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## Impulsivity in disorders of food and drug misuse

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## Abstract

**Background:** Evidence suggests some overlap between the pathological use of food and drugs, yet how impulsivity compares across these different clinical disorders remains unclear. Substance use disorders are commonly characterized by elevated impulsivity, and impulsivity subtypes may show commonalities and differences in various conditions. We hypothesized that obese subjects with binge eating disorder (BED) and abstinent alcohol-dependent cohorts would have relatively more impulsive profiles compared to obese subjects without BED. We also predicted decision impulsivity impairment in obesity with and without BED.

**Methods:** Thirty obese subjects with BED, 30 without BED and 30 abstinent alcohol-dependent subjects and age- and gender-matched controls were tested on delay discounting (preference for a smaller immediate reward over a larger delayed reward), reflection impulsivity (rapid decision making prior to evidence accumulation) and motor response inhibition (action cancellation of a prepotent response).

**Results:** All three groups had greater delay discounting relative to healthy volunteers. Both Obese subjects without BED and alcohol dependent subjects had impaired motor response inhibition. Only Obese subjects without BED had impaired integration of available information to optimize outcomes over later trials with a cost condition.

**Conclusions:** Delay discounting appears to be a common core impairment across disorders of food and drug intake. Unexpectedly, obese subjects without BED showed greater impulsivity than obese subjects with BED. We highlight the dissociability and heterogeneity of impulsivity subtypes and add to the understanding of neurocognitive profiles across disorders involving food and drugs. Our results have therapeutic implications suggesting that disorder-specific patterns of impulsivity could be targeted.

## Introduction

Converging evidence from preclinical and clinical studies suggest that impulsivity is a heterogeneous construct (Dawe *et al.*, 2004) which can broadly be subdivided into decisional and motor domains (Evenden, 1999). These multiple subtypes of impulsivity are associated with distinct yet overlapping neural networks and neurochemical substrates (Dalley *et al.*, 2011, Perry and Carroll, 2008). Impulsivity is important to substance use disorders as these clinical entities are commonly characterized by enhanced impulsivity both as a concurrent and predictive correlate (Perry and Carroll, 2008). Preclinical evidence suggests some overlap between disorders of pathological food and drug use (Avena, 2011, Ziauddeen *et al.*, 2012). Although elevated impulsivity has been associated with bulimia nervosa (binge eating with purging) and the bingeing-purging subtype of anorexia nervosa Fernández-Aranda *et al.*, 2006), here we focus specifically on obese subjects without purging and assess the role of binge eating disorder. This cross-diagnostic comparison of neurocognitive profiles may strengthen understanding of current psychiatric disease classifications and could allow tailoring of treatments to specific patterns of impairments (Robbins *et al.*, 2012).

Laboratory based cognitive measures of impulsivity are particularly useful as they may have better validity as predictors of state impulsivity than self-report questionnaires (Caswell *et al.*, 2013b). Recently, a range of impulsivity subtypes have been successfully characterized in Parkinson's disease, demonstrating the potential to subtype impulsivity in clinical populations (Nombela *et al.*, 2014).

Decisional impulsivity includes delay discounting, also known as impulsive choice, or the preference for an immediate small reward over a delayed but larger reward (Kirby *et al.*,

1999). Excessive delayed discounting is a central feature of multiple addictive and behavioral disorders and has been suggested to represent a ‘trans-disease’ process underlying choice behavior (Koffarnus *et al.*, 2013). Delay discounting may reflect multiple sub-processes that can be mapped onto neural regions including valuation of reward (ventral striatum, ventro-medial prefrontal cortex (vmPFC) and substantia nigra) cognitive control (anterior cingulate, lateral PFC) and prospection (medial temporal lobe) (Peters and Büchel, 2011). Reflection impulsivity involves making rapid decisions before evaluating sufficient evidence, and in a human fMRI study has been shown to involve a network including the ventral striatum, anterior insula, anterior cingulate and parietal cortex (Furl and Auerbeck, 2011). Preclinical evidence suggests a dissociation in measures of motor impulsivity which can be subdivided into motor response inhibition or the failure to stop a pre-potent motor response (Aron *et al.*, 2003) and anticipatory (premature) responding prior to the onset of a target. The neural regions implicated in response inhibition as tested using the stop signal task (SST) from lesional and imaging studies in rodent and human research include the right inferior frontal cortex, pre-supplementary motor area and caudate (Aron *et al.*, 2007, Aron *et al.*, 2003, Robbins, 2007). In premature responding, rodent studies have implicated the prelimbic cortex, nucleus accumbens and subthalamic nucleus (Dalley *et al.*, 2007, Desbonnet *et al.*, 2004, Pothuizen *et al.*, 2005, Risterucci *et al.*, 2003).

