Inhibition Training and Electrophysiology in Alcohol Use Disorder

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Dr. Mrunal Bandawar

Department of Clinical Neurosciences

National Institute of Mental Health And Neurosciences

Bengaluru, India

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I. Abstract

Alcohol use disorders are associated with impairments in inhibitory control. Computerised ‘inhibition training' interventions or mindfulness interventions may ameliorate these deficits and prompt reductions in alcohol consumption. The aim of this thesis was to test effects of the inhibitory control training with a smartphone game on alcohol use disorders. Three studies were planned, 2 with heavy drinkers and 1 with alcohol-dependent patients.

Study 1 had alcohol consumption related outcomes in heavy drinkers motivated to cut down drinking with a hypothesis that training would: (1) improve participants' performance in the training game and affect inhibitory control assessed by a stop-signal task (SST) (near transfer effects); (2) affect the attentional network assessed by a classical Stroop task (far transfer effects); and (3) help to cut down drinking in motivated heavy drinking participants (behavioural effects). The effects were compared with an active control group playing a game similar to the training version but didn't have any of the response inhibition components. 48 heavy drinkers motivated to cut down drinking, between 21 and 60 years of age were recruited and randomised to two groups playing the respective games for 2 weeks. The outcome measures were assessed prior to the intervention and at the follow-up. Alcohol consumption was assessed at the baseline with a 2-week timeline follow back diary and during intervention with a daily notification of the units of alcohol consumed on the previous day as a part of the game. 46 participants completed the 2-week intervention. Participants improved on the game task. No significant change in the inhibition related parameters or interference control was noted. No change in alcohol consumption was seen. No near and far transfer effects were noted with the inhibition training.

In the study 2, our aim was to compare the effects of a smartphone ‘inhibition training' intervention, Brief Mindfulness Intervention (BMI), and a computerised control intervention on inhibitory control and its event-related potential (ERP) markers in heavy drinkers. We randomly allocated 60 heavy drinkers to groups: the ‘inhibition training' group completed 30 minutes of a bespoke smartphone game that is designed to improve inhibitory control, the control group completed a similar smartphone game that did not train inhibitory control, and the BMI group received a 30 minute audiotaped mindfulness intervention. All participants then completed a Stop Signal Task whilst

their ERPs were measured using a Biosemi Active Two system. Results show that compared to the control group, the BMI group had blunted N200 ($t(38) = 2.13$, $P < 0.05$) and P300 ($t(38) = 2.52$, $P < 0.05$) ERP components during successful inhibition trials. The control and inhibition training groups did not differ (N200: $t(38) = 0.64$, $P = 0.53$; P300: $t(38) = 1.51$, $P = 0.14$). There were no group differences in behavioural inhibitory control performance (Stop Signal Reaction Time; $F(2, 57) = 1.211$, $P = 0.31$). Compared to the control intervention, a brief mindfulness intervention led to a short-term improvement in ERP components associated with inhibitory control. However, a brief inhibition training smartphone game did not lead to improvements in inhibitory control. Further work is required to investigate if mindfulness-induced improvements in inhibitory control are long-lasting and if they can lead to reductions in alcohol consumption in problem drinkers.

The aim of the study 3 was to observe changes in response inhibition, attention, interference control and error processing on training inhibitory control with a smart-phone based inhibition training game, in subjects with alcohol dependence syndrome (ADS), in comparison with the control training game. This study was performed at NIMHANS, Bangalore. Baseline comparison was made between 30 ADS subjects and 30 healthy controls (HC) on the inhibition and error processing tasks. Further, the 30 alcohol-dependent subjects were randomly assigned to an inhibition training or control training group, with one of the training for two weeks (10 minutes twice a day). The outcomes were assessed with a Go No-go (GNG) task and a stop-signal task (SST) measuring the inhibition; and a flanker task measuring the attention, interference control and error processing, with simultaneous electroencephalography recording for the Event-related potentials (ERP). On comparing the baseline data between ADS subjects and HC, significantly delayed stop-signal reaction time (SSRT) in SST along with a blunted N200 and P300 amplitudes were noted for the correct inhibitory trials performance in ADS subjects. Further, ADS subjects showed the blunting of N200 amplitudes with increasing inhibitory task difficulty, not noted in the HCs. In the GNG task, blunted P300 amplitudes were noted in the ADS subjects. In the flanker task, more error rate and a blunted error related late potential along with more negative early potential were noted in the ADS subjects. These findings validate the tasks ability to detect inhibition. On training, a significant rise in N200 negativity on correct performance of inhibitory trials in the SST was noted with inhibition training compared

to control training. No other changes were noted with the training. In conclusion, ADS subjects have an impaired inhibition and error processing, with a major difference in the conflict detection on an increased inhibitory demand. Multiple sessions of Inhibition training for two weeks improves the conflict monitoring process during a response inhibition.

In the last chapter, discussion about all 3 study findings and limitations of the thesis are discussed.

II. General Introduction

A. Alcohol use disorders: diagnosis and epidemiology

As per the latest (2010) World Health Organisation's global status report (World Health Organization, 2014), the worldwide consumption in aged 15 years or older was equal to 6.2 liters of pure alcohol consumed per person, which converts into 13.5 grams of pure alcohol per day. Globally, about 16.0% of drinkers in this age group engage in heavy episodic drinking. Also, 3.3 million deaths and 5.1% of the global burden of disease and injury is attributed as a health consequence of alcohol consumption.

There is a wide geographical variation in the proportion of alcohol consumption noted. The trend of increase in recorded alcohol per capita consumption in last decade was mainly seen in China and India, which could potentially be linked to the marketing strategy by the alcohol industry and the economic reforms in these countries. The per capita alcohol consumption in India has increased by 55% in last two decades from 1992 to 2012, the third highest increase in the world, after Russian Federation and Estonia (Franco, 2015). According to a recent report addressing alcohol consumption in India, 93% of the alcohol was consumed as spirits, 7% as beer and less than 1% as wine (World Health Organization, 2014). The rising consumption of alcohol and its changed pattern towards binge drinking increases the risk of diseases associated with the alcohol use.

The rising alcohol consumption is also a major concern in European countries including the United Kingdom. Twenty-four percent of adults in England, including 33% of men and 16% of women, showed a harmful pattern of alcohol consumption (McManus, Meltzer, Brugha, Bebbington, & Jenkins, 2009). Also, 4 % of adults in England are alcohol dependent (6% men; 2% women), involving a significant amount of addiction to alcohol, causing difficulty to reduce drinking or abstain despite increasingly serious harm (Drummond et al., 2004). Drinking alcohol is socially accepted in the UK. It is widely associated with use for relaxation and pleasure. Many people drink alcohol without experiencing harmful effects. However, the number of people experiencing physical, social and psychological harmful effects of alcohol are growing.

As per the previous UK safe drinking guideline, less than 21 units of alcohol per week in men and 14 units in women is safe (Royal College of Psychiatrists, 1986). The recent 2016 guidelines are not to drink more than 14 units a week on a regular basis to keep

health risks from alcohol to a low level (Department of Health, 2016). Those people who cross this level of drinking but have not yet experienced alcohol-related harm are regarded as hazardous drinkers. These people are at the probability of increased risk of harm in future if the pattern of drinking is continued. Apart from this, clinical guidelines for diagnosing alcohol use related disorder is as per International Classification of Diseases (ICD-10) (World Health Organization, 2004) and Diagnostic and Statistical Manual of Mental Disorders (DSM–5) (American Psychiatric Association, 2013).

International Classification of Diseases (ICD-10) (World Health Organization, 2004)

For the diagnostic purpose in clinical settings in India ICD-10 is used as the standard guideline. As per the ICD-10 guidelines, diagnosis of alcohol dependence is usually made only if three or more of the following criteria are met at some time during the past year. If 1 to 2 criteria are met, diagnosis of alcohol abuse is considered.

1. a strong desire or sense of compulsion to take the substance;
2. difficulties in controlling substance-taking behaviour in terms of its onset, termination, or levels of use;
3. a physiological withdrawal state when substance use has ceased or been reduced, as evidenced by the characteristic withdrawal syndrome for the substance; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms;
4. evidence of tolerance, such that increased doses of the psychoactive substances are required in order to achieve effects originally produced by lower doses (clear examples of this are found in alcohol- and opiate-dependent individuals who may take daily doses sufficient to incapacitate or kill non-tolerant users);
5. progressive neglect of alternative pleasures or interests because of psychoactive substance use, an increased amount of time necessary to obtain or take the substance or to recover from its effects;
6. persisting with substance use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking, depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning; efforts should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm.

Diagnostic and Statistical Manual of Mental Disorders (DSM–5) (American Psychiatric Association, 2013)

As per DSM–5 guidelines, anyone meeting any two of the 11 criteria during the same 12-month period receives a diagnosis of Alcohol Use Disorder (AUD). The severity of AUD—mild, moderate, or severe—is based on the number of criteria met.

The severity of the AUD is defined as:

Mild: The presence of 2 to 3 symptoms

Moderate: The presence of 4 to 5 symptoms

Severe: The presence of 6 or more symptoms

11 questions are asked regarding alcohol consumption in the past year. These are as follows:

1. Alcohol is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.
3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
4. Craving, or a strong desire or urge to use alcohol.
5. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.
7. Important social, occupational, or recreational activities are given up or reduced because of alcohol use.
8. Recurrent alcohol use in situations in which it is physically hazardous.
9. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.
10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of alcohol to achieve intoxication or desired effect.
    b. A markedly diminished effect with continued use of the same amount of alcohol.

11. Withdrawal, as manifested by either of the following:
    a. The characteristic withdrawal syndrome for alcohol.
    b. Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.

The treatment of alcohol use disorder generally has one of the two approaches regarding the drinking-related goals. One of this approach is abstinence target. In this approach, the aim is complete abstinence from alcohol. The objective of this pattern of management is with a view that, in the subjects with problem drinking, a return to moderate or 'controlled' drinking is difficult (Edwards & Gross, 1976; Schuckit, 2009). Further, for subjects with significant psychiatric or physical comorbidity (for example, depressive disorder or alcoholic liver disease), abstinence is the appropriate goal. Disulfiram, an alcohol deterrent, is commonly prescribed for this type of management. Even though the use of this strategy is decreasing, we still find it as a favourite for many clinics in India and the UK. Another management goal is harm reduction approach. This is possible for those with a low level of alcohol problem such as hazardous and harmful drinkers. The goal of this approach is to be able to achieve moderate alcohol consumption (Raistrick, 2006). These are the major treatment approaches for problem drinking both in India and UK.

In India and the UK, the approach towards subjects with severe problem drinking is common. The patient needing treatment is first detoxified depending on the presence of withdrawal symptoms. This is followed by the psychological treatment approaches such as motivational interviewing, psycho-education, group therapy, cognitive behavioural therapy and 12 step program. The anti-craving agents or disulfiram for relapse prevention are prescribed as per the needs and guidelines.

B. Neuroscience of addiction

Neurobiological theories of addiction are primarily based on studies performed on the animal models of addiction. The major consideration in this theory is the transition from infrequent substance user to dependence pattern. It consists of positive and negative reinforcements produced at different stages of substance use (Gilpin & Koob, 2008). Positive reinforcement is important in the early stages of substance use and abuse. Negative reinforcement can be important early in substance use in people self-medicating for the coexisting affective disorders. But the role of negative reinforcement more likely increases after the transition to dependence. The critical pathway involved

in addiction is the mesolimbic-fronto-cortical dopamine system (containing the mesolimbic and mesocortical dopamine systems), also considered as brain reward circuit (Wise, 1996). Dopamine has been implicated in the reinforcing effects of drugs, with drugs use resulting in the direct stimulation of dopamine and also an indirect increase in dopamine levels (Altman et al., 1996) responsible for initial positive reinforcement. Later, frequent use cause up-regulation of the dopamine and other receptors resulting in the requirement of more substance to receive the same positive reinforcement resulting in the development of tolerance for the substance. Further use of the substance starts producing untoward effects of substance withdrawal. To avoid these effects, substance use is continued for the negative reinforcement. This leads to disinhibition in the substance use.

There are several other theories attempting to explain the development and persistence of addictive behaviour. Reward-deficiency model mentions drug intake as a compensation to individual's deficiency of neural rewards (Blum, Gardner, Oscar-Berman, & Gold, 2012; Limbrick-Oldfield, van Holst, & Clark, 2013) along with a poor inhibitory control over drug-taking behaviour (Rita Z Goldstein & Volkow, 2011; Jentsch & Taylor, 1999; Volkow, 2002). The drug use may also cause associated neuro-adaptations in reward learning. This phenomenon biases behaviour toward drugs (Heinz, Beck, Meyer-Lindenberg, Sterzer, & Heinz, 2011). The dual process model of addiction suggests a conflict between automatic impulsive process and reflective process. The automatic impulsive process causes a tendency to approach drugs after repeated use and the reflective process may motivate to abstain from drugs in view of the long-term benefits (Bechara, 2005; Wiers et al., 2007). It is also suggested that, after repeated drug intake, the cues that are associated with drugs may activate the habitual behaviours associated with drugs (Everitt & Robbins, 2005). Approach and avoidance processes outside of conscious awareness are supposed causes for drug craving and relapse, even after years of abstinence (Heinz, Beck, Grüsser, Grace, & Wrase, 2009).

The neuronal model of addiction is considered to involve prefrontal cortex, striatum and basolateral amygdala and the circuits between them. The prefrontal cortex governs the motivation, inhibitory control and choices whereas the basolateral amygdala is associated with the link between a stimulus and an emotion. The striatum is suggested to be a place that processes reward and links emotions to actions. The circuit can be easily understood with help of an example of a choice between health food such as a

fruit and an unhealthy pleasure giving food such as cake. The pleasurable memories of cake eating are stored in the basolateral amygdala. Whenever there is a time to make a choice between a fruit and a piece of cake, pre-frontal cortex weighs the advantage and disadvantage of both. During this time, the basolateral amygdala would work as a suggestive part which is ruled by the previous experiences. The pleasure of the final activity will be seen in the striatum. The recent research has suggested that the chronic use of addictive substance leads to a generation of a new habit forming pathway that links the basolateral amygdala indirectly with the striatum, the locus of habituation (Everitt & Robbins, 2013). This connection can cause a direct activation of the striatum due to an activity in the basolateral amygdala, on presenting any substance-related cue that has stored emotions, bypassing the prefrontal area. This could explain the reason for the chronic use of substances even after being aware of the harms caused and so probably explaining the reason for the relapsing-remitting nature of the addictive disorders.

C. Deficits in self-control, self-regulation, and executive function in addiction

Self-control is defined as a preference for larger delayed rewards over smaller immediate rewards (Ainslie, 1975; Hoch & Loewenstein, 1991; Kirby & Herrnstein, 1995). Self-control is the process of advancing abstract, distal motives over concrete, proximal motives when the two motives directly conflict (Fujita, 2011). It is suggested that failure in the self-control occurs when an activation of the salient temptations cause an inability to inhibit impulses (Chaiken & Trope, 1999). So, a self-control requires recognising these impulses as undesirable and then inhibiting them. This inhibition process is believed to be initiated consciously and to require a sufficient cognitive and motivational resources. Three factors influence the self-control failure – the salient temptation activation, an intensity of impulse and decrements in cognitive and motivational resources (Fujita, 2011). The salient temptations activate impulses to get involved in those temptations. For example, when the smokers abstain from smoking have a significantly increased thoughts about the smoking when exposed to a lit cigarette (Sayette, Martin, Wertz, Shiffman, & Perrott, 2001). The other cause of failure of the self-control is strong impulses that are difficult to inhibit. For example, a strong positive self-association with alcohol and smoking increases the likelihood to drink and

smoke more (De Houwer, Custers, & De Clercq, 2006; Waters et al., 2007; Wiers & Stacy, 2006). It is also found that the demands on conscious resources can impair self-control. Cognitive load is suggested to aggravate the temporal discounting (Hinson, Jameson, & Whitney, 2003). Also, individual differences in the cognitive resource capacity such as working memory capacity (Whitney, Hinson, & Jameson, 2006) affect people's self-control and can predict problem drinking.

Self-control failure has been widely linked to several negative health outcomes where excessive impulsivity gives rise to the maladaptive behaviours including tobacco use (W K Bickel, Odum, & Madden, 1999), substance dependence (W K Bickel et al., 2007; MacKillop et al., 2011), pathological gambling (Alessi & Petry, 2003; MacKillop et al., 2011; MacKillop, Anderson, Castelda, Mattson, & Donovick, 2006a, 2006b; Petry, 2001) and overeating (Epstein, Salvy, Carr, Dearing, & Bickel, 2010). In relation with the substance use, self-control failure is considered to be a result of the drug modulating normal learning mechanisms further producing a dysfunctional reward processing (W K Bickel, Yi, Mueller, Jones, & Christensen, 2010). The decision making is distorted by overvaluing the drug-associated stimuli and undervaluing the other long-term rewards. This distortion is a result of the deregulated two valuation systems. Immediate reward valuation is due to greater activation of the strong limbic neural network, also known as the impulsive decision system. The future rewards valuation is controlled by the frontal cortices also termed as the executive decision system. It is suggested that less relative control by the executive decision system over the impulsive decision system is a reason for self-control failure in the substance use disorders.

The different components of executive function are attentional control, inhibitory control, working memory and cognitive flexibility (Miyake et al., 2000; A M Owen, Downes, Sahakian, Polkey, & Robbins, 1990; A M Owen, Roberts, Polkey, Sahakian, & Robbins, 1991; A M Owen, Sahakian, Semple, Polkey, & Robbins, 1995; Robbins, 1996). The unity in diversity explanation of executive function suggests that a complex executive task has a latent contribution from each of its subcomponents (Miyake et al., 2000). While executive function is factored into many components, inhibitory control is an important subordinate. According to Barkley's theory of executive function, it is built upon behavioral inhibition (Barkley, 1997). Behavioral inhibition prevents automatic prepotent responses. This provides an opportunity for executive functions to influence responding using other facets like working memory and planning response

analysis and synthesis.

A large proportion of individuals struggling with addiction exhibit some type of executive dysfunction (Bates, Pawlak, Tonigan, & Buckman, 2006). These deficits may affect addiction-related therapies. For example, the fundamental prerequisite of successful cognitive behavior therapy in addiction treatment are basic planning, inhibition, flexibility and memory skills (A Verdejo-García, López-Torrecillas, Giménez, & Pérez-García, 2004).

Attention is defined as one's ability to concentrate on one aspect of the environment while ignoring other aspects (Barkley, 1997). Sustained attention (Levine et al., 2006) and attentional bias (Sinclair, Nausheen, Garner, & Baldwin, 2010) are the appropriate features of attention relevant to the substance use disorder. Poor sustained attention has been observed in cigarette smokers (Yakir et al., 2007), alcohol-dependent patients (Schellekens et al., 2009) and substance dependence (Kalapatapu et al., 2011; J. Prosser, London, & Galynker, 2009; J. M. Prosser et al., 2008; Scholes & Martin-Iverson, 2009). Addicted individuals also show an attentional bias for the addiction-related stimuli. For example, Chanon, Sours, & Boettiger, (2010) in their study showed that the active smokers have an attention bias towards the smoking-related pictures while performing a visual probe task. Another component of executive function is the working memory. Working memory is the ability to retain some information active in a flexible way for a future use (Bledowski, Kaiser, & Rahm, 2010). Most commonly n back task is used for assessing the working memory function and Patterson et al., (2010) showed that the performance in this task can predict the time to relapse in abstinent smokers. Working memory is also found to be deficient in the alcohol-dependent (Beatty, Katzung, Moreland, & Nixon, 1995; Thoma et al., 2011) and other substance users (Kalapatapu et al., 2011; Ornstein et al., 2000). Deficit in the inhibitory control is also well documented in people with the substance use disorder (Colzato, van den Wildenberg, & Hommel, 2007; Salo, Ursu, Buonocore, Leamon, & Carter, 2009) especially in alcohol use disorder (Colder & O'Connor, 2002; Chella Kamarajan, Porjesz, Jones, Choi, et al., 2005).

Mindfulness

Mindfulness is also considered as a key training to train the self-control. Attention control, emotion regulation, and an improvement of self-awareness are three

components of mindfulness meditation that are shared with the self-control framework. There is an emerging evidence that mindfulness meditation has a potential to ameliorate the negative outcomes resulting from deficits in the self-control by regulating the same core neuronal regions of Anterior Cingulate Cortex (ACC), Prefrontal Cortex (PFC), and striatum (Rita Z. Goldstein & Volkow, 2011; Koob & Volkow, 2010; Yi-Yuan Tang et al., 2009; Yi-Yuan Tang, Hölzel, & Posner, 2015; Yi-Yuan Tang, Posner, Rothbart, & Volkow, 2015). Recently, a few rigorous and randomized studies have tested the effect of mindfulness meditation on addictions (Bowen et al., 2014; Tang, & Posner, 2013). For example, compared to the usual treatment, the eight weekly group sessions of a mindfulness-based relapse prevention technique resulted in a significantly lower risk of relapse to the substance use and heavy drinking among participants (Bowen et al., 2014). Another study (Sanger & Dorjee, 2016) studied mindfulness effect in the adolescents and found changes related to the inhibitory ERP component, raising the possibility to explore the effects of mindfulness in the addicted population to train inhibition. The effect of mindfulness to prevent responding to the internal cues could make it a possible tool in treating Alcohol use disorder.

D. Neuroscience of inhibitory control

Inhibition has 3 inter-related processes- a. inhibition of initial prepotent response to an event (action inhibition); b. stopping an ongoing response, permitting a delay in the decision to respond (action cancellation); and c. protect this period of delay and the self directed response that occur within it from disruption of competing events and responses (action change/interference control)

Inhibitory control is assessed majorly by two tasks, Go-Nogo (GNG) task and Stop-Signal Task (SST) (C.D. Chambers, Garavan, & Bellgrove, 2009; Dalley, Everitt, & Robbins, 2011; F. Verbruggen & Logan, 2008). In GNG, participants are asked to respond quickly to a frequently-occurring stimulus and inhibit responding whenever they encounter a different stimulus that is encountered infrequently. The quick responses to the frequent stimuli generate an automatic response tendency. This increases the requirement of inhibitory control to prevent responses for infrequent stimuli. So, the inhibitory control in this task is reflected by the proportion of correctly inhibited no-go trials. This task measures the action inhibition process of inhibitory control. In SST, participants are instructed to quickly respond to a stream of go stimuli (G.D. Logan, Cowan, & Davis, 1984). Infrequently, the primary stimulus is followed

by a stop cue indicating to cancel already initiated response. The delay of stop cue from the go stimulus is termed as stop signal delay (SSD). The inhibitory control in this task is indexed by stop-signal reaction time (SSRT). This task measures the action cancellation process of inhibitory control. Both the GNG and SST are supposed to have a common inhibitory pathway, along with general processes such as attentional monitoring and salience processing (Corbetta & Shulman, 2002; Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010; Li, Huang, Constable, & Sinha, 2006).

N200 and P300 are two ERP components related to inhibitory control associated brain activity. N200 is thought to reflect the top-down functioning required to stop the automatic tendency (Falkenstein, 2006; Kaiser et al., 2006), which correlates with the behavioural outcomes of inhibition (A. Dimoska, Johnstone, & Barry, 2006; Falkenstein, Hoormann, & Hohnsbein, 1999; Van Boxtel, Van der Molen, Jennings, & Brunia, 2001), along with conflict detection in the early phase of inhibitory control (Falkenstein, 2006; S. Nieuwenhuis, Yeung, Van Den Wildenberg, & Ridderinkhof, 2003). N200 is also said to an early cognitive index of processing necessary to implement inhibitory control rather than the actual inhibitory break. P300 is an another ERP component reflecting temporally late stage of an inhibitory process which is closer to the actual inhibition of the motor system (G.P.H. Band & Van Boxtel, 1999; A. Dimoska et al., 2006; A. Kok, Ramautar, De Ruiter, Band, & Ridderinkhof, 2004).

The localization of the inhibitory control-related activity in healthy individuals is mainly right lateralized, including the Inferior Frontal Gyrus (IFG), Anterior Cingulate Cortex (ACC) along with pre-Supplementary Motor Area (SMA) and dorsolateral prefrontal cortex (DLPFC). The subcortical areas including thalamus and basal ganglia also play a vital role (Christopher D. Chambers, Garavan, & Bellgrove, 2009; Garavan, Hester, Murphy, Fassbender, & Kelly, 2006; Simmonds, Pekar, & Mostofsky, 2008). Among these areas, right IFG is suggested to be the responsible for detecting the relevant inhibitory stimulus (no-go and stop-signal stimuli) (Hampshire et al., 2010; Li et al., 2006). This is done within conjugation with the inferior parietal lobe (IPL) and temporal parietal junction (TPJ), responsible for selective attention (Corbetta & Shulman, 2002; Hampshire et al., 2010). Further, the selection of appropriate response among the two contrary responses and later update the motor plan for the selected response is done by the ACC and pre-SMA (S.H. Mostofsky & Simmonds, 2008).

E. Deficits in inhibitory control in addiction and alcohol use disorder

The ERP components associated with inhibitory control are found altered in patients with alcohol dependence. Kamarajan et al., (2005) in their study observed that the accuracy was impaired in alcohol dependence patients compared to controls during GNG task performance, which corresponded with a lower amplitude of P300 both at go and no-go trials and less anteriorisation of topography during No-Go trials. A similar finding of blunted amplitude for P300 on no-go trials in alcohol dependence patients was also observed in some other studies (H. L. Cohen, Porjesz, Begleiter, & Wang, 1997; Colrain et al., 2011). Although lowered P300 amplitude for no-go trials in alcohol dependence patients suggests impairment in inhibitory control, lower amplitudes of P300 on go trials reflects more general deficits such as attention (H. L. Cohen et al., 1997; C. Kamarajan et al., 2005; Pfefferbaum, Rosenbloom, & Ford, 1987). On contrary, some studies didn't notice any difference on both go and no-go P300 amplitudes in alcohol dependence patients (Fallgatter, Wiesbeck, Weijers, Boening, & Strik, 1998; Karch et al., 2007). All these mentioned studies have difference in the methodology such as prepotency of no-go trials (Fallgatter et al., 1998; C. Kamarajan et al., 2005; Karch et al., 2007) and cueing of no-go trials (Fallgatter et al., 1998), probable reason for the mixed evidence (Luijten et al., 2014). Along with P300, N200 is also studied in some of the studies comparing alcohol dependence patient with controls. Pandey et al., (2012) in their study compared the N200 amplitude differences on an equal probability GNG task. They observed reduced N200 amplitudes both for go and no-go trials. Also, patients didn't show the change in amplitude from the Go to the no-go trials, as in the healthy controls having larger amplitudes for no-go trials than go trials. The GNG task was widely used for estimating inhibitory control ERP in alcohol dependence patients, but the variations in electrophysiological correlates of SST between patients and controls is perhaps not explored.

The research specifically studying the fMRI activation differences between alcohol-dependent patients and healthy control during an inhibition task performance is limited. Karch et al., (2008) in their study simultaneously acquired ERP and BOLD signals while performing a stop-signal task in subjects with alcohol dependence. Although they did not note any difference in the stop-signal reaction time between patients and healthy controls, they observed lower activation of the left dorsolateral prefrontal cortex during the inhibitory task performance. The similar activation pattern difference was also

noted in another study (Li, Luo, Yan, Bergquist, & Sinha, 2009). Further, after administration of modafinil (purported cognitive enhancer) increased activation in the left supplementary motor area and right ventrolateral thalamus, the components of an inhibitory control circuit, in the alcohol-dependent subjects with low baseline inhibitory control compared to placebo (Schmaal et al., 2013). This suggests the possibility of modulation in the neuronal circuit of inhibition.

F. Cognitive training interventions for alcohol use disorder

The training of executive function involves repeated activation of the involved neuronal circuits. This may help to treat some of the executive dysfunction seen in addiction (Vocci, 2008). For example, Bickel et al. (2011) trained working memory in stimulant addicts. They exposed a group of stimulant addicts to 4–15 one-hour sessions of a working-memory training battery, and compared with a control group that received the same task stimuli but were presented without any training component and repeated the same trials again. They observed a decrease in delay discounting rates in the working-memory training group compared to the control group. This suggested the generalisation of working memory training to another domain of the executive function of valuation of future events. This study did not include clinical variables in their outcome measures. Similarly, generalising the effects of working memory training towards the other cognitive domains are also noted in other studies (Gamito et al., 2014; T Klingberg, Forssberg, & Westerberg, 2002; Torkel Klingberg et al., 2005). This generates the possibility of demonstrating improvement in future event valuation of training different components of executive function.

There were some more studies training working memory components in population having alcohol drinking associated problem. A study conducted by Houben and colleagues (2011) in 48 problem drinkers via the Internet, with 25 sessions of either active or control working-memory training found reduced alcohol consumption, particularly in more impulsive individuals. The training consisted of 3 components: visuospatial WM task, a backward digit span task, and a letter span task. During the visuospatial WM task, several squares in a 4 × 4 grid on a computer screen changed colour in order and was expected to mark the sequence of changes for correct response. During the backward digit span task, several numbers were presented on the computer screen one at a time, and the correct response was to reproduce this sequence in reverse order. In the letter span task, several letters were presented one at a time in a circle on

the computer screen. One of the positions in this circle was then indicated, and participants had to enter the corresponding letter. Each of the three tasks consisted of 30 trials. In the training condition the intensity of the task changed according to participants' performance while, in the control condition it remained the same. WM improvements and decreased alcohol intake were demonstrated in the experimental group and these effects persisted 1 month after training cessation. This study was an internet based and lacked the lab-based alcohol consumption validation test.

Black & Mullan, (2015) did a computer-based planning ability training in 59 binge drinking college students with 4 sessions, modifying parameters of Tower of London task. The Tower of London task (TOL) requires participants to manipulate 3 different-coloured balls across 3 pegs; in order to achieve a goal state. 21 Successful completion of the minimum possible moves requires preplanning the series of response. They made 7 different versions of this task with 4 as equivalent difficulties and further 3 of increasing difficulty later. Task difficulty was manipulated using the number of minimum moves required and start-configuration ambiguity. Scores on the tasks reflected both total time and number of failed attempts and could range from -36 to +108, with higher scores representing better performance. They reported significantly reduced mean drinks per occasion and maximum drinks consumed on any occasion as per the AUDIT C scoring, compared to the control the control group performing a training of consistent difficulty levels. But no change was noted on the frequency of Heavy episodes drinking. They also mentioned of participants overplaying the sessions claiming of intervention to be more interesting.

Another type of cognitive training attempted in executive function group of training is training attention bias away from alcohol in the population with problem alcohol use. These training tasks were basically modified from visual probe task or an addiction Stroop task. Initially training attention bias was found to be effective in some of the laboratory-based studies. Field & Eastwood, (2005) trained a group of heavy social drinkers having a probable alcohol use disorder, allocating them to one of the 'Attend' or 'Avoid' group, who were trained to direct their attention toward or away from alcohol-related pictures, respectively. They noted an increased beer consumption in the Attend group compared to the Avoid group, demonstrating that attentional bias for alcohol cues had an underlying influence on alcohol craving and consumption. But the further attempt of replicating and extending these findings towards novel alcohol

pictures not used in the training task failed in subsequent studies (M. Field et al., 2007; T. Schoenmakers, Wiers, Jones, Bruce, & Jansen, 2007). Also, all these studies were single session training, so the effectiveness of these training is always questionable in the clinical scenarios.

There are some of the studies attempted multiple sessions of attention bias training. Fadardi & Cox, (2009) tested modified Stroop task training over problem drinkers recruited from the local community who were drinking alcohol at unsafe levels. The modified Stroop task training named as 'Alcohol Attention-Control Training Programme' consisted of a Stroop colour-naming task in which personalised alcohol-related pictures (e.g. of the participants' preferred brand of beer) were presented with a coloured border. Naming the colour of the border was the correct response. The difficulty level was increased by reducing the size of the border, presenting more than one stimulus at a time, and requiring quicker responses than on previous blocks. They reported of decrease in alcohol consumption by the intervention but lack of control group was the limitation of the study. Schoenmakers et al., (2010) in their study compared alcohol attention bias training with a control training (a different reaction time task, that also involved responding to alcohol pictures), for 5 session over 3 week duration on 43 alcohol-dependent patients. This study reported of generalisation of the effects of training and delaying the relapse but, the study had a small sample size. McGeary et al., (2014) tested 41 heavy drinking college students having a probable alcohol use disorder by allocating them to the Avoid alcohol group or Control group. They performed the tasks twice per week for four weeks at home. Results reported of a good compliance rate with 73% completing at least six ABM sessions over the four weeks. The Avoid group reported a reduction in the frequency of drinking over the course of the study period. Wiers et al., (2015) investigated the efficacy of multiple sessions of the attention bias training program delivered via the internet to heavy drinkers having a probable alcohol use disorder using the same task as in the previous studies comparing with an active control group. They reported of generalised decrease in alcohol consumption with no specific difference in the training condition. The results produced by attention bias monitoring are promising, also home environment based intervention showed better results (Kerst & Waters, 2014; McGeary et al., 2014).

Another type of training is approach bias training, which trains the approach bias for appetitive alcohol cues in people with problem alcohol use. Three studies trained

alcohol-dependent patients to avoid alcohol by training approach bias and found improvement in the approach bias compared to the sham training, further decreasing the relapse rate at 1year follow-up (Eberl et al., 2013, 2014; Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011c). This training along with the previously described attention bias monitoring and working memory training suggests the potential of these types of training as an add-on to the clinical management.

Inhibitory control training has recently been investigated for alcohol use disorder. There are 2 types of this training focus: associative types of inhibition training in which appetitive alcohol cues are paired with no-go or stop cues in an inhibitory task and by changing the prepotency of inhibitory trials or with the variation of the stop-signal delay, inhibition for the appetitive cue is trained. Another type of inhibition training is the non-associative inhibition training in which, similar to the associative training, changing the prepotency of inhibitory trials or with the variation of the stop-signal delay in an inhibitory task is the basis of training, but the inhibitory trials are not paired with appetitive cues and thus the goal is to strengthen the top-down inhibitory function. In this type of training, the outcomes of interest are first, change in the inhibitory task performance projecting the near transfer effects with improvement in the same cognitive domain. Second, change in other task performance measuring other components of executive function and change in the alcohol consumption or relapse rate, projecting the far transfer effects. For example, if the cognitive training is done for inhibitory control using a stop-signal task-based training, then the near transfer effects would be changes produced in a stop-signal task or inhibition per se and the far transfer effects would be changes produced by the same training on other cognitive functions like working memory and generalized changes in the associated behavior like decrease in alcohol consumption or increase in concentration span. A recent review by Simons et al., (2016) suggests that the brain training interventions have good near transfer effects but their potentials to generate far transfer effects are limited. They suggested a need for extensive randomized control trials to generate evidence for effectiveness for such type of training interventions.

Few studies have attempted training inhibition to alcohol cues through the associative type of training. Bowley et al., (2013) trained 50 college students with a single session of go-no-go task associative training and found decreased ad-lib alcohol consumption measured by taste test in the training group compared to control group receiving alcohol

go training. This effect of inhibition training did not sustain outside the lab when measured 1-week alcohol consumption post training. This study did not measure the near and far transfer effects on cognitive tasks. Another two studies also noted a similar ad-lib decrease in alcohol consumption with an associative inhibition training on go-no-go task (Houben, Nederkoorn, Wiers, & Jansen, 2011b) and stop-signal task (Jones & Field, 2013). Jones & Field, (2013) also reported near transfer effects of improvement in the behavioural inhibition in heavy drinkers having a probable alcohol use disorder but, did not note any decrease in alcohol consumption noted for 1-week post training outside the laboratory. Recent two meta-analysis performed to assess the effect of single-session appetitive inhibition reported robust but small effect size for these types of training (Allom, Mullan, & Hagger, 2016; Jones et al., 2016).

The effect of non-associative type of inhibition training has not been widely explored. In a recent study (Field et al., in prep), training inhibition in a non-associative pattern was attempted in heavy drinkers having a probable alcohol use disorder. They tested three types of training Alcohol No-Go, General inhibition training, and Cue-specific inhibition training delivered over 4-week period against a control group. They neither noted any intervention specific change in the inhibitory control nor further effect on the alcohol consumption. Another similar study (Field, Tiplady, & Jones, in prep), trained heavy drinkers having a probable alcohol use disorder using a mobile phone instead of the computerised task, twice per day for two weeks. The trained with one of the three tasks: training in which inhibition became more difficult over time; training with simply practicing a standard Stop Signal task; and a control training with only the reaction time component of the Stop Signal task. They noted a near transfer effect on inhibitory control task when training was done with constant stop signal delay task rather than variable one compared to the control task. This study suggests a possible advantage of using a mobile phone in the inhibition training.

G. Delivery of psychological interventions via computers and mobile phones (e-health and m-health interventions)

Many computer-based programs have been developed for monitoring treatment, providing psycho-education and therapy in many mental health conditions such as depression, anxiety disorders, stress, bipolar disorder, substance use disorders and eating disorders. These programs users showed a positive attitude towards their use

(Graham, Franses, Kenwright, & Marks, 2000) and are well accepted (Christensen, Griffiths, & Korten, 2002). Randomised controlled trials and meta-analyses have suggested good clinical efficacy and cost-effectiveness of eMental Health programs (Barak, Hen, Boniel-Nissim, & Shapira, 2008; Griffiths & Christensen, 2006). They have also shown a comparative effect similar to the face-to-face interventions (Andersson & Cuijpers, 2009; Cuijpers et al., 2009).

In past few years, the mobile technology has penetrated widely in the low and middle-income countries such as India (Annual Report, 2016). Mobile technologies are having wider availability along with the advantages of being portable. Utilising this technology in health care delivery may decrease the cost of services by using the existing wide infrastructure available (Zhang, Ho, Cheok, & Ho, 2015), as people carry mobiles with them all the time. As in India, there is a gross deficiency of mental health resources (Chadda & Prashanth, 2015), use of mobile technology for delivering mental health intervention will be advantageous as an add-on to the existing system.

A recent systematic review studied the use and efficacy of mHealth apps (Zhao, Freeman, & Li, 2016). They mentioned the long-term sustainability of effects of these apps is not studied. Also, they mentioned a high risk of bias among these studies as per the Cochrane guidelines. They found a high retention rate of about 75% in most of the studies in the intervention groups, suggesting a good response rate by the participants. Most of the studies included in their review were conducted in high-income countries, which they proposed as probably due to either because of their inclusion criteria of English language of reported studies or due to lack of the research of web interventions in the low and middle-income countries. They suggested that apps with a simple interface and better use of app design and technology may reduce the time required for users to participate in the intervention and improve retention. Also, the use Consolidated Standards for Reporting Trials (CONSORT) checklist for reporting web-based mHealth randomised controlled trials (RCT) and mHealth Evidence Reporting and Assessment (mERA) checklist may improve the reporting with decreasing the risk of bias.

With substance use disorders some mobile-based apps have been tested. Bricker et al., (2014) in their Randomised Controlled Trial (RCT) tested efficacies of comparable 2 mobile-based apps, "SmartQuit" and "QuitGuide", based on different behavioural principles delivered in smokers to quit smoking. They noted promising quit rate with

the customized app "SmartQuit" (13%) over the regular guidelines based one (8%), with a high retention rate of around 85% in both the groups for the 2-month study. Another study delivering the motivational enhancement therapy with the help of smartphone app in people with alcohol use disorder showed a promising increase in the percentage of abstinent days in the intervention group over a 6-week study compared to an internet-based therapy group (Gonzalez & Dulin, 2015). One other study tested an app built to improve self-determination in patients with alcohol dependence and found fewer risky drinking days with the intervention and a follow-up period of 12 months compared to control group with usual intervention (Gustafson et al., 2014). Although a large study conducted on the university college students to reduce alcohol consumption with an app did not find any differential effect (Gajecki, Berman, Sinadinovic, Rosendahl, & Andersson, 2014), the discrepancy in the result could be due to the different background theory for the basis of app and the population of interest along with the brief duration of the intervention. This also suggests having a strong theoretic background for the app to deliver behavioural intervention (Glanz & Bishop, 2010; Michie & Johnston, 2012; Webb, Joseph, Yardley, & Michie, 2010). If the apps are not designed on background research evidence, it may fail to yield the desired outcomes.

