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## Abstract

Binge drinking is associated with increased impulsivity and altered emotional processing. The current study investigated, in a group of university students who differed in their level of binge drinking, whether the ability to inhibit a pre-potent response and to delay gratification is disrupted in the presence of emotional context. We further tested whether functional connectivity within intrinsic resting-state networks was associated with alcohol use. Higher incidence of binge drinking was associated with enhanced activation of the lateral occipital cortex, angular gyrus, the left frontal pole during successful response inhibition irrespective of emotional context. This observation suggests a compensatory mechanism. However, higher binge drinking attenuated frontal and parietal activation during successful response inhibition within a fearful context, indicating the selective emotional facilitation of inhibitory control. Similarly, higher binge drinking was associated with attenuated frontopolar activation when choosing a delayed reward over an immediate reward within the fearful, relative to the neutral, context. Resting-state functional data analysis revealed that binge drinking decreased coupling between right supramarginal gyrus and Ventral Attention Network, indicating alcohol-associated disruption of functional connectivity within brain substrates directing attention. Together, our results suggest that binge drinking makes response inhibition more effortful, yet emotional (more arousing) contexts may mitigate this; disrupted functional connectivity between regions underlying adaptive attentional control, is a likely mechanism underlying these response inhibition effects associated with binge drinking.

## Introduction

A pattern of intake of large amounts of alcohol within a short time (e.g. during weekends) followed by a period of abstinence, is known as binge drinking and is habitually common among teenagers and university students (Townshend & Duka, 2002; Courtney & Polich, 2009). Adolescents and young adults may be particularly vulnerable to excessive alcohol use, due to the immaturity of inhibitory control processes, predisposing to a reduced ability to limit alcohol intake. Furthermore, alcohol itself can foster dysregulated alcohol use by modulating or disrupting the development of inhibitory control processes (López-Caneda *et al.*, 2014). Indeed, binge- and heavy-drinking adolescents and young adults show neural signatures of cognitive difficulties in elevated brain activity across frontoparietal regions during working memory, verbal learning, and inhibitory control tasks (for review see Cservenka & Brumback, 2017). Structurally, there is as systematic thinning of the prefrontal cortex, lower volumes in prefrontal and cerebellar regions, and indicators of delayed white matter maturation (Cservenka & Brumback, 2017; Smith *et al.*, 2017). Dysfunctional affective processing is observed among binge drinkers (BD) (for review see Stephens and Duka, 2008) and is accompanied by changes in neural reactivity within prefrontal and temporal regions (Maurage *et al.*, 2013). For example, when processing angry faces, BD showed lower right temporal pole and right cuneus activity than non-BD (Whelan *et al.*, 2014). Therefore, understanding how emotional states influence impulsive behaviours, which facilitate alcohol use, may be of particular importance in BD. The current study attempted to examine the role of emotional context in the control of impulsive behaviours.

Increased alcohol use and heavy episodic alcohol consumption among college students is tied to elevated impulsivity levels (Cyders *et al.*, 2009; Caswell, Celio, *et al.*, 2015). However, impulsivity is a multidimensional construct (Caswell, Bond, *et al.*, 2015; Herman *et al.*, 2018), and it is possible that distinct facets of impulsivity may not be disrupted equally in

BD. For example, BD show increased trait impulsivity compared to non-BD, particularly on dimensions of motor and 'non-planning' impulsivity (Sanchez-Roige *et al.*, 2014). Concerning behavioural motor impulsivity, Bø and colleagues (2016) observed that BD could not adjust behaviour after they fail to stop but otherwise show no differences in a measure of response inhibition. Therefore, it is possible that binge drinking and heavy alcohol use may be associated with disrupted behavioural adjustment mechanisms. Tests of the ability to delay gratification, i.e. temporal discounting, are mixed. Some studies indicate no differences between BD and non-BD (Banca *et al.*, 2016) while others suggest elevated temporal impulsivity in BD (Sanchez-Roige *et al.*, 2014).

Neuroimaging may resolve these conflicting observations from behavioural research. For example, while choosing a delayed reward over an immediate one, individuals with more severe drinking problems show increases in the activation of several brain regions involved in response inhibition and interoceptive processing, including right inferior frontal gyrus, supplementary motor cortex, and insula (Claus *et al.*, 2011), consistent with a need for problem drinkers to exert greater effort to overcome immediate bias. Moreover, despite no differences between BD and controls in behavioural measures of response inhibition, successful inhibition in BD is related to significantly higher activation of the right inferior frontal cortex, a brain region implicated in volitional aspects of inhibitory control. Thus, BD may need to recruit more neural resources for successful inhibition of behaviour (López-Caneda *et al.*, 2012). Interestingly, in a modified version of the Go/No Go (GNG) task, activation of prefrontal areas is decreased during successful inhibitory trials occurring in an emotionally-negative, compared to a neutral, context (Cohen-Gilbert *et al.*, 2017). The authors provided as a possible interpretation that negative emotional distractors elevate cognitive control demands in young adults with a heavier pattern of binge drinking, disrupting neural regulatory processes through reduced prefrontal activation. However,

participants in that study were not very heavy alcohol users (up to 30 U.S. drinks per month); thus, we propose an alternative hypothesis to explain the data by Cohen-Gilbert et al., (2017): The attenuation of prefrontal activity during action inhibition in the negative context relative to neutral context can reflect facilitation of inhibitory control in this condition. It is possible that the fearful context increases arousal in more binge drinking individuals making them more attentive; thus, facilitating inhibitory control. Indeed, it has been proposed that under-aroused individuals might show improved performance at cognitive tasks when stimulated (Hebb, 1955; Zuckerman, 1969; Barratt, 1985; Schmidt *et al.*, 2013). This may also apply to other aspects of self-control such as delay discounting. The present study aimed to test this hypothesis.

Cognitive and emotional processing alterations in heavy alcohol users have been associated with alcohol-induced grey- and white matter abnormalities within several brain regions including frontal lobe and limbic systems, basal forebrain, and cerebellum (Crews *et al.*, 2004; Sullivan & Pfefferbaum, 2005; Crews & Nixon, 2009). Emerging evidence suggests that chronic alcohol use affects the relationship between these regions at the level of functional connectivity (FC). The characterisation of interregional FC within the resting state (RS) brain networks provides a valuable tool to probe brain mechanisms underlying dysfunctional neurocognitive processes and neuropsychiatric disorders (e.g. De Luca *et al.*, 2006; van den Heuvel & Hulshoff Pol, 2010). Studies in heavy-drinkers and alcohol-dependent individuals point to selective abnormalities within RS networks, notably those related to cognitive and motor control, visual processing and reward sensitivity (Weiland *et al.*, 2014; Zhu *et al.*, 2017). These findings support the use of RS FC to identify brain-wise differences in functional integrity in heavy alcohol-users and could provide us with information about baseline functional alternations in brain activity. If the same brain regions

show disrupted activity pattern during task performance and at rest, stronger evidence would be provided for a dysregulated target neuronal network.

The current study examined whether emotional context affects temporal and motor impulsivity in a group of healthy college students who differed in their binge drinking. Since BD can show altered emotional processing, individuals who binge more, may be less affected by emotional stimuli at the behavioural level, i.e. perform better than individuals who binge less. As explained above, it is possible that emotional context (e.g. fearful) increases arousal in more binge drinking individuals making them more attentive. We also wanted to examine the neural correlates of impulsive behaviour in emotional context and its relationship with binge drinking. To our knowledge, the role of emotional context in temporal impulsivity and prepotent response inhibition in BD has not yet been examined using functional Magnetic Resonance Imaging (fMRI). Regarding motor impulsivity, previous research employed the affective version of the GNG task (Cohen-Gilbert *et al.*, 2017), a measure of action selection (to go or to stop) and restraint (due to the infrequency of Stop stimuli) (Winstanley, 2011; Herman *et al.*, 2018). In the current study we decided to study the neural correlates of inhibitory control in emotional context using the affective version of the Stop Signal Task (SST), which indexes a prepotent response inhibition (i.e. action cancellation; Herman et al., 2018; Winstanley, 2011), which has not been used before in BD. In fMRI, we predicted that diminished prefrontal activity during response inhibition would occur in the emotional vs neutral context in more binge drinking individuals. Finally, we explored the within and between RS networks FC associated with binge drinking to identify baseline differences in resting brain activity which may prove useful as biomarkers of alcohol-related problems.

## Materials and Methods

### Participants

30 volunteers (9 men) were recruited from the University of Sussex community. Participants had to be between 18 and 40 years old and right-handed. Exclusion criteria included history of any mental or neurological disorders, head injury, current treatment for any psychological or physical condition (including use of inhalers; excluding the contraceptive pill), pregnancy or breastfeeding, clinically significant impairment of vision, and any MRI contradictions (claustrophobia, and having any metal implants, teeth braces or bridges, or cardiac pacemakers).