Alcohol use disorders have been associated with greater decisional and motor impulsivity with greater delay discounting (Bjork *et al.*, 2004, Bobova *et al.*, 2009, MacKillop *et al.*, 2010, Petry, 2001). In rodent studies, increased premature responding has been associated with acute alcohol intake (Oliver *et al.*, 2009), the early phase of abstinence after chronic alcohol exposure (Walker *et al.*, 2011) and has been correlated with alcohol withdrawal severity (Gubner *et al.*, 2010). We also recently found elevated premature responding in

human abstinent alcohol dependent subjects (Voon *et al.*, 2014b). Although some studies have shown impaired motor response inhibition (de Zwaan *et al.*, 1994, Lawrence *et al.*, 2009a, b) significantly prolonged stop signal reaction times have not always been found with alcohol dependence (Li *et al.*, 2009, Schmaal *et al.*, 2013).

The relationship between impulsivity, eating disorders and alcohol misuse is complex. Correlation between obesity and addictive disorders is frequently low (Riggs *et al.*, 2012) and may be absent or negative (Kleiner *et al.*, 2004, Mather *et al.*, 2008). The prevalence of impulse control disorders have been found to be elevated in obesity and particularly high in obesity with binge eating (Schmidt *et al.*, 2012). In rats, binge eating of palatable food has been found to accelerate habitual control of behavior and be dependent on dorsolateral striatal activation (Furlong *et al.*, 2014). Although impulsivity appears important to both eating disorders and addictions, it is possible that other factors such as obsessive-compulsive features may also be relevant to characterizing and differentiating the disorders (Altman and Shankman, 2009). For instance, in the IMAGEN study involving adolescents (Montigny *et al.*, 2013), which assessed a broad range of eating disorders without investigating subtypes showed that eating disorders and alcohol misuse did not overlap in their relationship to externalizing constructs. Unlike binge-drinking, the broad range of eating disorders showed variance best explained by a compulsivity spectrum rather than an externalising factor suggesting that the relationship between substance misuse and eating disorders may be complex and multi-factorial. In contrast, this current study focuses on a specific subtype of pathological eating behavior comparing obese subjects with and without binge eating disorder with a disorder of drug addiction.

Preliminary evidence suggests that binge eating may represent a distinct subtype of obesity with greater similarities to disorders of addiction. In rodent studies, sugar bingeing displays addictive characteristics such as enhanced responding after abstinence, opiate-like withdrawal features, amphetamine cross-sensitisation and associated dopamine release in the nucleus accumbens (Avena *et al.*, 2008). In humans, preliminary evidence suggests binge eating disorder (BED) is associated with relatively higher impulsivity compared to obesity. For instance, obese subjects with BED as compared to those without BED exhibit elevated levels of questionnaire-based trait impulsiveness (de Zwaan *et al.*, 1994) and in a small study, greater motor impulsivity on the Barratt's Impulsiveness Scale (Nasser *et al.*, 2004). Both BED and obese subjects have been shown to discount delayed rewards at higher rates than normal controls (Manwaring *et al.*, 2011) and a study in females suggests that BED subjects may have greater delay discounting than obese subjects without BED (Manwaring *et al.*, 2011). Presenting food to obese human subjects with BED has shown to result in greater striatal dopamine release than in obese subjects without BED (Wang *et al.*, 2011). Evidence has also suggested BED to represent an extreme neurobehavioral phenotype of obesity with more prominent impulsivity (Carnell *et al.*, 2012). However, as studies have frequently not differentiated obese subjects with and without binge eating (Schag *et al.*, 2013b), relationships with impulsivity are yet to be firmly established. We have previously shown that premature responding is dissociable in disorders of food and drug use with greater premature responding observed in abstinent stimulant and alcohol dependent subjects with no differences observed in obese subjects with or without BED relative to healthy volunteers (Voon *et al.*, 2014b).