The validity of recently developed cognitive training tasks with an addition of serious game elements has been tricky (Boendermaker, Peeters, Prins, & Wiers, 2017). Although these training tasks become more attractive with the gamification, in the process it may hinder the core purpose of training if not designed appropriately. Some games have been introduced to train different cognitive processes in alcohol use disorders.

A facebook based game named “Cheese Ninja” (Boendermaker, Boffo, & Wiers, 2015) based on the go/no-go paradigm, aimed at retraining alcohol-related memory bias. This game has a basic character of a mouse with the user controls. The mouse runs through a tunnel, grabbing pieces of cheese and avoiding cats. These go and no-go cues are paired with images of alcoholic and non-alcoholic beverages in the background to train alcohol bias. The aim of this study was to access different platform based experience for users and so they did not measure the training effect on alcohol consumption. Gamito et al., (2014) used a set of gamified training targeting improvement of attention, working memory, and logical reasoning in alcoholic dependent patients, found a more

pronounced improvement in frontal lobe functions with the gamified training, compared to the control group receiving the usual treatment. These studies suggest that the gamification of existing training paradigms may result in even better training effects.

H. Statement of the general approach, aims, and hypotheses

The overall aim of this thesis was to train the inhibition of alcohol use disorder with the help of a smart-phone based training game. By focusing on this hypothesis we can attempt to develop an in-house smart-phone based inhibition training game using the previous training tasks. The importance of using the game based inhibitory control training is twofold – firstly, to use technology for providing a handy training tool helpful in increasing our understanding of addiction, and secondly, to make the regular training interesting enough to continue its use for a longer duration. As well as examining the behavioural effects of inhibition training, this thesis will also examine any possible changes produced by this training on neuronal markers of inhibition and further influencing the alcohol consumption.

Chapter Three describes the development of the inhibition training game. This chapter explains the process used for making the in-house game and its design. Furthermore, it is discussed the advantages and shortcomings in this game.

Chapter Four then sought to examine whether this game based training could be used in the field by heavy drinkers having a probable alcohol use disorder. A study was conducted on randomised groups of heavy drinkers having a probable alcohol use disorder motivated to cut down drinking, between inhibition training and control training for 2 weeks, and simultaneously measuring alcohol consumption using ecological momentary assessment. This study was conducted at the University of Liverpool. We investigated if the training produces a generalisable change in inhibitory control and other executive functions and if it prompts a reduction in alcohol consumption in heavy drinkers having a probable alcohol use disorder recruited from the local community.

Chapter Five attempted to examine whether a short-term inhibition training and mindfulness intervention produce any changes in the event-related potentials and behavioural markers of inhibition in heavy drinkers having a probable alcohol use disorder at University of Liverpool.

In Chapter 4 and 5, the term 'heavy drinkers' is used for the participants because these studies use community samples who are consuming more alcohol than the UK guidelines. This population would have scored more than 8 in AUDIT (increased risk). As per the DSM 5 (clinical criteria), they may classify as mild to moderate alcohol use disorder but might not come in severe criteria. As per ICD 10 (clinical criteria), they might classify as alcohol abuse with 1 or 2 positive criteria. Also, it was ensured that the participants don't overlap between two studies reported in chapter 4 and 5.

The study in chapter 4 required participants to be motivated to cut down on drinking. The study in chapter 5 was a one session training. The age range of 18 – 21 years in study in chapter 4 was excluded because it would have attracted more of the young students, which might have affected the outcomes by the predicted increase in drop out and false presentations. So the age above 21 years was decided to avoid this expected problem.

In Chapter Six, I examined whether this developed inhibition training would bring changes in subjects with alcohol dependence when trained for multiple sessions. For this, a study was conducted at NIMHANS, Bangalore on recently detoxified alcohol-dependent subjects. It was observed in the 2 weeks of training produce any comparable changes to the control training intervention in the behavioural and event-related potential outcomes of inhibition and error processing.

In the final chapter (Chapter Seven), I discussed the general findings from all the studies in support of my hypotheses, consistency across studies, theoretical implications, clinical implications, strengths and limitations and directions for future research.

Table 1 Details of all the studies in thesis

Study no.	Chapter no.	Place	Study population	Duration	Sample size
1	4	University of Liverpool	Heavy drinkers (probable AUD)	March 2015 to March 2016	Training group = 24 Control group = 24
2	5	University of Liverpool	Heavy drinkers (probable AUD)	April 2015 to April 2016	Training group = 20 Control group = 20 Mindfulness group = 20
3	6	NIMHANS	Patients with Alcohol dependent syndrome and healthy controls for comparison	October 2016 to May 2017	Training group = 15 Active Control group = 15 Healthy control = 30

III. Presenting 'Pento Plaza' – A smart-phone based Serious Game to train Response Inhibition in Alcohol Use Disorder: Components and Design

A. Introduction

There are two paradigms that are frequently used for training response inhibition: the go/no-go (GNG) and the stop-signal (SST) paradigm (Frederick Verbruggen & Logan, 2008). In GNG, participants need to respond to designated 'Go' stimuli but refrain from responding to 'No-Go' stimuli. In SST, the stimulus is delivered and instructions are to give a specified response to it. Infrequently, the stimulus is followed by a stop cue (visual or auditory) and the instruction is to prevent the pre-potent response for stimulus. It is seen that difficulty to prevent the response with the stop cue depends on the time delay between Go stimulus presentation and the stop cue. The longer the time delay, the more difficult the task gets (Berkman, Kahn, & Merchant, 2014; F Verbruggen & Logan, 2015; Frederick Verbruggen & Logan, 2009a). Lindqvist & Thorell, (2008) showed that task difficulty can be successfully manipulated in inhibitory control tasks by changing parameters in GNG (interstimulus interval, prepotency) and SST (stop-signal-delay, prepotency). Another way to increase the difficulty level in SST is to deliver the stop signal cue associated trials infrequently. As such, the GNG and SST paradigm are believed to target executive processes at the motor level (Gordon D. Logan & Cowan, 1984). These components we tried to incorporate into a game for training inhibitory control.

Another aspect of inhibition is to differentiate between automatic response inhibition and controlled response inhibition (Frederick Verbruggen & Logan, 2008). First, automatic response inhibition is a bottom-up process, developed by pairing certain stimuli consistently with a no-go or stopping response. Training automatic response inhibition is termed as associative inhibition training, in which repeated the exercise of such inhibitory cue combined stimulus can train automatic inhibition (Jones & Field, 2013; Frederick Verbruggen, Adams, & Chambers, 2012). For example, Jones & Field, (2013) used an SST training that consistently paired alcohol-related cues with stop-signal responses to strengthen the ability to inhibit responses to alcohol-related stimuli in heavy drinkers. Second, controlled response inhibition is a top-down process that can be used to actively inhibit a response. An indirect strategy to strengthen response

inhibition in a general context could be to train controlled response inhibition, often termed as non-associative inhibition training. For example, Liu & colleagues, (2015) successfully trained controlled response inhibition in young preschool children through a tablet computer game named ‘fruit ninja' based on the GNG paradigm.

Recently, several effective, evidence-based inhibitory control training paradigms have been developed that can improve response inhibition [e.g., Houben, Havermans, Nederkoorn, & Jansen, 2012; Jones & Field, 2013], and thus help controlling drinking behavior. A problem associated with these training paradigms is that they are often seen as long and boring (Prins, Dovis, Ponsioen, ten Brink, & van der Oord, 2011). Most of the interventions aiming decrease of alcohol use focus on changing the outcome behavior and not so much on motivating participants to complete the training. Also, people at risk for drinking behaviour that could benefit the most from these interventions, are often having difficulty in concentration and attention (Wilcox, Dekonenko, Mayer, Bogenschutz, & Turner, 2014). As these difficulties increase the likelihood of inefficient training in problem drinkers, it is necessary to develop a training corresponding with the needs along with motivating participants. This is where the use of serious gaming techniques may be of high relevance, as they have shown a capacity to increase participants' motivation to complete training [e.g., (Dovis, Van der Oord, Wiers, & Prins, 2013)]. Games can provide a safe training environment, personalized to an individual level of development, with a competitive and arousing theme (Granic, Lobel, & Engels, 2014). Moreover, using smart-phone for serious games can increase the adherence rate to the intervention (Höchsmann et al., 2017). In line with recent developments in the application of serious games to induce behavioral change (Boendermaker, Prins, & Wiers, 2015; Prins et al., 2011), we adapted the inhibition training paradigms by integrating it in a serious game, called ‘Pento Plaza’, developed for a smart-phone. In this game, response inhibition mechanism is targeted using evidence-based training principles (Field, Mcgrath, et al., in prep; Field, Tiplady, & Jones, in prep; Jones & Field, 2013). We also made a control version of the game not having the inhibitory component, to ensure a comparative effect to the training version of the game.

B. Methods

1. Game Interface description

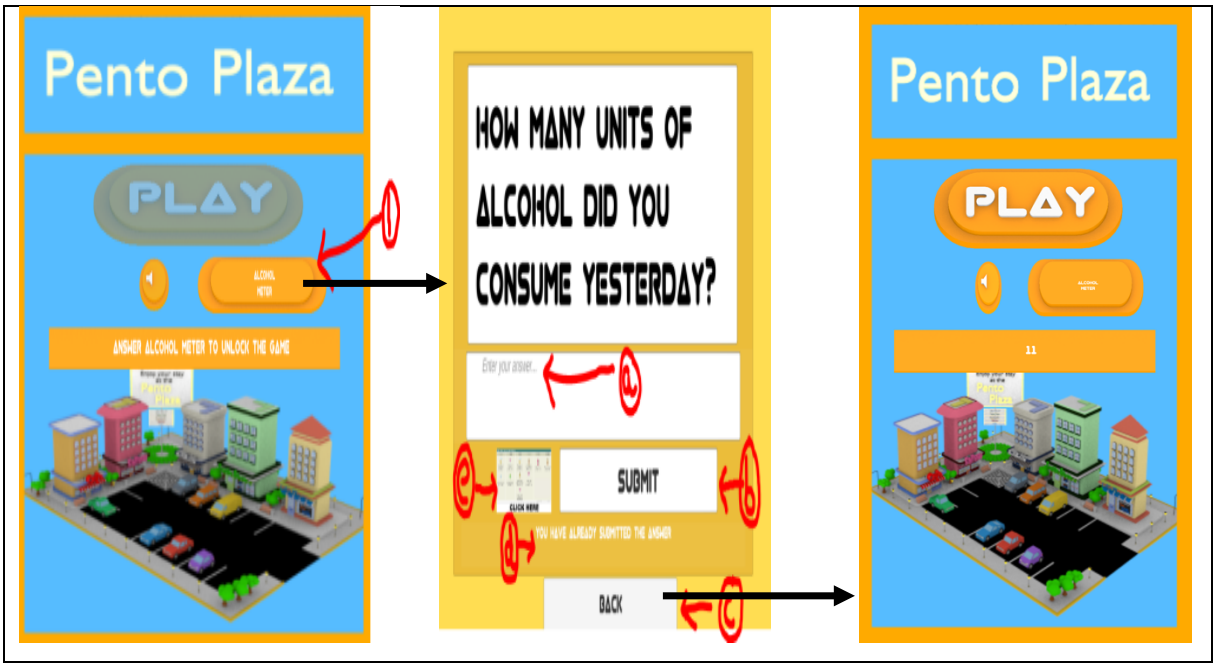
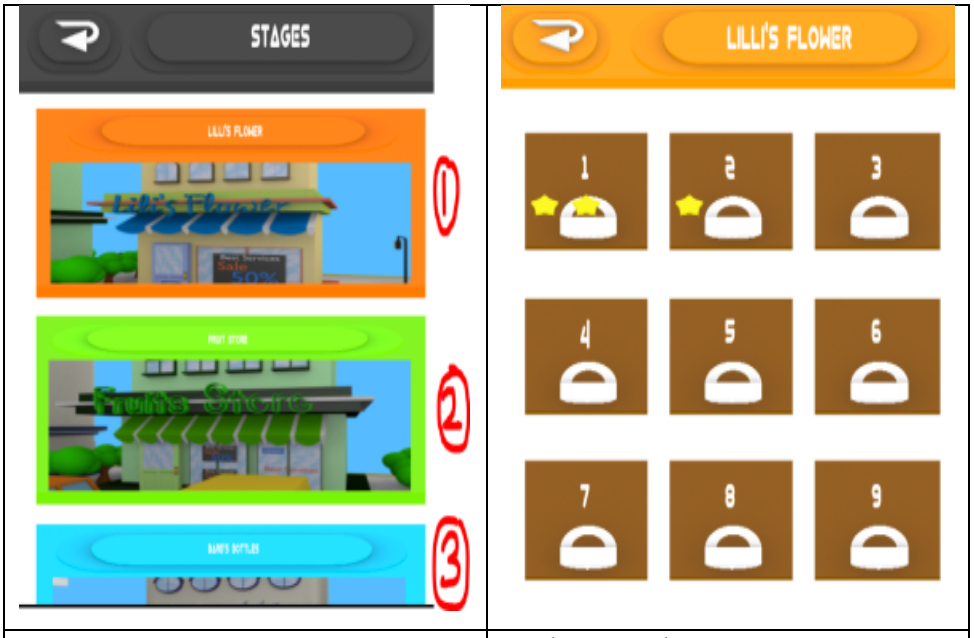


Figure 1 Game interface. (1) The screen at the start. (a) Space to enter the number (e) Guide to calculate the number of units (enlarge on selection)

Each time the app is opened, participants see the screen (see Figure 1) in which they could press one of two buttons labeled 'Play' and 'Alcohol Meter'. At the start of the day, the 'Play' key is greyed out (locked) until participants click on the 'Alcohol Meter' key; pressing this prompted the display of the daily alcohol diary (Figure 1) in which participants are instructed to record how many units of alcohol they had consumed yesterday. They are able to click the icon (indicated in Figure 1), which expanded to provide information about the number of units of alcohol in a number of different alcoholic drinks. After participants have entered this information, they return to the home screen. Now they will find the 'Play' key coloured and will able to press the 'Play' key to begin playing the game. The game is time locked to 10 minutes from the time logged in and is automatically timed out following it. This function is introduced in the game to avoid overplay.

The game graphics were designed in-house, using "blender" (Blender Foundation, 2014), a 3D modeling software. Further game programming was done in Unity 4.5. A log file is generated during each session consisting of performance data along with the date and time. The training is made more engaging by including a theme, storyline and reward aspects. The game theme has a character standing at the pavement of a three

storied building. The behavior of the character is controlled by the participant by tapping the smart-phone screen (touch sensitive), to move him left or right on the pavement. The storyline concept is to gather objects, which are pushed from the top of the building before it hits the ground, by moving the character. The game is made rewarding by allocating points for precise responses. The game is arranged in 5 stages (Figure 2a) and 9 difficulty levels (Figure 2b) in each stage. Stages 1 to 5 is arranged with an expectation of increasing difficulty while performing. The building in the background consists of 12 windows, with all the 3 stories having 4 columns of windows. On each trial, an object appears in one of the 4 windows' column.



a. Stages b. Levels

Figure 2 Stages and levels

2. Training game version

Three types of general category of stimuli are used. The frequent stimulus is termed the Go stimulus, which participants had to collect. The infrequent types of stimuli are No-Go and Go-Stop which participants should not collect. For No-Go stimulus, participants need to avoid collecting that stimulus. For Go-Stop stimulus, participants need to collect it, unless it changes into a Stop cue, in which case move the character away to avoid collection.

a) Description of Go-stimulus

Each stage had a theme and an important frequently appearing object to collect. The details of the Go-stimulus object for each stage are in Table 3. Collection of Go

stimulus objects is termed as correct response, whereas missed Go stimulus objects are termed as omission errors.

b) Description of No-Go stimulus

Each stage has No-Go stimulus object infrequently appearing between Go-stimuli and are to be avoided. A bomb is a common No-Go stimulus for all the stages. Alcohol bottles are introduced as a No-Go stimulus in stage 4 and 5. Collection of No-Go stimulus objects is termed as commission error.

c) Description of Go-stop stimulus

These start playing from stage 2 in the game and each stage later has a different Go-stop stimulus. These are infrequent stimulus and participants are asked to avoid collecting them. To make Go-stop stimuli, Go-stimuli is modified in such a way that they have a stop cue added to them but, maintain the basic visual characteristics of the Go-stimulus. The stop cue for the Go-stimulus appears after certain interval generating a conflict between collecting and avoiding the object. For example, in stage 2 the Go-stimulus fruit change their colour to black (stop-cue) after some time giving the signal not to collect it. Collection of Go-Stop stimulus object is termed as commission error.

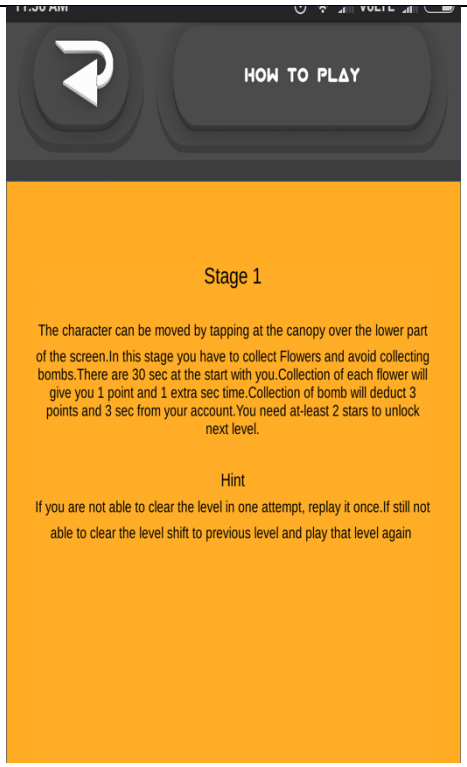
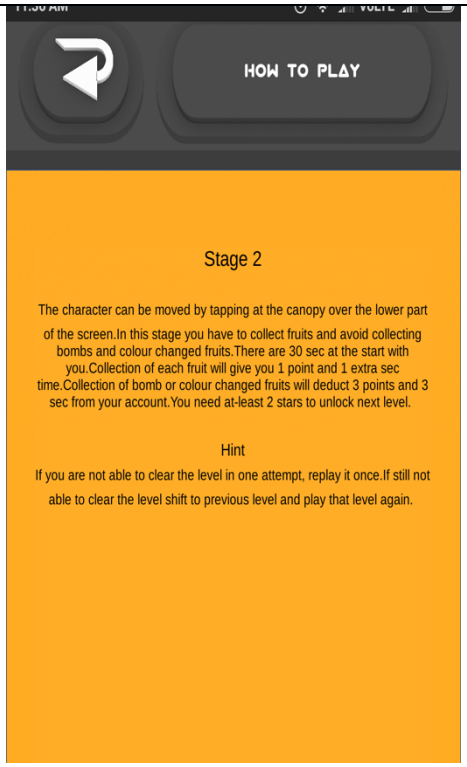
d) Scoring system

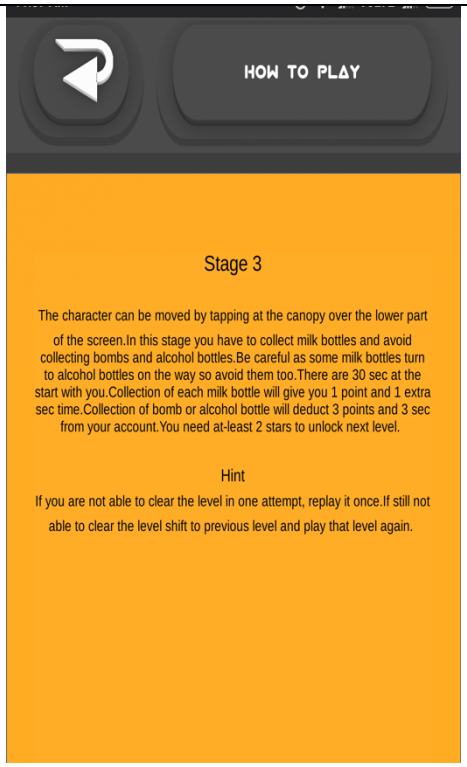
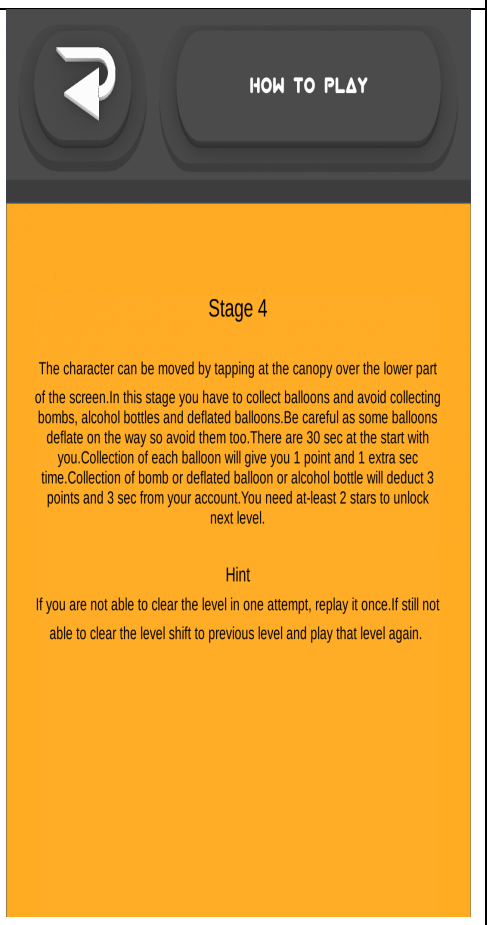
For incorporating the reward element, points are awarded. The errors are penalized by negative points and timeout. 30 seconds are allotted in the clock (represented on right upper corner of the screen) on starting each level. With each correct response, 1 point and 1 second are added. If participants make an omission error (failed to collect a Go stimulus), they lose one point and one second. If they make a commission error (collected a Go-Stop or a No-Go stimulus), they lose three points and three seconds. If participants reach 50 points, they receive a star (which was displayed at the top of the screen). If they reach 100 points, they are awarded a second star and could then progress to the next level if they wish, although they could keep playing at that level.

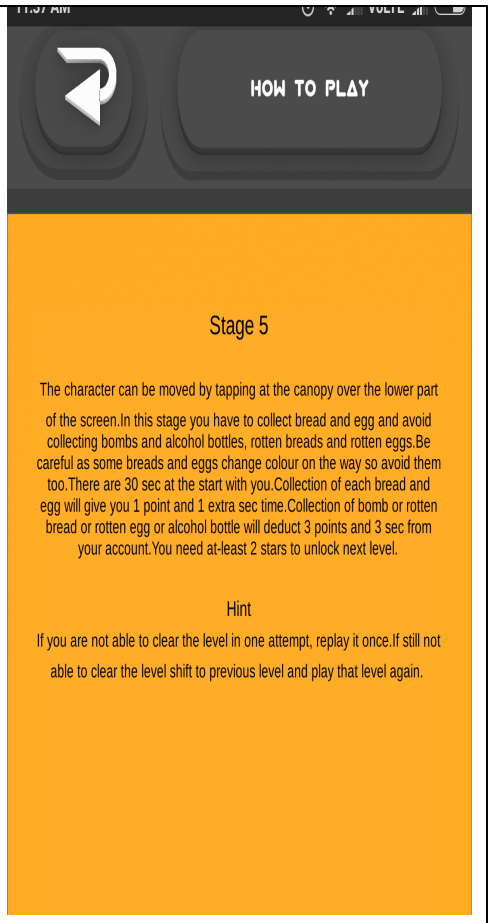
e) The flow of the game

There are 5 stages and 9 levels in each. Each stage depicts a theme shop, in front of which the falling objects are to be collected. Flower shop, fruits shop, bottles shop, balloon shop and a café are the theme shops from stage 1 to 5 respectively. Participants have to progress from level 1 to level 9 of stage 1 before they can proceed to level 1 of stage 2. At the beginning of each stage, instructions are provided on how to play and how to improve the performance (Table 2).

Table 2 Instructions for playing each stage

Stage No	Instructions
Stage 1	
Stage 2	

Stage 3	
Stage 4	

Stage 5	

f) Inhibitory control training variations

The task is manipulated by varying the following three parameters:

(1) By making the no-go/stop trials infrequent (frequency)-

The management of behavior of the objects as a Go stimulus, No-Go stimulus or Go-Stop stimulus is momentary. The total number of Go and No-Go stimulus or Go-Stop stimulus at any level was kept infinite, which means that participants can play any specified level until they have time on the level clock. A momentary system is used to assess the prepotency of the stimuli. In this, the proportion of Go stimuli is assessed after each stimulus delivery. If the proportion is < 50%, the next stimulus delivered will be a Go stimulus. If the proportion is between > 50% (so the average is 75%), either a Go or No-Go or Go-Stop stimulus will be delivered randomly. This prepotency algorithm is kept constant across all the levels of the game, making the delivery of Go stimuli around 75% and inhibitory stimuli around 25% at any time point.

(2) By changing the time lag for the stop cue (stop-signal delay)-

The positions of the window are used for changing the behavior of stimulus, as a landmark for transformation. Until level 4 in a stage, the position of a transformation of the object (stop cue) was set at the 1st row from the top, denoting the easy trials. From level 5 onwards, the position was set at 2nd row (increasing difficulty). The position was not dropped further, as such trials are impossible to be attempted correctly.

(3) By the amount of force, the object is pushed (speed)-

The specific force for each level is entered in the gaming system as a parameter, denoted in form of a number. Each number entered (mentioned in Table 4) denoted a specific speed of the object. The progressive levels are assigned a larger number to increase difficulty. The same pattern is followed in all the stages.

Table 3 Description of Stages

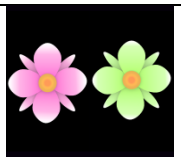
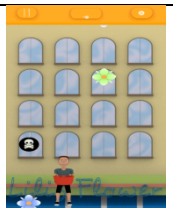
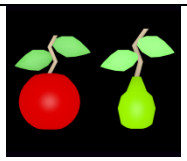
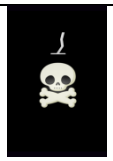
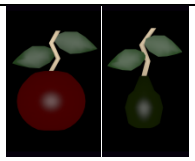
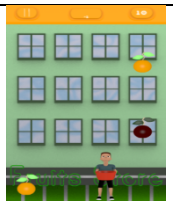
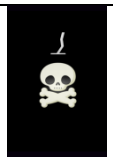
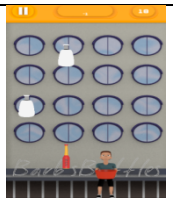
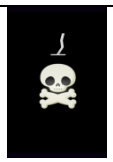
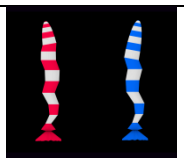
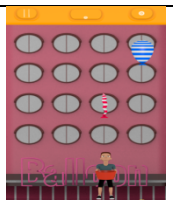
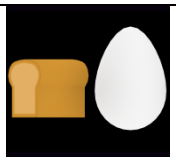
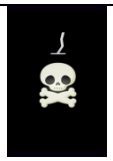
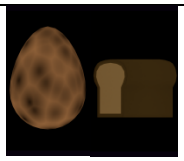
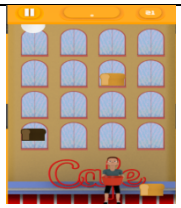
Stage	Go object	No-Go object	Go-Stop	Appearance in the Game
1	 Flowers	 Bomb	None	
2	 Fruits	 Bomb	 Black shaded	
3	 Milk	 Bomb	 Alcohol	
4	 Balloon	  Bomb, Alcohol	 Deflated Balloon	
5	 Bread, Egg	  Bomb, alcohol	 Blackened Bread, egg	

Table 4 Denotes the number entered in gaming system in the column for force with which the fruit should be thrown from the building

Level	1	2	3	4	5	6	7	8	9
Number	4	5	6	7	7.5	8	8.2	8.3	8.5

3. Control Game Version

The control game contains the same aspects as the training game, but participants are never required to inhibit (there are no No-Go or Go-Stop stimuli). Its basic principle is based on continuous uninhibited performance with no distractions. Care is taken to maintain the fun and rewarding element by maintaining the scoring system in the game. The speed component of the difficulty levels is the same, along with the points and time locking of levels. Points awarded and deducted for successfully catching target objects or failing to catch them are 1 and 3 respectively. However, in an attempt to match participants' progression through different stages, participants are required to reach 350 points before they could progress from level 6 to level 7, and so on.

C. Limitations

There are certain limitations to this game that should be mentioned. First, use of a game to prevent excessive alcohol use could cause problems associated with addictive gaming in some people. However, we tried to prevent this by using a time-out and avoiding excessive use, but this method to prevent addictive gaming is not yet tested and standardised. Second, the game we built lacks the capacity to measure stop-signal reaction time, due to the inherent nature of the game. The stimulus used in this game if not responded in a certain time will show as an error, but reaction times can't be calculated. Although errors can be some of the comparative outcome measures, this game is not favourable for assessment of inhibitory control. Also, the game was qualitatively validated in terms of the utility and usability, though it could not be validated in terms of as an assessment tool due to its inability to measure stop signal reaction time. The parameters of inhibition for the outcome can be calculated by another standard task on computer or mobile phone, to mark the improvement in core inhibition itself. Third, the alcohol meter recordings were based on the self-reporting. Although the self-reporting is an easy way to calculate the alcohol consumption, it is expected to be underreported (Boniface, Kneale, & Shelton, 2014). But, the self-reports can be

reliable and valid if retrospective recall errors are minimized by asking people to report their consumption every day rather than asking them to remember over a whole week or two (Field et al., in prep). This strategy used in our app may help to minimize recall bias. The use of some advanced ways to estimate the alcohol levels such as a transdermal alcohol level estimation would be helpful in the future app designs. Last we could not objectively qualify that gamification of the inhibitory tasks was at an appropriate level i.e., to put a check that the gamification is neither too little (affecting motivation to perform), or too much (distracting from the real goal). This was perhaps due to unavailability of any tool or protocol for the same.

D. Conclusions

This chapter aimed to introduce a new inhibitory control training game called 'Pento Plaza'. This game aims to offer, the population with alcohol use disorder, a motivating environment to increase their levels of inhibitory control, by training the top-down inhibitory control neuronal circuit. Effectivity of this game in terms of improvement in inhibitory control is evaluated in the studies mentioned in further chapters.

Although the popularity of serious game certainly had increased in last decade, it is very important to design these games on a firm scientific basis. One way to achieve this is by describing the development process and theoretical basis behind these games. This chapter may give awareness about some of the challenges faced while developing the serious game-based cognitive training and prospects these games have to offer. Training on a mobile phone can not only help us know the possible advantages of training for a longer duration but also determine if exhaustion after prolonged play may start to influence the performance. These games may be useful in bridging the gap between an evidence-based training paradigm and an attractive, motivating training environment.

IV. Smartphone Game based Inhibitory Control Training in heavy drinkers with a probable alcohol use disorder

A. Abstract

The aim of this study was to test effects of the inhibitory control training with a smart phone game on alcohol related outcomes in heavy drinkers having a probable alcohol use disorder motivated to cut down drinking with a hypothesis that training would: (1) improve participants' performance in the training game and affect inhibitory control assessed by a stop-signal task (SST) (near transfer effects); (2) affect the attentional network assessed by a classical Stroop task (far transfer effects); and (3) will help to cut down drinking in motivated heavy drinking participants having a probable alcohol use disorder (behavioural effects). The effects were compared with an active control group playing a game similar to the training version, but didn't have any of the response inhibition components. 48 heavy drinkers having a probable alcohol use disorder motivated to cut down drinking, between 21 and 60 years of age were recruited and randomised in two groups playing respective games for 2 weeks. The outcome measures were assessed prior to the intervention and at the follow-up. Alcohol consumption was assessed at the baseline with a 2-week timeline follow back diary and during intervention with a daily notification of the units of alcohol consumed previous day as a part of the game. 46 participants completed the 2-week intervention. Participants improved on the game task. No significant change in the inhibition related parameters or interference control was noted. No change in alcohol consumption was seen. No near and far transfer effects were noted with the inhibition training. Future inhibition training-related research should explore effects of other objective outcome measures such as objective assessments of alcohol consumptions and electrophysiological measures of inhibition. Longer duration of training may influence the behavioural measures of inhibition.

B. Introduction

Alcohol-related morbidity and mortality have an increasing prevalence, with a major concern among youngsters due to their binge pattern of consumption (Fuller & Hawkins, 2013). Designing interventions for controlling the heavy drinking episodes in a short period of contact are gaining a major research interest (Bertholet, Daeppen,

Wietlisbach, Fleming, & Burnand, 2005; Kaner et al., 2007; Moyer, Finney, Swearingen, & Vergun, 2002). For example, brief interventions have shown a significant impact in the reduction of alcohol consumption, particularly when delivered by the nurses (Platt et al., 2016). However, most of these interventions have an extrinsic approach, targeting the motivational improvement by loading information related to the harm and advantages of changing a behaviour (Warren K Bickel, Christensen, & Marsch, 2011).

Inhibitory control, an important component of the Executive Functions (EFs), is the ability to inhibit responses that are inappropriate (Gordon D. Logan & Cowan, 1984). It involves an ability to inhibit the pre-potent responses and manage the interference by the non-target distracting stimuli impacting on an ongoing information processing (Diamond, 2013). It can be assessed by a laboratory based go/no-go task (GNG) and stop-signal task (SST) which denotes the suppression of a pre-potent or automatic response (inhibition of action) (Brydges et al., 2012; Brydges, Anderson, Reid, & Fox, 2013). The go/no-go task assess the action restraint over a no-go cue, while in the stop-signal tasks' an emphasis is over an action cancellation on the stop cue (Schachar et al., 2007).

An inhibitory control training had demonstrated some degree of plastic changes. Manuel, Bernasconi, & Spierer, (2013) demonstrated that the SST task performance improved after a single session of an inhibition training. Similar plastic changes in the inhibitory control were noted by Berkman et al., (2014), with 10 sessions of an inhibition training across 3 weeks in healthy adults. They showed an improvement in the inhibitory control performance using a modified version of the SST. With the training, they observed a decreased activity in the Inferior Frontal Gyrus (IFG) while a stopping process. Although, many studies have reported a direct near transferred improvement in the inhibitory performance with training for a short duration (Dowsett & Livesey, 2000; Lindqvist & Thorell, 2008; Schapkin, Falkenstein, Marks, & Griefahn, 2007; Frederick Verbruggen & Logan, 2009a), some studies failed to replicate the similar effect when trained for long term. Studies by Field et al., (in prep) and Cohen & Poldrack, (2008) didn't notice the improvement in inhibitory control following four weeks and one week of multiple training sessions respectively.

Cognitive training has also demonstrated the far transfer effects. These effects refer to the generalizability of skills gained by training to other tasks or the same task in

different contexts (Willis, Blieszner, & Baltes, 1981). For example, Klingberg et al., (2005) showed that training the working memory could improve inhibitory control (assessed by Stroop task) and reasoning (assessed by Raven's Colored Progressive Matrices). The Stroop task is said to assess both interference control and inhibition (Friedman & Miyake, 2004) along with the attention as a latent variable. In this task, a name of a colour (e.g., "blue", "green", or "red") is printed in a colour that is not denoted by the name (e.g., the word "red" printed in blue ink instead of red ink). While naming the colour of the word, the interference effect is seen if the colour of the ink does not match the name of the colour. A study by Choi., et al (2012) had shown a possibility of a training-induced attentional improvement. As inhibitory control and attention are the components of executive function sharing a common domain (Friedman & Miyake, 2004; Miyake et al., 2000; Miyake & Friedman, 2012), training inhibition may bring an improvement in attention.

Training the inhibition has shown potentials of inducing a behavioural change. Inhibiting an alcohol-related appetitive cues have exhibited a decrease in ad-lib alcohol consumption (Jones et al 2013). Recently Jones et al., (2016) reported the robust effect on appetitive behaviours (food and alcohol consumption/choice) in the laboratory with a single session training. These type of training are the associative training, where participants are trained to inhibit cues embedded in a GNG and SST (Houben, 2011; Houben et al., 2012; Houben & Jansen, 2011; Jones et al., 2016; Veling, Aarts, & Papies, 2011). Although studies focusing on associative training of an inhibitory control have shown results, little is known about the effects of a non-associative motor inhibition training on the alcohol consumption. In a non-associative training, the top-down inhibitory neural circuits are attempted to make stronger.

Training the inhibition involves multiple components. One would be, to increase the level of difficulty in performance. For example, studies had suggested that if tasks were made more tedious by increasing the difficulty level to a moderate or high degree (Lindqvist & Thorell, 2008), this may produce a better neurocognitive change (Benikos, Johnstone, & Roodenrys, 2013; Berkman et al., 2014). The other would be, by making the training task more friendly, interesting and challenging. This can be done by using serious games with a touch-screen technology and motion-contingent interfaces (Ninaus et al., 2015). However, this may also have a negative effect if the motivational value of the gaming element is less than expected (Boendermaker, Sanchez Maceiras,

Boffo, & Wiers, 2016). In the current study, we designed an in-house game consisting of a graphical interface and a character plot to increase the aesthetic value of the training. We used the individualised approach, with a simple level of difficulty at the start and then a gradual increase in the difficulty as per the performance. The achievements in the difficulty level were rewarded and the performance was time locked. The detailed description of the game is given in the methods chapter.

The aim of this study was to test effects of this inhibitory control training game on the alcohol-related outcomes in heavy drinkers having a probable alcohol use disorder. The heavy drinkers could be considered as 'probable Alcohol Use Disorder', as they drink above government guidelines (therefore, probably causing themselves alcohol-related harm), and have high AUDIT scores of 'hazardous drinking'. We hypothesized that, in heavy drinkers having a probable alcohol use disorder motivated to cut down drinking, response inhibition training with the game would: (1) improve participants' performance in the training game and affect inhibitory control assessed by SST (near transfer effects); (2) affect the attentional network assessed by a classical Stroop task (far transfer effects); and (3) will help to cut down drinking in the motivated heavy drinking participants having a probable alcohol use disorder (behavioural effects). The effects were compared with an active control group. This group played a game similar to the training version, having a graded increase in the difficulty, but this version didn't have any of the response inhibition components. All the participants received a brief online intervention (Down Your Drink: DYD (Linke, Brown, & Wallace, 2004)) in order to ensure the motivation to reduce their alcohol consumption during the study period, before beginning the game intervention.

C. Methods

1. Sample Size Calculation

The sample size was calculated with the help of G*power software. The repeated measure Analysis of Variance was the predicted analysis strategy. The probability of type 1 error (α) was assumed to be 5 %. The expected power of the study was 80%. With the expected large effect size (0.7) based on Houben et al., 2012, the desired number for the study was 19. With the expected drop out of 20%, the ultimate sample size for the study in order to have a sufficiently acceptable statistical power was 24 in each group.

2. Participants

Forty-eight adult heavy drinkers having a probable alcohol use disorder from the university campus and surrounding area were recruited. In order to participate, individuals had to be a fluent English speaker aged between 21 and 60 years, and drink more than the UK Government Guidelines for sensible drinking in 2015 (14 units per week if female or 21 units per week if male) and motivated to cut down drinking for two weeks during the study. Individuals with a current or previous diagnosis of alcohol abuse or alcohol dependence or Attention Deficit Disorder (ADD) or prescribed methylphenidate (Ritalin) for ADD or similar conditions were excluded. Recruitment was done by advertising on the University intranet, in local newspapers, advertising websites and through the use of flyers. The study was approved by the University of Liverpool Research Ethics Committee.

3. Measures

a) Questionnaires

Participants completed a computer based questionnaire battery consisting of a two-week Timeline Follow-Back Diary (Linda C Sobell & Sobell, 1992) to assess their alcohol consumption over 2 weeks before the experiment, this was followed by the Alcohol Use Disorders Identification Test (AUDIT; (John B Saunders, Aasland, Babor, De La Fuente, & Grant, 1993), the Temptation and Restraint Inventory (Collins & Lapp, 1992) to examine preoccupation controlling alcohol consumption, the Barratt Impulsivity Scale version 11 (Patton, Stanford, & Barratt, 1995) to examine impulsivity and Readiness to change questionnaire (RCQ; (Gavin, Sobell, & Sobell, 1998)) for assessing the stage of motivation.