Participants who met study inclusion criteria, established initially via e-mail communication, were invited for a single session visit lasting up to 3 hours. Within this time inclusion criteria were confirmed, procedures were explained and written consent was provided. Participants also completed questionnaires and practised the tasks in a testing cubicle, before entering fMRI scanner. The study was approved by Brighton and Sussex Medical School Research Governance and Ethics Committee (reference number 16/023/DUK). The study conformed to World Medical Association Declaration of Helsinki.

### Questionnaires

Participants completed the Barratt Impulsiveness Scale (BIS, Patton, Stanford, & Barratt, 1995), which is an established measure of trait impulsivity, and the Alcohol Use Questionnaire (Mehrabian & Russell, 1978) to assess the approximate amount of alcohol consumed per week for the previous 6 months. The Alcohol Use Questionnaire provides a reliable measure of drinking quantity, but also of drinking pattern (Townshend & Duka, 2002). To assess alcohol drinking patterns, a binge score (BS; Townshend & Duka, 2002) is calculated based on the speed of drinking (number of drinks per hour), the number of episodes of alcohol intoxication in the past 6 months, and the percentage of alcohol

intoxications out of the total number of times of going out drinking (BS = speed of drinking x 4 + number of intoxications + percentage of times drunk x 0.2; (Townshend & Duka, 2002 based on Mehrabian & Russell, 1978). Alcohol intoxication in this context is defined as an experience of loss of coordination, nausea, and/or inability to speak clearly.

## Tasks

The investigation used an event-related fMRI paradigm. Prior fMRI session, all volunteers underwent training outside the scanner to familiarise themselves with the tasks and to ensure they follow the instructions correctly.

During scanning, the stimuli were back-projected onto a mirror mounted on the head coil and presented centrally against a homogenous grey background. We used the Cogent 2000 (Wellcome Dept., London, UK) in MATLAB (Mathworks Inc.) for stimulus presentation, the timing of stimuli and response events, and synchronisation with fMRI image acquisition. In both tasks, the emotional context was task-irrelevant (i.e. no instructions to perform the task referred to the emotional context – pictures of facial expressions).

### *Affective Stop Signal Task (ASST)*

ASST was based on a modified version of the SST based on previous work (Sagaspe *et al.*, 2011; Pawliczek *et al.*, 2013) with timings taken from the standard version of the task used in the lab which has been described previously (Nikolaou *et al.*, 2013). Instead of arrows, participants were presented with facial expressions from the FACES database (Ebner *et al.*, 2010) of males and females (50% each) displaying either fear or neutral expression (50% each).

Each trial started with a jittered (1200-1500ms) central fixation cross rest period. Presentation of the Go-stimulus (a facial expression surrounded by a white frame) followed, which on the Go-trials remained on the screen for the total stimulus display duration of 800ms. On the

Stop-trials, the Go-stimulus was replaced by the Stop Stimulus (the same picture surrounded by a yellow frame) after a variable stimulus onset asynchrony (SOA) (see Figure 1). The initial SOA was 200ms and was adjusted according to a staircase procedure (Verbruggen & Logan, 2009): the SOA increased or decreased by 50ms as a function of participants' performance. SOA increased 50ms every time the participant inhibited their response (Stop Success, SS) or decreased by 50ms every time the participant was unable to withhold their response (Stop Fail, SF). Such adjustments were made separately for each emotional condition (fearful and neutral), to obtain a probability of stopping 0.5 for each condition. The Stop-Signal Reaction Time (SSRT) was calculated separately for neutral (NeuSSRT) and fearful (FeaSSRT) trials by subtracting the mean SOA from the average reaction time (RT) to correct Go-trials (GoC; neutral or fearful, respectively). Further dependent variables included Go RT and Go Accuracy.

On the Go-trials, participants were instructed to respond with an appropriate button-press to indicate whether the face displayed on the screen was male or female (implicit emotional context) as quickly as possible and to try and withhold their responses when the frame surrounding the picture changed colour (Stop-trials). Participants were informed that speed and accuracy on task are equally important and that they should not be delaying their responses to see whether the frame would turn yellow.

Participants completed two runs of 160 trials each separated by a 1-minute break to allow them to relax. In total there were 120 Go Neutral, 120 Go Fearful, 40 Stop Neutral, and 40 Stop Fearful trials.

### *Affective Delay Discounting Task (ADD)*

The second task was a modified delay discounting task, which measures the ability to delay gratification. Participants were presented with black and white facial expressions of

(50%male, 50% female, 50% neutral, 50% fearful) from the NimStim database (Tottenham *et al.*, 2009) and Radbound (Langner *et al.*, 2010) Faces Databases. Each trial started with a jittered (1200-1500ms) central fixation cross rest period. Then, a facial expression was presented in the centre of the screen for 2 seconds, followed by a different face of a congruent emotional expression (fearful or neutral) and a hypothetical question with 2 possible answers was displayed below the photo, for example, "Would you prefer: £10 now, or £25 next week?" (see Figure 2). The order of the immediate and the delayed options display was randomised. Participants had to choose by pressing an appropriate button. The trial was terminated after a response button was pressed or 7s has elapsed, whichever came first. Moreover, the volunteers were instructed to pay attention to each facial expression presented on the screen and imagine that the person in the photo, asks them the question displayed below. Participants completed one run of 54 trials (27 neutral, 27 fearful trials in a randomised order) each. 27 questions were taken from the Monetary Choice Questionnaire (Kirby *et al.*, 1999) and another 27 items matched for k values to the original 27 questions were developed (see Supplementary Materials for details). For each emotional condition, a k value (log transformed) was computed.

### MRI experiment design

In the MRI scanner, first, a structural scan was obtained followed by a 7-minute resting-state scan (165 volumes) during which participants were instructed to rest with their eyes open without thinking of anything in particular and not falling asleep. Subsequently, ASST and ADD were completed. The total time spent in the scanner by each participant did not exceed 50 minutes. All participants were tested between 2 pm and 6 pm to control for possible time of day effects on attention level.

## MRI Acquisition

MRI was performed on a 1.5-Tesla MAGNETOM Avanto scanner (Siemens AG, Munich, Germany). Structural volumes were obtained using the high-resolution three-dimensional magnetization prepared rapid acquisition gradient echo sequence. Functional data sets used T2*-weighted echo planar imaging sensitive to blood oxygenation–level dependent signal (repetition time = 2.52 seconds, echo time = 43 ms, flip angle = 90°, 34 slices, 3-mm slice thickness, field of view = 192 mm, voxel size = 3 × 3 × 3 mm). Slices were angled -30° in the anteroposterior axis to reduce the signal loss in orbitofrontal regions (Deichmann *et al.*, 2003; Weiskopf *et al.*, 2006).

## Statistical Analysis

### Behavioural and trait measures

To investigate the relationship between impulsivity and binge drinking, we computed correlations between performance on the behavioural task and BS. Since BD show elevated trait impulsivity levels (Sanchez-Roige *et al.*, 2014), a correlation between BD and BIS was computed. Additionally, to look at the difference in performance between the emotional conditions, we calculated the subtraction scores (Fearful SSRT - Neutral SSRT, Fearful log k - Neutral log k). The analysis was conducted in SPSS v22.

## FMRI Data Preprocessing

Imaging analysis was performed using FEAT (FMRI Expert Analysis Tool) version 6.00, a part of FMRIB Software Library (FSLv6.0, Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). Pre-processing steps included (1) skull stripping of structural images with Brain Extraction Tool (BET), (2) removal of the first four functional volumes to allow for signal equilibration, (3) head movement correction by volume-realignment to the middle volume using MCFLIRT, (4) global 4D mean intensity normalization, (5) spatial smoothing

(6mm full-width half-maximum) and (6) noise signals removal, (7) temporal high-pass filtering (90s cut-off for task-related data, and 100s for resting-state data).

FMRI datasets were co-registered to the participant's structural image using affine boundary-based registration as implemented in FSL FLIRT (Jenkinson & Smith, 2001; Jenkinson *et al.*, 2002) and subsequently transformed them to MNI152 standard space with 2mm isotropic resolution using non-linear registration through FSL FNIRT (Andersson *et al.*, 2010). Noise signals were identified individually and removed using ICA-AROMA toolbox (Pruim *et al.*, 2015). ICA-AROMA incorporates probabilistic Independent Component Analysis (ICA) on the partly pre-processed single-subject fMRI data (following spatial smoothing and normalization but before high-pass filtering), identifies independent components (ICs) representing motion artefacts and removes them from the fMRI time-series using linear regression.