In the current study, decisional and motor impulsivity were investigated in obese subjects with and without BED and abstinent alcohol-dependent subjects (EtOH) compared with

healthy volunteers. As subtypes of impulsivity may assess different neurobiological processes, we hypothesize that impulsivity may dissociate in a disease-specific manner through different tests of delay discounting, reflection impulsivity, and impaired response inhibition. Based on previous evidence and our recent findings on motor impulsivity, we hypothesize that obesity with BED and abstinent alcohol-dependent cohorts would have relatively more impulsive profiles compared to obese subjects without BED. We also predicted decision impulsivity impairment in obesity with and without BED.

## **Methods and Materials**

### **Recruitment**

Subjects were recruited via community-based advertisements in the East Anglia area. Obese subjects had a body mass index (BMI) of 30 or more and those with BED also fulfilled BED criteria (Diagnostic and Statistical Manual of Mental Disorders, Version IV TR, DSM IV-TR) (American Psychiatric Association, 2000). EtOH subjects fulfilled DSM-IV criteria for alcohol dependence, and were abstinent for at least 2 weeks to one year prior to testing.

Subjects were included if they were 18 or older. Subjects were excluded if they had a current major depressive episode or a history of a severe psychiatric disorder (e.g. bipolar affective disorder or schizophrenia) or a current substance use disorder including regular cannabis use. All diagnoses were reviewed by a psychiatrist. Subjects were excluded if they tested positive for a drug urine screen (including cannabis) or alcohol breathalyzer test on the day of testing.

### **Procedure**

Following provision of written consent subjects undertook urine drug testing and an alcohol breathalyzer test on the day of testing. Subjects completed the Beck Depression Inventory-II (Beck *et al.*, 1996) to assess depressive symptoms and the UPPS-P Impulsive Behaviour

Scale to assess impulsivity (Whiteside and Lynam, 2001). Subjects were screened for comorbid psychiatric disorders with the Mini International Neuropsychiatric Inventory (MINI; (Sheehan *et al.*, 1998)). The National Adult Reading Test (NART; (Nelson, 1982)) was administered to obtain indices of premorbid IQ. The body mass index (BMI) and Binge Eating Scale (BES; (Gormally *et al.*, 1982)) scores were obtained for the Obese subjects and controls. The Alcohol Use Disorders Identification Test (AUDIT; (Babor and Grant, 1989)), units per day, duration, and days abstinent were assessed for the EtOH group. The Monetary Choice Questionnaire was used to assess delay or temporal discounting by evaluating the indifference point between preference for a small immediate or larger delayed reward. The SST was used to assess motor response inhibition by evaluating the capacity to inhibit a prepotent motor response. The Information Sampling Task (IST) was used to assess reflection impulsivity by evaluating the amount of evidence accumulated prior to a decision. The study was approved by the University of Cambridge Research Ethics Committee. Subjects were remunerated at a rate of £7.50 per hour including travel costs, with an additional £5 contingent on task performance.

## Measures

### Delay Discounting Task (DDT)

Delay discounting refers to the tendency to discount delayed rewards and is commonly measured using the Monetary Choice Questionnaire (Kirby *et al.*, 1999). The questionnaire is a 27-item, self-administered questionnaire in which participants choose between a small immediate reward, and a larger delayed reward (e.g. Would you prefer £14 today, or £25 in 19 days?). The primary outcome measure was the slope ( $k$ ) of the discounting curve calculated as follows:  $V = A/(1+kD)$  where  $V$  is the present value of delayed reward  $A$  at delay  $D$ . The higher the  $k$  value, the steeper the slope and the greater the discounting or



impulsive choice. The  $k$  value of small, medium and large magnitude choices were averaged for the final  $k$  value.