The "past two weeks" version of the Approach and Avoidance of Alcohol Questionnaire (AAAQ; McEvoy, Stritzke, French, Lang, & Ketterman, 2004) was administered to assess craving on three distinct sub-scales: inclined/indulgent, obsessed/compelled, and resolved/regulated. Finally, the Brief Mood Introspection Scale (BMIS; Mayer & Gaschke, 1988) was administered to assess mood and arousal on four continua: pleasant-unpleasant, arousal-calm, positive-tired, and negative-relaxed. Questions regarding participants' expectation (How much do you think you will benefit from this intervention, in terms of helping you to reduce your alcohol consumption?), motivation (How motivated are you to reduce your alcohol consumption?) and use of the mobile games ('Do you play games over mobile phone?

' (yes/no)) were also added. The expectation and motivation were assessed on a 5 point Likert scale (Not at all- Very much). At the final visit after a two-week interval, BMIS, AAAQ and subjective fulfilment of training were assessed on a 5 point Likert scale (How much do you think this intervention helped you to reduce your drinking?)

b) Executive Functioning tasks

The tasks were delivered on a computer screen at an eye-level kept at a meter distance away from the participants. They were designed and implemented using the Inquisit 3.0 (Millisecond software, 2008).

(1) *Near – Transfer Stop signal task (SST) (G. D. Logan, Schachar, & Tannock, 1997) :*

The task was programmed using the Inquisit 3.0 (Millisecond software, 2008). A standard version of the SST was used that incorporates arbitrary visual stimuli (the letters X and O) along with the tracking procedure to set the stop signal delay (SSD). Each trial had a letter X or O displayed in the centre of the screen. Participants needed to quickly categorise the letter by pressing 'V' or 'N' key respectively. Participants were asked to rest their fingers on the specified keys, to avoid confusion with other keys. These were the 'go' trials. On 25% of the trials an auditory tone occurred at a variable delay after the letter appeared. This auditory tone was a stop signal which signified participants to inhibit their categorisation response and wait for the next trial. The initial latency was set as 250 ms which increased by 50 ms after every successful inhibition, and decreased by 50 ms after every failure to inhibit.

Each trial started with a pre-trial pause for 250 ms followed by a stimulus on screen for 1250 ms. The inter-trial interval was fixed at 250 ms. The task was divided into 4 blocks. The first block was a practice block consisting of 16 trials (4 stop trials). This was followed by main task consisting of 3 blocks each with 64 trials. A break was provided between each block in which average reaction time and percentage of correct inhibitions on stop signal trials were displayed on the screen.

(2) Far- Transfer Classical Stroop Task (Jensen & Rohwer, 1966):

Participants were presented with the words 'red', 'green', 'blue' and 'black', each of which could be displayed in those colours. On each trial, participants were instructed to categorise the colour in which the word was printed, by pressing 'D', 'F', 'J' and 'K' keys for red, green, blue and black colours respectively, whilst ignoring the meaning of the word. Participants were asked to rest their fingers on the specified keys, to avoid

confusion with other keys. On the congruent trials, a word was printed in the same colour as its meaning (e.g. the word red printed in a red ink). On the incongruent trials, colour of the word and its meaning were incongruent (e.g. the word red printed in a green ink). On the control trials, a coloured block (3cm × 2cm) was presented. Each trial started with a stimulus appearing at centre of the screen, which remained on the screen until participants pressed one of the four response keys. The inter-trial interval was fixed at 200 ms. Participants were instructed to respond as fast as possible. In case of the incorrect response, an error message was displayed for 400 ms. This task had 1 block of 84 trials with an equal number of congruent, incongruent and control trials. The order of the trials was randomised.

4. Smartphone intervention games:

This consisted of 5 stages with each stage having 9 levels. The levels were designed with increasing difficulty. All the levels were locked apart from the level 1. Participants needed to play and get the required scores in order to progress to the next level in the hierarchy. The game had an inbuilt clock with 10 minute' timer on it. After 10 minutes, the game stops functioning and gets locked with an instruction of session ended. The game was set to have a maximum number of 4 sessions in a day. There were two versions of interventions as mentioned below:

a) Training intervention game

The training intervention game was designed on the principle of GNG and SST. The details of the stages and levels are provided in the methods chapter (add a reference here).

b) Control intervention game

The control intervention game contained the same graphics and difficulty hierarchy as the training game. The training intervention game was modified so that the GNG or SST components did not appear. Participants were made to continuously perform without stopping for no-go or stop signals. But, the aesthetic components of the game were maintained in order to engage the participants. The details of the control intervention game are available in method chapter.

5. low of the Study

Participants responded to advertisements by making the first contact with the researcher via email to express their interest in taking part in the study. Participants were then sent

a detailed participant information sheet; participants were then invited to contact the researcher again to arrange an initial visit to the laboratory.

a) Laboratory Procedures

Study procedures and measures are summarized in Table 5. Participants attended the laboratory and first provided the informed consent after discussion about the information sheet. An account was made on the downyourdrink.co.uk website. Participants were asked to take the quick version (10 minutes) of DYD (Linke et al., 2004) in order to increase motivation to reduce alcohol consumption. Participants then completed the questionnaire battery and the Stop-signal Task (SST) and Stroop tasks on a desktop computer in the lab. Participants were then randomly allocated to inhibition training or active control groups based on a predetermined group allocation sheet that was devised with a random number generator in an excel sheet (simple randomisation (Suresh, 2011)) . Group assignment was therefore single-blind, but not double-blind (because the researcher had to explain to each participant how to play the game). The researcher then explained to the participant how to use the alcohol meter and play the game, demonstrated gameplay, and then watched the participant play the game to ensure that they understood the instructions and how to progress through the levels and stages. As soon as participants were comfortable with how to use the app, they were loaned a smartphone (Samsung Galaxy Ace 3), given a printed sheet with instructions about how to access the app and how often to access it, and a follow-up lab visit (compliance check) was scheduled for one week later. Participants then left the laboratory and kept the DYD website information for future reference.

When participants returned to the lab for the compliance check visit after one week, data was downloaded from the phone; if they had not completed at least 75% of scheduled sessions, they were withdrawn from the study. One-week later, participants returned to the lab for the final visit where data was downloaded from the phone, and participants completed the questionnaires and SST and Stroop tasks on the desktop computer before being debriefed and receiving compensation for taking part. If participants completed fewer than 75% of assessments during the first week of the study, they were withdrawn from the study with a compensation of £20. If they completed fewer than 75% of sessions during the second week of the study, they were paid £50. If they completed more than 75% of the scheduled smartphone intervention sessions, they received £60 at the end of the study. If they completed the intervention

sessions 100%, an additional bonus of £20 was given. Payments were not contingent on the reduction of alcohol use.

b) Field Procedures

Participants were instructed to access the app twice per day when in a quiet location where they were unlikely to be disturbed and to play the game for 10 minutes. Participants were instructed to access the app once between 8:00 am and 1:30 pm, and once between 2:00 pm and 7:30 pm. Reminders were set on the phone for play timings. These reminders were set in the calendar of the mobile phone loaned for 8:00 am and 2:00 pm, so that they received notifications at the fixed time. Participants were requested to play the game when they received this notification. If they were not able to play at that time, they were advised to snooze the notification and take the intervention as soon as possible, but within the time duration of that particular session. On using the app first time in the day, participants were advised to note the previous day's total units of alcohol consumed in the app, before starting to play the game.

Table 5 Study procedures and measures.

Intervention/measure↓	**Instrument Type↓**					
		Base	Week 1	Visit 2	Week 2	Visit 3
Setting→		Lab	Field	Lab	Field	Lab
Inhibition/Control training	Mobile	✓	✓		✓	
Demographics	Computer	✓				
AUDIT	Computer	✓				
RCQ	Computer	✓				
BMIS	Computer	✓				
AAAQ	Computer	✓				✓
TRI	Computer	✓				✓
BIS-11	Computer	✓				
Alcohol use diary	Computer	✓				
Previous Games play information questions	Computer	✓				
Expectation check questions	Computer	✓				✓
Recording of previous day total alcohol consumption	Mobile	✓	✓		✓	
Data download	Mobile			✓		✓
SST	Computer	✓				✓
Stroop task	Computer	✓				✓
Debriefing	N/A	✓				
Compensation	N/A	✓				

AUDIT = Alcohol Use Disorder Identification Test, RCQ = Readiness to Chance Questionnaire, BMIS = Brief Mood Introspection Scale, AAAQ = Approach and Avoidance of Alcohol Questionnaire, TRI = Temptation and Restraint Inventory, BIS-11 = Barratt Impulsiveness Scale-11, SST = Stop-Signal Task.

D. Data reduction and analysis:

1. Questionnaires

All the statistical analysis was carried out with help of Statistical Package for the Social Sciences (SPSS – 16). The effect sizes were calculated for all the comparisons. For ANOVA, partial eta squares were calculated while for t-tests' cohen's-d were computed. For partial eta square, 0.01, 0.06 and 0.14 were considered as small, medium and large effect sizes respectively (A. Field, 2013). For cohen's-d, 0.2, 0.5 and 0.8 were considered as small, medium and large effect sizes respectively (A. Field, 2013). An independent t-test was performed on the baseline assessments to test for the between-group differences. On the craving scores, assessed with AAAQ at baseline and at 2nd follow-up, we performed a mixed design analysis of variance (ANOVA) with within-subject factors of subscale (3: inclined-indulgent, obsessed/compelled and resolved-regulated), time (2: pre-training, post-training) and a between-subjects factor of group (2: training, control). On mood scores, assessed with BMIS at baseline and at 2nd follow-up, we performed a mixed design ANOVA with 4 subscales (pleasant-unpleasant, arousal-calm, positive-tired and negative-relaxed) × 2-time points (baseline, following 2 weeks) × 2 groups (training, control).

2. Compliance and progress through the smartphone game

Independent t-test was performed to test for the between-group difference in compliance with the intervention. The maximum stage and level reached at the end of each day of gameplay, and the number of hours of training completed over the two-week training period was recorded. A 14 (days) * 2 group (training and control) MANOVA was performed to access performance in both types of intervention.

3. Computerised tasks

For Stop-Signal Task, Go reaction time (Go RT) and Stop Signal Reaction Time (SSRT) were calculated. Individual trials with errors or extreme outliers (trials with RTs ±2SD of the mean and RT greater than 2000ms) were removed from the analysis. For Go RT, mean of all the Reaction Times (RT) for go trials were considered. SSRT was calculated using the integration method (see Verbruggen & Logan, (2009)), by subtracting mean Stop Signal Delay (SSD) from the nth RT, where the nth RT is determined by multiplying the number of RTs in the go RT distribution by the overall proportion (respond|signal). For the Stroop task, mean RT and the proportion of errors were calculated for congruent, incongruent and control trials separately. Trials with RT

more than +2SD for the category of the trial were excluded. Mean colour word interference score (Stroop effect) was calculated by subtracting the average RT on congruent and control trials from the average RT on incongruent trials (Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006).

4. Outcomes related to alcohol consumption

Three variables were used for assessing alcohol consumption: Units of alcohol consumed, Number of heavy drinking days and Number of abstinent days. A weekly average for these variables was calculated and used in further analysis. For the variable of heavy drinking days, > 8 units in a day for male and >6 units for female were considered (NHS, 2016). A mixed design ANOVA (time (3: baseline, 1st week, 2nd week) × group (2: training, control)) was performed separately for each variable, followed by post hoc analysis for significant main effects and interactions.

E. Results

1. Demographic data (Table 6)

Groups were well-matched on demographic variables, alcohol use, impulsivity and performance on the Stop Signal and the Stroop tasks at the baseline assessment. There were also no between-group differences in expectation of improvement from the intervention ($t(46) = 0.894$; $p=.376$, $d = 0.26$) and motivation to cut down drinking ($t(46) = 1.00$; $p=.323$, $d = 0.29$). Participants in groups also did not differ on the experience of prior game playing on mobile phones (χ^2 (1, N = 48) = 0.375, p =.54). Table 7 shows the number of participants in each group at the different stage of motivation assessed by RCQ. There was no significant difference between groups (χ^2 (2, N = 47) = 3.09, p =.213).

Table 6 Baseline demography

Sr.no.	Condition	Training Group(n=24)	Control Group (n=24)	t(46)	p-value
1	Age in years	34.71 (±11.16)	31.50 (±10.93)	1.01	.32
2	Gender male(female)	7(17)	11(13)	1.42(χ^2)	.23
3	AUDIT	14.83(±4.68)	14.92 (±7.64)	0.05	.96
4	Units of alcohol consumed in previous two weeks	62.75 (±29.62)	66.15 (±55.10)	1.25	.22
5	BIS-11				
	Attentional subscale	21.04 (±2.88)	22.17 (±2.37)	1.47	.15
	Motor subscale	28.00 (±3.05)	27.52 (±3.15)	0.53	.60
	Non-planning subscale	26.29 (±2.49)	26.22 (±2.98)	0.09	0.93
6	TRI				
	CEP	30.25 (±12.85)	35.74 (±15.92)	1.30	.20
	CBC	21.67 (±9.14)	23.29 (±8.57)	0.67	.51
7	Expectation 1	3.88 (±0.85)	3.67 (±0.76)	0.89	.38
8	Expectation 2	4.00 (±0.72)	3.79 (±0.72)	1.00	.32
9	Play (yes/no)	15/9	17/7	0.38(χ^2)	.54
10	Expectation 3	2.83 (±1.07)	2.61 (±1.03)	0.70	.49

AUDIT = Alcohol Use Disorder Identification Test, TRI = Temptation and Restraint Inventory, BIS-11 = Barratt Impulsiveness Scale-11, TFBD = Timeline Follow Back Diary, CEP = Cognitive-Emotional Preoccupation subscale, CBC = Cognitive-Behavioural Control

Table 7 Stage of motivation assessed by readiness to change questionnaire

Group	Stage of change		
	Precontemplation	Contemplation	Action
Training	3	15	6
Control	0	16	7

2. Compliance and performance

From 48 participants who consented to take a part and were loaned a smartphone, 2 were excluded at the end of the first week (1 training group, 1 control group) as they completed fewer than 75% of the scheduled sessions. All the remaining participants completed 75% of the scheduled sessions during the first and second weeks of the training phase (mean 94.88%) of sessions. In the training group, participants finished 97.83% (4.69 hours (±0.32)) of sessions and the control group finished 91.93% (4.34 hours (±0.55)), which was statistically significant ($t(32.14) = 2.39$, $p = .02$, $d = 0.69$). Noting the performance in the game, a progressive improvement was noted. Participants gradually improved on the game as seen in Figure 3.

A 14 (days) * 2 group (training and control) mixed design ANOVA was performed to access performance in both types of intervention to compare the progress in the performance. There was a significant main effect of days ($F(1.81, 61.50) = 86.74$, $p < .001$, $\eta_p^2 = 0.72$) and a days * group interaction ($F(13,442) = 4.72$, $p < .001$, $\eta_p^2 = 0.122$). No significant main effect of group ($F(1, 34) = 2.75$, $p = .12$, $\eta_p^2 = 0.075$) was noted. The improvement in levels on subsequent days was noted in both the groups. For between group final level reached on 14th day, no significant difference was noted (training: $M = 3.95$, $SD = 1.60$; control: $M = 4.63$, $SD = 1.74$; $t(39) = 1.31$, $p = .20$, $d = 0.41$). For within group change for days, both the groups showed improvement over time.

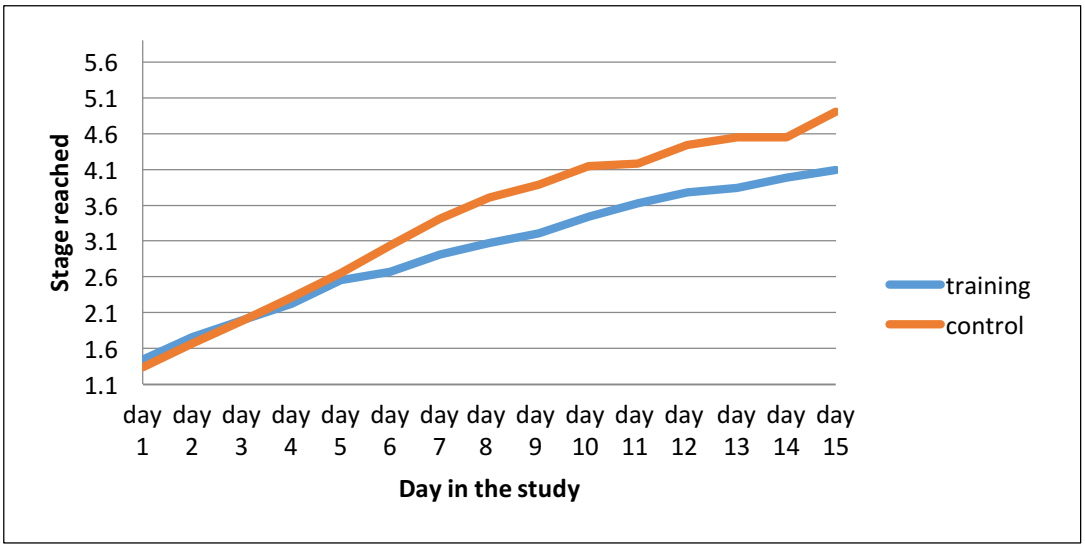


Figure 3 Shows the trajectory of game played in the respective groups

3. Effect of inhibition training on craving for alcohol, and mood (Table 8)

AAAQ scores were analysed using a mixed design analysis of variance (ANOVA) with within-subject factors of subscale (3: inclined-indulgent, obsessed/compelled and resolved-regulated), time (2: pre-training, post-training) and a between-subjects factor of group (2: training, control). We expected main effect of group and subscale * time * group interactions to be significant.

The main effect of time ($F (1, 44) = 6.10$, $p = .02$, $\eta_p^2 = 0.122$) was significant, whereas the main effect of group ($F (1, 44) = 0.06$, $p = .81$, $\eta_p^2 = 0.001$) was not significant. The subscale * time * group ($F (2, 88) = 1.43$, $p = .24$, $\eta_p^2 = 0.032$) interactions were also not significant.

The subscale * time interaction ($F (1.56, 68.69) = 20.94$, $p < .001$, $\eta_p^2 = 0.322$) was significant. The inclined-indulgent subscale ($M = 5.25$) had significantly higher score than obsessed/compelled ($M= 1.71$, $p < .001$) and resolved-regulated ($M = 2.46$, $p <.001$) subscales. The overall mean scores decreased over time (pre-training: $M = 3.31$, post-training: $M = 2.97$). Further for change in subscale scores over time, inclined-indulgent subscale (pre-training: $M = 5.92$, $SD = 1.46$; post-training: $M = 4.59$, $SD = 1.68$; $t (45) = 5.80$, $p<.001$) significantly decreased and resolved-regulated subscale (pre-training: $M = 2.16$, $SD = 1.66$; post-training: $M = 2.76$, $SD = 1.64$; $t (45) = 2.32$, $p=.03$) significantly increased. No significant change was observed in obsessed/compelled subscale (pre-training: $M = 1.86$, $SD = 1.65$; post-training: $M = 1.55$, $SD = 1.29$; $t (45) = 1.67$, $p=.10$).

For BMIS scores, MANOVA with 4 subscales (pleasant-unpleasant, arousal-calm, positive-tired and negative-relaxed) × 2 time points (baseline, following 2 weeks) × 2 groups (training, control) was performed. We expected main effect of group and subscale * time * group interactions to be significant.

The main effects of time (F (1, 44) = 0.73, p = .40, η_p^2 = 0.016) and group (F (1, 44) = 0.47, p = .47, η_p^2 = 0.012) were not significant. The subscale * time * group (F (3, 132) = 2.02, p = .11, η_p^2 = 0.044) interactions were not significant.

The subscale * time interaction (F (1.11, 48.85) = 5.98, p = .02, η_p^2 = 0.12) was significant. Further for change in subscale scores over time, pleasant-unpleasant subscale (pre-training: M = 3.91, SD = 7.45; post-training: M = 6.59, SD = 7.56; t (45) = 2.40, p=.02, d = 0.71) significantly decreased and negative-relaxed subscale (pre-training: M = 9.30, SD = 3.78; post-training: M = 8.04, SD = 3.82; t (45) = 2.26, p=.03, d = 0.66) significantly increased. The arousal-calm subscale (pre-training: M = 21.70, SD = 3.85; post-training: M = 20.87, SD = 3.66; t (45) = 1.36, p=.18, d = 0.39) and positive-tired subscale (pre-training: M = 9.59, SD = 2.97; post-training: M = 10.28, SD = 2.98; t (45) = 1.37, p=.18, d = 0.40) did not change significantly over time.

Table 8 Mood and alcohol craving scale

	Training Group		Control Group	
	Pre	Post	Pre	Post
AAAQ				
Inclined/indulgent	6.16 (±1.24)	4.50 (±1.88)	5.68 (±1.64)	4.68 (±1.50)
obsessed/compelled	2.25 (±1.76)	1.46 (±1.19)	1.47 (±1.46)	1.65 (±1.40)
Resolved/regulated	2.04 (±1.38)	2.64 (±1.78)	2.28 (±1.92)	2.87 (±1.52)
BMIS				
Pleasant/unpleasant	4.61 (±6.93)	8.35 (±7.18)	3.22 (±8.03)	4.83 (±7.05)
Arousal/calm	22.00 (±3.67)	20.00 (±3.99)	21.39 (±4.09)	21.74 (±3.14)
Positive/tired	9.96 (±2.29)	10.65 (±2.87)	9.22 (±3.54)	9.91 (±3.10)
Negative/relaxed	9.26 (±3.80)	7.00 (±4.10)	9.35 (±3.83)	9.09 (±3.29)

Note: Values are means(±SD); AAAQ: Alcohol Approach Avoidance Questionnaire; BMIS: Brief Mood Introspection Scale

4. Performance on the Stop Signal Task (SST) (Table 9)

For Go RT (Figure 4), mixed design ANOVA (time (2: baseline, following 2 weeks) × group (2: training, control)) was performed. We expected main effect of group and time * group interactions to be significant.

There was no significant main effect of time ($F(1, 44) = 1.35$; $p = 0.25$, $\eta_p^2 = 0.03$) or time x group interaction ($F(1, 44) = 0.36$; $p = .55$, $\eta_p^2 = 0.008$). There was no significant main effect of group ($F(1, 44) = 0.16$; $p = .69$, $\eta_p^2 = 0.004$).

For SSRT (Figure 5), mixed design ANOVA (time (2: baseline, following 2 weeks) × group (2: training, control)) was performed. We expected main effect of group and time * group interactions to be significant.

There was no significant main effect of time ($F(1, 44) = 1.76$; $p = .19$, $\eta_p^2 = 0.039$) or time * group interaction ($F(1, 44) = 1.77$; $p = .19$, $\eta_p^2 = 0.039$). No significant main effect of group was observed ($F(1, 44) = 1.72$; $p = .19$, $\eta_p^2 = 0.037$).

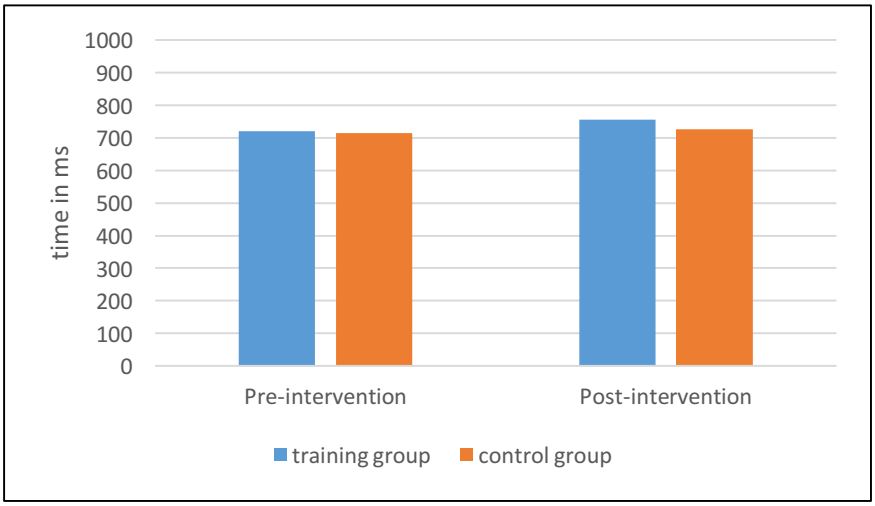


Figure 4 Go-RT

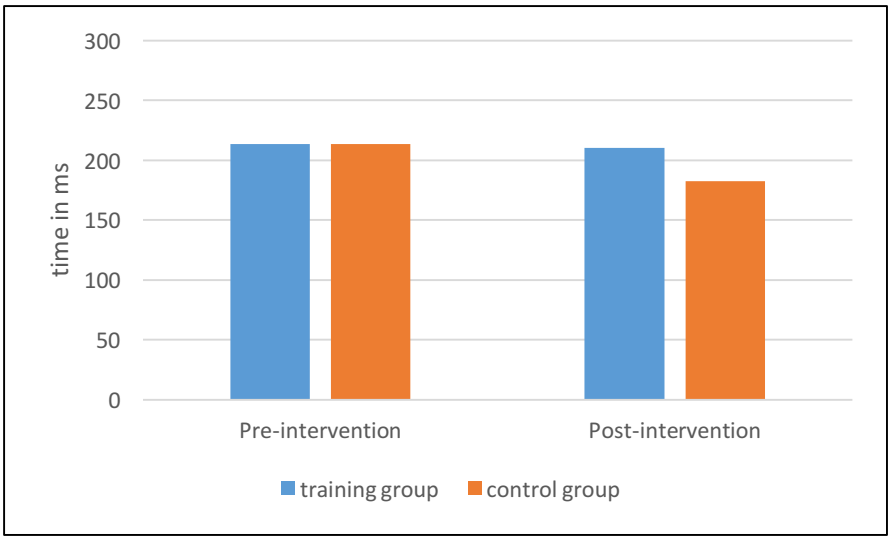


Figure 5 SSRT

Table 9 Stop-Signal Task

	Training Group		Control Group	
	Pre	Post	Pre	Post
Go RT	719.25 (±162.16)	756.47 (±196.10)	713.32 (±157.67)	725.31 (±173.17)
SSRT	213.35 (±67.85)	213.37 (±50.39)	210.54 (±54.27)	182.49 (±51.94)

Note: Values are means (±SD) GoRT = Reaction time on Go trials in milliseconds. SSRT = Stop Signal Reaction Time in milliseconds.

5. **Performance on the Stroop Task** (Table 10)

The reaction time data for Stroop task were analysed using a mixed design ANOVA (2 time (baseline, following 2 weeks) × 3 trial types (congruent, incongruent and control trials) × 2 groups (training, control)). We expected main effect of group, time * group and time * trial type * group interactions to be significant.

There was a significant main effect of time ($F (1, 44) = 33.96$; $p < .001$, $\eta_p^2 = 0.436$), with participants becoming faster in responding (baseline: $M = 997.55$ ms, $SE = 31.21$; Follow-up: $M = 906.30$ ms, $SE = 27.73$). There was a significant main effect of trial type ($F (1.45, 63.63) = 70.57$; $p < .001$, $\eta_p^2 = 0.666$), with the fastest response for the control trials ($M = 886.87$ ms, $SE = 26.25$), followed by congruent trials ($M = 919.08$ ms, $SE = 29.39$) and incongruent trials ($M = 1049.83$ ms, $SE = 33.00$).

There was no significant main effect of group ($F (1, 44) = 0.78$; $p = .38$, $\eta_p^2 = 0.017$). Also, time * group ($F (1, 44) = 0.01$; $p = .94$, $\eta_p^2 = 0.000$) and time * trial type * group ($F (2, 88) = 0.64$; $p = .53$, $\eta_p^2 = 0.014$) interactions were not statistically significant.

For interference score, a mixed design ANOVA (2 time (baseline, following 2 weeks) × 2 groups (training, control)) was performed. We expected main effect of group and time * group interactions to be significant. There was no significant main effect of time ($F (1, 44) = 1.40$; $p = .24$, $\eta_p^2 = 0.031$) or group ($F (1, 44) = 0.09$; $p = .76$, $\eta_p^2 = 0.002$). Also, the time * group interaction was not significant ($F (1, 44) = 0.01$; $p = .93$, $\eta_p^2 = 0.000$).

Table 10 Reaction time at the Stroop task

	Training Group		Control Group	
	Pre	Post	Pre	Post
Congruent	957.28 (±241.37)	821.92 (±184.40)	1002.12 (±238.14)	894.98 (±180.85)
Incongruent	1062.59 (±247.82)	993.20 (±240.44)	1109.07 (±234.60)	1034.47 (±235.22)
Control	895.77 (±193.37)	830.11(±18 0.84)	958.47 (±194.53)	863.11 (±175.96)
Interference	137.45 (±134.19)	176.10 (±126.05)	128.90 (±124.43)	163.81 (±126.15)

Note: Values are means(±SD) in milliseconds.

6. Inhibition training effects on alcohol consumption (Table 11)

A number of unit drinks in a week, Number of drinking days and Average drinks/drinking were calculated through TFLB diary for pre-intervention data. Daily recording of the number of drinking units entered during each day of intervention was used for analysis of the outcome of the intervention.

a) Units of alcohol consumed (Figure 6)

Mixed design ANOVA (time (3: baseline, 1st week, 2nd week) × group (2: training, control)) was performed for units of alcohol consumed during training. We expected main effect of group and time * group interactions to be significant. There were no significant main effects of time ($F(2, 88) = 1.21$, $p = .30$, $\eta_p^2 = 0.027$) or group ($F(1, 44) = 0.35$, $p = .56$, $\eta_p^2 = 0.008$). Also, the time * group interaction was not significant ($F(2, 88) = 0.76$, $p = .47$, $\eta_p^2 = 0.017$)

b) Number of heavy drinking days (Figure 7)

Mixed design ANOVA (time (3: baseline, 1st week, 2nd week) × group (2: training, control)) was performed for number of heavy drinking days during training. We expected main effect of group and time * group interactions to be significant. The main effect of time was significant ($F(2, 88) = 3.20$, $p = .05$, $\eta_p^2 = 0.068$), with drop in the heavy drinking days number in week 1 ($M = 1.49$, $SE = 0.21$; $p = .08$) and week 2 ($M = 1.41$, $SE = 0.23$; $p = .09$) of training compared to baseline ($M = 1.84$, $SE = 0.23$). The main effect of group was not significant ($F(1, 44) = 0.28$, $p = .60$, $\eta_p^2 = 0.006$). The time * group interaction was not significant ($F(2, 88) = 2.11$, $p = .13$, $\eta_p^2 = 0.046$).

c) Number of abstinent days (Figure 8)

Mixed design ANOVA (time (3: baseline, 1st week, 2nd week) × group (2: training, control)) was performed for number of abstinent days during training. We expected main effect of group and time * group interactions to be significant.

There was a significant main effect of time ($F(2, 88) = 3.32$, $p = .04$, $\eta_p^2 = 0.07$), with significant drop in the number of abstinent days in 2nd week of training ($M = 2.76$, $SE = 0.24$; $p = .02$) compared to the baseline ($M = 3.29$, $SE = 0.26$). The change in 1st week of training ($M = 3.07$, $SE = 0.26$; $p = .75$) compared to the baseline was not significant, along with the change from 1st week to 2nd week of training ($p = .59$).

The main effect of group was not significant ($F(1, 44) = 0.54$, $p = .47$, $\eta_p^2 = 0.012$). The time * group interaction was significant ($F(2, 88) = 3.27$, $p = .04$, $\eta_p^2 = 0.069$). On post hoc analysis for between group effect at each time point, no significant differences were noted at baseline ($t(45) = 0.74$, $p = .46$, $d = 0.21$), 1st week ($t(44) = 0.91$,$p = .37$, $d = 0.26$) or 2nd week ($t(44) = 1.53$, $p = .13$, $d = 0.44$). For training group, the change from baseline to week 1 ($t(22) = 0.62$, $p = .54$, $d = 0.13$) and to week 2 ($t(22) = 0.09$,$p = .93$, $d = 0.02$), and the change week 1 and week 2 ($t(22) = 0.61$,$p = .55$, $d = 0.13$), were not significant. For control group, the change from baseline to week 1 ($t(22) = 2.00$, $p = .06$, $d = 0.42$) was not significant but, baseline to week 2 ($t(22) = 3.56$, $p = .002$, $d = 0.74$) was significant, with decreased number of abstinent days noted. The change between week 1 and week 2 was not significant ($t(22) = 1.19$, $p = .25$, $d = 0.25$).

Table 11 Alcohol consumption

	Training Group			Control Group		
	Baseline	Week 1	Week 2	Baseline	Week 1	Week 2
alcohol consumption (units)	30.59 (±14.62)	27.35 (±18.37)	26.52 (±19.61)	33.42 (±28.10)	27.59 (±22.76)	33.94 (±31.41)
Heavy drinking days	2.04 (±1.60)	1.70 (±1.52)	1.30 (±1.36)	1.63 (±1.52)	1.26 (±1.32)	1.52 (±1.56)
Abstinent days	3.15 (±1.61)	3.30 (±1.79)	3.13 (±1.74)	3.43 (±1.46)	2.83 (±1.77)	2.39 (±1.53)

Note: Values are means (±SD)

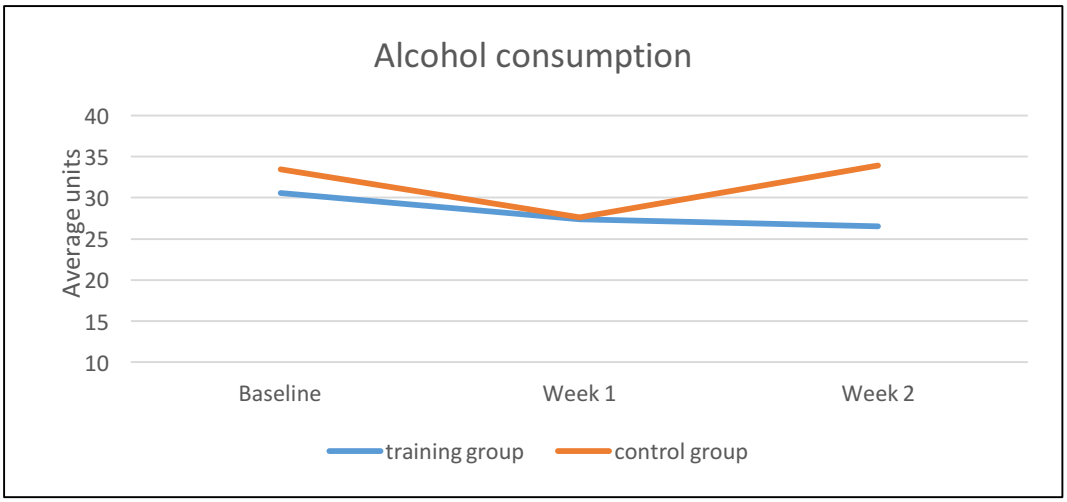


Figure 6 Per week units of alcohol consumption

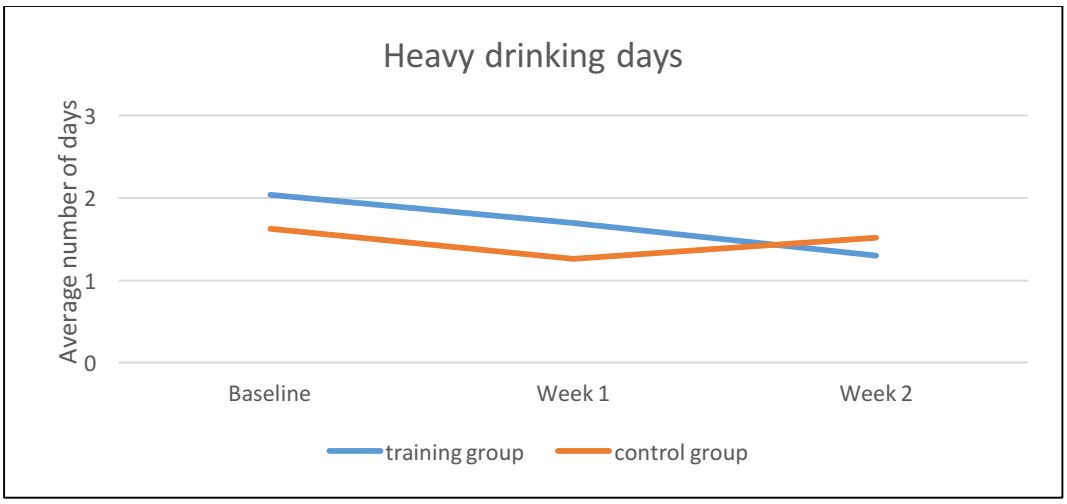


Figure 7 Heavy drinking days per week

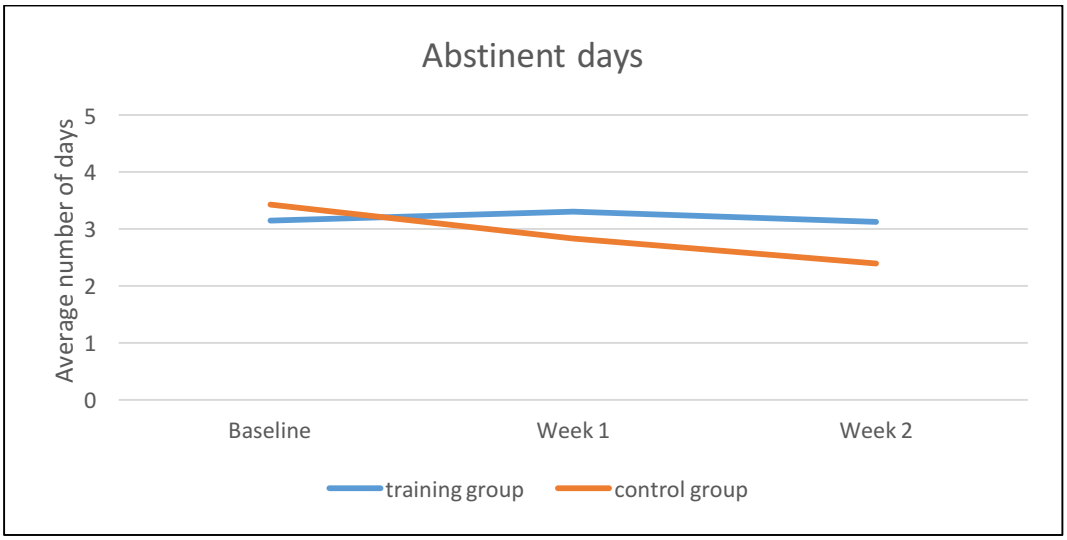


Figure 8 Abstinent days per weekPost-intervention subjective effect

A t-test was performed on the subjective scoring of intervention helped them in reducing alcohol consumption. After completing the 2-week intervention, there was no

significant difference noted in the subjective feeling of effect produced by the intervention (training: M = 2.83, S.D. = 1.07; control: M = 2.61, S.D. = 1.03; t (44) = 0.7; p= .488, d = 0.20).

7. Behavioural and alcohol-seeking associations (Table 12)

The changes in SSRT, Stroop interference score, alcohol consumption, number of heavy drinking days and abstinent days were plotted for correlation with the maximum stage reached during the training and total hours of training. Among the training group, changes in SSRT significantly correlated with the change in Stroop interference score (r = .59, p = .003). The other variables didn't correlate with each other for either training or control groups.