### Task-related fMRI Analysis methods

Statistical analyses were performed using the general linear model as implemented in FEAT. Customized square waveforms representing each event type and the duration of stimulus presentation were convolved with a double-gamma hemodynamic response function, and a high pass filter (90 s) was applied to remove low-frequency artefacts. For the ASST, events were modelled at the onset of the Go-stimuli. Several types of events were distinguished for the ASST for each condition (Neutral and Fearful) in order to compute contrasts: go correct (NeuGoC and FeaGoC), go incorrect (NeuGoI and FeaGoI), stop success (NeuSS and FeaSS), stop fail (NeuSF and FeaSF). For the ADD, 3 event types were identified for each emotional condition: face presentation (Neutral or Fearful), immediate (NeuImm and FeaImm) or delayed option chosen (NeuDel and FeaDel).

Functional MRI data were subsequently analysed using voxel-wise time series analysis within the framework of the General Linear Model. Mixed-effects analysis of group effects was carried out using the FMRIB Local Analysis of Mixed Effects (FLAME). Final Z statistical images were thresholded using Gaussian random field–based cluster interference with a height threshold of $Z > 2.3$ (family-wise error corrected) and a cluster significance threshold of $p < 0.05$ across the entire brain (Worsley, 2001; Heller *et al.*, 2006).

BS was added as a covariate of interest in all contrasts. Since there was a broad age range within our population (18-37 years old) and more females participated in the study, in all reported analyses demeaned age and gender were added as covariates of no interest at the second level group analysis. Moreover, since binge drinking has been linked to increased trait impulsivity (e.g. Sanchez-Roige et al., 2014), BIS score has been added in all fMRI analyses as a covariate, so that the results reflect solely the effect of BD beyond and above trait impulsivity.

Several contrasts of interest were computed. Specifically, for the ASST successful response inhibition regardless of the emotional context (SS>GoC, SS>SF), the main effect of emotional context (Fea-Neu), emotional context vs successful response interaction term ([SSFea-GoCFea]-[SSNeu-GoCNeu]). There were four contrasts of interest for ADD: making a decision relative to just passive facial expression viewing irrespective of the emotional context (Choosing – Face), choosing larger delayed versus smaller immediate rewards regardless of the emotional context (Del-Imm), main effect of emotion during making a decision (FeaChoosing – NeuChoosing), and interaction term of brain activity related to choosing a delayed and immediate reward in fearful vs neutral context ([FeaDel-FeaImm]-[NeuDel-NeuImm]).

## Resting state-data

### *Independent components analysis*

To decompose the RS data into various independent spatiotemporal components, Probabilistic Independent Components Analysis (PICA) was performed on the preprocessed functional scans using Melodic version 3.14 (Beckmann & Smith, 2004). A dimensionality estimation using the Laplace approximation to the Bayesian evidence of the model order (Beckmann & Smith, 2004) produced 11 spatiotemporal components. Following an approach described in (Reineberg et al., 2015), we statistically compared the spatial map of each independent component (IC) to a set of 7 reference RS networks from a previous large-scale RS analysis (Yeo *et al.*, 2011). We used FLS's "fslcc" tool to calculate Pearson's r for each pairwise relationship and kept only those ICs that yielded a significant spatial correlation (Pearson's $r > .3$) with one of the reference networks. This procedure identified and helped label 10 target ICs. The characteristic of each IC is presented in Table 1. Upon visual inspection, the remaining 1 IC was considered noise and was not subjected to further analysis.

## Dual regression

Next, we performed dual regression to generate subject-specific special maps and time courses from unthresholded group-level ICs maps (Beckmann *et al.*, 2009; Filippini *et al.*, 2009). The dual regression consists of (1) a spatial regression of the group-average set of ICs, which produces a set of subject-specific time series, one per group-level component, and (2) a temporal regression of those subject-specific time series, resulting in a set of subject-specific spatial maps, one per group-level component.

The within-network variation in functional connectivity depending on BS and subject-specific ICs was examined using Randomise, FSL's nonparametric permutation testing tool

(Winkler *et al.*, 2014), with 5000 permutations and threshold-free cluster enhancement (TFCE) with an alpha level of .05 to correct for multiple comparisons. Permutation testing was performed while controlling for age, gender and BIS score. The permutation testing procedure was run for each set of subject-specific RS networks (one for each group-level ICs of interest); thus, the resulting statistical images reveal how variation in RS FC predict differences in binge drinking. Following studies using similar procedures (Uddin *et al.*, 2013; Nomi & Uddin, 2015; Reineberg *et al.*, 2015; de Bézenac *et al.*, 2017), further correction for multiple component testing was not applied.

### *Between-network connectivity: FSL Nets*

To examine the relationship between BS and between-network FC, we employed the FSL Nets package implemented in Matlab (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLNets). This analysis involved correlation of the participants' time courses from the dual regression analysis and subjects them to between-network comparisons to determine how they are correlated with each other (Smith *et al.*, 2013). BS was then used to predict full and partial correlation values using FSL randomise with 5000 permutations.

The summary of RS data processing and analysis pipeline is presented in Figure 3.

## Results

### Exclusions

No subject was removed due to extensive motion in the scanner. Since 2 participants showed no discounting (consistently chose the delayed reward), they lacked events for delayed trials; therefore, they were excluded from the fMRI and behavioural analysis for the ADD task completely. As such, the sample for the ADD task consisted of 28 participants (9 males). No one was excluded from the ASST. The sample characteristic is presented in Table 2.

## Traits and Behaviour

Descriptive statistics is presented in Table 3. There was no relationship between BS and either trait impulsivity (BIS score) or performance on the tasks (*p*'*s* > .05). There was also no relationship between BS and difference in performance between Neutral and Fearful trials on the ADD (*p*'*s* > .05). However, the BS was negatively correlated with the FeaSSRT-NeuSSRT, $r(30) = -.376$, $p = .041$), indicating that the more the individuals were binge drinking, the better their response inhibition (less impulsive behaviour) in the fearful vs neutral condition (see Figure 4).

## Task related-fMRI

### ASST

Regression analysis revealed that increased BS was associated with increased activity in the lateral occipital cortex, angular gyrus, the left frontal pole during successful response inhibition (SS>SF, no suprathreshold voxels were found for SS>GoC), suggesting that individuals with higher BS need to engage more neural resources in order to successfully inhibit motor response (Table 4, Figure 5a). There was no main effect of emotion, but an interaction was found, [FeaSS-FeaGoC]<[NeuSS-NeuGoC], showing decreased activity in the left lateral occipital cortex, postcentral gyrus, superior parietal lobule, precuneus, and precentral gyrus bilaterally in the successful inhibition in the fearful vs neutral context (Table 4, Figure 5b).

### ADD

There was no relationship between BS and decision type (Del vs Imm) or emotional context (Fea vs Neu), but an interaction effect was found [FeaDel-FeaImm)<(NeuDel-NeuImm)], indicating that higher BD score was associated with decreased frontopolar activation bilaterally when choosing the delayed option over an immediate one in the fearful vs neutral context (Table 5, Figure 6).

## Resting State Functional Connectivity

### Within network

As seen in Figure 7, greater binge score was associated with the decreased coupling of the right supramarginal gyrus (peak MNI mm 62/-42/24, $p$-1 = 0.985) with IC 10, a network that correlated significantly with Ventral Attention Network template.

### Between network connectivity

No significant between-network FC results with regards to BS were found ($p_{FWE} > .05$).

## Discussion

This study sought to elucidate whether binge drinking status was associated with neural responses during impulsive actions and decisions and whether emotional context modulates these responses. We observed that higher BS is associated with increased neutral recruitment while successfully inhibiting prepotent motor responses, regardless of the emotional context. However, this effect was attenuated in the fearful context: higher BS was associated with decreased activation in several frontal and parietal areas during successful response inhibition in the fearful versus neutral context, a finding in line with our behavioural data indicating an association between an elevated BS and better response cancellation in the fearful vs neutral context. Moreover, increased BS was related to decreased frontopolar activation during choosing a delayed (over immediate) reward in the fearful vs neutral context, but no association between BS and performance on the temporal discounting task was found.

## ASST

Binge drinking score was positively associated with the lateral occipital cortex, angular gyrus and left frontal pole activity during successful response inhibition. This finding is consistent with previous reports showing that light alcohol consumption in young adults is related to compensatory recruitment necessary for motor inhibition implementation (López-Caneda *et*

*al.*, 2012; Hatchard *et al.*, 2017). Even though these past studies had younger samples (18-21 years old), it is still interesting to note that they reported similar results.