### **Stop Signal Task (SST)**

The SST is a task from the Cambridge Neuropsychological Test Automated Battery (CANTAB)(Aron *et al.*, 2003). Subjects viewed a computer screen and responded on a two-button response box using both index fingers. Subjects pressed the right or left button for a “Go” stimulus (arrow appearing within a circle pointing either left or right on screen until the subject responded. In 20% of the trials, they were required to withhold any response when an audible “beep” is sounded (Stop signal). The Stop signal starts at 250 milliseconds after the Go signal (Stop Signal Delay, SSD). The SSD then varies in a step-wise manner dependent on the previous response, decreasing by 50 milliseconds for a successful stop and increasing by 50 milliseconds for unsuccessful stops. Thus, successful stopping occurred at approximately 50% of the trials. The task had 5 blocks of 80 trials. The primary outcome measure was the stop signal reaction time (SSRT), which was calculated as follows:  $SSRT = \text{median Go reaction time} - SSD$  (Logan *et al.*, 1984) in which a higher score indicated greater impairment in response inhibition.

### **Information Sampling Task (IST)**

The IST task is also from the CANTAB (Clark *et al.*, 2006). Subjects viewed a 5x5 matrix of grey boxes on a touch screen monitor. Upon being touched, boxes opened to reveal one of two colours. The objective was to decide which of the two colours was predominant in the matrix, by opening a sufficient number of boxes in order to be able to make that decision. In the No Cost condition, subjects could win 100 points for correct choices or lose 100 points for incorrect choices regardless of the number of boxes opened. In the Cost condition, the

possible number of points for a correct answer started at 250, and decreased by 10 with every box opened. Thus subjects could win more points for earlier decisions. The penalty for a wrong answer remained the same at 100 points. Once subjects had made a decision they touched the corresponding coloured panel below the matrix. A message appeared for 2 seconds – “Correct! You have won [x] points” or “Wrong! You have lost 100 points”. There were 10 self-paced trials for each condition. An inter-trial interval (minimum 1 second) was adjusted so that each trial lasted at least 30 seconds to counteract delay-averse responding. The primary outcome measure was the average number of boxes opened. Secondary measures included total points and sampling errors (incorrect choices).

## **Statistics**

Subject characteristics were compared using independent t-tests and chi-squared tests as appropriate. The data were inspected for normality of distribution using Shapiro-Wilkes test and square root transformation was used on variables that were not normally distributed. The DDT K-value score was compared using independent t-test. The IST boxes opened, sampling errors and total points for both No Cost and Cost conditions were analysed as multivariate analyses to control for multiple comparisons. The go-trial reaction time (GoRT) and SSRT were also analysed as multivariate analyses to control for multiple comparisons. The effects of Cost on sampling errors and total points in the IST task were also analysed using a mixed measures ANOVA with Group as a between-subjects factor and Cost as a within-subjects factor.  $P < 0.05$  was considered significant for hypothesized outcomes. To assess the relationship with symptom severity and significant outcome measures, Pearson correlation was used to assess body mass index, Binge Eating Scale (BES) and AUDIT scores with significant outcome measures in EtOH subjects and Obese subjects without and without BED.

## Results

Thirty obese BED and 30 obese controls were compared to their own age- and gender-matched HV (Table 1). Thirty EtOH subjects (reported in mean (SD): weeks abstinent 15.60 (16.89); years heavy use: 12.78 (8.27); Units/day: 28.36 (14.58); Total units (=Units/day\*years heavy use\*365\*percent drinking days): 128573 (124490)) were compared with age- and gender-matched HV. EtOH subjects were on the following medications (acamprosate 2; disulfiram 1). The 3 index groups were compared with their own age- and gender-matched HV (1:2 (60 healthy volunteers) ratio for DDT; 1:1 (30 healthy volunteers) Ratio for IST and SST).

### *Delay discounting*

The K-value was square root transformed. Obese subjects with BED ( $t=2.59$ ,  $df=58$ ,  $p=0.012$ ), without BED ( $t=2.52$ ,  $df=58$ ,  $p=0.015$ ) and EtOH subjects ( $t=3.34$ ,  $df=58$ ,  $p=0.002$ ) had greater delay discounting compared to HV (Figure 1). The number of units per day positively correlated with the K-value (Pearson correlation coefficient  $R=0.53$ ,  $p=0.004$ ) in EtOH subjects. There was no correlation between BMI ( $R=-0.01$ ,  $p=0.93$ ) or BES ( $R=0.05$ ,  $p=0.68$ ) and K-value in Obese subjects with or without BED. There was no correlation between BDI ( $R=0.16$ ,  $p=0.42$ ) and K-value.