Table 12 Correlations between outcome variables in training group

		Heavy drinking days	Abstinent Days	Alcohol Consumption	Stroop Interference Score	SSRT	Hours of training	Stage
Heavy drinking days	Pearson Correlation	1	-0.37	.68	-0.24	0.26	0.14	0.03
	Sig.		0.07	0.00	0.26	0.22	0.50	0.87
Abstinent Days	Pearson Correlation	-0.37	1	-.62	-0.00	-.43	-0.21	0.26
	Sig.	0.07		0.00	0.97	0.03	0.33	0.21
Alcohol Consumption	Pearson Correlation	0.68	-0.62	1	0.04	0.28	0.40	-0.07
	Sig.	0.00	0.00		0.83	0.18	0.05	0.71
Stroop Interference Score	Pearson Correlation	-0.24	-0.00	0.04	1	.59	-0.18	-0.01
	Sig.	0.26	0.97	0.83		0.00	0.39	0.93
SSRT	Pearson Correlation	0.26	-0.43	0.28	0.59	1	-0.13	0.03
	Sig.	0.22	0.03	0.18	0.00		0.53	0.86
Hours of training	Pearson Correlation	0.14	-0.21	0.40	-0.18	-0.13	1	-0.13
	Sig.	0.50	0.33	0.05	0.39	0.53		0.54
Stage	Pearson Correlation	0.03	0.26	-0.07	-0.01	0.03	-0.13	1
	Sig.	0.87	0.21	0.71	0.93	0.86	0.54	

8. Qualitative evaluation

a) Interesting nature of the game

Participants mentioned the games were more engaging compared to the computerised assessment tasks. They mentioned the scoring system in the game made it more competitive.

b) Handy in use

Being the intervention on the mobile phone, this made it very handy for participants. Many participants mentioned that it was easy to carry the phone with them and play regularly. Some participants asked for loading the game on their personal phone but were convinced on explaining the comparability issue of results, if the game was not played on similar phones for all the participants.

c) Lock system

Many participants mentioned the lock in the game for not allowing to play overtime and having controlled number of sessions in a day, prevented their over-involvement. They mentioned the chances to overplay were more if they were not able to finish a level even after multiple attempts.

d) Monotonous after a long time

Some participants mentioned the game giving a monotonous feel in the 2nd week on training. They mentioned that initially the game engaged them, but later they didn't get motivated to play, leading to forgetting about the session after initial procrastination of play. These participants were mostly playing the control intervention.

e) Frustrating if stuck at one stage

Participants playing the training intervention mentioned they were stuck in the level 6 or 7 of stage 2. Most participants could cross it in a couple of sessions, but some couldn't clear it even until the end of the training. They mentioned this very frustrating.

f) The daily log of alcohol may be helpful

Some participants mentioned daily log of alcohol units were helpful for them to introspect about their drinking. This helped them to cut down further.

F. Discussion

This study aimed to develop an intervention, based on inhibition training with a smartphone game, to help in cutting down alcohol consumption in the motivated heavy drinkers having a probable alcohol use disorder. The comparison was made between

the training intervention and a look alike control intervention when trained for a two-week duration. Improvement was seen on both the training and the control game performance. Although, a good compliance was observed in both the groups, a significantly better adherence was with the training intervention. Contrary to the expectations, no significant near transfer effects were noted in the inhibition related task (primary hypothesis) with both the interventions with a very small effect size, even though participants improved on their games. No far transfer effects were detected in any of the groups, measured by the Stroop task with a small effect on the reaction time and a negligible effect on the interference. Although people may have been more motivated to engage with the experimental game rather than the control game, this increased motivation was not associated with improved alcohol-related outcomes. With parameters measuring the change in alcohol consumption, no significant change and a small effect of intervention on the number of alcohol units consumed was noted over time. There was an overall decrease in the number of days with a heavy drinking with a medium effect, but no significant difference was noted with the intervention type, although a small to medium differential effect for the intervention was noted. A significant decrease in the number of abstinent days were noted in a group with the control intervention but, no other significant differences in drinking pattern were seen while on the training. The change in the SSRT with the training intervention had a significant positive correlation with the change in the Stroop interference score. No other significant correlations were noted. Although the craving decreased over time, it was not differentially influenced by any of the intervention. The mood didn't significantly change over time.

The difference in the functionality of an assessment task (SST) used for the near transfer effect and the nature of training game could also be a contributing factor for the null effect in our primary hypothesis. The task assessed the stop signal reaction time during an action cancellation for the ongoing Go stimulus on presenting a stop signal cue. While the performance in the training game not only required an action cancellation for the Go stimulus as an inhibition component (not collecting the object on stop signal like change in colour of fruit), but also required a correction of the wrong response made (move the character collecting objects to a safe position avoiding collection of stop signalled object). Although the response switching is supported by the same neural systems as a response inhibition (Kenner et al., 2010), preparing to change the action

plans (i.e. adding an extra response or withholding the planned response) increases the cognitive load (Frederick Verbruggen & Logan, 2009b). The difference in this functionality may be the reason for a discrepancy in the observed results.

Previous studies had the alcohol consumption assessment with the help of a diary, after the training completion. For example, if the intervention is provided for 2 weeks, either the participants are given a take-home diary to fill daily (which may have more missing data) or at the end of the intervention, participants are asked to recall their number of drinks. On the other hand we did the assessment of consumption with an experienced sampling method, during the training (Houben et al., 2012; Houben, Nederkoorn, et al., 2011b; Houben, Wiers, et al., 2011; Wiers et al., 2015; Wiers, Rinck, Kordts, Houben, & Strack, 2010). This might be one of the contributors for the null effects on the units of alcohol consumption with the training. A recent study by Monk et al., (2015) examined the possible discrepancies between the real-time measurements and the retrospective accounts of alcohol consumption. They found that the retrospective accounts may underestimate the amount of actual, real-time alcohol consumed. These differences were exacerbated by an increased consumption, alongside interacting with the time frame given for reporting (weekly vs. daily retrospective). Similar findings were also noted by Townshend & Duka, (2002) were they observed an underestimation by ~12% on a retrospective sampling in the measures for alcohol intake and the number of times being drunk, compared with the real-time measures. Also, they noted that the high drinkers tended to underestimate their drinking behaviour, whereas the lower drinkers tended to overestimate. Our retrospective account was a fortnight recall, while the real-time account was a last day recall. The different ways to collect the data might have influenced the outcomes based on alcohol consumption. The baseline data was based on the prior 2 weeks memory, while during the study period daily alcohol units were registered before the intervention.

The participants, in our study, were recruited with an inclusion criterion of being motivated to cut down the drinking. This was assessed by a self-rating scale rating themselves on motivation to cut down drinking for the duration of the study and the readiness to change questionnaire, during the baseline assessment. Also, most of the participants were in the contemplation phase of motivation (table 6) and they received a brief intervention helping them to motivate in cutting down drinking, following which the participants rated themselves high on a motivation scale. Although people may have

been more motivated to engage with the experimental game rather than the control game, this increased motivation was not associated with improved alcohol-related outcomes. No overall decrease in the units of alcohol consumed during the study was observed compared to the baseline in both the groups. On the contrary, there was a significant decrease in the number of abstinent days noted in control group compared to the baseline. This is contrary to the study, where a reduction in the alcohol consumed was noted irrespective of the intervention (Field et al., in prep). Also, the findings are contrary to the Hawthorne effects noted in the control groups of any brief intervention study for reducing the alcohol consumption (Jenkins, McAlaney, & McCambridge, 2009; McCambridge, Kypri, Elbourne, Elbourne, & Sheeran, 2011). McCambridge et al., (2011) evaluated the size and nature of the effects observed in randomized manipulations of the effects of answering questions on drinking behaviour in brief intervention trials, with a small effect on the drinking behaviour, statistically significant for the college students ($z=2.46$). One of the reasons for no difference noted in the alcohol units consumed during the study could be the memory bias (Monk et al., 2015; Townshend & Duka, 2002), as the baseline was a 2-week recall and follow-up was real-time data. There was a significant reduction in the number of heavy drinking days with a medium effect noted in both the intervention groups. Although statistically not significant an about medium effect size was noted with the differential effect of the intervention on the heavy drinking days. There is one of the possibility that the inhibition training intervention participants were able to control their binge drinking and thus decreasing the heavy drinking days but the control intervention group tried to adopt a drinking cut down strategy by decreasing the number of abstinent days i.e., drinking on the abstinent days and redistribution of the alcohol units across week.

Our experience as per this study suggested a better compliance and adherence rate than the previous literature on the cognitive training with a smartphone app. Another RCT of an attention bias modification with an app to reduce the social anxiety, had around 25% drop-out by the end of the 4-week intervention, along with about 65% of training sessions completed (Enock, Hofmann, & McNally, 2014). One of the reasons for a high compliance rate could be the structured payment schedule for the compensation. Participants were rewarded with a bonus of 100% completion of the task. Also, the leap in the payment was high between <75% and >75% of the task completion. The financial gain could be a driving force for the high adherence rate noted in our study.

Gamification of the training could also be a major contributor for the compliance, as this makes the training more competitive and engaging (Boendermaker et al., 2017, 2016; Boendermaker, Prins, et al., 2015).

There were also other contributing features of gamification in the training intervention. First, a large proportion of our participants mentioned the 10minute time lock as useful, preventing them to overplay. We expect such a time-lock component in the game may help in preventing the overuse and problems associated with the overuse. Second, adding the gaming component to the principle of a regular training task increased the enthusiasm to play. This may increase an enthusiasm among the youngsters for the cognitive interventions. Finally, although initially interesting, due to the repetitive nature after a long time, the training may be booring and frustrating. This adds a need to keep variations in the game components. Also, this could be a reason for a significant difference in the total number of hours played among our two interventions. The training intervention had changing nature of the task at a regular interval, while the control intervention had only the monotonous collection of all the objects.

G. Limitations

There were limitations in our study. First, a smaller sample size limited our chances to notice any subtle changes. A previous meta-analysis of an associative inhibition training by Jones et al., (2016) suggested a small effect size for the inhibition training. Second, we collected the data for drinking only during the training period and didn't assess the alcohol consumption after the training period. The previous study noticed a decrease in the drinking in the follow-up recordings after completing a non-associative training (Houben, Wiers, et al., 2011), rather than during the training. Third, the self-report of alcohol consumption may be less than the actual use (Boniface et al., 2014). The participants in this study at the baseline had a recall assessment of the last 2 week of alcohol consumption. During the training period, they reported the units of alcohol consumed on the previous day. As all the participants followed the same protocol, the underestimation of alcohol use should have affected all the participants equally, irrespective of the training provided. Also, the self-reports can be reliable and valid if retrospective recall errors are minimized by asking people to report their consumption every day rather than asking them to remember over a whole week or two (Field et al., in prep). This strategy used in our study may help to minimize recall bias. Future studies of such type should incorporate both subjective and objective measures of alcohol

consumption. Fourth, the other psychopathology which can interfere with subject performance (e.g. Depression, Psychosis, Anxiety etc) were not assessed and excluded. This is one of the limitations of the study. But, as the participants in this study were recruited through newspaper and radio advert (community) or the university students, the probability of a dual diagnosis was expected minimal. Finally, a two-week duration of the training might not be sufficient to find the training associated changes. The combination of a high intensity and long duration of the training is considered to be important to stimulate a neuroplasticity in the brain (Cramer et al., 2011; Tedim Cruz et al., 2014).

In conclusion, this is perhaps the first study to use a gamified version of a non-associative inhibition training in the heavy drinkers having a probable alcohol use disorder. The gamification might have improved the adherence to the training along with the compliance, along with decreased the attrition rate (Boendermaker et al., 2017). Adding the experience sampling to the training game tool may be an important component in the field-based studies.

V. Brief inhibition training with a smartphone game and a brief mindfulness intervention lead to changes in the P300 during successful response inhibition in heavy drinkers with a probable alcohol use disorder

A. Abstract

Alcohol use disorders are associated with impairments in inhibitory control. Computerised ‘inhibition training' interventions or mindfulness interventions may ameliorate these deficits and prompt reductions in alcohol consumption. Our aim was to compare the effects of a smartphone ‘inhibition training' intervention, Brief Mindfulness Intervention (BMI), and a computerised control intervention on inhibitory control and its event-related potential (ERP) markers in heavy drinkers. We randomly allocated 60 heavy drinkers having a probable alcohol use disorder to groups: the ‘inhibition training' group completed 30 minutes of a bespoke smartphone game that is designed to improve inhibitory control, the control group completed a similar smartphone game that did not train inhibitory control, and the BMI group received a 30 minute audiotaped mindfulness intervention. All participants then completed a Stop Signal Task whilst their ERPs were measured using a Biosemi Active Two system. Results show that compared to the control group, the BMI group had blunted N200 ($t(38) = 2.13$, $P < 0.05$) and P300 ($t(38) = 2.52$, $P < 0.05$) ERP components during successful inhibition trials. The control and inhibition training groups did not differ (N200: $t(38) = 0.64$, $P = 0.53$; P300: $t(38) = 1.51$, $P = 0.14$). There were no group differences in behavioural inhibitory control performance (Stop Signal Reaction Time; $F(2, 57) = 1.211$, $P = 0.31$). Compared to a control intervention, a brief mindfulness intervention leads to a short-term improvement in ERP components associated with the inhibitory control. However, a brief inhibition training smartphone game does not lead to improvements in inhibitory control. Further work is required to investigate if mindfulness-induced improvements in inhibitory control are long-lasting and if they can lead to reductions in alcohol consumption in problem drinkers.

B. Introduction

Response inhibition is the ability to suppress or abort ongoing actions and it plays a crucial role in adaptive human behaviour (Stewart H Mostofsky & Simmonds, 2008).

The assessment of response inhibition in the laboratory can be done by using computerised tasks like the go-nogo task (GNG) and stop signal task (SST) (G. D. Logan et al., 1997). In GNG, two types of stimuli are presented in rapid succession. Subjects are required to respond to one of the stimuli and avoid responding to the another (Frederick Verbruggen & Logan, 2008). This task assesses action restraint, as the response has to be inhibited for only certain particular stimulus. While in SST, subjects are presented with 'go' stimuli in quick succession and are instructed to make designated motor responses. However, on a minority of the trials are accompanied by a stop signal which requires the suppression of ongoing response. This task assesses action cancellation, as it establishes a response conflict between rapid responding and successful inhibition (Guido P.H. Band, van der Molen, & Logan, 2003). A unique feature of SST is that it allows the calculation of the stop-signal reaction time (SSRT). SSRT is the time required to stop a response, estimated from the probability of stopping at different stop-signal delays, making the speed of the Go response and the speed of the Stop response independent (Logan and Cowan, 1984; Logan et al., 1984).

Alcohol use disorders (Goudriaan, Oosterlaan, de Beurs, & van den Brink, 2006) and other substance use disorders (Antonio Verdejo-García, Lawrence, & Clark, 2008) are associated with deficits in inhibitory control. A meta-analysis by Smith et al., (2014) suggested that alcohol affects the inhibitory capacity. They observed a significant deficit in inhibition of medium effect size ($g = 0.4–0.5$) for alcohol dependence and smaller deficit in heavy drinkers in the stop-signal task. We know that pre-morbid poor inhibitory control is a risk factor for alcohol misuse (Fernie et al., 2013). But, some studies also mention inhibitory control impairment as a consequence of binge drinking (López-Caneda et al., 2014; Maurage, Pesenti, Philippot, Joassin, & Campanella, 2009).

There are many neuronal markers of inhibition mentioned in the literature. Right Inferior Frontal Cortex (rIFA) is one of the most important areas of inhibitory control, both in the action restraint and action cancellation tasks (Aron, Robbins, & Poldrack, 2014). Also, dorsal Anterior Cingulate Cortex (dACC) is considered as an important structure related to response inhibition and error processing (Luijten et al., 2014). Event-related potentials (ERP) amplitude and latency are sensitive to activity-related changes in the brain (Kujala & Näätänen, 2010; Lillard & Erisir, 2011). For inhibitory control in ERP, N200 (a frontally maximal negative component peaking

around 200 ms after the onset of inhibition-evoking stimuli) (Johnstone, Pleffer, Barry, Clarke, & Smith, 2005; Janette L Smith, 2011)) and P300 (a positive component that has a Centro-parietal topography and peaks approximately 300 ms post-stimulus) (Randall & Smith, 2011; Janette Louise Smith & Douglas, 2011)) are most common target outcome measures. In SST, some argue that the inhibition process is best represented by the N200 (Falkenstein et al., 1999; Albert Kok, 1986), while others suggest that the P300 represents inhibition much better (Albert Kok, Ramautar, De Ruiter, Band, & Ridderinkhof, 2004; Randall & Smith, 2011; Janette L Smith, 2011; Janette Louise Smith & Douglas, 2011). The P300 is more fronto-central in the location on scalp topography and higher in amplitude (Aneta Dimoska, Johnstone, & Barry, 2006) for the successfully stopped events. This implies more frontal involvement in successful inhibition compared to unsuccessful inhibition (Ramautar, Kok, & Ridderinkhof, 2004). Onset latency of P300 is considered as the coinciding event in ERP to the SSRT in behavioural measures in SST (Wessel & Aron, 2015).

These neuronal markers of inhibition showed changes in substance use disorders. Luijten et al., (2014) in their review mentions that the N200 difference during the inhibitory task in EEG/ERP is consistent with dACC hypoactivation on fMRI in most of the substance use disorders. On the other hand, reduced amplitude of the P300, especially P300a (but not N200), is thought to be an endophenotype for alcohol dependence (Anja S Euser et al., 2012; Chella Kamarajan, Porjesz, Jones, Choi, et al., 2005). These P300 amplitudes were generated during novelty trials in a three-stimulus oddball task, which were found to be associated with brain activity related to the engagement of attention (Polich, 2003). A longitudinal study by Wetherill and colleagues suggested that hypo-activation of inhibitory circuitry during a GNG task in adolescents could predict later heavy drinking (Wetherill, Squeglia, Yang, & Tapert, 2013). This was indicative of neural vulnerabilities prior to the onset of alcohol use. Also, they showed that same inhibitory circuit hyper-activation while inhibiting responses after adolescents became heavy drinkers. This shows that poor inhibitory control can be both the cause and the consequence of excessive alcohol use (López-Caneda et al., 2014). So, if poor response inhibition is a risk factor for alcohol use disorders, then it might be possible to improve it and thereby reduce the risk of

developing an alcohol use disorder or reduce the risk of relapse to drinking after a period of abstinence.

In the present study, we investigated two different techniques that might improve response inhibition: inhibitory control training and a brief mindfulness intervention. Several studies targeted the training of neural circuits linked with Inhibitory Control (IC) in healthy individuals, used N200 and P300 both as the objective outcome measures. Schapkin et al., (2007), after three daily IC training sessions using the GNG task, found an increase in the frontal no-go N200 in successfully inhibited trials in healthy adults. This study did not have a control group. Another study trained response inhibition on GNG task, by instructing subjects to respond faster on go trials and alongside inhibiting their responses when unexpected no-go stimuli were presented. They showed electrophysiological changes with training, observed between 250 to 400 ms post-stimulus both in the go and no-go trials corresponding with the N2-P3 complex (Hartmann, Sallard, & Spierer, 2016). On source localisation, these changes corresponded to the change in the top-down inhibitory control activity from pre-frontal cortical areas with the training.

Training inhibition with different levels of difficulty may have a diverse effect on the electrophysiological outcomes. A study by Benikos & colleagues (2013) looked for between-group differential effects of inhibitory control training on GNG task performance and its electrophysiological parameters. They trained subjects to respond faster by manipulating extrinsic factors like cutting down the reaction time deadline and also instructing to respond fast. They found that for behavioural task measures, the improvement was optimised for moderate rather than low or high inhibitory demands. On the contrary for electrophysiological measures, training-related changes depended on the task related cognitive demand. They found an enhanced centro-parietal no-go P300 with low task difficulty, while an augmentation no-go>go P300 effect with high task difficulty when compared to the medium condition. A similar finding of a decrease in no-go P300 amplitude at the central electrode with the rising task difficulty was noted by Gajewski & Falkenstein (2013). The changes in P300 in these studies were mostly attributed to training-induced modulation in conflict resolution rather than the core inhibition itself.

Although the GNG training task related electrophysiological changes have been explored, few studies have used the stop signal task to train improvements in inhibitory

control. SST has an advantage over GNG that the task difficulties can be manipulated while undergoing the same session (Frederick Verbruggen & Logan, 2009a). This gives us a chance of examining within subject ability to deal with different task difficulties as an outcome of inhibition training, rather than using between-subject study design. Findings from Jones et al., (2013) suggests an influence of task instructions on the P300 amplitude in SST. They found lower P300 amplitude on correctly inhibited SST trials when the instructions were stressed on successful inhibition rather than rapid responding, changing the conflict generated in the task. So, use of SST for measuring behavioural and electrophysiological outcomes of inhibition training may help us in noting subtle change produced by short-term inhibition training on various task difficulties. These changes may go unnoticed when only behavioural measures are used for outcome assessment.

There are two potential problems with the inhibitory control training tasks used in previous studies. First, these tasks are not only tiresome, but also fail to engage participants for long time. When the target population is adolescents and young adults, such type of training tasks may fail to keep them involved in the performance for a long time (Giessen, 2015). Converting these training tasks into serious games may help. The intrinsic motivators in digital games may help to keep up the interest for training (Habgood & Ainsworth, 2011). In a recent review by Boendermaker and colleagues (2015) suggested a guideline for using tasks for designing a serious game. They also mentioned that if a proper use of game elements are not made, it may not produce the targeted behavioural change. Second, most of these tasks are computer-based. This limits their use along day to day life in a real-world scenarios. The use of smartphone-based serious games for the training purpose could solve this issue. The increasing mobile phone gaming tendency in the youth (Connolly, Boyle, MacArthur, Hainey, & Boyle, 2012) makes smartphone games a potential tool for the cognitive retraining. Connolly et al, (2012) had systematically reviewed the positive impact and outcome of digital games and suggested that more RCTs are required to provide rigorous evidence. Also, there is a dearth in literature with the use of smartphone games for inhibition training and its utility. In view of this, we designed this study for inhibitory control training with a smartphone game.

We know from previous research that performance in the inhibitory training depends on a level of difficulty in the task (Bowditch, Verbruggen, & McLaren, 2016; Frederick

Verbruggen, Best, Bowditch, Stevens, & McLaren, 2014). Most of the inhibition training research had a fixed degree of difficulty. If the difficulty level is kept at low the performance remained the same and if the difficulty level is raised to moderate or high, demands more cognitive input in the performance. The enhances allocation may show a better neurocognitive change (Benikos et al., 2013). With this in the background, we designed an in-house game consisting of a graphical output and with increasing level of difficulty in the stop signals. We kept in mind the individualised approach, with a simple level of difficulty at the start and then a gradual increase in the difficulty as per the performance. The detailed description of the game is given in the methods section.

The utility of the Mindfulness-Based Interventions (MBI) in mental health treatment has been increasing in the last decade. MBI has shown efficacy in treating versatile health conditions. The meta-analysis of MBI based research showed moderate to large effects (Hedges' g = 0.59–0.63) for anxiety and mood related disorders (Hofmann, Sawyer, Witt, & Oh, 2010), along with the psychosomatic symptoms associated with many other disorders such as diabetes, cancer, heart disease and chronic pain. MBI can be a cost-effective and a non-invasive alternative for dealing with the psychosocial aspects of many illnesses. However, its spiritual connection with Buddhism and lack of expertise among many of the trainers in the health services limits the exploration (Shonin, Van Gordon, & Griffiths, 2013).

Mindfulness meditation practice involves the adoption of a receptive mental awareness of present-moment sensations in the body and reframing of the ongoing experience as a phenomenon to be observed but not reacted upon (Gunaratana, 2002; Hart,1987; Lutz et al., 2007). In stages at the beginning, learning mindfulness involves focused attention on regular breathing and in the later stages, it involves observation of body sensations (Tang et al 2015). Research suggests that mindfulness involves enhanced ACC activation during breath awareness (focused attention) (Hölzel et al., 2007) and resting state (Yi-Yuan Tang et al., 2009) along with dorsal prefrontal cortical activation during executive processing tasks like Stroop (Allen et al., 2012). Moore et al., (2012) showed an increased negative potential of N200 and decreased P300 amplitude on the correct response of incongruent trials in the Stroop task, with 10minutes/day for 16 weeks, of mindfulness training in healthy adults. They also mentioned that this decreased P300 amplitude could be due to a decrease in neural resource allocation for attention. Further,

the more negative N200 could indicate better target detection and inhibition of automatic responses. Though the Stroop is not a classical task for assessing motor response inhibition, it has some components of it (Khng & Lee, 2014). Sanger & Dorjee (2016) reported an increase in the negativity of N200 in the non-target colour deviant stimuli in an oddball task following mindfulness training in adolescent school students, suggesting improvement in the attention allocation in the response inhibition. The divergent distractors in the oddball task are supposed to activate inhibitory circuit with the fronto-central topography of N2-P3 complex (Polich 2007). It is also noted that mindfulness-based therapies are effective in relapse prevention in patients with alcohol dependence (Chiesa & Serretti, 2014; Penberthy et al., 2015) and decrease in an urge to drink (Vinci et al., 2014) and consequences associated (Dvořáková et al., 2017) in college students. But the potential of mindfulness in improving inhibitory control in heavy drinkers is not well established. The heavy drinkers can be considered as a population which is developing the addiction. As explained in the introduction chapter, there is a probability that this population is forming the indirect addictive circuit in the brain connecting the amygdala and striatum. Looking at the action of mindfulness on both these areas and a modality to train the involuntary controlling capacity towards internal cues, mindfulness can be a potential tool modulating the evolving circuits in the heavy drinkers having a probable alcohol use disorder. So, in this study, we also planned to see effects produced by brief mindfulness session on ERP components.

Our aim in this study was to look at effects of both inhibitory control training game and brief mindfulness intervention in the heavy drinkers having a probable alcohol use disorder, on behavioural IC and neural correlates of IC and to compare both with an active control group, which played a control version of the game not having any component of inhibition training. The heavy drinkers could be considered as 'probable Alcohol Use Disorder', as they drink above government guidelines (therefore, probably causing themselves alcohol-related harm), and have high AUDIT scores of 'hazardous drinking'. We hypothesized that response inhibition training with a smartphone game in the specified training group or the Brief mindfulness intervention would: (1) improve participants' performance in the training game (not assessed in mindfulness group); and (2) training would produce difference in the ERP activity on correct responses in stop

signal task, as indicated by the N200 and P300 effects. We expect to find a difference in the amplitude of N200 and P300 and latency of P300.

C. Methods

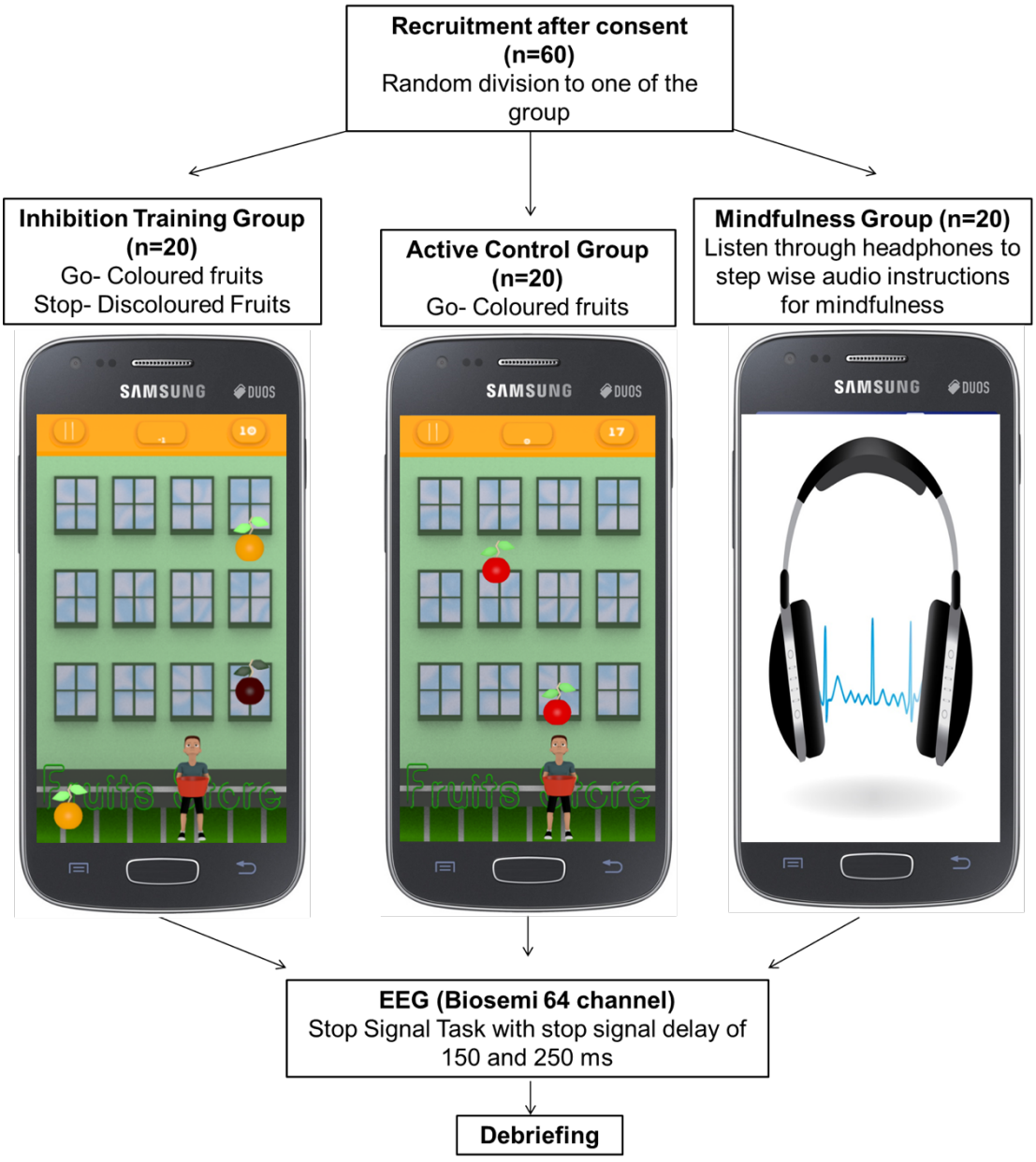


Figure 9 Flowchart. TFBD two-week alcohol Timeline Follow-Back Diary, AUDIT- Alcohol Use Disorders Identification Test, TRI- Temptation and Restraint Inventory, BIS-11- Barratt Impulsiveness Scales, FFMQ- Five-factor Mindfulness Questionnaire, TMS- Toronto Mindfulness scale.

1. Sample Size calculation and the recruitment

The sample size was calculated with the help of G*power software. The Analysis of Variance was the predicted analysis strategy. The probability of type 1 error (α) was assumed to be 5 %. The power of the study was expected to be 80%. With the expected

large effect size (0.7) based on Houben et al., 2012, and in view of the sensitivity of ERP for neurocognitive changes, the ultimate sample size for the study in order to have a sufficiently acceptable statistical power was 20 in each group.

60 participants who regularly consume alcohol in excess of UK government guidelines at the time (14 units per week for women, 21 units per week for men) (guidelines are changed from January 2016 after we finished our data collection) (Department of Health, 2016) , between age of 18 to 35 years and normal or corrected vision were recruited from the students of University of Liverpool and Liverpool community through flyers and intranet adverts. Participants currently or previously diagnosed with alcohol use disorders or Attention Deficit Disorder (ADD) or prescribed methylphenidate (Ritalin) for ADD or similar conditions were excluded.

2. Procedure (Figure 9)

a) Questionnaires

Questionnaire battery consisted of: two week alcohol Timeline Follow-Back Diary (L C Sobell et al., 2001), the Alcohol Use Disorders Identification Test (AUDIT) (J B Saunders, Aasland, Babor, de la Fuente, & Grant, 1993) and the Barratt Impulsiveness Scales (Patton et al., 1995). To assess participants' general degree of mindfulness, Five-Factor Mindfulness Questionnaire (FFMQ; Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006) was used consisting of questions around five facets: Observing, Describing, Acting with Awareness, Nonjudging and Nonreactivity. The Toronto Mindfulness Scale (TMS; Lau et al., 2006), having questions regarding two factors: "Curiosity" (awareness of the present moment, with the approach of curiosity) and "Decentering" (noticing feelings and thoughts, while maintaining distance from them) was used in this study as a manipulation check (used pre and post of the task) verifying whether mindfulness instructions increased state mindfulness (Vinci et al., 2014). The brief version of trait self-control scale (TSC; Tangney, Baumeister, & Boone, 2004) was used to measure subjective self-control. Questions were also asked to check the expectation from the intervention: "How much do you think you will benefit from this intervention, in terms of helping you to reduce your inhibition?" (Expectation in terms of improvement in inhibition) and "How motivated are you to take part in this intervention?" (Assess the motivation in participating for intervention). The response was noted on a 5 point Likert scale (Not at all- Very much).

b) Phase 1

Initially, participants contacted the study coordinator via email indicating their interest in the study. After being provided with detailed information about the study, those who were interested were scheduled to participate. The experimental phase of the study took place in the EEG laboratory between the hours of 12:00 p.m. and 7:00 p.m., Monday through Friday. During their visit, recruitment was started with the informed consent, which was approved by the University of Liverpool Research Ethics Committee. Following completion of the Questionnaire, participants were brought into an individual room for the rest of the experiment after setting up the EEG system electrodes. Participants were randomly assigned (via a random number table generated through an excel sheet for simple randomisation (Suresh, 2011)) to one of the three experimental groups: Smartphone-based stop-signal game training group, Active Control Game Group and Mindfulness intervention group. After completion of the training task, they performed the stop signal task (explained later) during which EEG was recorded. In the end, debriefing about the study was done following a questionnaire.

c) Phase 2

Tasks: The task is provided for a duration of 30 minutes with the help of a smartphone (Samsung Galaxy Ace 3). Participants were moved to a silent room and instructions were provided for the concerned task.

(1) Training group (see methods chapter for details of the game):

The game was built over Unity gaming platform. The full training game consisted of many stages and is described elsewhere (please see the other Chapter). Participants played the fruit stage (Stage 2) of the game for the 30 minutes of training duration, which was based on the principles of SST. They started with the level 1 of this stage and tried to complete as many levels as possible in the 30-minute duration.

(2) Active Control group (see methods chapter for details of the game):

This group played a control version game which was similar to the training one but without any of the stops cued fruits and bombs, for the same 30-minute duration. Similar to the training group, they started with level 1 of stage 2 and tried to complete as much as possible in the specified duration.

Mindfulness (Vinci et al., 2014): An audio recording of 30 minutes, focusing on the instructions to perform the initial step of Vipassana mindfulness meditation (Anapana)

in brief (described in appendix2), were played on the mobile phone connected with the earphones. Participants were instructed to follow the instructions.

d) Phase 3

3. EEG recording and Stop-signal Task (SST):

Biosemi Active Two system (Biosemi, Amsterdam, Netherlands) having 64 scalp electrodes based on the extended 10/20 system was used for EEG recording. Flat disc electrodes connected above and below the right eye and near to lateral canthus of both the eyes were used for recording vertical and horizontal electrooculogram (EOG) respectively parallel to EEG. All the signals were recorded at the sampling rate of 1024 Hz with the high pass and low pass filters set at 0.01 Hz and 100 Hz respectively. Default Biosemi referencing was used.

With Inquisit 3.0 (Millisecond Software: Seattle, Washington, USA), SST (Gordon D. Logan & Cowan, 1984) was coded and delivered to the participants on a standard monitor of 15 inch. In order to make the SST compatible for ERP acquisition and analysis, the components such as fixation point, for fixing start of one trial, and inter-trial interval, for making it flexible to cut epochs for further analysis, were added. Each trial started with a fixation point '+' in the centre of the screen for 500ms following which either 'X' or 'O' (go stimulus) was presented. Participants were required to classify them by pressing one of the assigned keys, using dominant hand, as quickly as possible. Stimulus time out of 1000 ms was used. Incorrect responses, or those that occurred after the timeout period was coded as errors of omission). An auditory stop-signal was presented on 25% of trials with a delay of either 150 ms or 250 ms after the onset of go stimulus. Participants were instructed to inhibit their response whenever they heard the stop signal. Failure to inhibit was coded as an error of commission. Inter-trial interval was 1500 ms. In all, the maximum length of one trial was 3000 ms. The task had 6 blocks with each having 64 trials of which 48 were go trials and 16 stop trials (8 at 150 ms and 250 ms each). Participants were given rest in between blocks. A practice was given at the start having 16 trials and indicators of correct and wrong responses. The total task took around 30 minutes. These parameters were the same used in the previous study (Jones, Field, et al., 2013).

a) Phase 4

Participants completed TMS. At the end of the study participants received £20 or course credit before being debriefed and discharged.

4. EEG analysis

MATLAB (2014a), EEGLAB (Delorme & Makeig, 2004) and ERPLAB (Lopez-Calderon & Luck, 2014) were used to analyse EEG data. The recorded online reference free EEG data was stored in a separated hard disk in a .bdf format. This data was later imported in the EEGLAB re-referenced to Cz electrode to avoid 40 dB notch noise. Default BESA channel locations were used for mapping the electrode locations. The data was later re-referenced to the average of all the electrodes, downsampled to 256 Hz and filtered with low pass of 35 Hz. The data was epoched for the different conditions (go, 150ms stop trials and 250ms stop trials). The correct and incorrect response trials were also separated. Epochs included 1000 ms before and 2000 ms after onset of the Go stimulus. The baseline was defined as the 200 ms preceding the stimulus. An Independent Components Analysis (ICA) was performed on the epoched data including all conditions. Independent components accounting for blink artefacts, gross muscle and electrode artefacts were visually identified and removed from the data. Trials affected by other artefacts caused e.g. by muscle tension and movement were rejected from further analysis with automatic artefact rejection keeping the amplitude fluctuation window of ±100 μV. Average for each condition was done for each individual participant. Finally, data was grand averaged for different groups. During cleaning the EEG data, different groups did not differ in the number of trials included in the study and lost during artefact rejection (for Stop signal at 150 ms: $F(2, 57) = 0.28$, $p = 0.76$; for Stop signal at 250 ms: $F(2, 57) = 0.47$, $p = 0.63$).

As per the methods used in previous studies [e.g. (Jones, Field, et al., 2013; Chella Kamarajan, Porjesz, Jones, Choi, et al., 2005; Chella Kamarajan, Porjesz, Jones, Chorlian, et al., 2005)], the P300 component was identified as the largest positive peak following presentation of the stop signal, between 450–600 ms for SSD 150 trials and 550-700 ms for SSD 250 trials. The N200 component was identified by searching backwards for the first negative peak occurring prior to the P300 (Sander Nieuwenhuis, Yeung, van den Wildenberg, & Ridderinkhof, 2003), which corresponded to the period 370–420 ms on trials with a 150 ms stop-signal delay, and the period 470–520 ms on trials with a 250 ms stop-signal delay. These time windows above were used to calculate mean amplitudes and onset latency for statistical analysis (Jones & Field, 2013). As the inhibitory potentials are located in midline on scalp topography, electrodes (Fz, Cz and Pz) were selected for analysis in accordance with previous research examining

inhibition P300 in alcoholics and other drug users (Jones & Field, 2013; Chella Kamarajan, Porjesz, Jones, Chorlian, et al., 2005). Onset latency for P300 was calculated by fractional peak latency method. In this method, first we find peak amplitude, and then we work backwards in time until we find the point at which the latency is a certain percentage of the peak value which in most case 50%, yields the highest reliability (Kiesel, Miller, Jolicoeur, & Brisson, 2008). For this latency calculation, looking at topographical distribution (Brydges et al., 2013), we took the P300 at Cz Electrode of the difference wave of the Stop trials and the Go trials, as amplitude was highest over central electrodes. The effect sizes were calculated for all the comparisons. For ANOVA, partial eta squares were calculated while for t-tests' cohen's-d were computed. For partial eta square, 0.01, 0.06 and 0.14 were considered as small, medium and large effect sizes respectively (A. Field, 2013). For cohen's-d, 0.2, 0.5 and 0.8 were considered as small, medium and large effect sizes respectively (A. Field, 2013).

5. Behavioural data analysis

The integration method was used to calculate SSRT (G. D. Logan et al., 1997). In this method, first, the individual reaction times on 'go' trials are ranked from fastest to slowest. Then, for each separate stop-signal delay, subtracting the delay (150 or 250 ms) from the Nth reaction time would be the SSRT. We get the *N*th reaction time from the ranked 'go' trials by multiplying the number of 'go' reaction times in the distribution by the probability of responding at a given delay. We calculated SSRT separately for the two stop-signal delays (150 ms and 250 ms) (Frederick Verbruggen & Logan, 2009a).

D. Results

1. Demographics and Baseline data (Table 13)

Participants consumed on average 23.00 (± 11.12) units of alcohol per week (1 unit = 8 g alcohol) and had a mean AUDIT score of 11.45 (± 4.84). There was no significant group difference in trait mindfulness, trait self-control and impulsivity (these data are shown in Table 2). There were also no significant group differences in the expectation from the effects produced by the intervention to be received, or motivation in participation (Question 1 and 2 in table 2).

Table 13 Demographics and questionnaire scores. Values are means (± Standard Deviation (SD)).