Hatchard and colleagues (2017)**,** investigated the impact of regular low-level alcohol consumption on response inhibition on the Go/No-Go task. Results indicated that, despite a lack of performance differences, compared to controls who did not use alcohol on a regular basis, those who used alcohol regularly showed significantly more activation during response inhibition in the left hippocampus, parahippocampal gyrus, superior frontal gyrus, precentral gyrus, right superior parietal lobule, and the cerebellum. It seems that even in low amounts, regular consumption of alcohol may be associated with changes in neurophysiological functioning in the developing brain during response inhibition (Hatchard *et al.*, 2017). Similarly, López-Caneda *et al.*, (2012) also using a GNG paradigm found that young binge drinkers show increased right inferior frontal gyrus activity as measured by event-related potentials during response execution and inhibition. In the current study, we report that increased BS is related to enhanced activity in several cortical regions, including lateral occipital cortex, angular gyrus and frontal pole, during successful response inhibition in the SST. The differences in anatomical location of areas showing an enhanced activity may be due to differences in samples and tasks used. However, the overall findings across these studies support a compensatory brain activity in frontal areas needed to implement response inhibition successfully.

Importantly, in our study individuals with the higher incidence of binge drinking needed to exert higher left frontopolar activation to implement inhibitory control successfully. Not only are decreased grey matter volumes of the frontal pole associated with harmful drinking, but also this relationship is mediated by impulsive behaviours (Gropper et al., 2016). Indeed, the frontal pole has been linked to top-down cognitive control, decision-making, evaluating self-generated decisions, and emotion regulation (Miller & Cohen, 2001; Tsujimoto *et al.*, 2009;

Neubert *et al.*, 2014; Orr *et al.*, 2015). If binge drinking is associated with impairment in this part of the brain, compensatory recruitment of neural resources (i.e. increased activation) may be needed to implement inhibitory control successfully.

Compensatory recruitment was also indicated by increased activation of the angular gyrus in more binge drinking individuals. Although the angular gyrus is not typically associated with response inhibition, a study on adolescence indicated that left angular gyrus activation during inhibition trials on the GNG task predicted higher levels of substance use and dependence symptoms 18 months later, particularly in those who initially showed frequent use (Mahmood *et al.*, 2013).

Moreover, on the behavioural level, increased BS was associated with improved inhibitory performance in the negative (fearful) vs neutral context. The neuroimaging results offer an explanation of these behavioural findings: more binge drinking individuals exhibited decreased neural recruitment in the fearful vs neutral context. Together, these results suggest that response inhibition is better among high BD in the negative context. Cohen-Gilbert and colleagues (2017) also showed reduced prefrontal activation in the presence of negative emotional distractors with increased binge drinking, but the authors interpreted their results as a failure to bring regulatory brain regions online in the negative context which elevates cognitive control demands. However, our behavioural and neuroimaging results taken together rather suggest that more binge drinking individuals find it easier to inhibit responses in a Fearful compared to a Neutral context. Possibly, BD are either less distracted by the emotional context or the emotional context brings about a state of arousal, which without inducing any emotional excitatory response, increases cognitive capacity and thus facilitates the behavioural control in the fearful context.

The decreased activity in response to inhibitory control implemented in the fearful vs neutral context was observed in brain areas important in cognitive processes associated with response inhibition, like the left superior parietal lobule, postcentral gyrus, precuneus and precentral gyrus bilaterally; but also in lateral occipital cortex, which plays a role in object recognition (Grill-Spector *et al.*, 2001) and multisensory integration (Beauchamp, 2005). The superior parietal lobule and neighbouring regions in the parietal cortex are thought to play a critical role in visuospatial attention (Corbetta & Shulman, 2002; Yantis *et al.*, 2002), switching processes (Piguet *et al.*, 2013) and working memory (Owen *et al.*, 2005). The precuneus seems to be involved in shifting and directing attention in space during action preparation and execution (Kawashima *et al.*, 1995; Cavanna & Trimble, 2006) as well as motor coordination (Wenderoth *et al.*, 2005). The precentral gyrus is involved in stimulus-response associations (Brass *et al.*, 2009) and is thought to be a key region for motor inhibition (Li *et al.*, 2006). Previously, an increased somatosensory (postcentral gyrus) activity in post-traumatic stress disorder patients during response inhibition tasks has been interpreted as a state of hyperactive sensory processing during inhibitory control (Falconer *et al.*, 2008). Analogously, in the current study reduced somatosensory cortex activity associated with binge drinking during inhibitory control in the fearful relative to neutral context, may reflect diminished sensory processing of emotional stimuli. Indeed, binge and heavy drinking have been related to altered emotional processing (Stephens & Duka, 2008; Maurage *et al.*, 2013).

Overall, these findings suggest that response inhibition was more efficient in the Fearful vs Neutral contexts in individuals with a higher incidence of binge drinking.

### ADD

In the temporal discounting task, we found no relationship between BD and performance. Therefore, it seems that the emotional context was not interfering or affecting choices between immediate and delayed rewards in binge drinkers in any way. Neuroimaging

analysis, however, showed that the higher the BS, the more the decrease in frontal pole activation when individuals made a delayed over immediate choice in the fearful vs neutral context. These results corroborate with our findings from the ASST, in that negative emotional context seem to require less neural resources in individuals who binge drink more, supporting further our hypothesis that BD become more aroused in the fearful condition and therefore more efficient for task performance.

Previous research indicated that prefrontal cortex (e.g. orbitofrontal cortex) plays a crucial role in temporal discounting (Sellitto *et al.*, 2010). Moreover, in a large-scale study, the grey matter volumes in the right frontal pole were predictive of the discounting parameter k, but not SSRT, suggesting that the right frontal pole may be a specific region associated with temporal discounting (Wang *et al.*, 2016). And in another study, it was suggested that the anterior dorsomedial prefrontal cortex (including frontal pole) is involved in representing temporally more distant reward (Wang *et al.*, 2014).

A recent study reported that alcohol dependence severity was positively associated with activation in paracingulate gyrus and frontal pole in delayed relative to impulsive, immediate decisions (Lim *et al.*, 2017). Our results extend those previous findings and demonstrate that the increased recruitment of prefrontal areas, particularly of frontal pole, may indeed be required to delay reward successfully. The presence of the fearful context could induce more efficient (less impulsive) decision making in individuals who binge more, as evidenced by the reduced recruitment of frontal pole. However, our behavioural data did not provide support for this assumption. In the context of these findings, it is important to note that the frontal pole is thought to be vital for behavioural control and emotional regulation (Orr *et al.*, 2015). Interestingly, the study on multiple detoxified alcoholics revealed that during emotion recognition task, the strength of connectivity between the insula and inferior frontal cortex

and frontal pole was negatively correlated with the number of detoxifications, the severity of alcohol dependency and control over drinking score (O'Daly *et al.*, 2012)**.**

### Resting-state functional connectivity

Our results suggest that in a sample of high-functioning university students, the level of binge drinking is associated with subtle changes in functional connectivity within the ventral attention network. However, in contrast to previous studies using alcohol-dependent individuals, there were no global differences in the between network architecture (Zhu *et al.*, 2017), suggesting that these may occur as a result of heavy drinking/dependence.

The level of binge drinking was associated with the decreased functional coupling of the right supramarginal gyrus and IC10, consisting of frontal regions, insular cortex, cerebellum (see Table 1), which matched the template of the Ventral Attention Network as identified by Yeo and colleagues (2011). The results indicate that less binge drinking individuals have more robust aforementioned Network, which expands further into the parietal lobe. Indeed the supramarginal areas are considered the part of the Ventral Attention Network (Vossel *et al.*, 2014). The Ventral Attention Network has been linked to attending to unexpected but goal-related stimuli (Vossel *et al.*, 2014). In accordance with this latter report, it is reasonable to suggest that decreased functional connectivity within the Ventral Attention Network with more binge drinking could result in attentional deficits. It is worth noting that we did not find any FC alternations in networks reported previously in alcohol-dependent individuals, such as the left frontoparietal network, the visual network, or the default-mode network (Weiland *et al.*, 2014; Zhu *et al.*, 2017), further indicating that these extended within and between-network connectivity changes might be a result of a heavy and long-term alcohol-use. Together with our task-related results, we find a consistent pattern of functional alterations within brain regions associated with attentional processes and executive control, with the

frontal pole as the most common hub. Such a finding provides strong evidence for the frontal pole being a neural biomarker for BD behaviour.

## Limitations

There are some limitations which should be considered when interpreting the study results. The cohort used in the current study consisted of university students, which is not a sample representative of the general population. Moreover, although participants were not diagnosed (in the past or currently) with alcohol or substance use disorder, and were instructed not to consume any recreational illicit substances five days prior to participation in the study, no formal assessment of substance use took place.

Another potential limitation may be individuals' socioemotional functioning, which is missing from our data, and which could be related to one's sensitivity to emotional faces as well as exposure to social situations (e.g. parties), in which alcohol use is likely to occur. In this context, it is possible that more binge-drinking individuals are more popular and may show enhanced emotional functioning.