### *Stop Signal Task*

GoRT and SSRT were assessed as multivariate analyses for each index group and their age- and gender-matched healthy volunteers. In all groups, the percentage of successful stops was at approximately 50% suggesting efficacy of the staircase SSD adjustment (HV 49.13% (SD

5.54); BED 50.79% (SD 5.91); Obese 50.59% (SD 7.08); EtOH 51.64% (SD 6.99)). Obese subjects without BED had impaired motor response inhibition ( $F=9.39$ ,  $p=0.003$ ) with no differences in GoRT (HV: 432.32 (SD 104.17), Obese: 449.85 (SD 89.57)  $F=1.36$ ,  $p=0.247$ ) compared to healthy volunteers (Figure 1). EtOH subjects had impaired motor response inhibition ( $F=8.26$ ,  $P=0.005$ ) and slower GoRT (HV: 429.12 (SD 108.21), EtOH: 494.62 (162.90)  $F=4.09$ ,  $p=0.047$ ). In BED subjects, there were no significant differences in GoRT (HV: 435.82 (106.11, BED: 483.69 (SD 137.59)  $F=0.009$ ,  $p=0.923$ ) or SSRT ( $F=0.024$ ,  $p=0.878$ ) compared to healthy volunteers. On an exploratory basis, we compared the same variables in Obese subjects with and without BED covarying for age and gender using multivariate analyses. Obese subjects without BED compared to those with BED also had greater impairments in motor response inhibition ( $F=9.657$ ,  $p=0.003$ ) with no differences in GoRT ( $F=1.240$ ,  $p=0.270$ ).

There was a trend towards a positive correlation between BMI ( $R=0.25$ ,  $p=0.061$ ) but not BES ( $R=-0.22$ ,  $p=0.119$ ) with SSRT for Obese subjects with and without BED. There was no correlation between the number of units per day and SSRT for EtOH subjects ( $R=-0.09$ ,  $p=0.631$ ). There was no association between BDI and SSRT FOR EtOH or Obese subjects ( $R=0.02 - 0.20$ ,  $p>0.05$ ).

### *Information Sampling Task*

Boxes opened, sampling errors, and total points for both Cost and No Cost conditions were assessed using multivariate analyses (Figure 2). Obese subjects without BED made more sampling errors in the No Cost condition ( $F=4.397$ ,  $p=0.040$ ) and accumulated fewer total points ( $F=7.109$ ,  $p=0.009$ ) as independent associated factors compared to healthy volunteers.

There were no other significant differences between Obese subjects without BED and healthy volunteers ( $F=0.020 - 0.724$ ,  $p>0.05$ ). There were no significant differences between healthy volunteers and BED subjects ( $F=0.012 - 2.994$ ,  $p>0.05$ ) or EtOH subjects ( $F=0.028 - 0.530$ ,  $p>0.05$ ). To assess the impact of Cost on sampling errors and total points, we also conducted a mixed measures ANOVA comparing obese subjects without BED and healthy volunteers. For total points, there was a main effect of Group ( $F(1,58)=5.630$ ,  $p=0.021$ ) in which Obese subjects scored fewer points compared to healthy volunteers. There was an interaction between Group x Cost ( $F(1,58)=8.343$ ,  $p=0.005$ ) in which Obese subjects performed worse with Cost relative to No Cost compared to healthy volunteers. There was no main effect of Cost ( $F(1,58)=0.083$ ,  $p=0.967$ ). For sampling errors, there was no main effect of Group or Cost or interaction effect ( $p>0.05$ ).

In Obese subjects with and without BED, there was a negative correlation between BES and sampling error ( $R=-0.341$ ,  $p=0.008$ ) and a positive correlation between BES and total points ( $R=0.415$ ,  $p=0.001$ ). Thus, those with lower BES scores or those less likely to have BED, had greater sampling errors and accumulated fewer total points. There were no significant correlations between BMI and errors or points ( $p>0.05$ ). There were no significant correlations in EtOH subject between AUDIT scores and sampling errors or total points ( $R=-0.326 - 0.177$ ,  $p>0.05$ ).