Variables	Training (n = 20)	Active control (n = 20)	Mindfulness (n = 20)
Gender male(female)	11 (9)	7 (13)	10 (10)
Age in years	24.75 (± 4.18)	23.75 (± 5.00)	23.65 (± 3.95)
BIS-11 (total)	76.00 (± 5.40)	74.00 (± 3.49)	75.30 (± 5.17)
-Attentional	21.70 (± 2.77)	21.10 (± 2.51)	22.50 (± 1.79)
-Motor	27.05 (± 3.18)	26.95 (± 2.39)	26.95 (± 3.05)
-Non-planning	27.25 (± 3.19)	25.95 (± 1.93)	25.85 (± 3.40)
AUDIT	10.60 (±5.14)	11.20 (± 4.46)	12.55 (± 4.95)
Alcohol (unit) consumed/ week	21.22 (± 10.28)	26.32 (± 13.49)	21.46 (± 8.89)
TSC	3.17 (± 0.41)	2.80 (± 0.63)	3.01 (± 0.68)
FFMQ (total)	123.05 (± 12.73)	123.40 (± 13.98)	118.55 (± 17.89)
-Observe	26.20 (± 4.95)	28.00 (± 5.19)	25.00 (± 4.80)
-Describe	26.30 (± 6.74)	27.40 (± 5.33)	26.85 (± 4.91)
-Act with awareness	22.10 (± 5.75)	25.10 (± 5.76)	22.90 (± 6.15)
-Non-judge	26.50 (± 6.69)	21.45 (± 6.47)	26.15 (± 7.60)
-Non-react	20.95 (± 3.68)	22.35 (± 3.44)	22.75 (± 4.03)
Question 1	2.85 (± 1.23)	2.90 (± 1.02)	2.75 (± 1.02)
Question 2	4.00 (± 0.92)	3.60 (± 0.88)	3.70 (± 0.98)

Values are means (± Standard Deviation (SD)).

AUDIT- Alcohol Use Disorders Identification Test, BIS- Barratt Impulsiveness Scales, TMS- Toronto Mindfulness Scale, FFMQ- Five-Factor Mindfulness Questionnaire, TSC- Trait Self-control, Question 1- How much do you think you will benefit from this intervention, in terms of helping you to reduce your inhibition? Question 2- How motivated are you to take part in this intervention?

2. Performance in the game

As all the participants started from the level 1, they were expected to progress in levels in the 30 minutes of task duration. On average they reached level 5.00 (± 2.00) in the

training version and level 7.00 (± 2.00) in the control version after 30 minutes. The difference was statistically significant (t (38) = 2.81, p = .01).

3. Manipulation check for mindfulness (table 3)-

We performed a mixed ANOVA, with 2 time (pre and post) × 2 subscales (curiosity and decentring) × 3 groups (mindfulness, training, active control). These was no significant main effect of time (F (1,57) = 0.15, p = 0.70, η_p^2 = 0.003). The time * group interaction was not significant (F (2, 57) = 1.62, p = 0.21, η_p^2 = 0.054). The main effect of subscale was not significant (F(1,57) = 0.48, p = 0.49, η_p^2 = 0.008). The subscale * group interaction was significant (F(2,57) = 3.91, p = 0.03, η_p^2 = 0.121). The time * subscale interaction (F(1,57) = 1.15, p = 0.29, , η_p^2 = 0.020) and time * subscale * group interaction (F(2,57)=2.12, p = 0.13, , η_p^2 = 0.069) were not significant. The main effect of group was not significant (F(2,57) = 0.48, p = 0.62, , η_p^2 = 0.017). On for post hoc analysis of subscale * group interactions, mean score of both time points for each subscale was calculated. There was no significant difference between training and active control group (curiosity: t(38) = 0.60, p = 0.55, *d* = 0.19 ; decentring: t(38) = 1.09, p = 0.28, *d* = 0.34). There was no significant difference between mindfulness and active control group (curiosity: t(38) = 0.06, p = 0.95, *d* = 0.02 ; decentring: t(38) = 1.55, p = 0.13, *d* = 0.49). There was significant difference between mindfulness and training group for decentring score (curiosity: t(38) = 0.59, p = 0.56, *d* = 0.19, decentring: t(38) = 2.72, p = 0.01, *d* = 0.86), with a higher decentring score for mindfulness group (22.68 ±2.47) than training group (19.90 ±3.83).

A further detailed analysis was performed. Paired sample t-tests were first utilized to determine whether the mindfulness intervention significantly increased in level of mindfulness (according to TMS subscale scores) from Phase 1 (pre-intervention) to phase 4 (post-intervention). Results indicated that TMS subscale scores, from phase 1 to phase 4, didn't change for curiosity (mindfulness, t(19) = 0.33, p = 0.74, *d* = 0.07; training, t(19) = 1.27, p = 0.24, d = 0.28; Active Control, t(19) = 0.64, p = 0.53, *d* = 0.14) or Decentering (mindfulness, t(19) = -1.47, p = 0.16, *d* = 0.33; training, t(19) = -0.28, p = 0.78, *d* = 0.06; Active Control, t(19) = 1.48, p = 0.15, *d* = 0.33).

To examine the effectiveness of the mindfulness intervention compared to the other interventions at phase 4, a mixed ANOVA was utilized with intervention type (Mindfulness vs. training vs. Active Control) entered as the independent variable (IV) and TMS subscales scores (Curiosity and Decentering) as the dependent variables

(DV). Results indicated that Curiosity did not differ between groups following the mindfulness intervention (at phase 4), ($F(2,59) = 0.13$, $p = 0.88$, $\eta_p^2 = 0.005$). For the Decentering subscale, groups significantly differed following the mindfulness intervention, ($F(2,59)=4.97$, $p=0.01$, $\eta_p^2 = 0.148$). Post hoc testing revealed that the Mindfulness group had significantly higher scores in Decentering compared to the training ($p = 0.005$) and Active control groups ($p = 0.014$).

Table 14 Toronto Mindfulness Scale (TMS) scores

	Training		Active Control		Mindfulness	
	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention
TMS (total)	41.55 (± 7.86)	41.1 (± 7.59)	42.80 (± 6.56)	40.85 (± 7.41)	42.5 (± 6.08)	44.00 (± 7.02)
Curiosity	21.75 (± 4.54)	21.10 (± 4.84)	20.90 (± 3.65)	20.40 (± 4.30)	20.70 (± 4.32)	20.45 (± 5.28)
Decentering	19.80 (± 4.53)	20.00 (± 3.73)	21.90 (± 4.61)	20.45 (± 3.70)	21.80 (± 2.97)	23.55 (± 4.20)

4. Stop-signal task (Table 15)

Table 15 Dependent measures from the stop-signal task, shown separately across groups

Group	Go reaction time (ms)	SSRT at 150 ms SSD	SSRT at 250 ms SSD	Errors at 150 ms SSD	Errors at 250 ms SSD
Training	548.64 (± 84.90)	340.60(± 99.23)	215.75 (± 97.54)	14.27 (± 10.78)	13.23 (± 10.61)
Active control	538.30 (± 69.70)	301.90 (± 54.60)	187.00 (± 47.84	11.98 (± 9.07)	9.69 (± 8.20)
Mindfulness	523.21 (± 68.44)	296.70 (± 57.98)	207.30 (± 78.97)	8.85 (± 5.05)	8.54 (± 6.75)

Values are means (±standard deviation (SD)). SSRT- Stop-signal reaction time, SSD- Stop signal delay, Errors are the proportion of commission errors. The Go and SSRT is in milliseconds.

To examine the effects of experimental condition on response inhibition, ANOVA was conducted on go reaction time, SSRT and proportion of commission errors for 150 and 250 ms stop signal delay (SSD) separately for each (Table 3). The groups did not differ

in Go reaction time (F (2, 57) = 0.57, P = 0.56, η_p^2 = 0.02), SSRT at 150 ms SSD (F (2, 57) = 2.13, p = 0.13, η_p^2 = 0.07), SSRT at 250 ms SSD (F (2, 57) = 0.73; p = 0.49, η_p^2 = 0.025), errors proportion at 150 ms SSD (F (2, 57) = 1.98, p = 0.15, η_p^2 = 0.065) and errors proportion at 250 ms SSD (F(2, 57) = 1.59; p = 0.21, η_p^2 = 0.053).

5. ERP data

a) P300 mean amplitude (Figure 10)

To explore the effect of group on the P300 we performed a 3 (electrode: Fz, Cz, Pz) × 3 (group: training, control, mindfulness) × 2 (SSD: 150 ms, 250 ms) mixed design analysis of variance (ANOVA). We expected the main effect of group and SSD * group along with SSD * electrode * group interactions to be significant.

There were significant main effects of electrode (F (1.35, 76.81) = 48.40, p<.001, η_p^2 = 0.459), suggesting larger amplitudes at central and parietal electrodes (Frontal = 0.65 μV, Central = 4.00 μV and Parietal = 3.93 μV). The main effect of group was also significant (F (2, 57) = 7.89, p = .001, η_p^2 = 0.217). The SSD * group interactions were not significant (F(2,57) = 1.86, p = .17, , η_p^2 = 0.061). The SSD * electrodes * group (F(4, 114)= 2.43, p = .05, η_p^2 = 0.079) interactions were significant.

On further running a 3 (electrode: Fz, Cz, Pz) × 3 (groups: training, control, mindfulness) ANOVA at the 150 ms SSD only, the electrode * group interaction was not statistically significant (F(4, 114) = 0.52, p = .72, η_p^2 = 0.018). However, there was a significant main effect of group (F (2,57) = 5.55, p = .006, η_p^2 = 0.163), with mindfulness group (M=1.82 μV, SD=1.75) having lowest amplitude, followed by training group (M=2.88 μV, SD = 1.55) and control group (M=3.68 μV, SD = 1.98). Post-hoc tests revealed that the difference between training and control groups were not statistically significant (t(38) = 1.43, p = .16, d = 0.45), whereas the difference between mindfulness and control group was significant (t(38) = 3.14, p = .003, d = 0.99). The training and mindfulness groups differences were also statistically significant (t(38) = 2.02, p = .05, d = 0.63).

Later, on running a 3 (electrode: Fz, Cz, Pz) × 3 (groups: training, control, mindfulness) ANOVA at the 250 ms SSD only, the electrode * group interaction was also not statistically significant (F(4, 114) = 1.75, p = .15, η_p^2 = 0.058). However, again, there was a significant main effect of group (F (2,57) = 8.89, p < .001, η_p^2 = 0.238), with mindfulness group (M=1.63 μV, SD=1.94) having lowest amplitude, followed by training group (M=2.98 μV, SD = 1.75) and control group (M=4.16 μV, SD = 2.01).

Post-hoc tests revealed that the difference amplitudes were lower in both training (t(38) = 1.98, p = .05, d = 0.62) and mindfulness (t(38) = 4.06, p < .001, d = 1.27) groups compared to the control group. The training and mindfulness groups differences were also statistically significant (t(38) = 2.32, p = .03, d = 0.73).

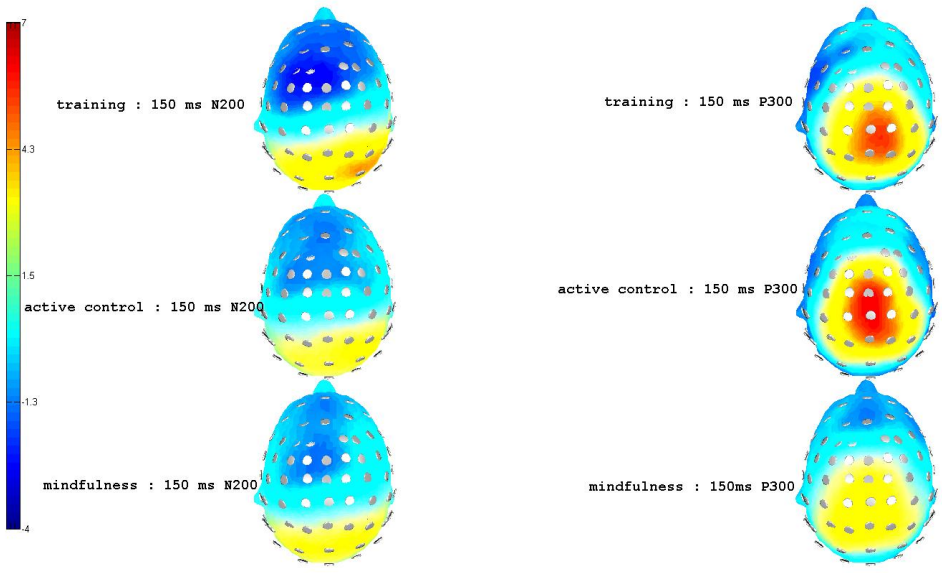
b) N200 mean amplitude

To explore the effect of group on the N200, we performed a 3 (electrode: Fz, Cz, Pz) × 3 (groups: training, control, mindfulness) × 2 (SST timing: 150 ms, 250 ms) mixed design analysis of variance (ANOVA). There were no significant main effects or interactions (e.g. electrode * SSD * group (F (4, 114) = 0.78; P = 0.54, η_p^2 = 0.027).

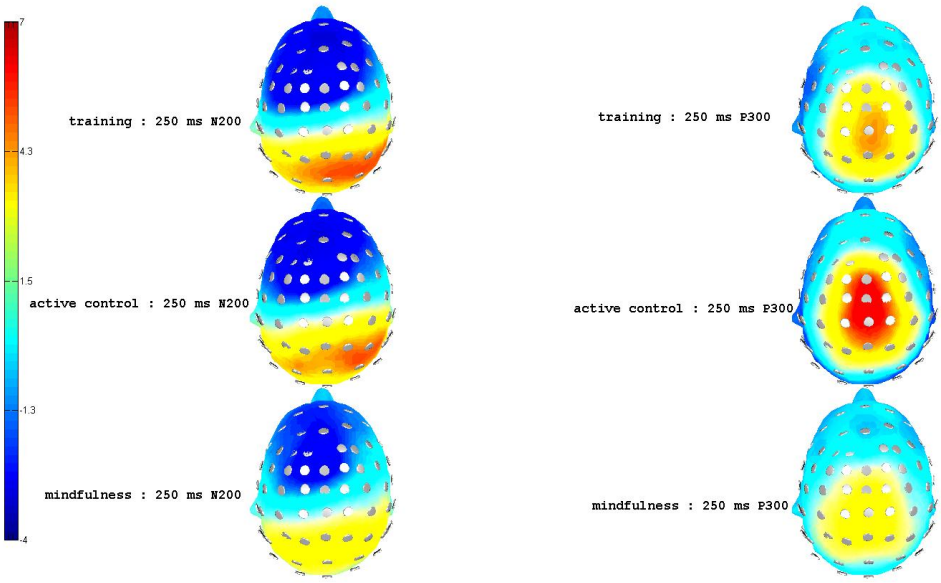
c) P300 Onset Latency calculations

We performed one-way ANOVA separately for both latency calculations at 150 and 250 ms SSD. There were no significant group differences (SSD=150 ms: F (2, 57) = 2.296, P=0.11, η_p^2 = 0.075; SSD=250 ms: F (2, 57) = 0.864, P=0.42, η_p^2 = 0.029), which accords with the behavioural data. Further to compare the effect of different intervention with active control group, we performed independent t-test separately at each SSD. At 150 ms SSD, training (t(38)= -0.42, p=0.676, d = 0.13) and mindfulness (t(32)= -1.78, p=0.084, d = 0.56) group did not significantly differ. Also at 250 ms SSD, training (t(38)= 1.06, p=0.294, d = 0.33) and mindfulness (t(38)= -0.24, p=0.814, d = 0.08) did not significantly differ.

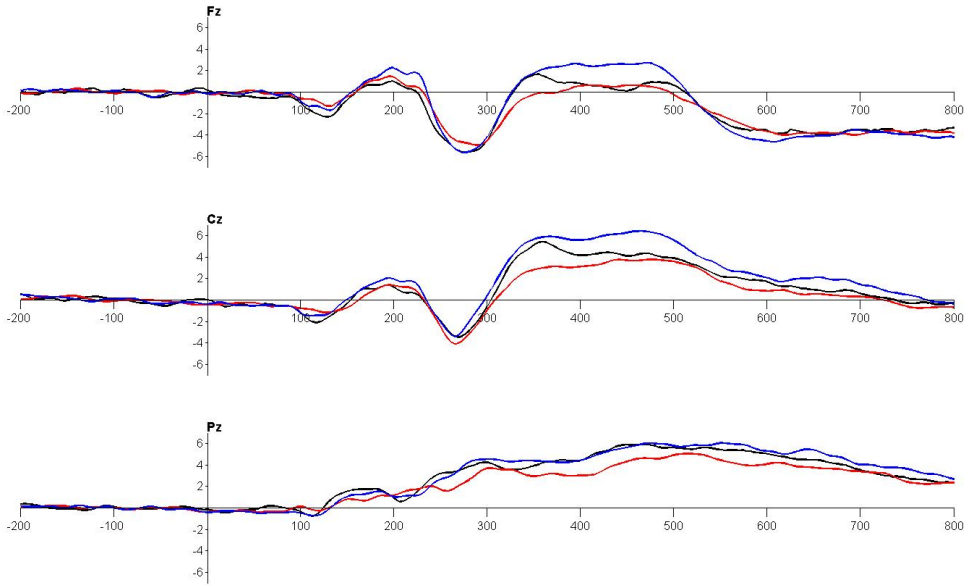
A: Topoplots at stop signal delay of 150 ms



B: Topoplots at stop signal delay of 250 ms



C: Waveform at 150 ms



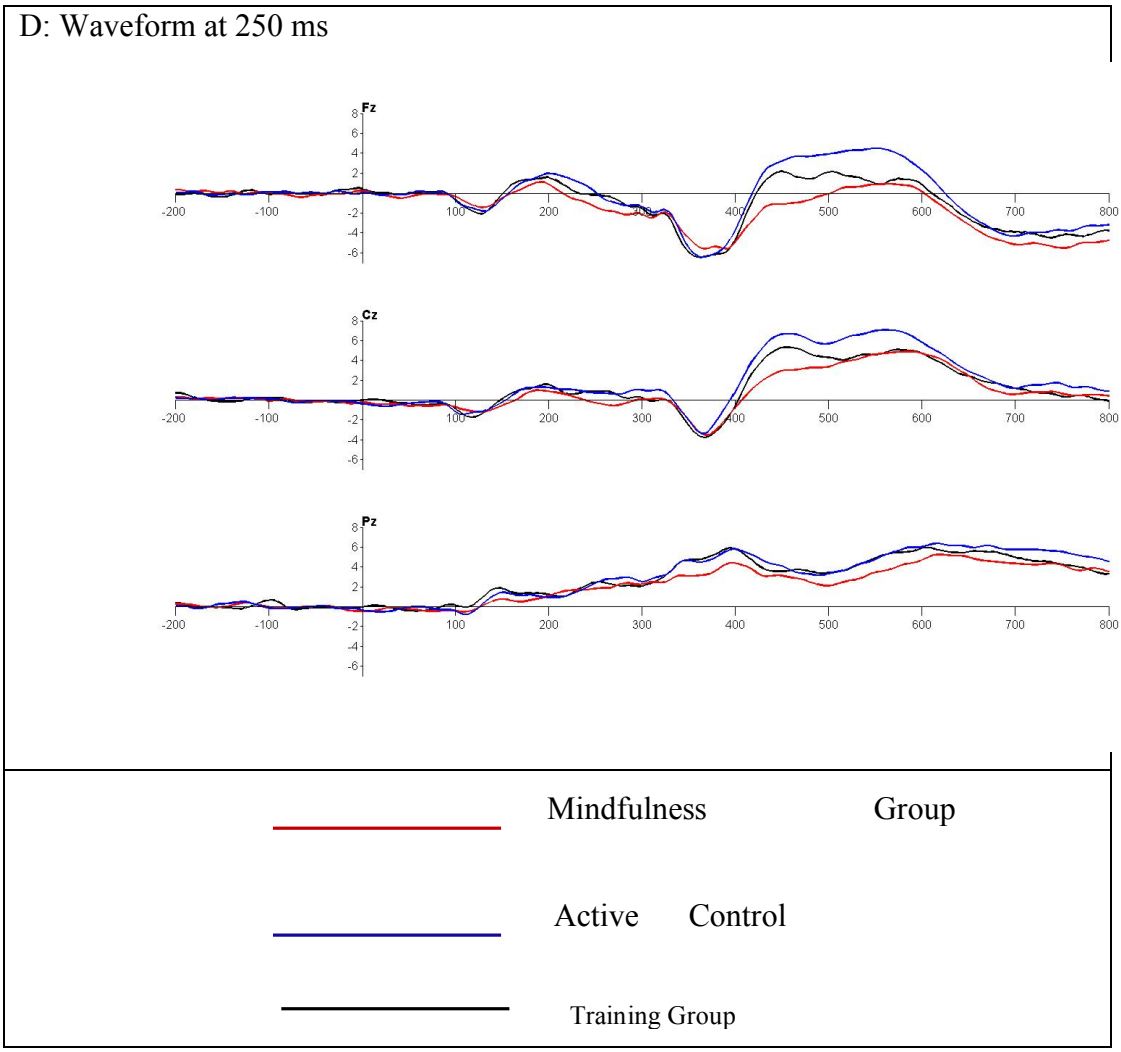


Figure 10 (A & B) Grand average isopotential Scalp maps of N200 and P300 components in all the groups at stop-signal task delays of 150 ms (A panel) and 250 ms (B panel). The topographic maps show the distribution of electrical potentials as seen from a top view. Negativity is plotted in blue colour and positive in red colour. (C & D) A comparison of ERPs along the midline electrodes (Fz, Cz and Pz) shown for all the groups 150 ms (C panel) and 250 ms (D panel) stop-signal delays. Training, active control and mindfulness group separate average waveforms are plotted using bold lines in blue, black and red colours respectively.

E. Discussion

The primary aim of this study was to explore the effects produced on response inhibition parameters, by a brief session of an inhibitory control training game and a mindfulness intervention in the heavy drinkers having a probable alcohol use disorder. Participants were randomly allocated to one of the intervention, either a smartphone based inhibition training game, a brief mindfulness intervention or an active control game. They were trained for 30 minutes following which they performed SST with a continuous EEG recording. The three groups did not differ at the baseline characteristics assessed by different questionnaires. With both the game interventions,

participants' performance improved in their respective games. With the BMI, participants scored more on TMS decentring subscale after intervention. Behavioural measures of Go RT and SSRT, assessed after intervention with SST, didn't show any statistically significant group differences with small effect sizes of the respective interventions. ERPs recorded while performing SST, were analysed. Significant differences in the P300 amplitude on successfully inhibited stop trials in the intervention groups were observed compared to the control group with large effect sizes of the respective interventions on the amplitudes. On trials with 150ms SSD, BMI group showed lower P300 amplitude. Further, on trials with 250ms SSD, both BMI group and inhibitory control training group showed lower P300 amplitudes compared to the control group. Also, the BMI group and the training group differences for P300 amplitudes for both 150 ms and 250 ms SSD, were statistically significant. The differences didn't reach significance for P300 latencies and N200 parameters.

1. Inhibitory control training

The important components in the ERPs during response inhibition are N200 and P300. N200 is considered as an early cognitive potential and P300 as a late one. The literature suggests that N200 recorded during response inhibition can be attributed to conflict detection arising from detection of the stop signal (Albert Kok et al., 2004). At the moment of N200-P300 complex generation, fMRI studies suggest an activation of inhibitory circuit areas like right PFC and dACC (Luijten et al., 2014). The most consistent finding of the P300 amplitude is that it is elevated in situations calling for a response suppression or changes (e.g., Kropotov, Ponomarev, Hollup, & Mueller, 2011; Randall & Smith, 2011). Previous findings from Jones et al., (2013) suggests an influence of the task instructions on the P300 amplitude in a SST. They found a lower P300 amplitude on correctly inhibited SST trials when the instructions were stressed on successful inhibition rather than rapid responding, changing the conflict generated in the task, and thereby less neuronal resources allocation for a conflict resolution.

In our study, we observed lower P300 amplitude on correctly inhibited SST trials after the participants were trained for the inhibitory control, with an in-house designed training game delivered through a smartphone. This change was only noted on the difficult trials of SST (with 250 ms SSD having a large effect size) and not on the relatively easier trials (with 150 ms SSD having a moderate effect size), which implies inhibitory control improvement on the difficult part of the task. This finding of lowered

P300 amplitude with difficult part was similar to the previous study by Benikos et al., (2013). They experimented the effect produced by the different difficulty levels of inhibitory control training in a GNG task, where between moderate and high task difficulty group, a decrease in the no-go P300 potential was observed. Similar observation of a decreased no-go P300 amplitude with the rising task difficulty was also noted in an another study (Gajewski & Falkenstein, 2013). Our findings add to the literature that the short-term inhibitory control training might first improve subtle conflict resolution. This can be initially noted only while the brain utilises a large number of cognitive reserves, such as when the task is difficult. These changes may go unnoticed on behavioural measures and when the demands on inhibitory control are relatively small (i.e. with a 150ms SSD).

Previous studies used a GNG task for an inhibitory training and assessment with EEG for monitoring the neuronal markers (Benikos et al., 2013; Gajewski & Falkenstein, 2013; Hartmann et al., 2016). For difficulty levels, they used extrinsic components like a rapid response on go trials by the instructions or by decreasing the response cut off timings of the Go trials. Also, the graded difficulty levels were assigned to different groups. Our study shows the advantage of using SST for inhibitory training assessment rather than the GNG, as it gives a freedom of having within-subject analysis with different stop signal delays (difficulty levels) in the same task. The P300 potentials generated by different SSDs in the same task gives a live example of the effective neuronal allocations at the different difficulty levels. So, the subtle difficulty associated with differential changes produced by the short-term inhibitory training can be noted. These changes may go unnoticed if a task with fixed difficulty is used for outcome measurements. The other possible reason for the differential effect of a significance noted at two SSD could be the effect sizes for the study. The study was designed in view of a large effect produced by the inhibition training on the outcome variables. In our study, the 250 ms of SSD showed a large effect size and so could reach to a statistical significance while the 150 ms of SSD showed a moderate effect size and the difference was not statistically significant. The change in the sample size of the study might have brought statistical differences at both the SSDs.

The training devices in the previous studies were designed by simple paradigm modulations and delivered on a computer screen (Houben, 2011; Houben & Jansen, 2011; Houben, Nederkoorn, et al., 2011b; Jones & Field, 2013). They lacked the

graphical inputs and associated fun elements with it. The inhibition training intervention in our study was delivered in the format of an engaging game delivered on a smartphone. It was also modified with the gaming elements and had a graphical appeal, making it more enjoyable. Participants also mentioned that the game based training was more interesting and engaging than the inhibition assessment SST task. They showed an improvement in the levels of training, in a short 30 minute duration, for both the games. Our experience with game training suggests that these trainings have a capability to produce similar neuro-cognitive changes found with computerised versions of the training. Also, the smartphone training showed effects on the computerised task, though electrophysiological, which have different stimuli than those used in the training game but are based on the same principle. This may be called as a near transfer effects demonstrated by different studies (Enge et al., 2014; Rass et al., 2015; Owen et al., 2010). As we demonstrated the changes with the mobile game happening at a neurocognitive level, this raise a possibility of producing far transfer effects sharing same cognitive domain if the same training is carried out for a longer term, as seen in many studies (Klingberg, 2010; Klingberg et al., 2005; Thorell, Lindqvist, Nutley, Bohlin, & Klingberg, 2009; Zinke, Einert, Pfennig, & Kliegel, 2012; Olesen, Westerberg, & Klingberg, 2004). But, studies using mobile phones for bringing the far transfer effects is very limited. So, future studies should explore the far transfer effects of these new mobile-based tools.

The N200 component is thought to represent a controlled mismatch detection process (Näätänen & Picton, 1987) and is therefore related to the stimulus discrimination (Johnstone, Barry, & Anderson, 2001; Johnstone, Barry, Anderson, & Coyle, 1996). We didn't observe any significant between-group changes in the N200 amplitude, following any type of training in our experiment. Also a small effect was noted on the N200 amplitude with the interventions. It is interesting to note that very few of the previous inhibition training studies have reported changes in N200 amplitude. These studies noted changes after multiple sessions of training (Schapkin et al., 2007) and at the later stages of task-related learning (Luu, Tucker, & Stripling, 2007). With shorter durations of training, the changes in N200 were not observed (Benikos et al., 2013; Gajewski & Falkenstein, 2013; Hartmann et al., 2016).

2. Mindfulness

Previous literature suggested an increase in TMS score with the mindfulness-based interventions. Lau et al 2006 in their study validating TMS showed a decentering sub-scale correlating with the clinical outcome of stress reduction with the mindfulness-based intervention and changed after the intervention. Vinci et al 2014 used TMS for a manipulation check with the brief mindfulness intervention. They found both changes in the curiosity and decentering subscale with a BMI. In our study, the decentering score with the BMI was trending towards significance at the post-intervention level. The within-group changes in any of the group were not statistically significant but had a moderate effect size. TMS is a subjective scale, the statistically non-significant changes could be due to the low sample size. Given that the Decentering subscale measures an individual's ability to distance oneself from thoughts, feelings, and physical sensations, it is possible the BMI targeted these measures in our sample.

We observed a blunted P300 amplitude on the correctly inhibited stop trials in the SST after participants were delivered a brief mindfulness intervention and had a large effect. The training in BMI was to enable focus on breathing and so prevent mind wandering. This may improve the inhibition task associated components, such as a stimulus detection and resource allocation for detecting a conflict in the stimuli and resolving it. This blunting of a P300 with BMI might be a sign of ease in a conflict resolution and needing less neuronal resource allocation for it. Moore et al., (2012) in their study in adults with a long-term mindfulness training also found a decrease in P300 amplitude in the Stroop task on the correctly identified incongruent trials, likely to suggest the decrease in resource allocation for an interference effect due to a mismatch between colours and words. On the contrary, in an another study by Sanger 2016, they found more negative N200 in the adolescent with a mindfulness training rather than any change in the P300, on trials of a visual oddball task requiring a response inhibition for its execution. The difference in our findings might be due to a difference in the participant population, duration of the training and the nature of the outcome task itself. Findings from our study suggest that mindfulness may help with a minimal resource allocation in the conflict resolution during an inhibition task in the heavy drinkers having a probable alcohol use disorder. There is also a possibility that a lowered P300 amplitude noted in our study are due to the relaxation gained after a mindfulness meditation helping to better concentrate. Better comparative results could be gained in

future studies by including groups performing the only relaxation and also by performing the intervention for a longer duration.

In this study, the differences between the P300 amplitudes with a brief inhibition training and a BMI were different, with more attenuation seen for mindfulness compared to the inhibition training. This difference could be due to the difference in the mechanism of action between the two interventions. According to the theoretical model for addiction, the general inhibition training is expected to strengthen the top-down executive/reflective system, while the mindfulness is believed to act on both the bottom-up impulsive system and the top-down reflective system (Verdejo-Garcia, 2016). The dual action of mindfulness might play a vital role in producing a more robust effect on the inhibitory control and having a large statistical effect with a brief intervention compared to the brief inhibition training which have a small to moderate statistical effect.

F. Limitations

First, as this was a pilot study, we used between-subject design. We generated ERPs only at one time-point, which was post-intervention. This design helped us to show between-group differences after the intervention but lacked the power predict whether these changes in the participants' performance was due to intervention or they had an inherent difference even prior to the intervention. Although the baseline subjective questionnaires didn't show any significant differences between groups, neuronal resource allocation with respect to inhibition may differ. This drawback can be overcome by acquiring ERP data both, prior to and after intervention (Woodman, 2010). Secondly, both the inhibition training and BMI were for a short duration of 30 minutes. The long-term practice may produce more robust results improving inhibition (Gladwin, Wiers, & Wiers, 2016). We also did not measure the cigarette smoking, a variable that is known to influence the amplitude of the P300 (Anokhin et al., 2000), in our participants. Third, it is difficult to comment on the changes we noticed in the inhibition related ERP with mindfulness. There is a possibility that the mindfulness training improved inhibition as discussed. However, the changes might be due to the relaxation of the participants with the mindfulness. In that case, simultaneous assessments of other executive function related components would have been used for comparison. Future studies can address this shortcoming by a simultaneous assessment of other executive functions along with the inhibition. Finally, we opted to use only two

stop-signal delays (150 and 250 ms) in order to generate a reliable pattern of electrophysiological activity at each stop-signal delay. The observation of a significant difference only over 250 ms SSD with the training game could be more efficiently described if more levels of SSD changing the difficulty like a range of delays which make inhibition very easy (e.g. 50 ms) in addition to delays which make inhibition almost impossible (e.g. 450 ms) in SST (Jones, Field, et al., 2013).

G. Conclusion

To conclude, this study was perhaps the first attempting to evaluate the objective ERP effects produced by a mobile phone inhibitory control game training and a brief mindfulness intervention in the heavy drinkers having a probable alcohol use disorder. We observed that the mean P300 amplitude could be a good objective tool for assessing the short-term effects of an inhibition training which, may be missed on a behavioural data analysis. Smartphone games can be used to train the inhibitory control. Further studies planned should aim for longer training duration and include series of EEG over time to observe within-subject effects of the training with a better sample size.

VI. The impact of multiple sessions of a smartphone inhibition training game on the electrophysiological markers of response inhibition and error processing in the alcohol-dependent patients

A. Abstract

The inhibitory control deficit and error processing anomaly is noted in subjects with alcohol dependence and is said to have a causal relationship. The event-related potentials generated during an inhibitory task performance are said to be reliable markers of the inhibition and its associated neuronal activities. Aim of this study was to observe changes in the response inhibition, attention, interference control and the error processing on training the inhibitory control with a smart-phone based inhibition training game, in subjects with the alcohol dependence syndrome (ADS), in comparison with the control training game. Baseline comparison was made between 30 ADS subjects and 30 healthy controls (HC) on the inhibition and error processing tasks. Further, the 30 alcohol-dependent subjects were randomly assigned to an inhibition training or control training group, with one of the training for two weeks (10 minutes twice a day). The outcomes were assessed with a Go No-go (GNG) task and a stop-signal task (SST) measuring the inhibition; and a flanker task measuring the attention, interference control and error processing, with simultaneous electroencephalography recording for the Event-related potentials (ERP). On comparing the baseline data between ADS subjects and HC, significantly delayed stop-signal reaction time (SSRT) in SST along with a blunted N200 and P300 amplitudes were noted for the correct inhibitory trials performance in ADS subjects. Further, ADS subjects showed the blunting of N200 amplitudes with increasing inhibitory task difficulty, not noted in the HCs. In the GNG task, blunted P300 amplitudes were noted in the ADS subjects. In the flanker task, more error rate and a blunted error related late potential along with more negative early potential was noted in the ADS subjects. These findings validate the tasks ability to detect inhibition. On training, a significant rise in N200 negativity on correct performance of inhibitory trials in the SST was noted with inhibition training compared to control training. No other changes were noted with the training. In conclusion, ADS subjects have an impaired inhibition and error processing, with a major difference in the conflict detection on an increased inhibitory demand. Multiple

sessions of Inhibition training for two weeks improves the conflict monitoring process during a response inhibition.

B. Introduction

Executive functions consist of a group of cognitive facets controlled by the frontal lobe, one of which is the inhibitory control. In subjects with the alcohol dependence syndrome (ADS), for instance, a difficulty in inhibiting the initial impulse to drink alcohol, or aborting the ongoing process of drinking becomes challenging due to an underlying deficit in the response inhibition. This imbalance between the bottom-up impulsive system and the top-down reflective system in ADS is considered as one of the causative factor for dependence (Jarmolowicz et al., 2013).

The inhibitory control can be assessed by electrophysiological markers such as the event-related potentials (ERP). These markers related to an inhibition process are found altered in patients with an ADS. Kamarajan et al., (2005) in there study observed that the accuracy was impaired in alcohol-dependent subjects compared to the controls during a Go No-Go (GNG) task performance, which corresponded with a lower amplitude of P300 both at the go and no-go trials and decreased anteriorisation of a topography during the No-Go trials. A similar finding of a blunted amplitude for P300 on the no-go trials in ADS patients was also observed in some other studies (H. L. Cohen et al., 1997; Colrain et al., 2011). All these studies suggest an impaired response inhibition associated neuronal activity in ADS subjects. Along with response inhibition, the processing of error is also found to be impaired in subjects with an ADS. Padilla et al., (2011) in their study found larger Error-related negativity (ERN) amplitudes following the incorrect responses while performing the Flanker task in the abstinent alcohol-dependent male subjects compared to the controls.

The cognitive training methods, connected to the neuroplasticity mechanisms in order to enhance a cognition related to impaired neural system, had shown a promising evidence in the substance use disorders (SUD), along with the other psychiatric disorders [for details see Keshavan, Vinogradov, Rumsey, Sherrill, & Wagner, (2014)]. In the SUD, Bickel & Collegues, (2011) trained the working memory with computerized tasks in the stimulant users for between 4 to 15 sessions in about 25 days and found a reduced impulsivity and delay discounting compared to the control intervention. Brooks et al., (2017) in their recent study exploring the effects of a working memory training in the methamphetamine-dependent patients for 20 hours

across 4 weeks, found an improvement in the self-reported impulsivity and a lack of planning compared to the patients receiving a usual clinical treatment.

In the alcohol use disorder, two types of cognitive training interventions are tried for training the imbalance between the impulsive and reflective system. One type of training is said to improve the overactive bottom-up impulsive system and another type to strengthen the weak top-down executive system. One of the study training an approach bias (training impulsive system) in the alcohol-dependent patients with 4 brief sessions for 15 minutes on 4 consecutive days, transformed the approach bias for alcohol into an avoidance bias. This later translated behaviorally by decreasing the relapse rate over 1 year when compared with the control groups (Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011a). Gamito et al., (2014) in a study training the working memory (training executive system) using a smart-phone game in the alcohol-dependent patients, with each session of 60 minute duration with 2-3 sessions/ week over the usual 4 to 6 week period of treatment, found an improvement in the overall frontal lobe function with the training compared to patients receiving the treatment as usual. These studies suggest that both the type of training can prove effective in the ADS subjects.

There is some evidence suggesting that training a response inhibition is possible and could further influence peoples' alcohol consumption. There are two types of inhibition training attempted: the associative inhibition training with an aim to train automatic response inhibition devaluating the alcohol-associated cues and the non-associative/general inhibition training aiming to strengthen the top-down function of controlling an impulse (Antonio Verdejo-Garcia, 2016). Many studies had attempted the associative inhibition training, by coupling an objective cue with the inhibitory trial (Jones et al., 2016). For example, Houben & colleagues, (2011) in their study coupled the alcohol-related cues with the no-go trials in a GNG training task. On training the heavy drinking college students to inhibit an alcohol cue, they found a decrease in the weekly alcohol consumption compared to the group trained to go for the alcohol cues. Similarly, Jones & Field, (2013) found an improvement in the inhibition and a decrease in alcohol consumption by training the automatic response inhibition with the stop-signal task (SST) in heavy drinkers.

There are only a few studies which attempted the non-associative inhibition training. Bartsch et al., (2015) trained the inhibitory control in heavy drinkers for 4 consecutive

days and compared with a control placebo training. They neither found improvement in the inhibition (near transfer) nor a decrease in alcohol consumption (far transfer) with the training. Similar, null effects were noted in an another study training the inhibition for a 4-week duration (Field et al., in prep). Although these studies did not show any significant effect of the intervention (Field et al., in prep; Bartsch, Kothe, Allom, Mullan, & Houben, 2015), the evidence about the non-associative type of training is limited and needs further research.

It has been a general observation that a cognitive training can produce near transfer effects (changes in the same training component) but fails to generalise the training effects (far transfer: changes in the other cognitive components than that of the training) (Simons et al., 2016). However, some the previous studies tried training executive function in the ADS subjects, with an aim to train the impaired top-down reflective system, found a generalisation of the training effects (Gamito et al., 2014). Their training not only improved a performance of the ADS subjects in the same task (near transfer effects) but also improved the other task performances controlled by the frontal lobe (far transfer effects). Similarly, the response inhibition training may also bring transfer effects to the domains shared in an executive functioning with the inhibition (Miyake et al., 2000), such as the attention and interference control.

The response inhibition can be trained using a task used for measuring the inhibition such as the GNG task and the Stop-signal task (SST). Training the inhibition on a mobile phone has its own advantages. Subjects with the alcohol dependence are shown to have an inability to sustain attention for a longer duration (Jarmolowicz et al., 2013). If an intervention is booring and does not attract attention for a longer duration, we may not observe an expected result. For this, a gamified version of the training may prove helpful. Also, the training provided on a mobile phone makes it handy and can be delivered in the field. Our inhibition training game designed on the similar principles might produce the targeted change in the ADS subjects.