## Conclusions

The current study provides evidence that more severe binge drinking is associated with enhanced activation of inhibitory brain areas during execution of successful response inhibition suggesting that binge drinkers require more effort to inhibit a prepotent motor response. This effect of binge drinking may be counteracted in the presence of the emotional (more arousing) context leading to a lower activation in frontal and parietal areas when compared to neutral context, areas supporting attentional processing. Also, higher binge drinking was associated with lower activity in the frontal pole (one of the key regions for intertemporal decision-making), when choosing a delayed over an immediate reward in the emotional context. Moreover, disrupted functional connectivity within the Ventral Attention Network in more binging individuals may suggest disrupted attentional processing providing

supporting evidence for the brain signature associated with binge drinking  These findings taken together highlight the important role that emotional situations play in modulating inhibitory control in BD, and the significance of applying RS FC in understanding the role of related neuronal network malfunctioning in these populations. Longitudinal research on changes in FC as individuals' transition from social drinking to dependence could further improve our understanding of what are the predisposing factors leading to alcohol drinking as well as what are the alcohol-induced changes in the whole-brain connectivity pattern.

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## Conflict of interest

The authors declare no conflict of interest.

## Author contributions

AH, HC and TD were responsible for the study concept and design. AH carried out the study and the data analysis. AH and TD interpreted the findings. AH drafted the manuscript. HC and TD provided critical revisions of the manuscript for important intellectual content.

## Data Accessibility

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Abbreviations

ADD – Affective Delay Discounting Task

ASST – Affective Stop Signal Task

BD - Binge Drinkers

BIS - Barratt Impulsiveness Scale

BS – Binge Score

Del – Delayed option

FC – Functional Connectivity

Fea – Fearful Condition

FeaSSRT – Stop-Signal Reaction Time computed for Fearful trials

fMRI - functional Magnetic Resonance Imaging

GNG – Go/No Go

GoC – Go Correct

GoI – Go Incorrect

IC – Independent Component

ICA - Independent Component Analysis

Imm – Immediate option

Neu – Neutral condition

NeuSSRT - Stop-Signal Reaction Time computed for Neutral trials

PICA - Probabilistic Independent Components Analysis

RS – Resting State

RT – Reaction Time

SF – Stop Fail

SOA - Stimulus Onset Asynchrony

SS – Stop Success

SSRT - Stop-Signal Reaction Time

SST – Stop Signal Task

TFCE - Threshold Free Cluster Enhancement

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## Tables

**Table 1** Resting-state Independent Components (IC number) identified in the current study and their characteristics. Template refers to networks identified in a previous large scale study (Yeo et al. 2011). DMN – Default Mode Network

| IC Number | Matching Template Network | Correlation with the Template (Pearson's r) | Regions | Lateralisation | Number of Voxels |
|---|---|---|---|---|---|
| 1 | Visual | 0.745 | Cuneal Cortex, Intracalcarine Cortex, Occipital pole | bilateral | 1138587 |
| 2 | DMN | 0.746 | Precuneus, Lateral Occipital Cortex, Middle Frontal Gyrus | bilateral | 761539 |
| 3 | Dorsal Attention/ Visual | 0.579/0.359 | Lateral Occipital Cortex, Occipital Pole, Middle Frontal Gyrus, Middle Temporal Gyrus, Precentral Gyrus, Precuneus | bilateral | 1003173 |
| 4 | DMN | 0.469 | Frontal Pole, Precuneus, Middle Temporal Gyrus, Subcallosal Cortex, Superior Frontal Gyrus | bilateral | 266631 |
| 5 | DMN | 0.548 | Frontal Pole, Angular Gyrus, Supramarginal Gyrus, Frontal Orbital Cortex, Inferior Frontal Gyrus, Middle Frontal Gyrus, Cerebellum | bilateral | 670689 |
| 6 | Ventral Attention | 0.454 | Supramarginal Gyrus, Inferior Frontal Gyrus, Frontal Pole, Latreal Occipital Cortex, Precentral Gyrus, Frontal Operculular Cortex, Insula, Cingulate Gyrus | bilateral | 181331 |
| 7 | Somatomotor | 0.746 | Postcentral Gyrus, Precentral Gyrus, Insula, Lateral Occipital Cortex, Cingulate Gyrus | bilateral | 898845 |
| 8 | Frontoparietal | 0.329 | Middle Frontal Gyrus, Lateral Occipital Cortex, Occipital Fusiform Gyrus, Middle Temporal Gyrus, Frontal Pole | left | 944938 |
| 9 | Frontoparietal | 0.513 | Middle Frontal Gyrus, Lateral Occipital Cortex, Middle Temporal Gyrus, Cerebellum, Paracingulate Gyrus, Cingulate, Frontal Pole, Insular Cortex | right | 689400 |
| 10 | Ventral Attention | 0.301 | Frontal Pole, Paracingulate Gyrus, Cerebellum, Superior Frontal Gyrus, Frontal Opercular Cortex, Juxtapositional Lobule, Insular Cortex, Occipital Fusiform Gyrus | bilateral | 211073 |

**Table 2** Sample Demographics, alcohol use, cigarette smoking and impulsivity personality trait ratings. BIS – Barratt Impulsiveness Scale

| **Variable** | **Mean** | **SD** |
|---|---|---|
| Age | 23.40 | 5.01 |
| Number of Cigarettes smoked a day | 1.27 | 3.31 |
| Total number units* of alcohol per week over a 6 months period | 13.23 | 15.78 |
| Binge Score | 21.85 | 19.95 |
| BIS Total | 65.30 | 11.39 |

*1 unit = 8g of alcohol

**Table 3** Group performance on the ASST and ADD tasks in the fearful and neutral conditions. ASST – Affective Stop Signal Task, ADD – Affective Delay Discounting, SSRT – Stop Signal Reaction Time

| **Dependent variable** | **N** | **Mean** | **SD** |
|---|---|---|---|
| SSRT Neutral (ms) | 30 | 305.77 | 35.08 |
| SSRT Fearful (ms) | 30 | 299.69 | 44.72 |
| ADD Log k value Neutral | 28 | -2.00 | .98 |
| ADD Log k value Fearful | 28 | -1.77 | .83 |
| SSRT Difference Fearful-Neutral | 30 | -6.07 | 51.39 |
| ADD log k Difference Fearful-Neutral | 28 | .22 | .97 |

**Table 4** Local maxima for each cluster of regions identified for the ASST successful response inhibition contrast (SS>SF) and the ASST interaction effect [(NeuSS>NeuGoC) > (FeaSS>FeaGoC)]. Cluster index refers to a group of voxels encompassing multiple brain areas. 'Voxels' refer to the number of voxels within each cluster. The Harvard-Oxford cortical and subcortical probabilistic atlases were used to identify each region.

| Cluster index | Voxels | P | Z-Value | MNI Coordinates [mm] | | | Side | Region |
|---|---|---|---|---|---|---|---|---|
| | | | | x | y | z | | |
| **CONTRAST SS>SF** | | | | | | | | |
| 1 | 422 | .010 | 3.67 | -24 | 66 | 20 | L | Frontal Pole |
| 1 | | | 3.42 | 6 | 70 | 12 | R | Frontal Pole |
| 1 | | | 3.35 | -18 | 60 | 16 | L | Frontal Pole |
| 1 | | | 3.34 | -20 | 60 | 2 | L | Frontal Pole |
| 1 | | | 3.11 | -14 | 62 | 18 | L | Frontal Pole |
| 1 | | | 3.06 | -10 | 70 | 12 | L | Frontal Pole |
| 2 | 608 | < .001 | 3.85 | -48 | -62 | 24 | L | Lateral Occipital Cortex |
| 2 | | | 3.65 | -50 | -52 | 28 | L | Angular Gyrus |
| 2 | | | 3.27 | -46 | -52 | 18 | L | Angular Gyrus |
| 2 | | | 3.05 | -42 | -56 | 42 | L | Angular Gyrus |
| 2 | | | 2.95 | -56 | -68 | 28 | L | Lateral Occipital Cortex |
| 2 | | | 2.87 | -62 | -60 | 36 | L | Lateral Occipital Cortex |
| **CONTRAST [NEUSS>NEUGOC] > [FEASS>FEAGOC]** | | | | | | | | |
| 1 | 415 | .010 | 3.74 | -50 | -64 | 4 | L | Lateral Occipital Cortex |
| 1 | | | 3.74 | -54 | -72 | 14 | L | Lateral Occipital Cortex |
| 1 | | | 3.42 | -42 | -72 | 12 | L | Lateral Occipital Cortex |
| 1 | | | 3.02 | -42 | -78 | 22 | L | Lateral Occipital Cortex |
| 1 | | | 2.93 | -52 | -66 | 20 | L | Lateral Occipital Cortex |
| 1 | | | 2.54 | -58 | -60 | -4 | L | Middle Temporal Gyrus |
| 2 | 540 | .002 | 3.51 | 56 | -18 | 48 | R | Postcentral Gyrus |
| 2 | | | 3.21 | 46 | -12 | 58 | R | Precentral Gyrus |
| 2 | | | 3.07 | 46 | -34 | 56 | R | Postcentral Gyrus |
| 2 | | | 2.99 | 52 | -26 | 58 | R | Postcentral Gyrus |
| 2 | | | 2.97 | 42 | -34 | 62 | R | Postcentral Gyrus |
| 2 | | | 2.89 | 28 | -2 | 56 | R | Middle Frontal gyrus |
| 3 | 3323 | < .001 | 4.31 | -20 | -68 | 54 | L | Lateral Occipital Cortex |
| 3 | | | 4.01 | -36 | -46 | 60 | L | Superior Parietal Lobule |
| 3 | | | 3.9 | -6 | -40 | 52 | L | Precuneus Cortex |
| 3 | | | 3.67 | -14 | -26 | 68 | L | Precentral Gyrus |
| 3 | | | 3.61 | -4 | -12 | 68 | L | Juxtapositional Lobule Cortex |
| 3 | | | 3.48 | -38 | -44 | 54 | L | Superior Parietal Lobule |