## Discussion

We show a dissociation in contrasting subtypes of impulsivity between disorders of food and drug use. Our results reveal novel similarities and differences between neurocognitive endophenotypes of the three disorders. Obese subjects without BED were dissociated from those with BED.

### *Delay Discounting*

Delay discounting was elevated across all groups corroborating that this form of impulsivity is a core abnormality across these disorders. We showed that Obese subjects either with or without BED as well as EtOH subjects discounted delayed hypothetical monetary rewards to a greater extent than healthy volunteers. Our finding of an association between alcohol dependence and increased delay discounting is in line with other studies (Koffarnus *et al.*, 2013, Petry, 2001). Similarly, Obese subjects with and without BED have been shown to have greater delay discounting (Davis *et al.*, 2010, Manwaring *et al.*, 2011, Weller *et al.*, 2008). These findings converge with a body of literature demonstrating greater delay discounting in multiple substance use disorders including those at risk for the development of substance use disorders (Bickel *et al.*, 2013). Thus, delay discounting may be a behavioural marker for pathological disorders across both food and drug use. Further work on identifying specific impairments in Obesity with and without BED including salience of the immediate reward, uncertainty tolerance, delay aversion or diminishing marginal utility would be indicated.

Discounting deficits may reflect changes in the delayed discounting subprocesses and their neural correlates that include reward valuation, cognitive control and prospection (Peters and Büchel, 2011). We have also recently shown that obese subjects with BED as compared to those without BED have lower volumes in bilateral medial orbitofrontal cortices extending into ventromedial prefrontal cortices (Voon *et al.*, 2014a), regions implicated in the representation of reward.

### *Reflection Impulsivity*

Reflection impulsivity has been relatively under-investigated compared to other impulsivity subtypes (Clark *et al.*, 2006), and can be tested using the IST which has less visual and memory demands than previous Iowa Gambling and Matching Familiar Figures Tasks (Solowij *et al.*, 2012). In this study, no impairment in reflection impulsivity as measured by the number of boxes opened (evidence sampled) in any of the index groups relative to healthy volunteers was found. Alcohol dependent subjects have not been shown to exhibit significant differences in information sampled on either the IST or Matching Familiar Figures Task (MFFT) compared to healthy volunteers (Lawrence *et al.*, 2009b, Weijers *et al.*, 2001). In early compared to later-onset alcohol dependence, a non-significant increase in reflection impulsivity has been detected (Joos *et al.*, 2013b). After acute alcohol however, healthy participants have shown increased reflection impulsivity, which has been attributed to alcohol expectancies (Caswell *et al.*, 2013a). Impairments in reflection impulsivity have been shown using the MFFT in obese children (Braet *et al.*, 2007) although we did not demonstrate this in obese adults. Reflection impulsivity has also been found in opiate, amphetamine (Clark *et al.*, 2006) and cannabis users (Clark *et al.*, 2006, Solowij *et al.*, 2012).

Although in this study there were no differences in evidence sampled, we show that relative to healthy volunteers, obese subjects without BED accumulated fewer total points and more specifically performed worse in the later Cost condition when penalized for the amount of evidence accumulated. BES scores similarly reflected the same association with sampling errors and total points accumulated. This is in line with findings that increased sampling errors may be found in addiction disorders including alcohol dependence and problem gamblers (Lawrence *et al.*, 2009b). Overall, our findings suggest that Obese subjects without BED may be more impaired at integrating information after multiple trials to optimize

outcomes despite evaluating the same amount of evidence. Reduced performance after the subsequent introduction of cost could also be a result of fatigue effects as the cost condition was introduced after the no-cost condition. This could indicate poorer sustained vigilance or effort effects in obese subjects. Task performance deterioration after multiple trials has similarly been seen in increased BMI in women (Nederkoorn *et al.*, 2006b) and children (Guerrieri *et al.*, 2007a).