Inhibitory control is assessed majorly by two tasks, a Go-Nogo (GNG) task and a Stop-Signal Task (SST) (C.D. Chambers et al., 2009; Dalley et al., 2011; F. Verbruggen & Logan, 2008), measuring two different attributes of the inhibitory control. The GNG task measures action restraint ability and the SST focus on the action cancellation ability. In a GNG, participants are asked to respond quickly for a frequent stimulus and to restraint their action by inhibiting the infrequent one. The inhibitory control in this

task is reflected by the proportion of correctly inhibited no-go trials. In a SST, participants are instructed to quickly respond to a stream of go stimuli (G.D. Logan et al., 1984). Infrequently, the primary stimulus is followed by a stop cue indicating to cancel an already initiated action. The delay of a stop cue from a go stimulus is termed as a stop signal delay (SSD). The inhibitory control in this task is indexed by a stop-signal reaction time (SSRT). Both the GNG and SST are supposed to have a common inhibitory break, along with general processes such as an attentional monitoring and a salience processing (Corbetta & Shulman, 2002; Hampshire et al., 2010; Li et al., 2006).

The N200 and P300 are two ERP components related to the inhibitory control associated brain activity. The N200 is thought to reflect the top-down functioning required to stop an automatic tendency (Falkenstein, 2006; Kaiser et al., 2006), which correlates with the behavioural outcome of an inhibition (A. Dimoska et al., 2006; Falkenstein et al., 1999; Van Boxtel et al., 2001), along with the conflict detection in an early phase of inhibitory control (Falkenstein, 2006; S. Nieuwenhuis et al., 2003). The N200 is also said to be an early cognitive index of processing, which is necessary to implement the inhibitory control rather than an actual inhibitory break. The P300 is an another ERP component reflecting the temporally late stage of an inhibitory process which is closer to the actual inhibition of the motor system (G.P.H. Band & Van Boxtel, 1999; A. Dimoska et al., 2006; A. Kok et al., 2004).

In the previous study of this thesis (please see Chapter 4 for details), we trained response inhibition for a short duration of 30 minutes in the heavy drinkers. The training showed an improvement in the ability to resolve a conflict when dealing with a difficult inhibitory situation. This was suggested by a blunted P300 amplitude on the correct performance at a difficult inhibitory trial. Training the inhibition for multiple sessions in subjects with the alcohol dependence might enhance the effects produced by a short-term training. Also, the training for multiple sessions might bring a N200 associated change. As our training game (described in chapter 2) has components of both an action restraint and an action cancellation inhibition training, this training may show the changes differentially in both the processes. So, both the GNG task and the SST were used for an inhibitory outcome assessment in this study.

Error processing is noted to be aberrant in the ADS subjects (Luijten et al., 2014). It shares the neuronal network with inhibition processing. Apart from this, attention and interference control has also been seen to share cognitive networks with inhibition

(Miyake et al., 2000; Miyake & Friedman, 2012). The inhibition training might produce far transfer effects on these cognitive abilities of executive function.

In the present study, our first aim was to compare the ADS subjects with HC to confirm that the assessment tasks are capable of detecting the behavioural and ERP impairments associated with the inhibition. Further, we trained the ADS subjects with the smartphone-based inhibition training (IT) game or the other game with similar graphics but without an inhibition training (control training (CT)). The second aim was to test the effect of a repeated performance of the smartphone game on the inhibition related behavioural and neural markers showing impairment. The hypothesis was that the 2 weeks of an IT intervention would bring a near transfer effect of an improvement in the inhibition and a far transfer effect of an improvement in the attention and interference control at the behavioural level and an error processing at the neuronal level, compared to the CT intervention. The outcome assessments used to explore the near transfer effects were a GNG task for the action restraint process of an inhibition and a SST for the action cancellation process of an inhibition. For assessing the far transfer effects of an inhibition training on the attention, interference control and error processing, the Flanker task was used. The simultaneously acquired event-related potentials during these task performances were used to explore the transfer effects at a neuronal level.

C. Methods

1. Sample size calculation

The sample size was calculated with the help of G*power software. The mixed Analysis of Variance (ANOVA) was the predicted analysis strategy for a baseline comparison of the outcome measures between the ADS subjects and healthy control and the repeated measure ANOVA was the predicted analysis strategy for a comparison the effect of interventions in the ADS. The probability of a type 1 error (α) was assumed to be 5 %. The expected power of the study was 80%. The ERP is a sensitive measure of a cognitive load (expecting a large effect size of 0.8), the ultimate sample size for the study for a baseline comparison between the ADS subjects and healthy controls, in order to have a sufficiently acceptable statistical power, was 21 in each group. Further, with the expectation of a large effect size (0.8) based on Houben et al., 2012, the desired number for comparing the effect of an intervention on the ERP in the ADS subjects was 15. With the expected drop out of 10% (as the study was conducted in an inpatient

setting), the ultimate sample size for determining the effect of our intervention, in order to have a sufficiently acceptable statistical power, was 16 in each group.

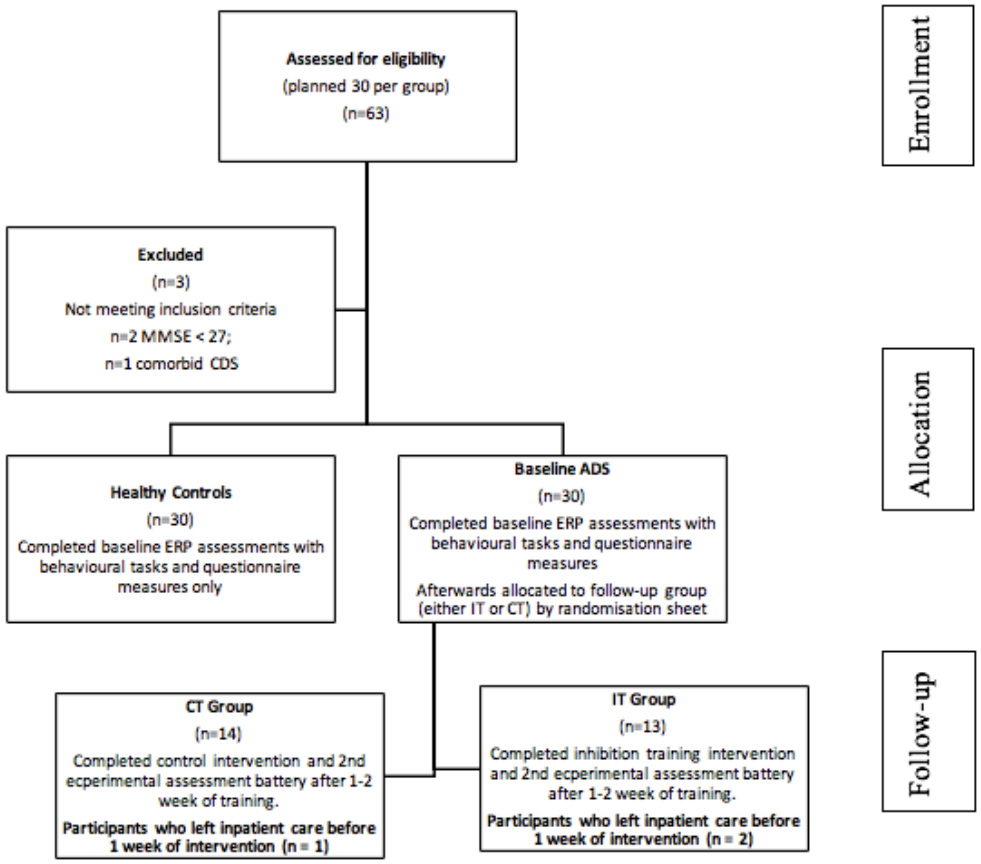


Figure 11 CONSORT diagram to describe how healthy controls (HC) as well as Alcohol Dependence Syndrome (ADS) participants were recruited to either the Inhibition training (IT) group or the control training (CT) group.

2. Participants:

See Figure 11 for CONSORT (Consolidated Standards of Reporting Trials) recruitment diagram. 33 ADS individuals and 30 healthy controls (HC) aged between 18 and 60 were initially invited for a screening to further take part in the study, at an in-patient clinic, the Centre for Addiction Medicine, National Institute of Mental Health and Neurosciences (NIMHANS) in Bangalore, India. On completing the study, 27 ADS in-patient subjects were incorporated in the data analysis (n = 2 did not meet the inclusion criteria on screening and n = 3 patients dropped out and returned home before completing the experiment/programme). The mean duration of alcohol exposure prior to the admission for the participants who completed the study over 2 weeks was 14.96

years (s.d. = 7.04). According to the clinicians, all patients in the study were abstinent from alcohol use for a minimum duration of a week before being randomised to one of the two groups (via a random number table generated through an excel sheet for simple randomisation (Suresh, 2011)). After completing a baseline questionnaire, the ADS participants were given either (a) the inhibition training game (n = 15) or (b) the control training game (n=15). In addition, both the groups received a treatment as usual for the in-patient duration as per the hospital protocols. The study was approved by the NIMHANS Ethics Committee.

The inclusion criteria for the ADS group were as follows: (a) Satisfies criteria for Alcohol dependence as per ICD-10 (b) No co-morbid psychiatric disorder- namely schizophrenia, bipolar and other affective disorders, pervasive developmental disorder, obsessive-compulsive disorder, anxiety disorders; (c) No co-morbid medical or neurological disorder that might significantly influence brain structure & function.

Inclusion criteria for the HC group were as follows: (a) no history of abusive substance use including alcohol (excluding nicotine); (b) no current or previous history of psychiatric disorder (including clinical anxiety, depression and occasional drug use) as confirmed by screening questionnaires.

3. Clinical settings

The ADS patients were recruited from an in-patient, the CAM. The usual treatment program runs for a total of 3-week duration. The Treatment as Usual (TAU) involved 1-h daily sessions of a group therapy from Monday to Friday for 3 weeks, a total of 21 one hour sessions. In addition, patients attended the psycho-education sessions addressing a basic and social skill development and the in-patient physical activities. In the clinical management, 1st week was a detoxification period when the patients with withdrawal symptoms were detoxified with benzodiazepines such as lorazepam with a loading dose regimen (Kattimani & Bharadwaj, 2013). Following the detoxification, patients were started with an anti-craving agent such as the naltrexone, baclofen and acamprosate. To make a note, the initial 1 week of the program was considered as an induction period and so the researchers did not interview the patients during this phase. Thereafter a post 72 hours the last dose of detoxification, researchers were given 2 weeks for conducting the study; for IT and CT groups, this contained a baseline and a follow-up questionnaire and daily 10 minutes twice a day of an allotted game intervention.

4. Clinical measures

a) Clinical interview at the treatment centre

In the first week, all patients undertook a routine one-to-one interview with a trained clinician to establish the diagnosis and comorbidities, ascertaining the AUD and a need to prescribe any medication. Based on the knowledge from clinical interviews and after a go-ahead from the clinical team, we recruited the currently abstinent in-patients with a minimum of 72 hours after the last detoxification dose and subsided withdrawal symptoms. The patients who were likely to take the whole 3-week program at the in-patient setting were recruited.

b) Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998)

The M.I.N.I. was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Both patients and healthy controls were screened for major psychiatric disorders in order to fit for the inclusion criteria. This was used to exclude the dual diagnosis among the participants.

c) International Classification of Diseases (ICD 10) checklist alcohol use disorder (Janca et al., 1994)

This contains questions about the symptoms associated with alcohol use, to establish any 3 of the total 5 criteria of a dependence, craving, tolerance, withdrawal, salience and persistent use despite harm. This scale was used on the ADS subjects to confirm the diagnosis.

d) Alcohol Use Disorders Identification Test (AUDIT) interview version (John B Saunders et al., 1993)

AUDIT is a screening questionnaire for detecting the hazardous or harmful drinking habits. This gives a total score ranging from 0 to 40, with the higher scores indicative of a more severe alcohol use disorder. This scale was used in the HC to rule out a problem drinking.

e) Barratt Impulsiveness Scale version 11(BIS-11) (Patton et al., 1995)

Barratt Impulsivity Scale (BIS) questionnaire contains 30 items. It is meant to measure individual impulsivity. The Items are scored on a scale (rarely/never, occasionally, often, almost always/always) to derive six first-order factors (attention, motor, self-control, cognitive complexity, perseverance and cognitive instability), three second order factors (attentional, motor and non-planning) and a total impulsivity score. This

scale was used both on the ADS subjects and HC to get a subjective measure of impulsivity.

5. Tasks

The tasks were delivered on an LCD screen placed at the eye level of the participants at a one-meter distance in a quiet isolated room. The responses were collected through a response button device having 5 buttons in a row. An EEG recording was performed simultaneously during all these task performances.

a) Stop signal task

The stop-signal task had 2 symbols, cross ‘X' or circle ‘O', displayed at the centre of the display. Participants were instructed to press the ‘one' key of response box upon presentation of ‘X' and the ‘two' key upon presentation of ‘O', using a different finger of the right hand. The go stimulus was uninterrupted on 75% of trials. On 25% of trials a visual ‘stop' signal, a red box surrounding the symbol was presented at one of the four delays (150 ms, 200 ms, 250 ms and 300 ms) after an onset of the go stimulus, which signalled participants to inhibit their prepotent motor response.

Each trial started with a fixation point at the centre of screen for 200 ms followed by a stimulus, with a timeout of 1000 ms. The inter-trial interval was kept as 1500 ms. The task had 10 blocks, each block had 64 trials in which 48 were go trials and 16 were stop trials (4 with each SSD of 150 ms, 200 ms, 250 ms and 300 ms) randomly presented. The main task preceded with a practice block of 16 trials having 8 Go trials and 8 stop trials (150 ms SSD). Each block was followed by a 30-second break. The task took 30 minutes to complete.

The SST task used in this study had a visual inhibitory cue in form of red box around the go stimuli, while in the previous 2 studies SST contained auditory stop signal cue. In the previous study, the SST task had 2 different stop-signal delays (SSD) of 150 ms and 250 ms. The task used in this study had four SSDs, 150 ms, 200 ms, 250 ms, and 300 ms. This was planned to find the difference in performance ranging from an easy to difficult inhibitory trial. In order to get at least a minimum of 10 artefact free trials for each SSD for the averaging, a total of 40 trials were included in the task for each SSD. As total frequency of the stop trials cannot exceed 25% (infrequent trials) for measuring the inhibitory ability, the task was prolonged. But, adequate care was taken by interim small breaks to avoid a fatigue.

b) Eriksen Flanker task (A S Euser, Evans, Greaves-Lord, Huizink, & Franken, 2013)

A modified version of an Eriksen Flanker task (Eriksen & Eriksen 1974) was used for assessing the error related cognitions. The behavioural and ERP data was collected while performing this task. The task consisted of four different arrow strings (<<<<<, <<><<, >>>>> and >><>>, n = 400), randomly presented at an equal probability. The arrows were either congruent (<<<<<, >>>>>, n=200) or incongruent (<<><<, >><>>, n=200), appearing in black on a white background. The subjects were instructed to respond with speed and accuracy to the central target arrow (< or >) of a shown arrows' string. The response was asked to be made with a response button device having 5 buttons in a row. The 3rd and 4th buttons were used for the response to the central arrow of a string. Instructions were to press the 3rd button with their left index finger if the central arrow was directed towards left (<) and the 4th button with their right index finger for a central right arrow (>). The trial started with a 150 ms fixation cross (+) were the central arrow from the string would appear on the screen. Arrows were presented for 58 ms. After the stimulus, a blank screen was presented for 642 ms during which the subjects had to respond. The responses were followed by a feedback screen (duration 500 ms) about the correctness of the trial (Correct (in blue) for a correct response, Incorrect (in red) for an incorrect response, respectively). When no response was made within the response period, a feedback (no response (in red)) was given informing that their response was not fast enough. Before the next trials, a blank screen was visible for 100 ms. The experimental session was preceded by a practice block of 32 trials. The experimental phase was divided into four blocks of 100 trials each followed by an intermediate short break of 30 seconds. The total duration of the task was approximately 15 minutes.

c) Go No-go task

The task consisted of two types of stimulus (‘X' (75%) and ‘O' (25%), n = 128), randomly presented. The response was asked to be made with a response button device having 5 buttons in a row. The 1st button was used for the trial response. Participants were instructed to respond with a speed and accuracy to X (Go trial) by pressing the button with the right index finger and to prevent response for an O (No-go trial). The trial started with a 200 ms fixation cross (+) followed by either of the X or O stimulus with a response time out of 1000 ms. The inter-trial interval was 1500 ms. The task

was presented in 3 blocks, containing a practice block and 2 main blocks. The practice block contained 16 trials with 12 go trials and 4 no-go trials. Each main block had 64 trials with 48 go trials and 16 no-go trials. Between each block, a break of 30 seconds was provided.

6. Game interventions

a) Inhibition Training (IT) intervention game

This was the training version of the game, consisting of multiple stages and levels targeting the inhibitory control. The details of the game are mentioned in the methods chapter. Participants started from level 1 of 1st stage and proceeded ahead.

b) Control Training (CT) intervention game

This was a placebo control intervention with came graphics and theme as with the IT game, but not having components targeting the inhibitory control. Refer to the methods chapter for details about this game.

7. Procedure

The candidate ADS participants recognised by the clinical staff, were interviewed by the researcher using the screening questionnaires at CAM. For the HC group, the screening questionnaire interview was conducted at the Centre for Brain Mapping lab (NIMHANS). The screening questionnaire for the ADS participants included MINI, ICD-10 Alcohol use disorder checklist, OCDS and BIS-11. For the HC participants screening questionnaire included MINI, AUDIT and BIS – 11.

After screening, the eligible ADS participants were invited to the Centre for Brain Mapping (NIMHANS) to assess the outcome parameters under the study. All the Participants (ADS and HC) took part in an EEG session, which lasted for approximately 90 minutes. They were seated on a chair in an isolated room with the light and sound-attenuation. After the EEG electrodes were attached, subjects completed a stop signal task. Subsequently, the Eriksen Flanker Task was administered in order to examine the error-processing. After completion of the Flanker Task, participants performed a Go-NoGo task. Later, the EEG electrodes were detached.

The HC participants were debriefed about the experiment. For ADS participants, completing the EEG experiments, were introduced to either the IT or CT game loaded over a smartphone-tablet (Lenovo). They were directed with the instructions to play. Later, the 1st session of the training was completed by the participants. The ADS participants were advised to complete their respective scheduled play session (10

minutes) daily between 8 am to 2 pm and 2 pm to 7 pm under observation, while in the ward. After 2 weeks, the EEG session was repeated and the ADS participants were debriefed. The participants in this study were not given any monitory benefits for the participation. The attendance was on the voluntary basis.

8. EEG recording and processing

The EEG was recorded using a 128-channel HydroCel Geodesic Sensor Net (Electrical Geodesics, Inc., Eugene, OR). All electrodes were kept below 50 KΩ (Ferree et al., 2001). The recording was performed with a reference as Cz electrode.

The continuous EEG was band-pass filtered at 0.1–35 Hz with the zero-phase shift FIR filters. The data were then segmented in stimulus-locked epochs of 2000 ms for the SST (500 ms before and 1500 ms after Go stimulus) and the GNG (500 ms before and 1500 ms after stimulus) and response-locked epochs of 800 ms for the flanker task (100 ms before and 700 ms after response). Only correct response to the respective trials was included in the analysis. The epoch durations were similar as in the previous study (chapter 4). Trials were then sorted according to the task and load. The trials that exceed a voltage threshold of 100 μV and those with blinks or ocular movement artefacts were excluded. The trials with more than 10 bad channels were also excluded. These cleaning of trials was first carried out with an automatic tool. They were later manually inspected for the excluded trial. The data were then averaged and re-referenced to the average reference. The periods of 200 ms pre-stimulus for the SST and GNG and 100 ms pre-response for the flanker task served as a baseline.

For the SST and GNG, a median latency for peak amplitude was considered as a mark and mean amplitude was measured between ± 100 ms of median latency of positive peak amplitude for P300 and ± 50 ms of median latency of negative peak amplitude for N200. The range of duration used for measuring the mean amplitude as in Table 16. As per the grand average, the ERN component for flanker task was derived as a mean value in the 25–100 ms time window after onset of a response from error trials and CRN component was derived from same time window from correct trials. Pe component was defined as a mean value in the 200–350 ms time window and was derived from error trials (A S Euser et al., 2013).

There were some differences in the EEG acquisition and analysis between the present study and the previous study (chapter 4). The EEG acquisition in the previous study was carried out by the Biosemi 64 channel system, while the present system acquisition

was with the 128 channel EGI geodesic system. For the analysis purpose, in previous study Matlab based EEGLAB and ERPLAB tool boxes were used, while the present study used the net-station tool. The parameters used for epoch duration were same between these studies. In the previous study, the artefacts were cleaned using the independent component analysis, while the present study used both the manual and automatic method of an artefact detection. In the previous study (chapter 4), for P300 and N200 latencies the between-group differences were not noted, so the standard time durations of the P300 and N200 amplitude extraction was used. In this study, on grand averaging the waveforms, a latency difference between groups was observed visually. So, the median latency method was used to capture most of the amplitudes of respective waves under the mean amplitude calculation.

Table 16 Range of time used for mean amplitude calculation in the Go No-go task and Stop signal task.

Median	Healthy controls	Alcohol dependent subjects Baseline	Alcohol dependent subjects Follow-up
Go No-go task			
N200			
Go	160 – 260 ms	150 – 250 ms	170 – 270 ms
No-Go	180 – 280 ms	160 – 260 ms	170 – 270 ms
P300			
Go	280 – 480 ms	260 – 460 ms	270 – 470 ms
No-Go	280 – 480 ms	370 – 570 ms	360 – 560 ms
Stop signal task			
N200			
Stop-signal delay 150 ms	300 – 400 ms	300 – 400 ms	300 – 400 ms
Stop-signal delay 200 ms	350 – 450 ms	360 – 460 ms	360 – 460 ms
Stop-signal delay 250 ms	410 – 510 ms	410 – 510 ms	410 – 510 ms
Stop-signal delay 300 ms	450 – 510 ms	490 – 590 ms	460 – 560 ms

P300			
Stop-signal delay 150 ms	460 – 660 ms	490 – 690 ms	450 – 650 ms
Stop-signal delay 200 ms	500 – 700 ms	560 – 760 ms	510 – 610 ms
Stop-signal delay 250 ms	540 – 740 ms	620 – 820 ms	560 – 760 ms
Stop-signal delay 300 ms	610 – 810 ms	680 – 880 ms	630 – 830 ms

D. Statistical analysis

1. Behavioural data

All the statistical analysis was carried out with help of Statistical Package for the Social Sciences (SPSS – 16). The effect sizes were calculated for all the comparisons. For ANOVA, partial eta squares were calculated while for t-tests' cohen's-d were computed. For partial eta square, 0.01, 0.06 and 0.14 were considered as small, medium and large effect sizes respectively (A. Field, 2013). For cohen's-d, 0.2, 0.5 and 0.8 were considered as small, medium and large effect sizes respectively (A. Field, 2013).

a) Stop-signal task

The Go reaction time (GoRT) and SSRT were two different behavioural outcomes derived from the SST. The SSRT was calculated by an integration method (G. D. Logan et al., 1997) separately for all SSDs. In this method, a reaction time for correct 'go' trials is ranked in an ascending order of speed (fastest to slowest). Then Nth reaction time is obtained from the ranked 'go' trials by multiplying the number of 'go' reaction times in the distribution by the proportion of commission errors. The Nth reaction time was calculated individually for each SSD from their respective commission errors. Later SSD was subtracted from the Nth reaction time to get the individual SSRT (Frederick Verbruggen & Logan, 2009a).

The effects on response inhibition were assessed by performing multiple mixed design ANOVA and MANOVA. For baseline assessment, 4 SSD (SSRT 150, SSRT 200, SSRT 250 and SSRT 300) * 2 group (HC and ADS baseline) mixed design ANOVA was performed, followed by a post hoc analysis. For the intervention-related changes, 2-time points (ADS baseline and follow-up) * 4 SSD (SSRT 150, SSRT 200, SSRT

250 and SSRT 300) * 2 interventions (IT and CT) MANOVA was performed. For the GoRT analysis, an independent t-test was performed for the ADS baseline comparison with HC and 2-time points (ADS baseline and follow-up) and 2 interventions (IT and CT) mixed ANOVA was performed for assessing the intervention effects.

b) Flanker task

To analyse behavioural data for the flanker task, first the baseline assessments of patients were compared with the healthy controls, later the effects of intervention in patients were processed. To proceed with the baseline assessments, two sets of 2 * 2 mixed analyses of variance (ANOVAs) were performed with Group (Patients versus Healthy Controls) as between-subject factor, Congruency (congruent versus incongruent) as within-subject factor (Group * Congruency), and consecutively the percentage of errors and the percentage of missing responses as the dependent variables. For response time (RT) data, two sets of 2 * 2 repeated-measures ANOVAs were employed: (1) Group * Congruency (RTs on congruent versus incongruent trials); and (2) Group * Correctness (RTs on correct versus incorrect trials). For analyzing effect of intervention on the patients, two sets of 2 * 2 * 2 multivariate analyses of variance (ANOVAs) were performed with intervention (inhibition training versus Control training) as between-subject factor, Congruency (congruent versus incongruent) and time points (baseline versus follow-up) as within-subject factor (Intervention * Congruency * time points), and serially the percentage of errors and the percentage of missing responses as the dependent variables. Later for response time (RT) data, two sets of 2 * 2 * 2 multivariate ANOVAs were employed: (1) Intervention * Congruency *time point (RTs on congruent versus incongruent trials); and (2) Intervention * Correctness * time points.

c) Go No-go task

Go reaction time (GNGRT) and proportion of commission errors (CE) were taken as dependent variables. For baseline comparison, independent t-tests were performed for differences between HC and ADS baseline. For comparing effects of the intervention, 2 time-points (baseline and follow-up) * 2 interventions (IT and CT) MANOVA was performed separately for both dependent variables.

2. EEG data

a) Latency

The latency of the peak amplitudes was taken at the Pz electrode for GNG task. The analysis was separately carried out for N200 and P300 latencies. Later, for assessing effects of interventions on ADS patients, 2 time-points (baseline and follow-up) * 2 interventions (CT and IT) separately were performed for go and no-go trials.

b) Amplitudes

(1) SST

SST amplitudes were analyzed at Fz, Cz and Pz electrodes (Jones, Field, et al., 2013). A 2 * 3 * 2 mixed ANOVA was performed with 4 SSD wave types (SSD 150, SSD 200, SSD 250 and SSD 300), three electrode amplitudes (Fz, FCz and Cz) and 2 groups (patients and healthy controls). Further t-tests were performed for post-hoc analysis of significant interactions. A similar analysis was also performed for both N200 and P300 waves amplitudes separately.

(2) Flankers task

For ERN-CRN amplitudes were analyzed at Fz, FCz and Cz electrodes (A S Euser et al., 2013). A 2 * 3 * 2 mixed ANOVA was performed with two wave types (ERN and CRN), three electrode amplitudes (Fz, FCz and Cz) and 2 groups (patients and healthy controls). Further t-tests were performed for post-hoc analysis of significant interactions. A similar analysis was also performed for Pe waves amplitudes (wrong/right responses) at Cz, CPz and Pz electrodes (A S Euser et al., 2013).

(3) GNG task

GNG amplitudes were analyzed at Fz, Cz and Pz electrodes. A 2 * 3 * 2 mixed ANOVA was performed with 2 trial types (Go and no-go trials), three electrode amplitudes (Fz, Cz and Pz) and 2 groups (patients and healthy controls). Further t-tests were performed for post-hoc analysis of significant interactions. A similar analysis was also performed for both N200 and P300 waves amplitudes separately.

E. Results

Results are presented as per the outcome variables. First, the primary outcome measures to see near transfer effects with training are reported. Second, the influence of training on secondary outcome measures for far transfer effects are reported. While reporting each outcome measure related to task performance, first the baseline comparison of the

task is reported by relating the difference in the performance of ADS subjects and HCs. Later, the comparison is reported between IT and CT interventions.

1. Comparison of demographic variables for task validation between Alcohol-dependent subjects and Healthy Controls (Table 17)

There was a significant age difference between ADS patients and HC ($t(41.50) = 4.33$, $p < .001$). For education status, there was no significant differences in the HC and ADS baseline ($\chi^2(4, N = 60) = 9.29$, $p = 0.06$). AUDIT score was low in HC (mean = 1.1, s.d. = 0.5). The nicotine dependence was frequently noted in ADS subjects (80%) than in HC (26.67%). There was a significant difference in the BIS-11 score between ADS patients and HC ($t(57) = 2.39$, $p = .02$). As the ADS patients and HC had a significant difference in age and total BIS-11 score, ANCOVA was tried as an exploratory analysis with age and total BIS-11 score as a covariate for all the outcome variables. As co-variation of these variables not affected the outcome measures significantly, simple mixed design ANOVA results are reported. The ADS subjects were most commonly prescribed Baclofen as an anti-craving agent (Baclofen: n = 21, Acamprosate: n = 5, Naltrexone: n = 4). Due to small sample size, differential analysis for the specified drugs was not performed.

Table 17 Demographic variables

	Healthy Controls (n = 30)	All baseline Alcohol dependent subjects (n = 30)	Inhibition training group (n = 13)	Control training group (n = 14)
Age in years (mean, s.d.)	29.63 (3.37)	35.83 (7.08)	35.00 (5.88)	36.67 (8.22)
Duration alcohol intake in years	-	14.96 (7.04)	14.85 (5.67)	15.07 (8.33)
Education, n (%)				
Literate but no formal education	0	4	2	1
No matric	2	5	3	2
Matric	16	15	5	9
Graduate	10	3	1	1
Postgraduate	2	3	2	1
BIS 11 total score	71.86 (4.74)	76.08 (6.04)	75.17 (8.35)	74.44 (4.80)
Attentional	22.40 (3.02)	19.80 (3.17)	20.83 (2.71)	19.11 (3.41)
Motor	24.10 (3.24)	26.33 (2.99)	26.50 (4.04)	26.22 (2.33)
Non-planning	25.17 (2.78)	28.60 (3.64)	27.83 (2.64)	29.11 (4.26)

ADS = Alcohol-dependent subjects; IT group = Inhibition Training Group; CT group = Control Training group; s.d. = standard deviation; BIS = Barrat Impulsivity Scale

2. Comparison of demographic variables between Inhibition Training and Control Training interventions (Table 17)

There was no significant difference in age among intervention groups ($t(28) = 0.64$, $p = .53$). There was no significant difference in duration of alcohol use in both the intervention groups ($t(28) = 0.08$, $p = .94$). For education status, there was no significant differences between intervention groups ($\chi^2(4, N = 27) = 1.47$, $p = 0.83$).

There was no significant difference for BIS-11 score between intervention groups in ADS subjects (t(25) = 0.21, p = .83).

3. Intervention related variables

An independent t test was performed on the number of hours of intervention between Inhibition training (IT) and control training (CT) groups. There was no significant difference between IT (mean = 3.82 hrs, s.e. = 0.24) and CT (mean = 4.00 hrs, s.e.=0.21) groups in the number of hours of intervention (t(25) = 0.57, p = .78) provided.

4. Near transfer effects: Inhibitory control

a) Comparison between Alcohol-dependent subjects and Healthy Controls for task validation

(1) Action restraint process of inhibition (Go Nogo task)

(a) Behavioural variables (Table 18)

For assessing the behavioural performance differences with the GNG task, an independent t-test was performed separately on the reaction time (GNGRT) and the commission errors (CE). We expected that the ADS subjects would have more CE than HC.

On comparing CE between group, there was no significant difference noted (t (46.81) = 1.63, p = .11, d = 0.42). This suggests that the groups did not differ significantly on restraining their action while inhibiting.

An unexpected slowing of the ADS subjects was noted, with significantly larger GNGRT for ADS subjects than HC (t (44.27) = 6.98, p < .001, d = 1.80).

Table 18 Dependent measures from the Go-Nogo task shown separately across groups and interventions. Values are means (standard deviation).

	Healthy Controls (n = 30)	All baseline Alcohol dependent subjects (n = 30)	Inhibition training group (n = 13)	Control training group (n = 14)
GNGRT in milliseconds	296.59 (43.44)	410.97 (76.75)	395.09 (57.08)	409.26 (49.80)
CE (%)	14.53 (15.18)	9.11 (9.43)	4.16 (7.12)	5.06 (7.83)

GNGRT: Go trials reaction time in GNG task; CE: proportion of commission errors

(b) Event-Related Potentials variables

(i) Amplitude N200

A 2 waves (go and no-go) * 3 electrodes (Fz, Cz, Pz) *2 groups (ADS baseline and HC) mixed design ANOVA was performed. The main effect of wave and wave * electrode * group interactions were expected to be significant.

The main effect of waves was significant ($F(1,55) = 16.81$, $p < .001$, $\eta_p^2 = 0.234$), with the no-go (1.27) amplitude less than go (2.22). This is suggestive of the decrease in N200 amplitude on a change in the trial from go to no-go, as expected.

The wave * electrode * group ($F(2,110) = 2.58$, $p = .08$, $\eta_p^2 = 0.045$) interactions were not significant, suggesting that the groups did not majorly differ in N200 amplitudes for the go and no-go trials together. A post hoc analysis was further performed to see the variation differences for each trial type.

The main effect of the electrode was significant with the Pz electrode having a least amplitude. Other main effects and interactions were not significant.

(a) Post hoc analysis for Go trials N200 amplitudes

An electrode (Fz, Cz and Pz) * group (ADS baseline and HC) mixed ANOVA was performed. It was expected that the main effects of group and electrode*group interactions will not differ.

As hypothesized, no significant main effect of group ($F(1, 55) = 3.40$, $p = .07$, $\eta_p^2 = 0.058$) and electrode * group interactions ($F(2,110) = 0.45$, $p = .64$, $\eta_p^2 = 0.008$) were noted. This indicate that the activity for the go trials did not differ between groups. The overall amplitudes were lower in the ADS subjects (m = 1.87, s.e. = 0.27) than in the HC (m = 2.57, s.e. = 0.27).

(b) Post hoc analysis for No-go trials N200 amplitudes

An electrode (Fz, Cz and Pz) * group (ADS baseline and HC) mixed ANOVA was performed. It was expected that main effects of group and electrode*group interactions will be significant.

The main effect of group ($F(1, 57) = 0.50$, $p = .48$, $\eta_p^2 = 0.009$) and the electrode * group interactions ($F(2,114) = 1.92$, $p = .15$, $\eta_p^2 = 0.033$) were not significant, indicating that the N200 activity did not differ between groups for no-go trials.

(ii) Amplitude P300

2 waves (go and no-go) * 3 electrodes (Fz, Cz, Pz) *2 groups (ADS baseline and HC) mixed design ANOVA was performed. The main effect of wave and wave * group interactions were expected to be significant.

The main effect of wave was significant ($F(1,55) = 29.97$, $p < .001$, $\eta_p^2 = 0.353$), with no-go (4.70) amplitude more than go (2.96). This suggests that the P300 amplitudes significantly increased when trials changed from go to no-go.

The wave * group ($F(1,55) = 4.50$, $p = .04$, $\eta_p^2 = 0.076$) interactions were significant, suggesting that the P300 amplitudes differed between groups for different waves. A post hoc analysis was performed to further simplify the results.

Also, the main effect of the electrode was significant with maximum amplitude at the Cz electrode followed by the Pz electrode, suggesting the centro-parietal distribution of the P300. The other interactions were not significant.

(a) Post hoc analysis for Go trials P300 amplitudes

An electrode (Fz, Cz and Pz) * group (ADS baseline and HC) mixed ANOVA on go trials P300 amplitude was performed. It as expected that the main effect of groups is not significant.

No significant main effect of group ($F(1, 55) = 0.10$, $p = .75$, $\eta_p^2 = 0.002$) was noted, suggestive of no difference between groups on P300 activity of Go trials. The other interactions were also not significant.

(b) Post hoc analysis for No-go trials P300 amplitudes (Figure 12)

An electrode (Fz, Cz and Pz) * group (ADS baseline and HC) mixed ANOVA was performed. It as expected that the main effect of group is significant.

There was a significant main effect of group ($F(1, 57) = 4.29$, $p = .04$, $\eta_p^2 = 0.07$), with ADS subjects (mean = 3.90, s.e. = 0.54) having blunted amplitudes than HC (mean = 5.46, s.e. = 0.53). This suggests of overall lower amplitudes of P300 for no-go trials for ADS subjects.

The electrode * group interactions ($F(2,114) = 4.35$, $p = .02$, $\eta_p^2 = 0.071$) were significant also significant and are reported in Figure 12. The significant differences between groups were localized to centro-parietal location.

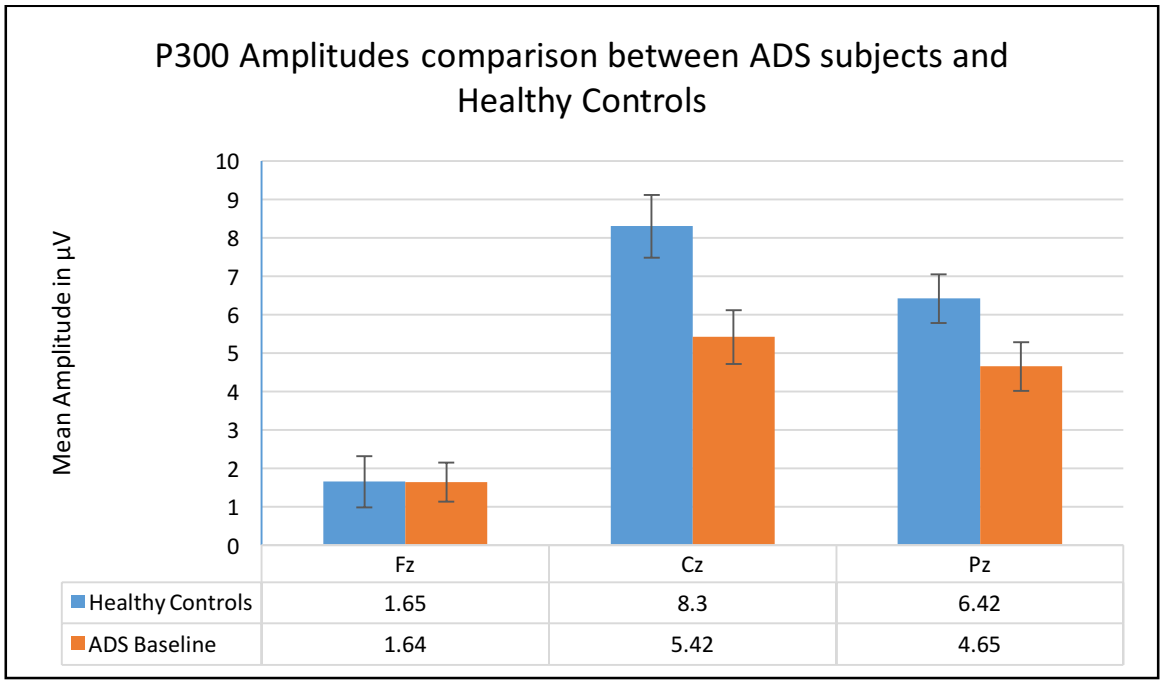


Figure 12 Comparison of P300 amplitudes on no-go trials in ADS patients and healthy controls

(iii) Latencies for N200 and P300

A 2 wave (go and no-go) * group (ADS baseline and HC) mixed design ANOVA was performed separately for the N200 and P300. The N200 did not differ between groups. The no-go P300 latencies were significantly delayed in ADS patients ($F(1,54) = 16.43$, $p < .001$).

(2) Action cancellation process of inhibition (Stop-signal task) (Table 4)

(a) Behavioural variables

(i) Go reaction time (GoRT)

A comparison was done for the GoRT between groups with the independent t-test. The ADS subjects had a significantly longer reaction time than HC ($t(56) = 4.66$, $p < .001$, $d = 1.21$), suggesting that ADS subjects were slower than HC on reacting at Go trials.

(ii) Stop-signal reaction time (SSRT)

The difference in SSRT between ADS subjects and HC was analysed using mixed ANOVA comparing SSRT at 4 stop-signal delays (SSD 150, SSD 200, SSD 250 and SSD 300) * 2 groups (ADS subjects and HC). The main effect of group and the SSD * group interactions were expected to be significant.

There was a significant main effect of group ($F(1, 56) = 23.84$, $p < .001$, $\eta_p^2 = 0.299$), but no significant SSD * group ($F(3, 168) = 0.24$, $p = .87$, $\eta_p^2 = 0.004$) interactions. This suggests that the groups differ in the SSRT (Figure 13), but the variance for the changing SSD is similar in both the groups.

