes in young heavy drinkers. The one exception was Pe amplitude, which was significantly larger for controls compared to heavy drinkers, possibly indicating greater conscious awareness of errors in controls (Murphy et al., 2012, O'Connell et al., 2007). Note that this effect contrasts with our previous examination of Pe in a different Go/NoGo task (Smith et al., 2017), where we observed no group difference in Pe amplitude.

In contrast to the cued-Go/NoGo task, behavioural data from the stop-signal task displayed some evidence of sex-specific differences in inhibition among heavy drinkers and controls, however, these were not as expected. Based on previous research (Nederkoorn et al., 2009, Smith et al., 2016), we expected female heavy drinkers to show poorer inhibitory capacity (longer SSRT, and lower probability of successful inhibition) than female controls, with a reduced or even a small reversed effect for male heavy drinkers. In contrast, we observed similar probability of inhibition and SSRT for female heavy drinkers vs. controls, but a strong group effect for males. Further follow-up investigations of these effects revealed that male heavy drinkers did not perform exceptionally well (being no different to female heavy drinkers), but rather, male controls performed exceptionally poorly. Because this result differs so greatly from previous studies, more research is needed to further investigate the nature of sex differences in the relationship between heavy drinking and disinhibition. If the current result is a nonreplicable anomaly, and female heavy drinkers are in fact poor inhibitors, then we reiterate our argument regarding the need to understand this relationship better for prediction of treatment outcomes, and/or therapies which increase inhibitory control, and how these might be effective for only one sex. However, if the current result represents the true state of affairs, then again, more work is needed to investigate inhibitory capacity in young male controls and heavy drinkers. It is perhaps unsurprising that our young male sample displays impulsivity (e.g., Bjorklund and Kipp, 1996), yet it is difficult to understand why this effect is limited to controls – is it possible that heavy drinking is protective among young males? Further research will be required to understand this phenomenon.

ERP results were also not as expected, relative to previous research, and relative to the cued-Go/NoGo task in the same set of participants. Although we observed the expected failed > successful inhibition effect for N2 amplitude, we did not observe the robust increase in P3 amplitude for successful inhibition (e.g., Kok et al., 2004, Dimoska and Johnstone, 2007). Our results also did not mirror those from our similar previous study using the stop-signal task (Smith et al., 2016), which found a marginally larger successful > failed P3 effect for heavy drinkers (similar for males and females, but see also O'Halloran et al., 2019, for relationships in the opposite direction). In contrast, here we observed a small successful > failed effect for females only, and although we observed a sex x group interaction for P3, there were no interactions between group and trial type for N2 or P3 (similar to the cued-Go/NoGo task).

Further, the Pe results for the stop-signal task (male heavy drinkers showed a large Pe) contrast with those from the cued-Go/NoGo task here (Pe larger for men than women and for controls compared to heavy drinkers). Although it is possible that these anomalous results are due to our use of a visual rather than auditory stop-signal, as in our previous research (Smith et al., 2016), we think it unlikely, as Ramautar et al. (2006) have showed that similar N2 and P3 effects are observed for auditory and visual modalities. We point out also that recruitment criteria were similar across the two studies. Thus, the lack of consistency between studies, and with standard effects in the stop-signal task, is disconcerting, and more work will be required to understand the reasons for the disparity.

All in all, we saw little evidence of inhibitory impairment among heavy drinkers, let alone sex effects with greater impairments among female heavy drinkers. Since we published our meta-analysis of inhibitory deficits in heavy drinkers and other groups (Smith et al., 2014), there have been several new studies which have also failed to observe alcohol-related impairments in inhibition (e.g., Bø and Landrø, 2017, Hu et al., 2016, Franken et al., 2017, Watson et al., 2016), calling into question the small effect reported for heavy drinkers in our meta-analysis (Smith et al., 2014). For this reason, we suggest that future investigations of relationships between inhibitory control and substance use should focus on dependence only. Questions that are relevant might include whether cognitive control deficits can predict treatment outcomes (e.g., Rupp et al., 2016, Czapla et al., 2016, Goudriaan et al., 2008, Steele et al., 2014), and whether cognitive training (e.g., attentional bias modification, inhibitory control training) may serve as a useful treatment adjunct for people with a dependence (e.g., Jones and Field, 2020).

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