#### *Motor Impulsivity: Response Inhibition*

We demonstrate impaired motor response inhibition in both EtOH subjects and obese subjects without BED as measured using the SST, which assesses motor cancellation or inhibition of ongoing motor responses. Alcohol dependence has been associated with significantly impaired motor response inhibition with prolonged Stop Signal Reaction Times (SSRT) in some (Lawrence *et al.*, 2009b) but not all studies (Li *et al.*, 2009, Schmaal *et al.*, 2013). Further, in non-dependent light and heavy adult drinkers, no SSRT differences were observed (Yan and Li, 2009). Several lines of evidence have linked SSRT with Alcohol. SSRTs are particularly prolonged in alcohol-dependence when go-stimuli are changed to an alcohol cues rather than a neutral stimuli indicating approach behaviours towards certain cues may be more difficult to inhibit (Zack *et al.*, 2011). After acute alcohol, SSRT in moderate drinkers has been shown to also increase (Loeber and Duka, 2009, McCarthy *et al.*, 2012, Ramaekers *et al.*, 2011). Non-dependent, heavy-drinking subjects with a family history of alcoholism may be less sensitive to the effects of alcohol on the SST (Kareken *et al.*, 2013) suggesting that family history may also be relevant to motor impulsivity.

The link between alcohol dependence and impaired action cancellation has been further shown by pharmacological manipulation. Trials of quetiapine (Moallem and Ray, 2012), topiramate (Rubio *et al.*, 2009) but not modafinil (Joos *et al.*, 2013a) have improved SSRTs



in alcohol dependent subjects. Impaired motor response inhibition with the SST has been shown in both subjects with cocaine dependence and their unaffected family members demonstrating a role for this form of impulsivity in predicting cocaine use disorders (Ersche *et al.*, 2012).

Our findings suggest greater similarities in the domain of motor impulsivity in obese subjects without BED and substance use disorders. Other studies have shown greater motor impulsivity in obesity with BED compared to without BED on the SST (Svaldi *et al.*, 2014) and on a go/no-go task (Mobbs *et al.*, 2011) which tests action cancellation and action restraint respectively. As with our findings, the overall relevance of motor impulsivity to obesity has been shown through associations with increased BMI (Guerrieri *et al.*, 2007a, Nederkoorn *et al.*, 2006a, Verbeken *et al.*, 2009) and food consumption (Guerrieri *et al.*, 2007b). As well as being a potential maintaining factor for obesity, poorer SST performance has predicted poorer treatment outcomes with reduced weight loss (Nederkoorn *et al.*, 2007). During a weight reduction treatment camp, progressive reductions in SSRT have also been demonstrated (Kulendran *et al.*, 2013). However, significantly increased motor impulsivity associated with elevated BMI has not always been observed (Hendrick *et al.*, 2012). The shared findings of SSRT deficits in both EtOH and Obesity without BED suggest there may be an overlap in neural substrates involving structural (Tabibnia *et al.*, 2011) or functional (Ray Li *et al.*, 2008) regions required in the SSRT such as the right inferior frontal cortex, pre-supplementary motor area and caudate. Whether our results represent a state factor or may represent a predictive risk factor for the development for obesity remains to be established.

The relationship between motor response inhibition and behavioural addictions is less clearly established. Pathological gambling has been associated with behavioural impairments in the SST in some (Odlaug *et al.*, 2011, Wu *et al.*, 2013), but not all studies (de Ruiter *et al.*, 2012, Grant *et al.*, 2011, Lipszyc and Schachar, 2010). These studies and a meta-analysis (Lipszyc and Schachar, 2010) suggest that motor response inhibition is not always impaired in other forms of behavioural addictions. That Obese subjects with BED were impaired predominantly on decisional impulsivity but not on motor response inhibition dovetails with a recent study on another form of a behavioural addiction, gaming use disorder (Irvine *et al.*, 2013). Here the authors suggest that the lack of impairment in motor inhibition may be related in part to practise effects from videogaming. Although we did not show that obese subjects with BED were impaired in motor response inhibition as hypothesized, this does not exclude other patterns of impairment that may fit with a disorder of addiction. Although our findings are compatible with both a conceptualization of BED as an extreme neurobehavioural subtype of obesity, we note that there were no differences in BMI between the two subject groups. Here we are interested in both similarities and differences in neurocognitive profiles to better characterize mechanistic differences that might underlie different subtypes of behavioural and substance addictions. Our findings are compatible with both a conceptualization of BED as an extreme neurobehavioural subtype of obesity and BED having similarities with other behavioural and substance addictions.