The post hoc analysis revealed SSRT for ADS subjects was significantly larger than HC (HC: mean = 195.21 s.d. = 24.97 s.e. = 6.53; ADS Baseline: mean = 240.32 s.d. = 240.32 s.e. = 6.53; $t(56) = 4.88$, $p < .001$, $d = 1.27$), suggesting of delayed SSRT in ADS subjects.

Table 19 Dependent measures from the stop-signal task shown separately across groups and interventions. Values are means (standard deviation).

	Healthy Controls (n = 30)	All baseline Alcohol dependent subjects (n = 30)	Inhibition training group (n = 13)	Control training group (n = 14)
GoRT	525.35 (59.44)	598.82 (60.63)	567.50 (53.86)	587.14 (48.31)
SSRT 150	199.14 (39.53)	240.17 (59.30)	214.91 (29.10)	218.00 (45.85)
SSRT 200	185.93 (45.47)	237.41 (53.15)	187.45 (41.76)	215.14 (34.74)
SSRT 250	194.59 (32.46)	239.62 (51.59)	197.36 (43.39)	213.14 (52.49)
SSRT 300	201.17 (39.34)	244.07 (45.45)	216.36 (32.55)	207.36 (39.09)

SSRT: stop-signal reaction time in milliseconds; GoRT: Go trials reaction time in milliseconds

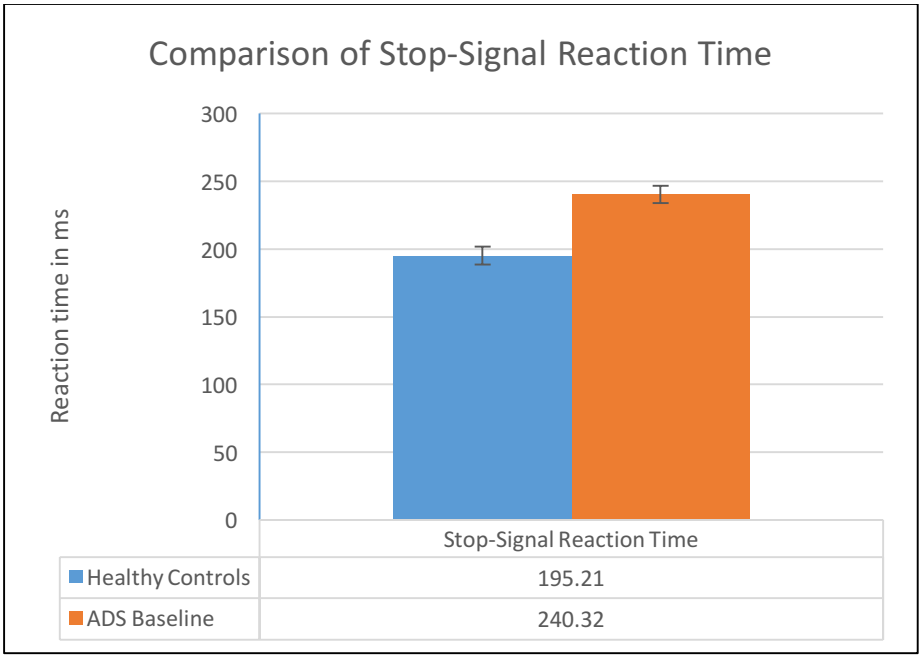


Figure 13 Comparison of Stop-Signal Reaction Time between ADS patients and healthy controls

(b) Event-Related Potentials variables

(i) N200 Amplitudes (Figure 14)

A 4 SSD (SSD150, SSD200, SSD250 and SSD300) * 3 electrodes (Fz, Cz and Pz) * 2 groups (patients and HC) mixed design ANOVA was performed. The main effect of

group, SSD * group and SSD * electrode * group interactions were expected to be significant.

The main effect of group (F (1,57) = 4.46, p = .04, η_p^2 = 0.073) was significant. The mean amplitudes were significantly higher in the ADS subjects than in HC (ADS baseline: mean = 1.96, s.e. = 0.33, HC: mean = 0.98, s.e. = 0.33). This suggests of blunted negative amplitudes for ADS subjects.

The SSD * group (F (3, 171) = 3.72, p = 0.01, η_p^2 = 0.061) interactions were significant, where as the SSD * electrode * group (F (6, 342) = 1.57, p = 0.16, η_p^2 = 0.027) interactions were not significant. This suggests a difference in the amplitude variation between groups on different SSDs, irrespective of the electrode site.

On further post hoc analysis for between group differences at each SSD by independent t-test, a significant difference was noted at SSD 300 trials (ADS baseline: mean = 2.86, s.e. = 0.62; HC: mean = 0.67, s.e. = 0.45, t (57)= 2.85, p = .01, d = 0.74), where as amplitudes for trials with SSD 150 (ADS baseline: mean = 1.25, s.e. = 0.42; HC: mean = 0.72, s.e. = 0.35, t (57)= 0.98, p = .33, d = 0.25), SSD 200 (ADS baseline: mean = 1.53, s.e. = 0.42; HC: mean = 1.16, s.e. = 0.33, t (57)= 0.69, p = .49, d = 0.18) and SSD 250 (ADS baseline: mean = 2.20, s.e. = 0.37; HC: mean = 1.35, s.e. = 0.32, t (57)= 1.71, p = .09, d = 0.44) did not differ significantly. On performing within group comparisons with paired t tests separately for each group, the mean amplitudes did not significantly change in HC, on trials with step wise increase in SSD [SSD 150 – 200: t(28) = 1.44, p = .16, d = 0.27; SSD 200 – 250: t(28) = 1.16, p = .26, d = 0.22; SSD 250 – 300: t (28) = 1.78, p = .09, d = 0.33; SSD 150 – 300: t (28) = 0.13, p = .89, d = 0.02; SSD 200 – 300: t (28) = 1.46, p = .16, d = 0.27]. In ADS subjects, amplitudes significantly increase with the SSDs, noted between SSD 200 – 250 (t(29) = 2.02, p = .05, d = 0.37), SSD 150 – 300 (t(29) = 2.21, p = .04, d = 0.40) and SSD 200 – 300 (t(29) = 2.41, p = .02, d = 0.44). The differences did not reach significance between SSD 150 – 200 (t (29) = 0.78, p = .44, d = 0.14) and SSD 250 – 300 (t(29) = 1.18, p = .25, d = 0.22). These results are suggestive of significant increase in blunting of N200 amplitudes with increasing SSD in ADS subjects, while no significant change in HC (Figure 14).

The main effect of electrodes was significant, with Pz electrode showing least amplitude. Other interactions were not significant.

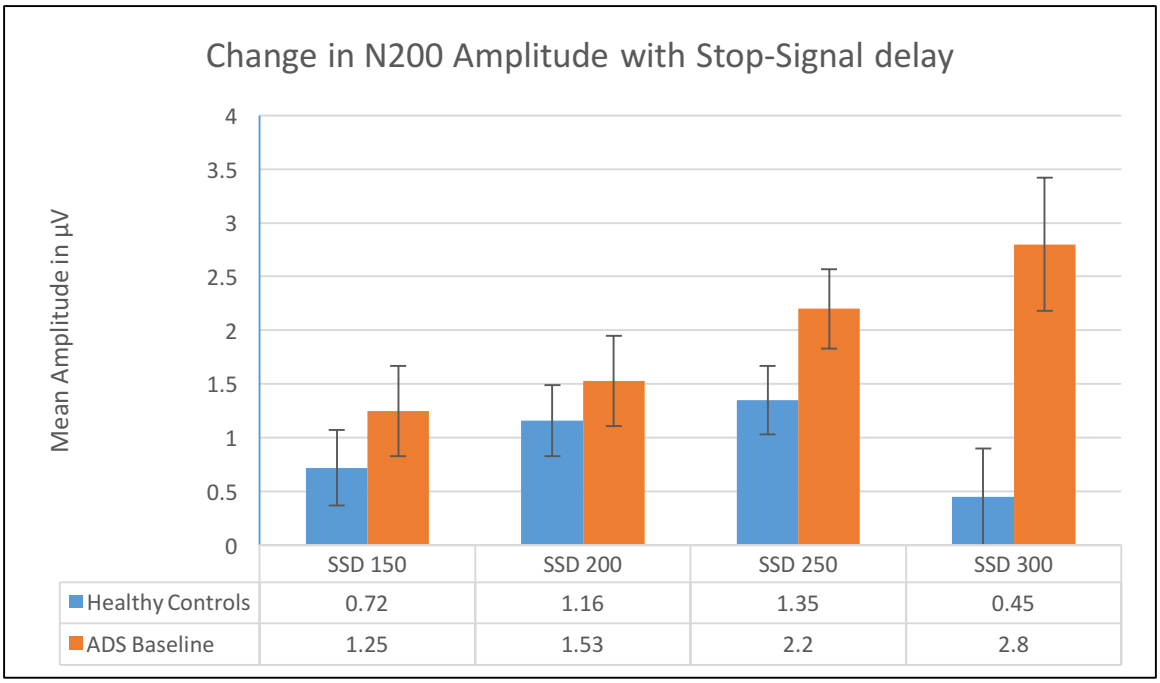


Figure 14 Comparison of N200 amplitude with Stop-signal delay in ADS patients and healthy controls

(ii) P300 Amplitude (Figure 15)

A 4 SSD (SSD150, SSD200, SSD250 and SSD300) * 3 electrodes (Fz, Cz and Pz) * 2 groups (patients and HC) mixed design ANOVA was performed. The main effect of group, SSD * group and SSD * electrode * group interactions were expected to be significant.

The main effect of group ($F(1,57) = 6.44$, $p = .01$, $\eta_p^2 = 0.102$) was significant. The mean P300 amplitudes for ADS subjects (5.09) were significantly lower than HC (6.58). Electrode * group ($F(2,114) = 5.12$, $p = .007$, $\eta_p^2 = 0.082$) interactions were significant, with the differences in the amplitudes localized to centro-parietal electrodes (Figure 15).

The SSD * group ($F(3, 171) = 2.25$, $p = .09$, $\eta_p^2 = 0.038$) and SSD * electrode * group ($F(6,342) = 0.48$, $p = .83$, $\eta_p^2 = 0.008$) interactions were not significant. This suggests that the P300 amplitudes did not vary between group with changing SSD. The other interactions were not significant.

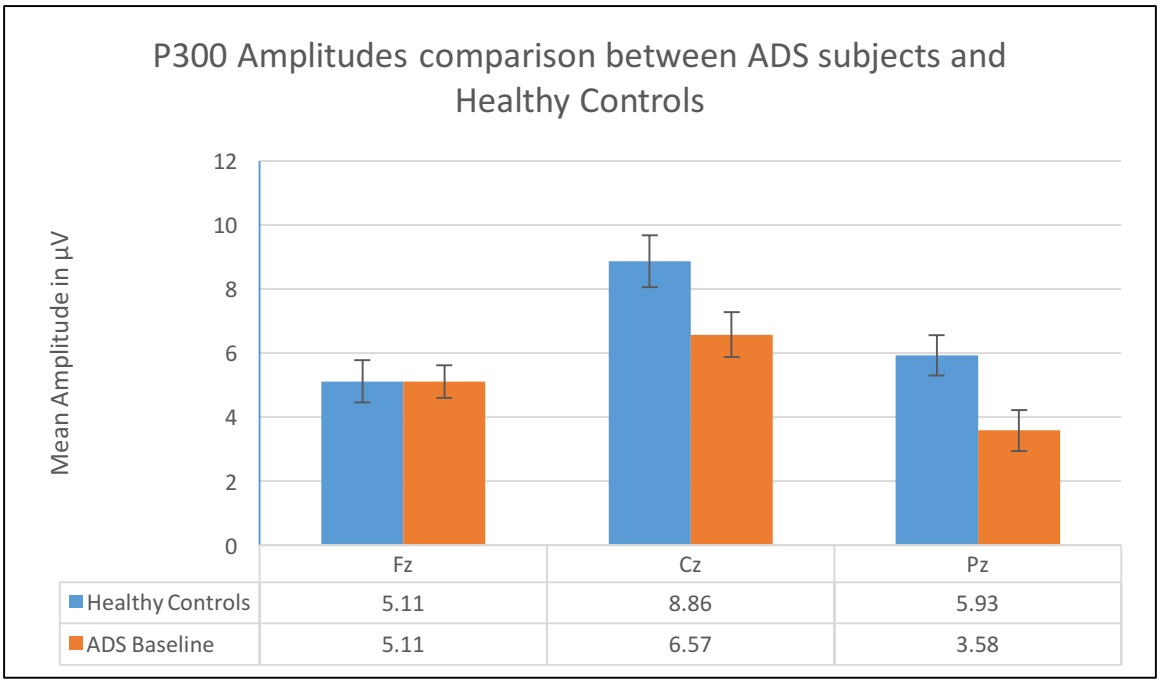


Figure 15 Comparison of P300 amplitudes at electrodes for stop trials in the stop-signal task in ADS patients and healthy controls

b) Comparison between Inhibition Training and Control Training interventions for near transfer effects

(1) Action restraint process of inhibition (Go No-Go task)

(a) Behavioural variables

(i) Reaction time (GNGRT)

For effect of intervention over time in ADS on GNGRT, no significant main effect of time ($F(1,22) = 0.35$, $p = .56$, $\eta_p^2 = 0.016$) or intervention ($F(1, 22) = 0.47$, $p = .50$, $\eta_p^2 = 0.021$) was noted. There were no significant time point * intervention interactions ($F(1, 22) = 0.02$, $p = .89$, $\eta_p^2 = 0.001$). This suggests that there was no significant change in the response speed.

(ii) Commission errors (CE)

A 2 time (baseline and follow-up) * 2 interventions (IT and CT) MANOVA was performed. It was expected that main effect of time and time * intervention interactions are significant.

No significant main effect of time ($F(1,22) = 4.08$, $p = .06$, $\eta_p^2 = 0.156$) and time * intervention interactions ($F(1, 22) = 1.31$, $p = .26$, $\eta_p^2 = 0.056$) were noted. The CE decreased from baseline to follow-up (Baseline: mean = 10.12, s.e. = 1.99, Follow-up: mean = 4.61, s.e. = 1.53). This suggests that the action restraint inhibition improved over time, but the type of intervention did not have any specific effect on this change.

(b) Event-Related Potentials variables

(i) Amplitude N200

A 2 time (baseline and follow-up) * 3 electrodes (Fz, Cz and Pz) * 2 interventions (IT and CT) MANOVA was performed for no-go N200 amplitudes. The main effect of time with time * intervention and time * electrode * intervention interactions were expected to be significant.

The main effect of time ($F(1,22) = 2.93$, $p = .10$, $\eta_p^2 = 0.118$) was not significant. This suggest that over time there was no significant change in the N200 amplitude of action restraint inhibitory trials. Also, time * intervention ($F(1,22) = 2.17$, $p = .16$, $\eta_p^2 = 0.09$) and time * electrode * intervention ($F(2,44) = 1.19$, $p = .31$, $\eta_p^2 = 0.051$) interactions along with the other interactions were not significant. This suggests no effect of intervention on N200 amplitude while restraining the on going action.

(ii) Amplitude P300

A 2 time (baseline and follow-up) * 3 electrodes (Fz, Cz and Pz) * 2 interventions (IT and CT) MANOVA was performed for no-go N200 amplitudes. The main effect of time with time * intervention and time * electrode * intervention interactions were expected to be significant.

The main effect of time ($F(1,22) = 1.13$, $p = .30$, $\eta_p^2 = 0.049$) was not significant. This suggest that over time there was no significant change in the P300 amplitude of action restraint inhibitory trials. Also, time * intervention ($F(1,22) = 1.90$, $p = .18$, $\eta_p^2 = 0.079$) and time * electrode * intervention ($F(2,44) = 0.60$, $p = .55$, $\eta_p^2 = 0.027$) interactions along with the other interactions were not significant. This suggests no effect of intervention on P300 amplitude while restraining the on going action.

(iii) Latencies of N200 and P300

There was no significant main effect of time or its interventions with the interventions for both N200 and P300 latencies.

(2) Action cancellation process of inhibition (Stop-signal task) (Table 19)

(a) Behavioural variables

(i) Go trials reaction time (GoRT)

For GoRT, there was a significant main effect of time point ($F(1,23) = 7.49$, $p = .01$, $\eta_p^2 = 0.246$) with decrease in GoRT over time (Baseline: mean = 602.90, s.e. = 12.47, Follow-up: mean = 577.32, s.e. = 10.23). There was no significant main effect of

intervention (F (1,23) = 0.87, p = .36, η_p^2 = 0.012) and time * intervention (F (1,23) = 0.87, p = .36, η_p^2 = 0.036) interactions. This suggests that the subjects were faster in responding over time but not interaction with intervention for this effect.

(ii) Stop-signal reaction time (SSRT)

A 2 time (baseline and follow-up) * 4 SSD (150, 200, 250 and 300 ms) * 2 intervention (IT and CT) MANOVA was performed. The main effect of time, with time * intervention and time * SSD * intervention interactions were expected to be significant.

A significant main effect of time (F (1,23) = 20.86, p < .001, η_p^2 = 0.476) was noted, with decrease in SSRT over time (Baseline: mean = 244.72, s.e. = 8.97, Follow-up: mean = 208.72, s.e. = 5.47). This suggests that the subjects improved in the inhibitory reaction time.

The time * intervention (F (1,23) = 2.22, p = .15, η_p^2 = 0.088) and time * SSD * intervention (F (3,69) = 0.85, p = .47, η_p^2 = 0.036) interactions were not significant. This suggests that there was no differential effect of the intervention in the improvement in the inhibitory reaction time. Also, the intervention did not affect differentially for the different SSDs. The other interactions were not significant.

(b) Event-Related Potentials variables

(i) N200 amplitudes (Figure 16)

A 2 time (baseline and follow-up) * 4 SSD (150, 200, 250 and 300 ms) * 3 electrodes (Fz, Cz and Pz) * 2 intervention (IT and CT) MANOVA was performed. The main effect of time and time * intervention, time * SSD * intervention and time * SSD * electrodes * intervention were expected to be significant.

The main effects of time (F (1, 24) = 2.38, p = 0.14, η_p^2 = 0.09) was not significant. This suggests that over the time the N200 amplitude did not change significantly. The time * intervention (F (1, 24) = 4.74, p = 0.04, η_p^2 = 0.165) interactions were significant. But, the time * SSD *intervention (F (3, 72) = 1.72, p = 0.17, η_p^2 = 0.067) and time * SSD * electrode * intervention (F (6, 144) = 1.99, p = 0.07, η_p^2 = 0.076) were not significant. This suggests that the overall N200 amplitude differentially changed over time with the intervention type. The other interactions were not significant.

Further, a 4 SSD (150, 200, 250 and 300 ms) * 3 electrodes (Fz, Cz and Pz) * 2 intervention (IT and CT) mixed ANOVA was performed for baseline N200 amplitudes. SSD * intervention and SSD * electrodes * intervention interactions with main effects of intervention were expected not to be significant. The main effect of interventions (F

(1, 28) = 0.45, p = 0.51, η_p^2 = 0.016) was not significant. The SSD * intervention (F (3, 84) = 1.21, p = 0.31, η_p^2 = 0.041) and SSD * electrode * intervention (F (6, 168) = 0.72, p = 0.64, η_p^2 = 0.025) interactions were not significant. This suggests that the groups did not differ significantly before intervention.

Later, a 4 SSD (150, 200, 250 and 300 ms) * 3 electrodes (Fz, Cz and Pz) * 2 intervention (IT and CT) mixed ANOVA was performed for followup N200 amplitudes. SSD * intervention and SSD * electrodes * intervention interactions with main effects of intervention were expected not to be significant. The main effect of interventions (F (1, 24) = 1.98, p = 0.17, η_p^2 = 0.076) was not significant. The SSD * intervention (F (3, 72) = 0.71, p = 0.55, η_p^2 = 0.029) and SSD * electrode * intervention (F (6, 144) = 1.35, p = 0.24, η_p^2 = 0.053) interactions were not significant. The electrode * intervention (F (2, 48) = 3.08, p = 0.05, η_p^2 = 0.114) interactions were significant. This suggests that the interventions had differential effect on the overall amplitudes at electrodes. To analyze this difference, mean of all SSD at each electrode was calculated. The post hoc analysis showed that the amplitudes did not significant differ for Fz (IT: mean = 5.35, s.e. = 0.75; CT: mean = 4.35, s.e. = 0.62; t (25) = 1.03, p = .31, d = 0.40), Cz (IT: mean = 0.63, s.e. = 0.88; CT: mean = 2.39, s.e. = 1.01; t (25) = 1.30, p = .21, d = 0.51) and Pz electrode (IT: mean = -3.76, s.e. = 1.08; CT: mean = -1.21, s.e. = 0.80; t (25) = 1.91, p = .07, d = 0.74). So, the intervention had maximum effect at Pz electrode, with more negative amplitude at this electrode for IT intervention group.

Furthermore, time (baseline and follow-up) * SSD (SSD 150, 200, 250 and 300) * electrode (Fz, Cz and Pz) MANOVA was performed separately for IT and CT intervention. Here, the main effect of time and time * electrode interaction was expected to be significant for IT intervention but not for CT intervention.

For IT intervention, the main effect of time (F (1,12) = 3.96, p = .07, η_p^2 = 0.248) was not significant. The time * electrode (F (2, 24) = 3.30, p = .05, η_p^2 = 0.215) interactions were significant. On post hoc analysis, a significant decrease in the amplitude was noted at Pz (baseline: mean = -1.24, s.e. = 0.55, follow-up: mean = -3.76, s.e. = 1.08; t (12) = 2.38, p = .04 d = 0.66), while the amplitude at Cz (baseline: mean = 1.53, s.e. = 0.51, follow-up: mean = 0.63, s.e. = 0.88; t (12) = 1.46, p = .17, d = 0.40) and Fz (baseline: mean = 5.61, s.e. = 0.97, follow-up: mean = 5.35, s.e. = 0.75; t (12) = 0.38, p = .71, d = 0.11) did not change significantly. For CT intervention, the main effect of time (F (1,12) = 0.79, p = .39, η_p^2 = 0.062) and time * electrode (F (2, 24) = 1.54, p = .24, η_p^2 = 0.114)

interactions were not significant. This suggests that the negativity of N200 amplitude significantly increased with the IT intervention (Figure 16).

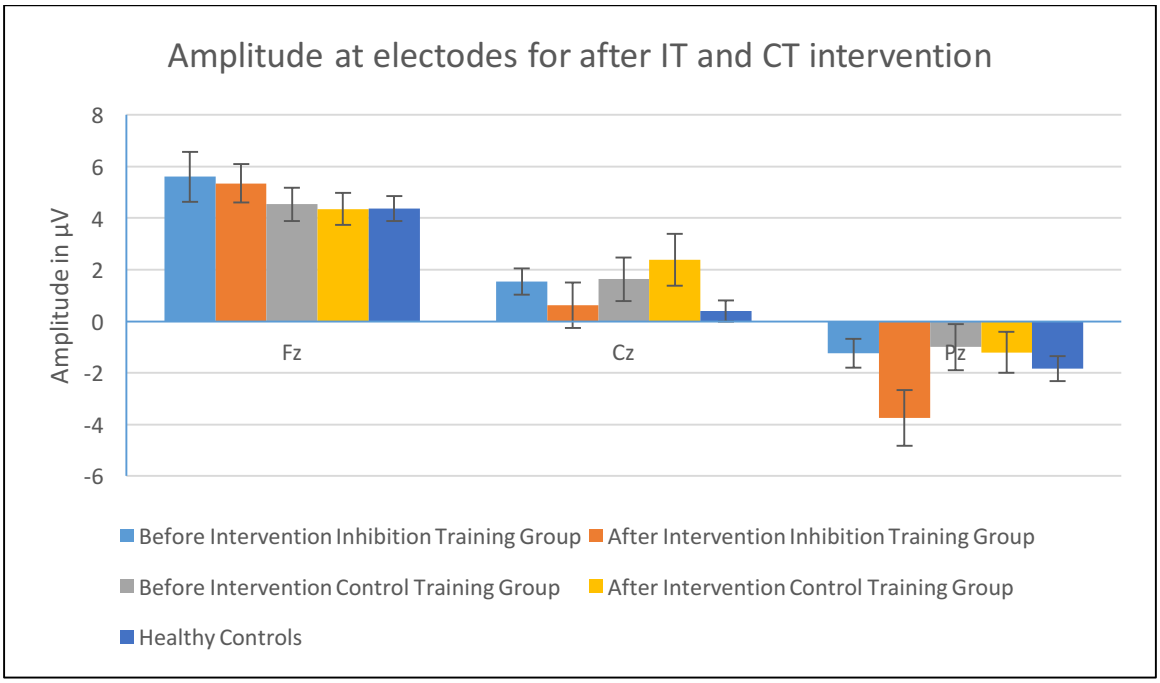


Figure 16 Change in amplitude at different electrodes after Inhibition training intervention and control training intervention (indicates significant difference)*

(ii) P300 amplitudes

A 2 time (baseline and follow-up) * 4 SSD (150, 200, 250 and 300 ms) * 3 electrodes (Fz, Cz and Pz) * 2 intervention (IT and CT) MANOVA was performed. The main effect of time and time * intervention, time * SSD * intervention and time * SSD * electrodes * intervention were expected to be significant.

The main effect of time ($F(1,24) = 2.15$, $p = .16$, $\eta_p^2 = 0.082$) was not significant. The time * interventions ($F(1,24) = 0.56$, $p = .46$, $\eta_p^2 = 0.023$), time * electrode * interventions ($F(2,48) = 2.51$, $p = .09$, $\eta_p^2 = 0.095$) and time* SSD * electrode * interventions ($F(6,144) = .91$, $p = .49$, 0.037) interactions were not significant. This suggested that the interventions did not influence P300 amplitudes.

5. Far transfer effects: attention, interference effect and error processing (Flanker task)

a) Comparison between Alcohol-dependent subjects and Healthy Controls for task validation

(1) Behavioural variables

(a) Percentage of errors (Interference effect)

A 2 trial congruency (congruent vs incongruent) * 2 groups (ADS subjects and HC) mixed ANOVA was performed. The main effect of trial congruency and group with groups * trial congruency interactions were expected to be significant.

A significant main effect of the trial congruency ($F(1,57) = 58.20$, $p < .001$, $\eta_p^2 = 0.505$) was noted. More errors were made on the incongruent than on congruent trials (33.96% versus 18.38%, respectively). This validates the interference effect in the task.

The main effect of groups ($F(1,57) = 62.29$, $p < .001$, $\eta_p^2 = 0.522$) was significant. More errors were committed by ADS subjects (40.93%) than in the healthy controls (11.40%). The groups * trial congruency interaction effect reached statistical significance ($F(1, 57) = 6.54$, $p = .013$, $\eta_p^2 = 0.103$).

On post hoc analysis, patients made significantly more errors for both congruent [ADS subjects: M= 30.53, SD = 20.82; Healthy Controls: M= 6.23, SD= 7.97; $t(35.8) = -5.88$; $p < 0.001$, $d = 1.53$] and incongruent trials [ADS subjects: M= 51.33, SD = 22.66; Healthy Controls: M= 16.58, SD= 8.66; $t(35.8) = -7.72$; $p < .001$, $d = 2.01$]. The congruency effect (difference between errors on incongruent trials and congruent trials) was of larger magnitude in ADS subjects than healthy controls [ADS subjects: M= 20.79, SD = 21.72; Healthy Controls: M= 10.35, SD= 5.24; $t(31.1) = 2.52$; $p = .02$, $d = 0.66$]. This suggested that due to interference in the trial, ADS subjects committed more errors than HC, indicating ADS subjects not able to manage the interference efficiently.

(b) Percentage of misses (attention)

A 2 trial congruency (congruent vs incongruent) * 2 groups (ADS subjects and HC) mixed ANOVA was performed. The main effect of group was expected to be significant.

The main effect of Group ($F(1,57) = 40.11$, $p < .001$, $\eta_p^2 = 0.413$) was significant. The ADS subjects missed more responses than healthy controls (15.76% versus 1.3%,

respectively). This suggested ADS subjects' inability to attend many of the fast series of stimuli.

(c) Reaction time (Interference effect)

A 2 trial congruency (congruent vs incongruent) * 2 groups (ADS subjects and HC) mixed ANOVA was performed for the congruency effect on reaction time. The main effect of the trial congruency and group with groups * trial congruency interactions were expected to be significant. The main effect for the trial congruency on RTs ($F(1,57) = 33.48$, $p < .001$, $\eta_p^2 = 0.37$) was significant. The RTs to incongruent trials were longer than to congruent trials (404.82 ms versus 381.84 ms, respectively). This showed that the participants had a processing time difference between the two type of trials. The main effect of group was not significant [ADS subjects: M= 402.50, SE = 12.31; Healthy Controls: M= 384.15, SE= 12.11; $F(1,57) = 1.13$; $p = .29$, $\eta_p^2 = 0.019$]. This suggests the groups did not differ in response timings. A significant group * trial congruency interaction was noted ($F(1,57) = 13.77$, $p < .001$, $\eta_p^2 = 0.195$). The post hoc analysis showed that healthy controls had significantly more RT for incongruent (M= 403.01, SD = 32.32) than congruent trials (M= 365.30, SD= 30.56) ($t(29) = -12.01$; $p < .001$, $d = 2.19$). This change in RT with congruency was not significantly different in ADS subjects [congruent: M= 398.38, SD= 83.71; incongruent: M= 406.62, SD = 99.03; $t(28) = -1.11$; $p = .28$, $d = 0.20$]. This suggested that HC had a significant processing time for managing the interference effect, while ADS subjects respond to both the trials similarly and not able to manage the interference effect.

Table 20 Dependent measures from the Flanker task shown separately across groups and interventions. Values are means (standard deviation).

	Healthy Controls (n = 30)	All baseline Alcohol dependent subjects (n = 30)	Inhibition training group (n = 13)	Control training group (n = 14)
Accuracy				
% Errors congruent	7.38 (8.28)	30.53 (20.81)	22.35 (23.65)	22.89 (24.89)
% Errors incongruent	18.00 (8.63)	51.33 (22.66)	45.80 (30.06)	47.07 (31.39)
% Misses congruent	0.98 (2.02)	13.09 (12.66)	5.70 (6.21)	7.35 (9.04)
%Misses incongruent	1.74 (2.18)	18.43 (13.86)	17.10 (28.16)	16.17 (19.78)
Reaction Time in milliseconds				
Congruent	304.15 (30.44)	398.38 (83.71)	356.59 (104.17)	375.47 (80.81)
Incongruent	338.12 (29.45)	406.62 (99.03)	376.81 (105.06)	398.31 (103.34)

(2) Event-Related Potentials related variables (error processing)

(a) Early Potentials

A 2 wave (ERN and CRN) * 3 electrodes (Fz, FCz and Cz) * 2 groups (ADS subjects and HC) mixed ANOVA was performed. The main effect of wave and group with wave * group and wave * electrode * group interactions were expected to be significant.

The main effect of wave ($F(1,57) = 63.33$, $p < .001$, $\eta_p^2 = 0.526$) was significant. The negative amplitude was more after incorrect response (ERN = -1.67 μV versus CRN = 0.39 μV). This validates the ability of the task to monitor error associated negativity. The main effect of Group ($F(1,57) = 11.19$, $p = .001$, $\eta_p^2 = 0.164$) was significant. The ADS subjects (-1.23μV) had overall more negative potentials than healthy controls (-

0.05μV). This more negativity in ADS subjects was irrespective of the outcome of the trial.

The wave * group interactions (F (1, 57) = 25.05, p < .001, η_p^2 = 0.305) and wave * electrode * group interactions (F(2, 114) = 28.30, p<.001, η_p^2 = 0.332) were significant. For understanding these interactions further analysis was carried out.

(i) Incorrect response related early potential (ERN)

A 3 electrodes (Fz, FCz and Cz) * 2 groups (ADS subjects and HC) mixed ANOVA was performed. The main effect of group and electrode * group interactions were expected to be significant.

The main effect of group was not significant (F(1,58) = 0.00, p = .97, η_p^2 = 0.00). The electrode * group interactions were significant (F(2,116) = 7.92, p = .001, η_p^2 =0.12). On post hoc analysis for between group effect, the amplitude was more negative at Fz electrode for ADS subjects than HC (ADS baseline: mean = -1.83, s.e. = 0.32; HC: mean = -0.79, s.e. = 0.32; t (58) = 2.14, p = .04, d = 0.56), whereas the differences were not significant at FCz electrode (ADS baseline: mean = -1.88, s.e. = 0.37; HC: mean = -2.14, s.e. = 0.42; t (58) = 0.47, p = .63, d = 0.12) and Cz electrode (ADS baseline: mean = -1.11, s.e. = 0.37; HC: mean = -1.84, s.e. = 0.43; t (58) = 1.29, p = .20, d = 0.34). This suggested of a differential pattern of activation between groups only limiting to the frontal electrode showing more negativity of ADS subjects on incorrect response.

(ii) Correct response related early potential (CRN)

A 3 electrodes (Fz, FCz and Cz) * 2 groups (ADS subjects and HC) mixed ANOVA was performed. The main effect of group and electrode * group interactions were expected to be not significant.

The main effect of group was significant (F(1,57) = 35.22, p < .001, η_p^2 = 0.382), with amplitude more negative for ADS subjects (mean = -0.85, s.e. = 0.29) than HC (mean = 1.62, s.e. = 0.30). The electrode * group interactions were significant (F(2,114) = 10.19, p < .001, η_p^2 = 0.152). On post hoc analysis for between group effect, the amplitude was lower at Fz electrode (ADS baseline: mean = -1.53, s.e. = 0.26; HC: mean = -0.06, s.e. = 0.28; t (57) = 3.92, p < .001, d = 1.02), FCz electrode (ADS baseline: mean = -1.07, s.e. = 0.29; HC: mean = 1.60, s.e. = 0.38; t (57) = 5.66, p < .001, d = 1.47) and Cz electrode (ADS baseline: mean = 0.07, s.e. = 0.31; HC: mean = 3.33, s.e. = 0.47; t (57) = 5.79, p < .001, d = 1.51) for ADS subjects than HC.

(b) late Potentials

A 2 wave (ERN) * 3 electrodes (Cz, CPz and Pz) * 2 groups (ADS subjects and HC) mixed ANOVA was performed. The main effect of wave and group with wave * group and wave * electrode * group interactions were expected to be significant.

A significant main effect of wave ($F(1,57) = 86.58$, $p < .001$, $\eta_p^2 = 0.603$) was noted. The over all potentials increased after wrong response (Pe (wrong response) = 3.78 μV versus Pe (right response) = 0.87 μV). This validates the tasks ability to generate late potentials after incorrect response.

The main effect of Group ($F(1,57) = 17.59$, $p < .001$, $\eta_p^2 = 0.236$) was significant. The ADS subjects (0.73μV) had lower potentials than healthy controls (3.81μV).

The Group * wave interaction effects were of statistical significance ($F(1, 57) = 85.52$, $p < .001$, $\eta_p^2 = 0.60$), but wave * electrode * group interactions ($F(2, 114) = 1.56$, $p=.21$, $\eta_p^2 = 0.027$) were not significant. For understanding these interactions further analysis was carried out.

(i) Incorrect response related late potential (Pe incorrect) (Figure5)

A 3 electrodes (Cz, CPz and Pz) * 2 groups (ADS subjects and HC) mixed ANOVA was performed. The main effect of group was expected to be significant.

The main effect of group was significant ($F(1, 58) = 43.99$, $p < .001$, $\eta_p^2 = 0.431$). The amplitudes were larger for HC (6.32) than ADS baseline (0.74). This suggested that the Pe amplitudes were blunted for ADS subjects than HC. The electrode * group interactions were significant ($F(2, 116) = 14.72$, $p < .001$, $\eta_p^2 = 0.202$).

(ii) Correct response related late potential (Pe correct)

A 3 electrodes (Cz, CPz and Pz) * 2 groups (ADS subjects and HC) mixed ANOVA was performed. The main effect of group was expected to be not significant.

The main effect of group was not significant ($F(1, 57) = 0.14$, $p = .71$, $\eta_p^2 = 0.002$). The electrode * group interactions were not significant. This suggested that the Pe amplitudes did not differ between the groups on correct responses.

(iii) Change in Pe amplitude on incorrect response compared to the correct response

A 2 wave (ERN) * 3 electrodes (Cz, CPz and Pz) mixed ANOVA was performed separately for ADS subjects and HC. The main effect of the wave was expected to be significant for HC but not for ADS subjects.

For HC the main effect of wave was significant ($F(1, 28) = 119.35$, $p < .001$) while for the ADS subjects the main effect of wave was not significant ($F(1, 29) = .00$, $p = .96$). This suggested that the Pe activity changed for HC on an incorrect response, but the incorrect response did not affect HC.

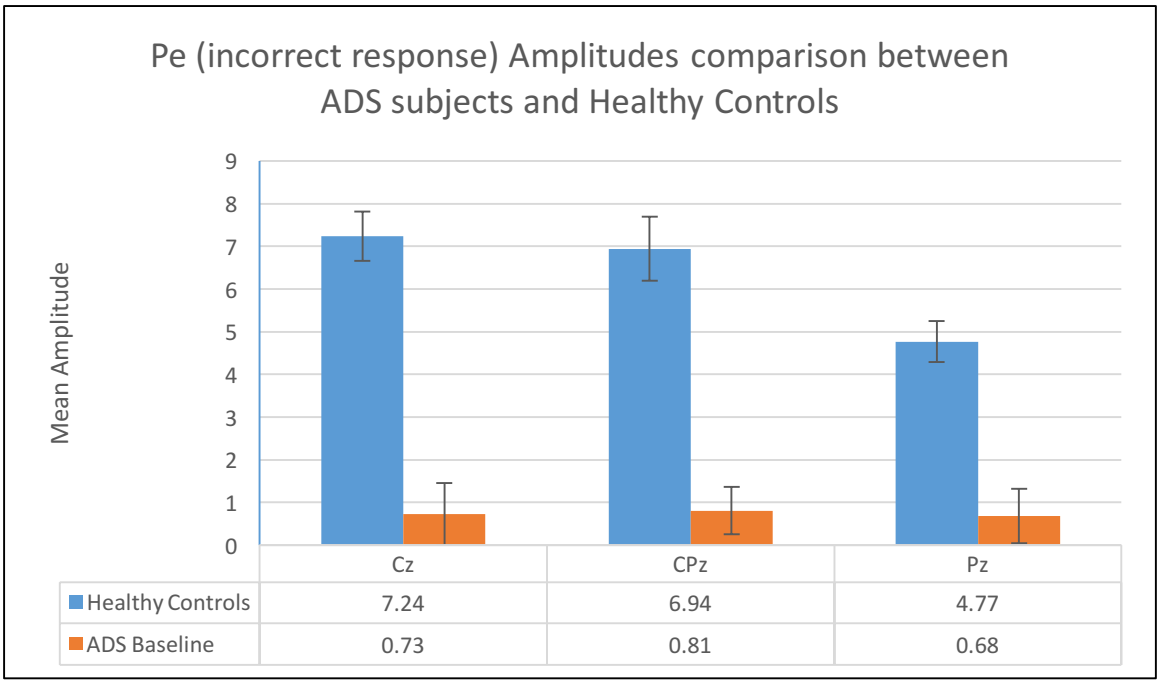


Figure 17 Comparison of Pe amplitudes at electrodes for incorrect responses in Flanker task in ADS patients and healthy controls

b) Comparison between Inhibition Training and Control Training interventions for far transfer effects

(1) Behavioural variables

(a) Percentage of errors (effect on interference)

A 2 time (baseline and follow-up) * 2 trial congruency (congruent and incongruent) * 2 interventions (IT and CT) was performed. The main effect of time and intervention with time * intervention and time * congruency * intervention interactions were expected to be significant.

The main effect of time ($F(1,22) = 7.14$, $p = .014$, $\eta_p^2 = 0.245$) was significant with decrease in errors over time and intervention ($F(1, 22) = 0.03$, $p = .87$, $\eta_p^2 = 0.001$) was not significant. No significant time * intervention ($F(1, 22) = 0.04$, $p = .85$, $\eta_p^2 = 0.003$) and time * congruency *intervention ($F(1, 22) = 0.16$, $p = .69$, $\eta_p^2 = 0.007$) interactions were seen. This suggests of no effect produced by any interventions on interference control.