**Table 5** Local maxima for the cluster of regions showing significant interaction effect for ADD task interaction effect [(FeaDel-FeaImm) < (NeuDel-NeuImm)]. 'Voxels' refer to the number of voxels within each cluster. The Harvard-Oxford cortical and subcortical probabilistic atlases were used to identify each region.

| **Voxels** | **P** | **Z-Value** | **MNI Coordinates [mm]** | | | **Side** | **Region** |
|---|---|---|---|---|---|---|---|
| | | | x | y | z | | |
| 325 | .019 | 3.92 | 6 | 66 | -8 | R | Frontal Pole |
| | | 2.94 | -6 | 70 | -6 | L | Frontal Pole |
| | | 2.91 | 16 | 72 | 0 | R | Frontal Pole |
| | | 2.85 | 8 | 72 | 0 | R | Frontal Pole |
| | | 2.79 | 4 | 74 | 8 | R | Frontal Pole |
| | | 2.53 | 24 | 74 | 4 | R | Frontal Pole |

## Figure captions

**Figure 1** The Affective Stop Signal Task. The panel on the left shows an example of a go trial (neutral condition), during which participants had to indicate with the appropriate button-press a gender of the face presented in the picture, irrespective of the emotional expression. Participants had up to 1000ms to respond. The panel on the right shows an example of the stop trial (fearful condition). The sudden change of the colour of the frame surrounding the picture (a stop signal) meant that participants had to withhold (inhibit) their response to indicate gender and not press any buttons. The change of the frame's colour during stop trials (stop-signal delay) was adjusted online based on participants' performance: after a successful response inhibition, on the next stop trial of the same emotional condition, the delay period was increased, making it more difficult to stop, while following an unsuccessful stop trial, the delay was decreased, making it easier to withhold a response.

**Figure 2** The Affective Delay Discounting Task. Each trial began with a presentation of a fixation cross (jittered between 1.2-1.5s). Next, a facial expression was presented on a screen for 2s, followed by different expression of the same emotion (fearful or neutral) and a question, asking the participants to choose between a smaller monetary reward available immediately and a larger reward available after a delay. Participants had to make a choice by pressing an appropriate button. They had up to 7s to decide.

**Figure 3** Resting-state functional fMRI data preprocessing and analysis pipeline. RS – Resting state, ICA - Independent Component Analysis, ICs – Independent Components, RSNs – Resting State Networks (See Methods, subsection "Resting-state data" for details).

**Figure 4** Relationship between the binge score (BS) and inhibitory control failure (SSRT) in the Fearful vs Neutral contexts (FeaSSRT – NeuSSRT); SSRT – Stop Signal Reaction Time.

**Figure 5** Brain regions which showed association with BS during ASST performance. Images are presented in the radiological convention. (A) Brain regions (Lateral Occipital Cortex/Angular Gyrus region and the Frontal Pole) which show a relationship between BS and Successful response inhibition (SS>SF). X = -50 Y = -54 Z = 18. (B) Brain regions (Lateral Occipital Cortex, Pre- and Postcentral gyrus and Superior Parietal Lobule) which show a relationship between BS and successful response inhibition contrasted with Go response in the neutral vs fearful context ([NeuSS>NeuGoC] > [FeaSS>FeaGoC]), X = -52 Y = -60 Z = 4. Scatterplots illustrate the relationship between individuals' BS and parameter estimate extracted from the regions depicted in the circles (as examples of these relationships). ASST – Affective Stop Signal Task, SS – Stop Success, SF – Stop Failure, GoC – Go Correct, Neu – Neutral, Fea – Fearful.

**Figure 6** Brain regions which showed significant relationship between the binge score and delay gratification contrasted with immediate gratification in the Fearful vs Neutral context ([FeaDel-FeaImm] < [NeuDel-NeuImm]), X = 4 Y = 64 Z = -6. Scatterplot illustrates the relationship between individuals' BS and parameter estimate extracted from the regions depicted in the circle. Images are presented in the radiological convention. Del – Delayed Choice, Imm – Immediate Choice, Neu – Neutral, Fea – Fearful.

**Figure 7** Binge score and functional connectivity within the IC10 (Ventral Attention Network). The IC overlay derived at the group level is depicted in warm colours, and the region of decreased coupling with the network associated with increased binge score is represented in blue. In the bottom right corner, the illustration of the correlation between the binge score and the parameter estimates extracted from the supramarginal gyrus (indicated by blue arrows), X = 62 Y = -42 Z = 24. Images are presented in the radiological convention. A-anterior, I-inferior, L-left, P-posterior, R-right, S-superior. IC – Independent Component.