#### *Motor Impulsivity: Premature Responding*

In a previous study, we demonstrated that EtOH subjects had elevated premature responding, a form of motor impulsivity characterized by anticipatory responses, whereas Obese subjects with and without BED did not differ in this measure from healthy volunteers (Voon *et al.*, 2014b, Voon *et al.*, in press). Although the five-choice serial reaction time task (5-CSRTT)

and SST both measure motor impulsivity, the two forms of impulsivity can be dissociated in their neural networks and underlying neurochemistry. In a previous study, we also did not observe any correlations between premature responding and measures including SSRT or delay discounting (Voon *et al.*, 2014b). Dissociated performance on premature responding and SSRT may thus implicate different mechanisms involved in the two tasks. The SST involves inhibition of an already initiated motor response whereas the 5-CSRTT requires ‘waiting’ before responding. Serotonin depletion increases 5-CSRTT premature responding in rodents and healthy humans (Harrison *et al.*, 1997) (Worbe *et al.*, 2014) without affecting SSRT (Eagle *et al.*, 2009) or delay discounting (Worbe *et al.*, 2014). Moreover, lesions of the nucleus accumbens core increases impulsivity on 5-CSRTT (Christakou *et al.*, 2004) but may not influence SRTTs (Eagle and Robbins, 2003).

### *Limitations*

There were several limitations in our study. As the alcohol dependent subjects were in recovery whilst the obese subjects with and without BED were not, it is possible that abstinence may contribute to group differences. In the obese subjects with and without BED, testing subjects who are dieting, under food restriction or using food as an outcome may influence results (Schag *et al.*, 2013a). We are currently addressing the question of whether testing under food restriction may influence premature responding. Similarly subjects with more severe forms of obesity may also respond differently. Further studies in obese subjects who are dieting subjects are indicated. As monetary outcomes used in the delay discounting task were similarly impaired across groups, money may act as a common conditioned reinforcer. Using the same outcome as a conditioned reinforce across different disorders also allows for comparisons across groups without the confounder of motivation. In addition,

how closely eating disorders are related to impulsivity as compared to an obsessive-compulsive spectrum further remains to be seen. When considering impulsivity and obesity, other mediators of energy balance including energy expenditure, appetite and satiety and environmental influences should also be taken into consideration (Ziauddeen *et al.*, 2012). Gathering further clinical details on duration of binge eating, number of vomiting episodes would also be informative.

### *Conclusions*

Through different pathogenic mechanisms, alcohol and eating disorders may differentially influence neurocognitive systems subserving impulsivity. Our findings highlight the variability and dissociability in impulsivity. Delay discounting is impaired in alcohol use disorders and obesity irrespective of binge eating emphasizing its role as a core impairment across disorders whereas motor response inhibition is impaired as a function of BMI but not of binge eating. The differential role of impulsivity subtypes in disorders of food rewards may have implications for tailoring therapeutic strategies in obesity and addiction disorders.

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## Legend

Table 1. Subject characteristics and behavioural measures in alcohol-dependent subjects and obese subjects with and without BED

Table 2. Summary of impulsivity findings

Figure 1. Delay discounting and stop signal task

A. K-values of delay discounting task. B. Stop Signal Reaction Time (SSRT) values.

**\*\*** $p < 0.005$  **\*** $p < 0.05$  of index group compared to their own healthy volunteer controls. Error bars represent standard error of the mean. Abbreviations: HV = healthy volunteers; BED = Obese subjects with binge eating disorder (BED); Obese = Obese subjects without BED; EtOH = abstinent alcohol dependent subjects

Figure 2. Information sampling task

Information sampling task outcomes for number of boxes opened, sampling error and total points accumulated. **\*** $p < 0.05$  in Obese subjects without binge eating disorder compared to healthy volunteers on multivariate analysis. Error bars represent standard error of the mean.

Abbreviations: HV\_BED = healthy volunteers that were age and gender-matched to the binge eating disorder group; HV\_Obese = healthy volunteers that were age and gender-matched to the obese group; HV\_EtOH = healthy volunteers that were age and gender-matched to the alcohol dependent group; BED = Obese subjects with binge eating disorder (BED); Obese = Obese subjects without BED; EtOH = abstinent alcohol dependent subjects