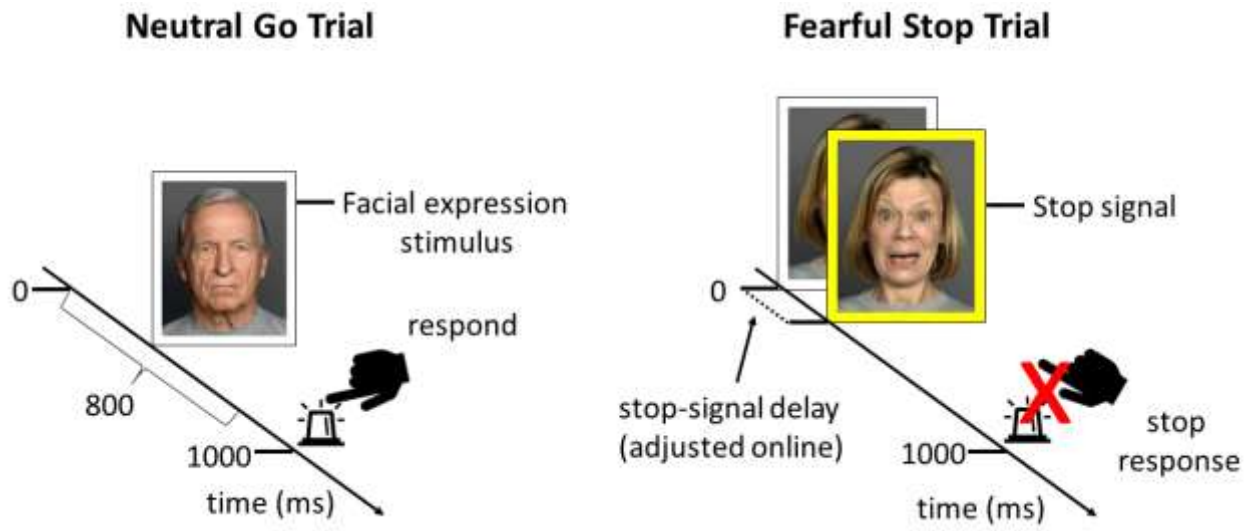


*Figure 1*

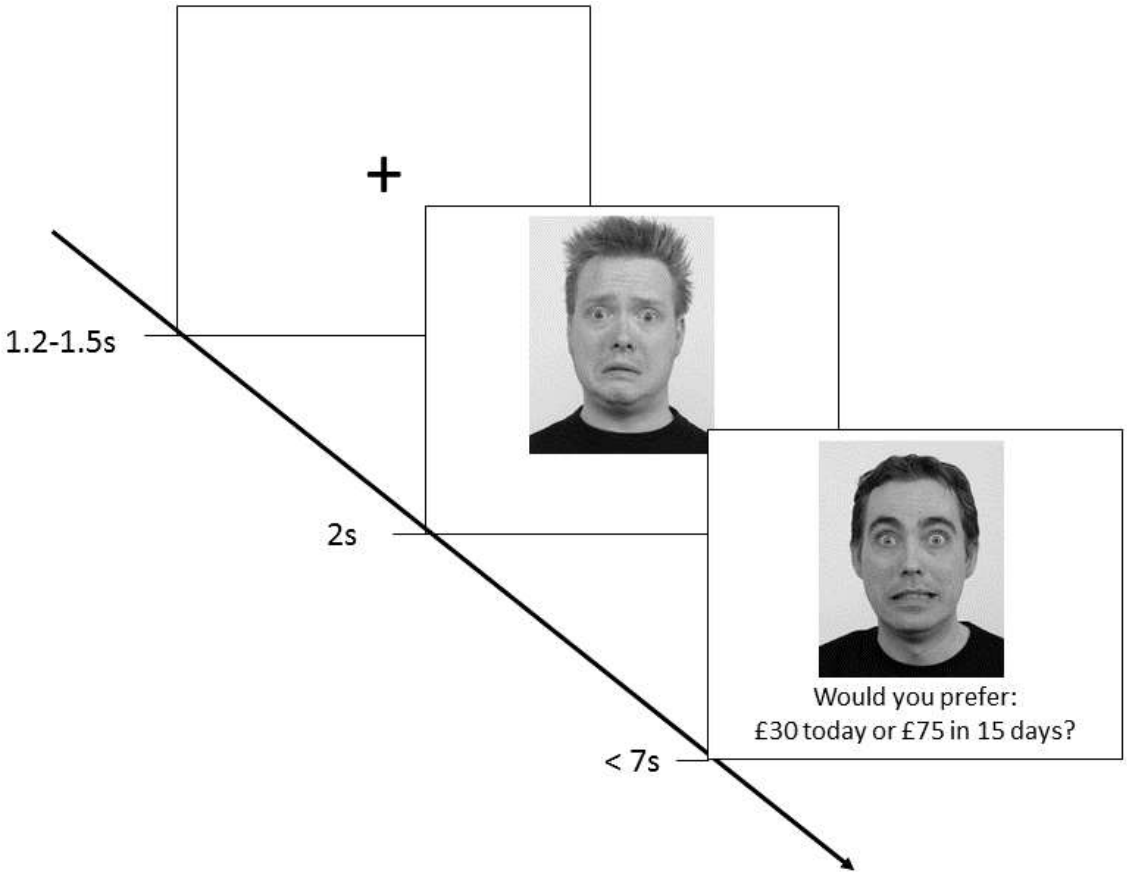


*Figure 2*

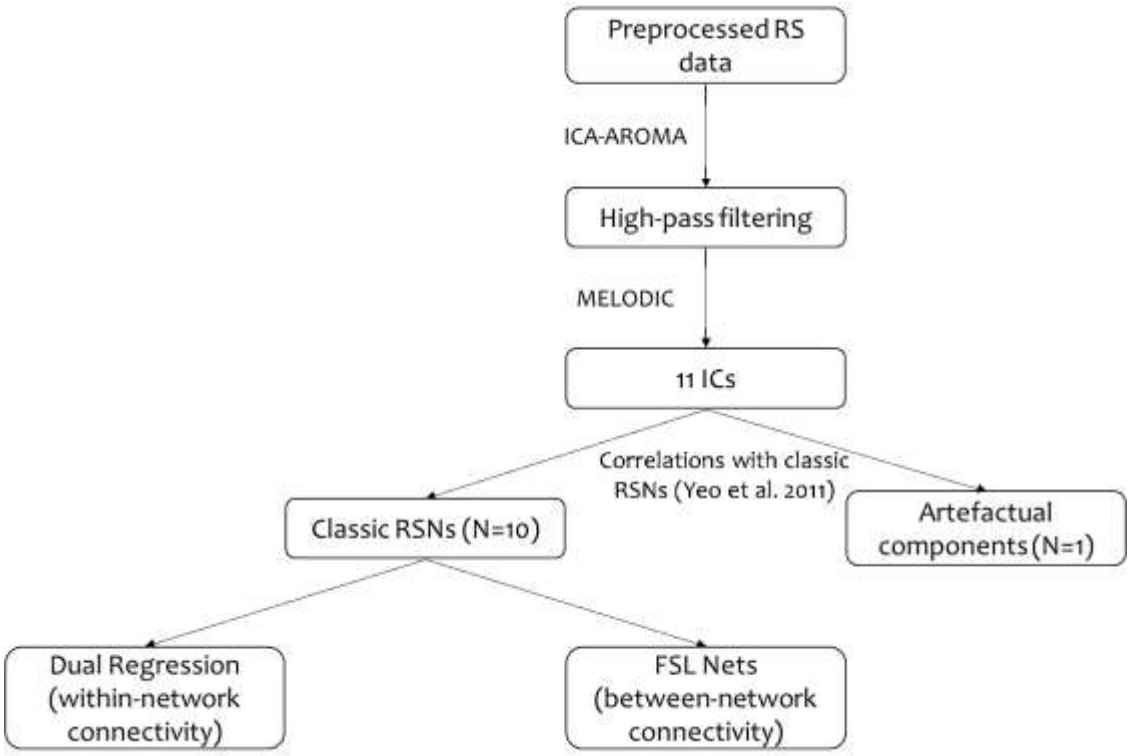


*Figure 3*

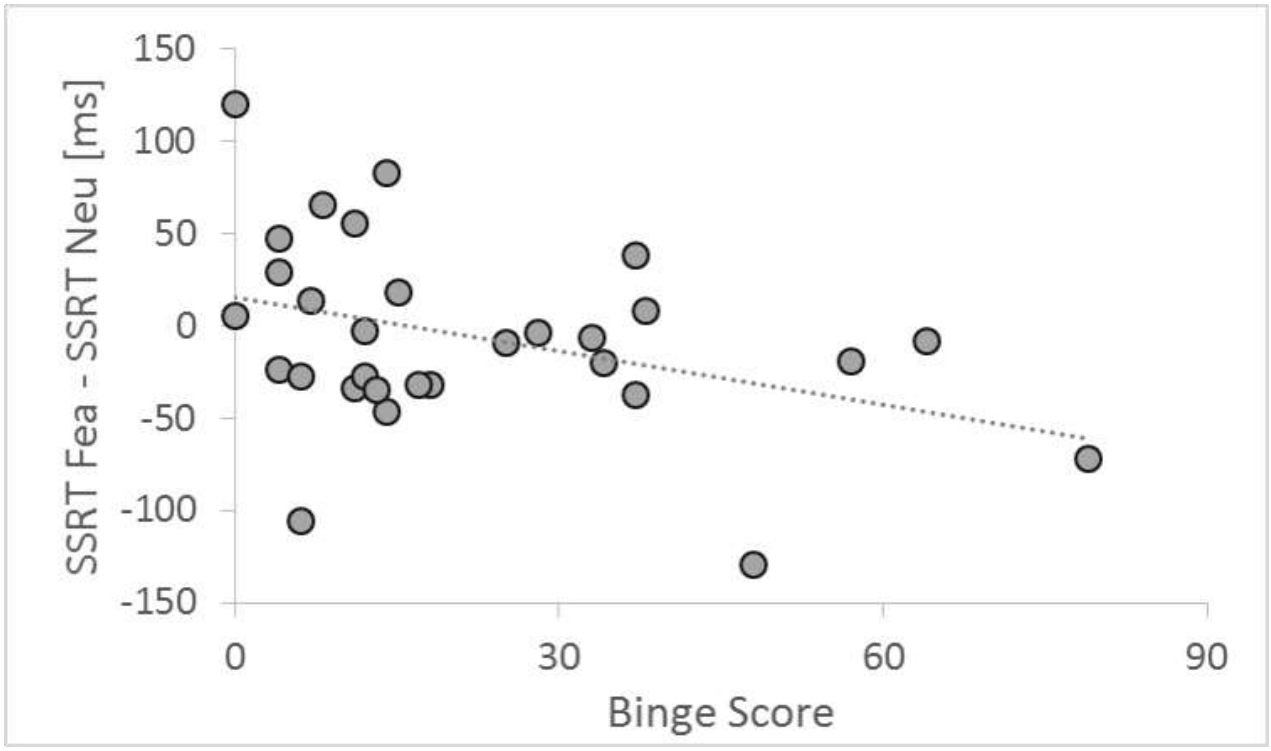


*Figure 4*

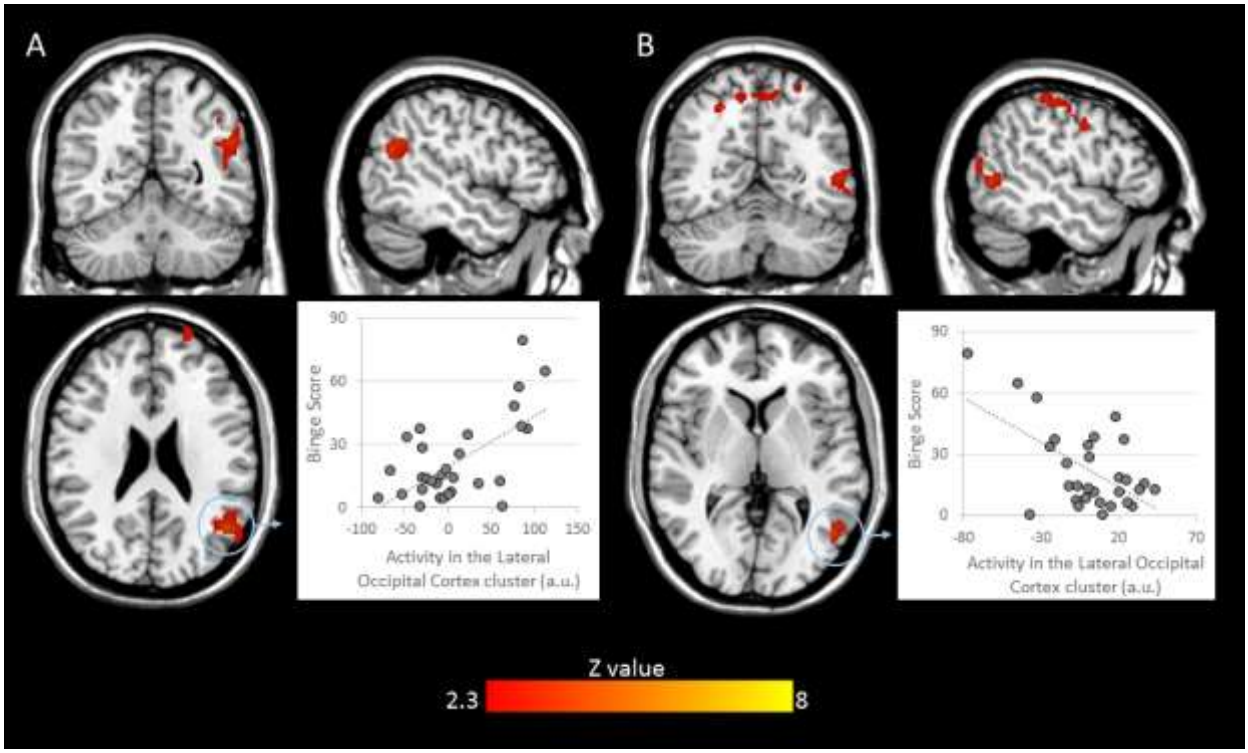


*Figure 5*

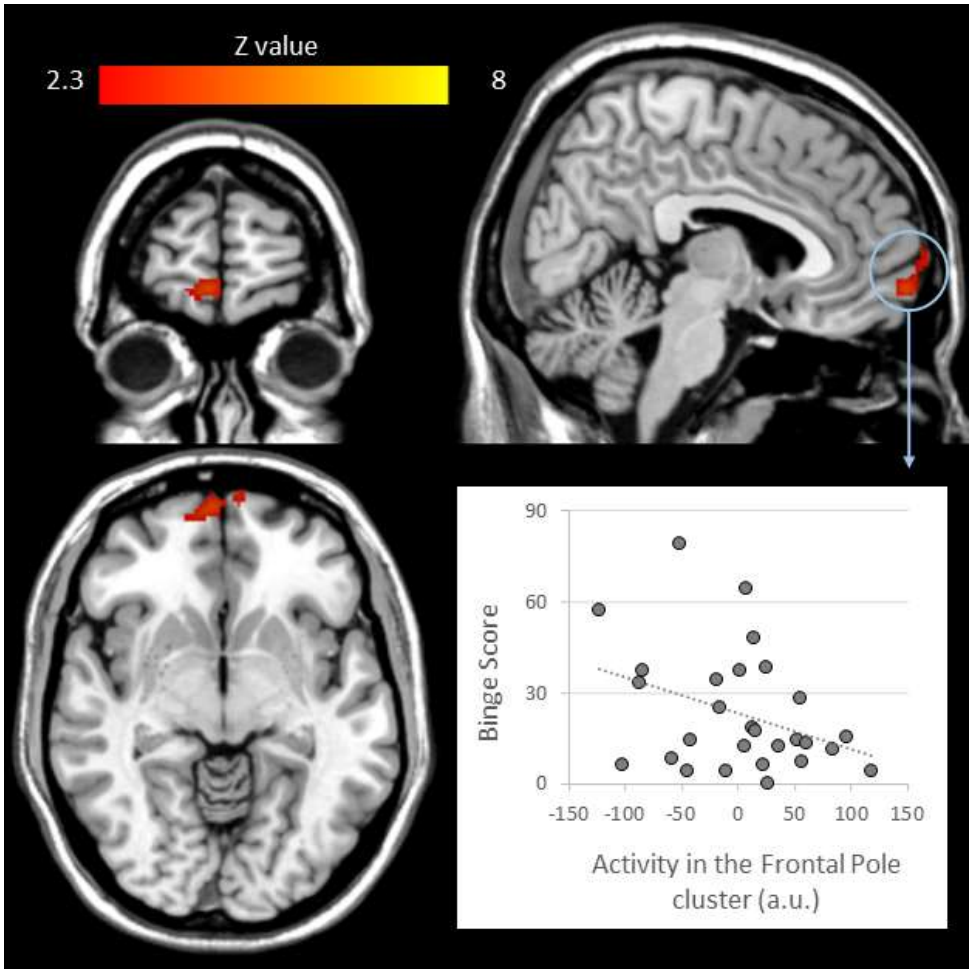


*Figure 6*

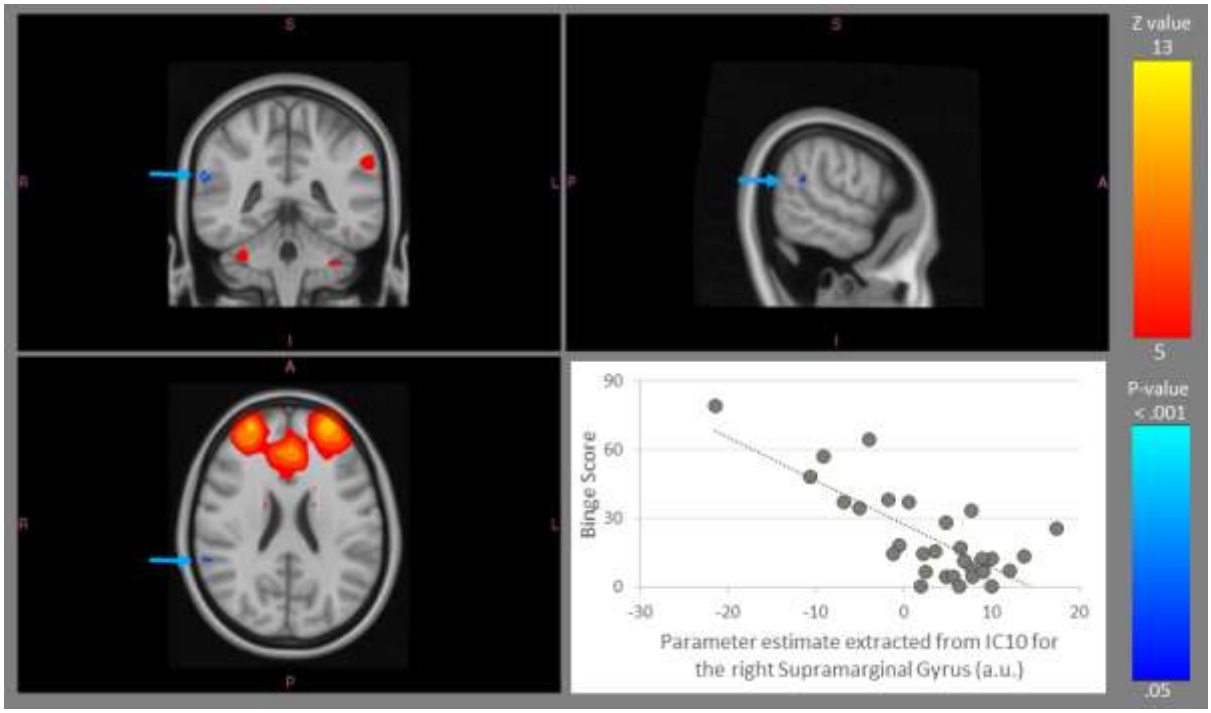
S
R
L
I
S
P
A
I
A
R
L
P
90
60
30
0
Binge Score
-30
-20
-10
0
10
20
Parameter estimate extracted from IC10 for the right Supramarginal Gyrus (a.u.)
Z value
13
5
P-value
< .001
.05

*Figure 7*