(b) Percentage of misses (effect on attention)

A 2 time (baseline and follow-up) * 2 trial congruency (congruent and incongruent) * 2 interventions (IT and CT) was performed. The main effect of time and intervention with time * intervention were expected to be significant.

No significant main effect of time ($F(1, 22)= 1.98$, $p = .18$, $\eta_p^2 = 0.082$) and intervention ($F(1, 22)= 0.00$, $p = .98$, $\eta_p^2 = 0.000$) was noted. Also, there were no significant time * intervention ($F(1, 22)= 0.01$, $p = .91$, $\eta_p^2 = 0.001$). This suggested that the intervention did not have any effect on attention.

(c) Reaction time (effect on interference)

A 2 time (baseline and follow-up) * 2 trial congruency (congruent and incongruent) * 2 interventions (IT and CT) was performed. The main effect of time and intervention with time * intervention and time * congruency * intervention interactions were expected to be significant.

No significant main effect of time ($F(1, 22)= 3.39$, $p = .08$, $\eta_p^2 = 0.133$) and intervention ($F(1, 22)= 0.76$, $p = .39$, $\eta_p^2 = 0.033$) was noted. Also, no significant time * intervention ($F(1, 22)= 0.50$, $p = .49$, $\eta_p^2 = 0.22$) and time * congruency * intervention ($F(1, 22)= 0.47$, $p = .47$, $\eta_p^2 = 0.021$). This suggested that the intervention did not affect the reaction times and interference control.

(2) Event Related Potentials variables (Effect on Error processing)

(a) Early Error related Potentials

A 2 time (baseline and followup) * 3 electrode (Fz, FCz and Cz) * interventions (IT and CT) MANOVA was performed. The main effect of time and intervention with time * intervention and time * electrode * intervention interactions were expected to be significant. The main effects of time ($F(1, 24) = 4.05$, $p = .06$, $\eta_p^2 = 0.144$) were significant with increase in negative potential the over time. The effects of intervention ($F(1, 24) = 0.106$ $p = .75$, $\eta_p^2 = 0.004$) were not significant. The interactions of time * intervention ($F(1, 24) = 0.57$, $p = .46$, $\eta_p^2 = 0.023$) and time * electrode * intervention ($F(2, 48) = 2.97$, $p = .09$) were not significant. This suggested of no effect of intervention on error related early potentials.

(b) Late Error related potentials

A 2 time (baseline and follow-up) * 3 electrodes (Cz, CPz and Pz) * interventions (IT and CT) MANOVA was performed. The main effect of time and intervention with time * intervention and time * electrode * intervention interactions were expected to be

significant. A significant main effect of time (F (1, 24) = 6.55, p = .02, η_p^2 = 0.214) was noted. The Pe amplitude for incorrect responses increased over time from baseline (0.60) to follow-up (1.43). The time * intervention (F (1,24) = 1.97, p =.17, η_p^2 = 0.076) and time * electrode * intervention (F(2,48) = 0.11, p = .90, η_p^2 = 0.005) were not significant. This suggested of no differential effect of the intervention on changing late potentials over time.

F. Discussion

The first aim of the present study was to compare subjects with alcohol dependence syndrome (ADS) with healthy controls (HC), on their performance and event-related potentials (ERP) on the inhibitory tasks: Go Nogo (GNG) task (action restraint) and stop-signal task (SST; action cancellation); and error processing task: flanker task. The second aim was to test the effect of multiple sessions of the smartphone inhibition training game in ADS subjects on the behavioural and neural markers found impaired on these tasks. With the intervention, near transfer effect on inhibitory control (near transfer: change in same cognitive function as of training) and far transfer effects (far transfer: change in other cognitive function other than the trained cognitive function) on attention, interference control and error processing were expected. The comparison was made with a placebo intervention similarly delivered with a smart-phone game intervention but not expected to train inhibition.

At baseline, the ADS subjects displayed impaired inhibitory control and error processing in comparison to the HC subjects. Following brief training in inhibitory control, with the smartphone game in a subset of the ADS subjects, contrary to expectations, there were no improvements on the behavioural (neuropsychological) parameters of inhibition and error processing, compared to compared to the control intervention, given to the other ADS subjects. However, there were observed changes in the Event-Related Potentials (ERP) related to the tests of inhibitory control suggesting possible near transfer effects, but no far transfer effect of game training in terms of changes in attention, interference control and error processing.

1. Near transfer effects: Inhibitory control

a) Baseline comparison

On comparing the performance on the inhibitory tasks between ADS subjects and HC, the ADS subjects demonstrated reduced inhibitory control. This was evident from a

significantly longer stop-signal reaction time (SSRT) noted in the ADS subjects when compared to HC. Further, the ADS subjects had blunted N200 amplitudes on stop signal task (SST) and blunted P300 amplitudes on both go nogo task (GNG) and SST, on correctly inhibited trials. Most of the statistically significant comparisons between the ADS subjects and HC had a large effect size. These findings suggest that ADS subjects had impairments in the inhibitory control and neuronal resource allocation on correct performance of an inhibitory control. The N200 amplitudes are thought to reflect the neuronal resources allocated for detecting/monitoring the conflict in an inhibitory task, while P300 amplitudes signifies allocation to resolve the detected conflict. The GNG task is an inhibitory task which assesses the action restraint part of inhibition, while the SST assesses the action cancellation part of inhibition. Looking at the ERP differences on the GNG task between ADS subjects and HC, blunted P300 amplitudes in the ADS subjects may perhaps signify that they had less neuronal resources allocated for resolving the conflict generated while restraining the action on no-go trials. The N200 amplitudes for the no-go trials did not differ significantly between groups and had a small effect size, on the contrary, the N200 amplitudes on the Go trials were trending towards significance. No statistical difference in the errors of commission between two groups and a related small effect size difference, might therefore suggest that the ADS subjects were nonetheless able to manage to restrain their ongoing action. One of the other possibility of no difference in the N200 in no-go trials could be that the ADS subjects already had a negative defection at the go trials which was trending to significance, and presentation of the no-go trial did not make any change in the N200. While in the HC, the no-go trail brought a negative deflection. Among the SST variables, the raised SSRT in the ADS subjects suggests of a delayed start in the cancellation process while suppressing the action of the ongoing motor activity in an inhibitory trial after presentation of a stop cue. Furthermore, the blunted N200 amplitudes suggest of an inability to allocate ample of neuronal resources for detecting the conflict generated in the stream of go trials. Blunted P300 amplitudes further suggests of inability to resolve the conflict generated. These differences in the ERP appear to indicate that even though the ADS subjects successfully inhibit their activity, the neuronal processing of inhibition is not similar to the HC and they have subnormal resource allocation. A recent meta-analysis showed a significant gray matter volume reduction in the ADS subjects in the cortico-striatal-limbic circuits, including the areas

of dorsal lateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) (Yang et al., 2016). These are the areas noted to play a crucial role in the inhibitory control (Luijten et al., 2014). The neurotoxic effects produced by a long-term alcohol use may lead to a loss in the neuronal resources controlling inhibition.

Further, we assessed how the ADS subjects manage the differential amounts of inhibition requirements while managing with the limited resources available. We assessed this by increasing the stop-signal delays (SSD) in SST. The SSD signifies the time delay in the stop cue delivery to abort an ongoing response for a go trial. The more the delay in delivering a stop cue, the more difficult it would be to cancel an already started action to respond. We used 4 SSD times of 150 ms, 200 ms, 250 ms and 300 ms, expecting that the increasing SSD timings would increase the difficulty. While performing the trials with increasing difficulty, the SSRT and associated ERP activities did not significantly change in HC subjects and the increase in the difficulty level had a small effect. The variation in the SSD also did not reach significance with the increase in inhibitory demand for ADS subjects. However, ADS subjects displayed incremental blunting of N200 amplitudes with increasing inhibitory difficulty and had a moderate effect size. As the N200 amplitude denotes an amount of brain activation on detecting a conflict in the ongoing 'go' response on presenting a stop cue, the progressive blunting of N200 amplitude with an increasing SSD suggests a decrease the brain activation with increasing conflict in an ongoing response. As we know about the limited availability of inhibitory resources in the ADS subjects, the increase in the inhibitory demand limits the further utilization of the available neuronal resources. During a difficult period, the ability of ADS subjects to sense an inhibition requirement further worsen, enhancing the probability of taking an impulsive decision. This might explain the dynamics of an inhibitory resource adjustment in the ADS subjects with an increase in the inhibitory demand.

The ADS subjects were consistently slower in responding to the go trials on both GNG task and the SST task. Further, while processing an inhibitory activity in both the tasks, the latencies of N200 and P300 waves were longer for ADS subjects than HC. These differences in the response timings and the timings of neuronal processing of inhibition are suggestive of sluggish processing of activities in the ADS subjects. This perhaps could be due to the persisting effects of alcohol or that of benzodiazepines used for detoxification. The previous literature suggests of benzodiazepines affecting the

reaction times (Jansen, De Gier, & Slangen, 1986) and lowering the processing speed. The latencies of N200 and P300 waves are said to vary with time and number to repeated measurements (Kinoshita, Inoue, Maeda, Nakamura, & Morita, 1996). Also, such differences were not noted in studies assessing inhibition in children of alcoholics (Kamarajan et al., 2005), perhaps suggesting that the latencies do not represent a trait marker but change with the state.

Our findings of poor inhibitory control in ADS subjects compared with HC, are similar to the previous findings. The blunted P300 amplitudes for the successfully inhibited trials in the GNG task were also noted in other studies (Colrain et al., 2011; Fallgatter et al., 1998; C. Kamarajan et al., 2005). No difference noted in the N200 amplitude in our study on GNG task contradicts the findings of a previous study by Pandey et al., (2012). They noted lowered N200 amplitudes in the ADS subjects with alcohol dependence on performing inhibitory trials. The variation in the prepotency of the inhibitory trials in the GNG task used could be the reason for the discrepancy.

b) Effects of the inhibition training on inhibitory control

Following the inhibition training and the control intervention using the smartphone based games in the ADS subjects, there was an overall reduction in the commission errors (CE) and SSRT in the GNG task and SST tasks respectively, across both the intervention groups, suggesting improvements in inhibition. However, there was no specific interaction noted with any specific type of the provided interventions. The cause of this non-specific reduction may be simply the self-monitoring of the task-related activities, leading to a Hawthorne effect (McCambridge, Witton, & Elbourne, 2014). Hawthorne effect is a change in the behavior seen due to their awareness of being observed. Alternatively, the regular treatment in the ward with motivational interviewing and anti-craving medications might have produced a non-specific effect on improving inhibition (Goncalves et al., 2014). It could also be due to a practice effect.

However, the inhibition training group of ADS subjects showed an increase in the negativity of the N200 amplitudes with a large effect size, (which were blunted in comparison to the HC subjects on prior assessment at the baseline). This effect might be due to an increase in the neuronal allocation for detecting a stop cue linked conflict in an ongoing series of go trials. This may also suggest an improvement in the ability to recognize the moment of an inhibitory requirement and detection of the time to

cancel of an ongoing motor activity. No other near transfer effects were noted in the inhibitory task performance. The reason for this could be the limited two-week duration of training. Apart from a few recent studies with a null near transfer effect of general inhibition training for 4 days (Bartsch, Kothe, Allom, Mullan, & Houben, 2015) and 4 weeks (Field et al., in prep), there is no literature about training the inhibition for a longer duration in the alcohol use disorder. Inhibition training for a longer period of 6 month in the population with eating disorder (Lawrence et al., 2015) and for 1 years in the older adults (Wilkinson & Yang, 2016) have previously documented changes in the outcome measures related to the training. Also, previous studies with training the executive functions in older adults, specifically working memory training for improving the top-down functioning, for a longer duration have shown the strengthening of the specified training network along with the improvement in the behavioural parameters (Rebok et al., 2014). This suggests that our intervention might show an improvement in the training for a longer duration, as in 2 weeks, our training could produce some changes in the brain activations. Future studies should try attempting such type of training for extended periods.

In our previous study training inhibition for a single session in heavy drinkers, blunting of P300 amplitudes were noted for difficult trials of inhibition suggesting improvements in the ability to resolve the detected conflict efficiently (please see chapter 4). The present study did not show any changes in the P300 amplitudes with training inhibition. There could be several reasons for this difference. First, the population being trained was different. The present study was performed on ADS subjects, in whom the inhibitory control related parameters are impaired. The previous study trained heavy drinkers, where the inhibitory control is suggested to be a state change factor with momentary changes in the inhibitory control (Jones & Field, 2013; Jones, Field, et al., 2013). Second, the duration of training. In the previous study, we trained for a short duration of 30 minutes, while this present study trained for multiple sessions over 2 weeks. It could be possible that our training targets different components of inhibitory control at the different time. Initially, it may train neuronal resources responsible for P300, while later on further training it may train N200 associated resources. Future studies should focus on changes produced by inhibitory control training of different duration. This may help us in deciding the optimal amount of training required to bring desired changes.

Our finding of an increase in the negativity of the N200 amplitude with inhibitory control training corresponds to findings of the similar previous studies. It can be noted that three weeks of inhibition training, in a previous study, reported increased no-go N200 amplitude (Schapkin et al., 2007). But, this study did not have a control intervention group for comparison. Benikos & colleagues (2013) in their study reported decreased N200 amplitude training inhibition for short duration of 45 minutes. They mentioned that the reduced N200 amplitudes with training are suggestive of more efficient stimulus discrimination. Manuel et al., (2010) in their study training inhibition with GNG training task for 40 minutes, showed electrophysiological topographic modulations around 150 ms post-stimulus for no-go trials. In another of their study with inhibition training for 60 minutes, showed modulations around 200 ms post-stimulus for inhibitory trials (Manuel et al., 2013). Both these training studies showed changes corresponding to the temporal dynamics of inhibitory control (Falkenstein et al., 1999; Schmajuk, Liotti, Busse, & Woldorff, 2006). All these mentioned studies attempted training inhibition in healthy adults. Our study is perhaps the first one to report the changes with inhibition training in ADS subjects. As the baseline comparison of ADS subjects and HC suggested of blunted N200 amplitudes in ADS subjects, enhanced N200 negativity may suggest improvement in the ability to recognize the timing when they need to stop responding to their impulsive drive. But, learning the actual stopping to the impulsive response is not seen in the 2 weeks of training.

2. Far transfer- attention, interference control and error processing

a) Baseline comparison

We used the Eriksen's flanker task for assessing the attention and interference control. On initial comparison of behavioural variables between the ADS subjects and HC, there were evident differences in the interference processing with large effect sizes. When trials changed from congruent to incongruent, HCs showed a significant increase in the reaction time (RT), whereas in the ADS subjects the RT did not change significantly. This discrepancy in RT is further reflected by the error proportions where there were significant interactions with congruency. The overall error rate was higher in the ADS subjects, and the change in trial congruency induced more errors when compared with the HCs. The longer difference in the RT with a congruency change in the HCs suggests that they detect the change in the trial dynamics and then successfully change their responses. In the ADS subjects, this change in the congruency is not adequately judged,

leading them to commit more errors in the changing trial dynamics. These differences in the congruency management between two groups suggest the ADS subjects to have relative impairments in the interference processing. Additionally, an increase in the proportion of trials without a response (missed trials) in the ADS subjects, is indicative of their inability to attend the fast frequency of trials. This shows their deficits in an attention processing compared to the HCs.

On commission of an error, the HC subjects appeared to respond by generating an early negative potentials (ERN), widely distributed over fronto-central sites, followed by large positive late potentials (Pe). The ADS subjects, on the other hand, responded, with a weak negative potential limited to frontal sites, without any changes in the positive potential in response to an error. The early potentials following an error is a neuronal marker for an initial and automatic error detection, while the late potential signify more conscious evaluation of an error and its awareness, as also the motivational significance attributed to an error. Initial deflection in the early potentials for ADS subjects only on the frontal site, compared to the generalized fronto-central negative deflection in HC, is suggestive of their sub-optimal brain activation in automatic error detection (large effect size). It is implied that if the error is not detected optimally, the evaluation process for the error may not occur, affecting the late potentials in the ADS subjects. This impaired processing of error in the ADS subjects might be the reason for them not learning from the mistakes made and thus repeating them, leading to a high proportion of errors.

Some of the previous studies have shown findings similar to our study for error processing in the ADS subjects (Padilla et al., 2011; Schellekens et al., 2010). The error processing is also found to be sub-optimal in the children of alcoholics when compared to the same age children (Hardee, Zucker, & Heitzeg, 2015). Also, late potentials related to the processing of error are found blunted in the heavy drinkers (J L Smith, Mattick, & Sufani, 2017). These findings may suggest impaired error processing as a trait marker and may play a causative role in the development of a problem alcohol use. Similar findings are also noted in other substance dependence, such as nicotine dependence (Franken, van Strien, & Kuijpers, 2010; Luijten, Van Meel, & Franken, 2011) and stimulant dependence (Franken, van Strien, Franzek, & van de Wetering, 2007; Marhe, Van De Wetering, & Franken, 2013), where a decreased negativity was noted on incorrect responses compared to HC. This suggests that the population who

are at risk for developing substance associated problems are not able to generate an understanding of a mistake and thus not learning from them to avoid the same mistake. Also, they may not be able to learn from the harm caused to them by the substances and thus continue to use them in a harmful pattern. This may further worsen the error processing due to neurotoxic effects of these substances.

b) Effects of inhibition training on attention, interference control and error processing

With 2 week interventions in ADS subjects, there was a decrease in the error rate over time with no interaction with the intervention type. This might be the practice related effect noted (Kelley & Yantis, 2009). Apart from this, no change in the reaction time was noted with the intervention suggesting that there were no transfer effects of inhibition training on interference control. Also, the lack of change in the proportion of trials with missed responses, suggest the lack of improvement in attention to inhibition training. With intervention, no changes in error processing relating to both early and late potentials were noticed. This may be taken to conclude that the inhibition training in this study did not induce any far transfer effects on attention, interference control and error processing.

Previous studies using a non-associative type of inhibition training also did not find any far transfer effects. They assessed the far transfer effects of inhibition training in heavy drinkers on alcohol consumption and did not find any intervention related specific decrease in alcohol use (Field et al., in prep; Bartsch et al., 2015). However, other study training executive function in ADS subjects found generalized improvement in the frontal lobe associated cognitive functions (Gamito et al., 2014). As these neurocognitive areas under the executive function are linked (Miyake et al., 2000), it is predicted that improvement in one function may influence the development of even in the other ones. There are many studies showing the far transfer effects (Warren K. Bickel et al., 2011a; Björkdahl, Åkerlund, Svensson, & Esbjörnsson, 2013; Houben, Nederkoorn, Wiers, & Jansen, 2011a; T Klingberg et al., 2002; Takeuchi et al., 2010; Verbeken, Braet, Goossens, & van der Oord, 2013). However, this ability to transfer improvement to other functions is still doubtful (Simons et al., 2016). It may be possible that if all the cognitive facets of executive function are tuned simultaneously in one training program, it may produce generalized behavioural changes. Further studies

should try developing a generalized training package rather than just training one cognitive function.

G. Limitations

This study, the first to examine whether inhibitory control training alters inhibitory control parameters and their neuronal markers in those being treated for the alcohol dependence, has some limitations that deserve emphasis. Firstly, the subjective outcome measures such as craving measures were not taken to measure the far transfer effects produced by the inhibitory control training. At the time of recruitment, the ADS subjects were already under treatment, so most of them subjectively mentioned of no craving. This made difficult for us to record such measures. Given that the previous studies with a cognitive training in the substance dependence found positive behavioral changes (Brooks, Wiemerslage, Burch, Maiorana, Cocolas, Schiöth, et al., 2017; Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011b), taking clinical measures such as craving improvement and relapse rate, would have added chances to explore the clinical effects. Secondly, it would also have been better to collect subjective measures of the cognitive training process, to gauge whether the ADS subjects felt any benefits of the inhibition training during their daily schedule. Furthermore, given various constraints, we were unable to increase the number of participants measured and unfortunately, 3 dropped out during their standard treatment. This could have affected the ability of this study to note subtle changes produced by the training (Button et al., 2013). This could be another reason for no other near transfer effects could be the small sample size of the study apart from a large effect on the N200. The small and medium effects on SSRT and the P300 respectively were not detected as significantly different. A larger sample size might have some different result.

Another limitation is that we did not have a 'treatment as a usual' group not receiving any cognitive training, to compare intervention effects with the natural course of a disease. Looking at the crucial phase of illness when the intervention was provided, many confounding factors may play role in the changes noted with the intervention (McCambridge et al., 2011). The use of anti-craving medications might be one of the reason of the change as it affects impulsivity (Pettorruso et al., 2014), even though the effects are not specifically tested on a larger scale. Previous studies have given cognitive training over longer periods and observed more generalization of the training effect. Nevertheless, our preliminary data of the effects of inhibition training with a

smart-phone game on ERP measures directs towards the further exploration before offering cognitive trainings as a formal intervention, particularly as other re-searchers examining different cohorts with impulse control deficits (e.g. ADHD and cocaine use) have shown positive effects of other trainings (Benikos et al., 2013; Berkman et al., 2014; Warren K. Bickel et al., 2011b; Boendermaker, Prins, et al., 2015; Brooks, Wiemerslage, Burch, Maiorana, Cocolas, Schiöth, et al., 2017; Houben, Nederkoorn, et al., 2011b; Torkel Klingberg et al., 2005). Also, the data in this study is related to the male participants. Noting the gender differences in the ERPs of inhibitory task performance in a previous study (Melynyte, Ruksenas, & Griskova-Bulanova, 2017), a generalization of our results in females needs to be explored.

H. Conclusion

This study suggests that the inhibitory control is impaired in ADS subjects. The defect is evident from a longer inhibitory reaction time and subnormal brain activation while doing an inhibitory activity. Further, on 2 weeks of inhibition training in the ADS subjects, there is an increase in the brain activation while a conflict detection moment of correct processing of an inhibition. This may be suggestive of better ability to identify the moment of an inhibition requirement. No other near or far transfer effects were seen with the inhibition training. A longer duration of similar training may extend the improvements noted in this study at a behavioural level. Further studies should explore the effects produced by this type of training for a longer term.

VII. General Discussion

The aim of this thesis was to develop an in-house game targeting the inhibitory control and test this game for an improvement in the inhibitory control markers in population with an alcohol use disorder. The game was developed on "unity" platform for designing the game dynamics. This had a graphical user interface and could provide a personalized training as per the ability of the subject. We used this game in 3 different studies. The first 2 studies were conducted at the University of Liverpool on heavy drinkers having a probable alcohol use disorder. The third study was conducted at NIMHANS, Bangalore on the patients with alcohol dependence syndrome. In all the studies, outcomes were compared between the inhibitory control training intervention and a control intervention.

The first study aimed to observe, in heavy drinkers having a probable alcohol use disorder, near and far transfer effects with a 2-week of the above inhibition training assessed by a stop signal task (SST) for inhibition and the Stroop task for attention. We also assessed the effect of training on alcohol consumption by the ecological momentary assessment. Although small to moderate effects were noted on the outcome measures, no significantly different near and far transfer effects were observed, along with a null effect on alcohol consumption.

In the second study, we explored effects produced by a short-term (30 minutes) inhibition training and a mindfulness training on the behavioural measures and event-related potentials (ERP) of an inhibitory control. Mindfulness was noted to reduce P300 amplitude for all the inhibitory trials, while the inhibitory control game training showed a significant reduction of P300 amplitude only for the difficult inhibitory trials which had a large effect. A moderate effect was also noted on P300 at the less difficult inhibitory trials though did not differ statistically. On the contrary, N200 and SSRT showed no significant difference. This suggested that ERPs could be a sensitive outcome measure to note subtle changes produced by our interventions.

In the third study conducted at NIMHANS, we trained the patients with alcohol dependence using the smart-phone games for 2 weeks. We also collected healthy control (HC) subjects' data for outcome measures in order to compare the baseline differences associated with the inhibitory control. To get a better understanding of the effects our training could produce on different difficulty levels of an inhibitory control, we used, for assessing the outcomes, a stop-signal task with 4 different difficulty levels

instead of two as with our second study. We also added a Go No-go task assessment to observe the variation in the effects produced by our training on action restraint, apart from the action cancellation process assessed by SST. The stop-signal task and the Go No-go task were the assessments used for a near transfer effect with the training. We added the error processing assessment, Flanker task, to explore the difference produced by an inhibition training on processing of an error (far transfer effects). Regarding the behavioural indices of an inhibition, SSRT was higher (worse inhibitory control) in patients compared to HC along with overall errors committed in the error processing task. We also noted that the ADS patients have less negative N200 and a blunted P300 amplitude while correctly performing the inhibitory trials, and more negative error-related negativity on an error response when compared with HC. With the inhibitory control training, patients showed an increase in the negativity of the N200 amplitude while correctly performing the inhibitory trials. There was no differential effect of the training on different levels of difficulties of the inhibitory trials. Also, on the action restraint task (Go No-go task), no change in the activity level was noted. The other indices of an inhibitory control and error processing did not show any significant change.

A. How the inhibition training influences ERP?

The finding associated with the inhibition training from both ERP studies were mostly with the changes in a stop-signal task linked ERP components due to a large training related effect on them. The study in chapter 4 noted a blunting of P300 amplitude with the inhibition training, while the study in chapter 5 noted an increase in the N200 negativity following the training. The similarities between both the studies were the use of a same gamified version of the training and the results compared with a control training intervention which was not expected to produce changes in the inhibitory control. The major differences between these two studies were in the population trained and the duration of training provided.

First, the study in chapter 4 was conducted in the United Kingdom on heavy drinkers having a probable alcohol use disorder while the study in chapter 5 was performed at NIMHANS population on the alcohol-dependent subjects. These both the population differ in the baseline inhibitory control. In a previous study exploring differences in the inhibition processing between heavy and light drinkers, the deficits in the inhibition associated ERP components (both N200 and P300) in heavy drinkers having a probable

alcohol use disorder were not evident (Franken, Luijten, van der Veen, & van Strien, 2017). This suggested that heavy drinkers having a probable alcohol use disorder had an optimal inhibition processing neuronal resources. So, the conflict monitoring/detection process (N200 related) and the conflict resolution process (P300 related) during an inhibition evaluation functions similar to the light drinkers. Further, in the context of heavy drinkers having a probable alcohol use disorder, disinhibition is said to be a state phenomenon rather than a trait phenomenon and the momentary fluctuation in the inhibitory control is suggested to influence the alcohol consumption (Jones, Christiansen, Nederkoorn, Houben, & Field, 2013). The blunting of P300 amplitude with both the inhibition and mindfulness training was noted in the heavy drinkers having a probable alcohol use disorder but no significant effect was noted on the N200 amplitude. This suggests that our training might have helped heavy drinkers having a probable alcohol use disorder in smoothening the conflict resolution process without utilizing much of the neuronal resources on a correct performance for the inhibitory trials. The attenuation of P300 amplitude in heavy drinkers having a probable alcohol use disorder with the inhibition training, but not to the control training also suggests that the inhibition process wasn't a novel activity for this group. While the control group got exposed to the inhibition directly in the stop-signal task so had a larger P300 amplitude.

In the study described in chapter 5, the training was performed in the alcohol-dependent subjects in Indian settings. This population has been shown to have deficits in the inhibitory control processing from previous studies (Luijten et al., 2014) and also from our comparative findings with respect to healthy controls from chapter 5 study. The blunted N200 on correctly inhibiting in alcohol-dependent subjects suggests an inability to detect a conflict produced by changing the task trial and had a large effect size. This could be due to less neuronal resources available after the long-term use of alcohol causing the neurotoxic effects. It is expected that if the conflict monitoring/detection processing is impaired, further conflict resolution process reflected by P300 may not be seen leading to a blunted P300. On training inhibitory control in these subjects, an increased N200 negativity was seen. In view of the defective processing of a conflict monitoring/detection (blunted N200), an increase in the N200 negativity can be looked as an improvement in the resource allocation for a conflict detection in the inhibitory performance. This change with the training may be either due to an increase in the

number of synapses in an inhibition circuit or by strengthening the already existing synapses, brought by multiple stimulations over a period of time. This gives a hope of possibility to bring plastic changes in an inhibitory control of the alcohol-dependent subjects, looking at the gross deficits in them. No change noted in P300 could be due to the less duration of training provided (2 week). A longer duration of training may further even influence the conflict resolution process.

The second factor which might have influenced the difference in the findings of 2 studies could be the duration of training. In the study performed in the UK described in chapter 4, the training was a single session short-term training of 30-minute duration. The other study described in chapter 5 had multiple sessions of training performed over 2 weeks. It might be possible that the shorter duration of training induces changes in the conflict resolution process (P300 related) while on further extending the training duration the changes are even seen in a conflict detection process (N200 related). This may suggest that, instead of one neuronal circuit operational for an inhibitory control, there are two separate networks, one monitoring the conflicting activities and detecting the conflict. Later, this circuit updating another circuit which resolves the conflict by taking an action ahead. It may be possible that our inhibition training initially improves the conflict resolution circuitry, while the longer-term use of training further starts affecting the conflict detection circuitry. The only contradicting finding for this hypothesis of change between our studies is no change noted with P300 amplitudes in the alcohol-dependent subjects. The null effect on P300 in the ADS subjects might be due to deficits in the neuronal resources noted in alcohol-dependent subjects. Further understanding can be generated if different time points of recordings are done for the same sample of training population.

The pattern of variation in the changes produced postulated to be due to a variable duration of training can be observed in some of the previous studies. Previously when trained for a brief term, the inhibition training showed changes in the P300 amplitudes while correctly inhibiting stop trials. Hartmann & colleagues (2016) in their study, training inhibition with a GNG task for a short-term showed change in P300 amplitude associated with the correct performance of the inhibition trials. A similar finding was also noted in an another study (Benikos et al., 2013). Though their finding was an increase in the no-go P300 amplitude, which is opposite to our result, the reason for the discrepancy could be due to the nature of an assessment task and the target population.

We used SST for the training and assessment, which is based on an action cancellation process and our target population was the subjects with alcohol use disorder. They used a GNG task for the training and assessment, which is based on an action restraining process and tested the healthy adults. The difference in the neuronal reserves in the subjects with alcohol use disorder could be a reason for the opposite pattern of activation with the training (Rangaswamy & Porjesz, 2014). On longer term of the inhibition training, the conflict detection associated N200 amplitudes change were noted. Previous studies with a longer term of an inhibition training (Berkman et al., 2014; Liu et al., 2015), N200 changes in the ERP study and the inferior frontal gyrus (IFG) activation change in fMRI study were noted, similar to our study. The study targeting inhibitory control with the ERP outcome showed an increased N200 amplitude negativity with the training in preschool children (Liu et al., 2015). The IFG activation, an area which correlates with the N200 activity in ERP, increased during an inhibition task performance when trained for a longer-term (Berkman et al., 2014), is in line with our findings. We may infer from the findings that an initial shorter training course focuses on the P300 reflecting the neuronal components of a conflict resolution, while after the long term of training the N200 linked neuronal modulation takes place related to a conflict detection.

The game we used in our studies showed the capability to train components of an inhibitory control, similar to the previous computer and mobile-based training tasks (Benikos, Johnstone, & Roodenrys, 2013; Berkman, Kahn, & Merchant, 2014; Field, Mcgrath, et al., in prep; Field, Tiplady, & Jones, in prep; Jones & Field, 2013; Liu, Zhu, Ziegler, & Shi, 2015). In the computer-based training, Benikos et al., (2013) trained the inhibition with a computerized modifying Go No-go (GNG) task by changing the reaction time deadline of go trials, and thus increasing a conflict in the performance. In our training game stages, the increasing speed of trials with consecutive levels was expected to produce a similar effect. In another study, the training based on the stop signal task (SST) consisted of a changing stop-signal reaction time (SSRT) as the conflict modulatory agent. The increasing SSRT was expected to generate more conflict in responses while the training task performance (Field, Mcgrath, et al., in prep; Jones & Field, 2013). Training with the SST based training task showed improvements with both computerized (Jones & Field, 2013) and mobile-based training (Field, Tiplady, et al., in prep). On the training of gamified version of the SST, training with a game "Fruit

Ninja" showed the ERP changes in preschool children (Liu et al., 2015). Our training game contained both GNG and SST based training with increasing SSRT as the training advances and have a gamified training to increase the interest of participants in the training. As the game was based on previous literature, effects were expected in the similar lines.

One of the common findings for all our studies was that we didn't find any change in the behavioural indices of an inhibition with the training, although ERP changes were noted. These null effects noted were similar to another study (Field, Mcgrath, et al., in prep), having no changes in the behavioural measures with the web-based inhibition training. They trained heavy drinkers having a probable alcohol use disorder for both the general and cue-specific inhibition training in randomized groups for a 4-week duration. Another study by Bartsch & colleagues (2015) trained heavy drinkers having a probable alcohol use disorder with a non-associative inhibitory control training for 4 consecutive days, with the behavioural changes in SST and alcohol consumption as outcome measures. They did not find any change with the inhibitory control training neither in the behavioural measures nor in the alcohol consumption.

Looking at the limited evidence for an effectiveness of the non-associative inhibition training perhaps may be possible that the training effects are not tapped by the behavioural outcome measures of the stop-signal task. The other possibility is that longer duration of the training may produce the required behavioural changes. The other laboratory-based single-session studies demonstrated change in the behavioural measures with an inhibition training (Houben et al., 2012; Houben, Nederkoorn, et al., 2011b; Jones et al., 2016; Jones & Field, 2013), but these studies used an automatic inhibitory control training approach aiming the bottom up inhibition circuit, while our training aimed at the top-down inhibition circuit with developing the neuronal reserve associated with this circuit.

B. Theoretical implications of the inhibition training

As per a theoretical model behind the causality of addiction described in chapter 1, substance use for longer period of time disrupts the two complementary systems, the impulsive system and the reflective or executive system (R.Z. Goldstein & Volkow, 2011; R Z Goldstein & Volkow, 2002; A Verdejo-García & Bechara, 2009). The impulsive system is said to be overactive towards substance-related stimulus with a decreased response for other reinforcements, while the reflective or executive system

is said to be under active or impaired leading to difficulty in suppressing the impulsive response. Although the efficacy of the cognitive training interventions in generalizing the effects is not clear (Au et al., 2015; Au & Buschkuehl, 2015; Adrian M Owen et al., 2010), these pieces of training have shown some good results in the previous studies when trained in an alcohol use disorder.

The previous response inhibition trainings (Houben et al., 2012; Houben, Nederkoorn, et al., 2011b; Jones & Field, 2013) were mostly an associative type of training where an alcohol cue are paired with the inhibitory cues. In these studies, the mechanism relevant to the training would be a buffering of the impulsive system due to the nature of training, even though the training is mediated through an inhibitory task (Verdejo-Garcia, 2016). This type of training is said to reorient the action-value representation of the alcohol-associated cues and devaluing alcohol cues. The inhibition training, we used, is of a non-associative type and is expected to act on the reflective system and strengthen it. Our findings of an improvement in the inhibitory ERP components suggest changes associated with the executive neuronal circuit responsible for the inhibitory control. The previous study of an inhibition training in the healthy volunteers suggested most of the training associated changes in the inferior frontal gyrus, correlating with the improvement of an inhibition (Berkman et al., 2014). Noting the significant deficits in the inferior frontal gyrus in the substance users (Feil et al., 2010), our training might have influenced this area.

Our training is expected to produced effects on the inhibition in a similar manner as the previous working memory training in addiction. This is because the previous working memory also targeted the deficient reflective system in this population, helping them to control impulse. Although the working memory training associated changes in the imaging is not assessed in the studies with this training in the substance use disorder, similar training in the attention deficit hyperactive disorder has shown changes in the prefrontal cortical areas (Wesley & Bickel, 2014), commonly associated with the executive function and impulsivity.

C. Mindfulness

Hypothetically, the aim of mindfulness training is to improve the coordination of goal representation and a feedback loop if deviate from the goal-directed path. If considered at the neuronal level, mindfulness strengthens the integration between the lateral prefrontal areas (dorsolateral and ventrolateral prefrontal cortex (VLPFC)) and the

medial cortical areas (medial prefrontal cortex, anterior cingulate and insula) (Verdejo-Garcia et al., 2015; Verdejo-Garcia, Clark, & Dunn, 2012). This can be observed from a study on smokers where 2 weeks of mindfulness training increased the resting-state activity in the VLPFC and the medial prefrontal cortex/anterior cingulate cortex along with the reduction in tobacco use (Yi-Yuan Tang, Tang, & Posner, 2013). A recent model of the executive function suggests cognitive flexibility as one of the independent component of the executive system along with the working memory and response inhibition (Miyake & Friedman, 2012). Mindfulness training seems to add a cognitive flexibility to the treatment regimen of addiction and improve the reward-based decision making (Alfonso, Caracuel, Delgado-Pastor, & Verdejo-García, 2011). In our study, mindfulness training for a brief duration showed a blunting of P300 amplitudes on correct performance of inhibition trials, suggestive of resolving a conflict in the inhibitory tasks. This improvement in the inhibition ability may be due to the mindfulness training, helping them to make a goal-directed decision to inhibit a response when inappropriate, and strengthening the executive system controlling the automatic tendency to respond. More detailed research is further required to observe the effects on other neurocognitive domains and change produced in the drinking pattern with mindfulness training.

D. Mobile health

In all the three studies, the major finding was a strong adherence to the therapeutic intervention. This adherence was seen across the intervention groups, suggesting the effect to be of the device used for training rather than the intervention per se. Participants in all the study explicitly mentioned that the games were more interesting than the computer-based assessment tasks (done for pre-post assessments). Use of smart-phone for the therapeutic intervention has an advantage of a convenient usage. We expected some resistance from the patients at NIMHANS in view of the lower electronic literacy among the general inpatients we get in the hospital. But the participants easily adapted to the game and expressed the interest in playing. As the smartphone has increased its penetration into a day to day utility even in the developing countries, using this device for delivering interventions requiring frequent sessions or feedbacks would be helpful and may affect the outcome differently. Using smart-phones for measuring a real-time variable (ecological momentary assessment) such as, a daily alcohol consumption with eDiary or measuring daily fluctuation in the

behavioural activities, can help us understand the nature of change in the disease outside a laboratory. In the alcohol use disorder, implementation of strategies from prevention of the disease development, to improve the relapse rate, all can be managed by utilizing the smartphones. In a developing country like India, utilizing the smart-phone can reduce the treatment cost and even the accessibility in the interiors of India.

Looking at the effects produced by the inhibitory control training and the working memory training in tuning the executive functions, the combination of both these trainings could help in getting a better outcome in the alcohol use disorder. This may help in a better valuation of the long-term goals promoting to control the alcohol use and prevent overvaluing the immediate rewards. Integrating the gamification in an appropriate manner and avoiding dilution of the main effects of the training intervention (Boendermaker et al., 2017), can be advantageous when the training is designed for a population with the substance use. This may help in maintaining the motivation in the training when attempted for a longer duration. The output from the study in chapter 3, having no significant changes in outcome measures also suggests of chances of failure in case the outcome assessment measures are not influenced by the intervention per se.

VIII. Limitations

Even though our sample size for each study was comparable with the other studies in this field (Benikos et al., 2013; Berkman et al., 2014; Liu et al., 2015), the studies conducted for assessing the effect of training had a limited sample size. All the three studies had a lower sample size, considering the pilot nature of the studies and the limited time. The small sample sizes were capable of showing significant differences in comparisons having large effects and might have affected our ability to detect some subtle changes, also could be the contributor for null effects of the behavioural parameters which showed smaller effect sizes. The result using larger sample sizes may differ.

The maximum duration of training in our studies was of 2 weeks. Perhaps, the limited duration of training might be one of the reasons for not finding changes in the behavioural measures. With this short term of training, the changes were noted on electrophysiological measures. Training for a longer term may translate these changes to the behavioural level.

Another limitation was that the smoking-related indices of patients and heavy drinkers having a probable alcohol use disorder were not considered. The previous study had shown that cigarette smoking could influence ERP amplitudes (Anokhin et al., 2000). Another confounding variable which might have influenced our findings is IQ. We didn't measure IQ of the participants in any of the study. Even though this may not have a direct effect on the inhibitory variables, its strong genetic influence can't be neglected (Friedman et al., 2008).

The game training was designed on the principle of an inhibitory task, similar to the previous computerised training tasks. In this process, we gamified the trials of an inhibitory training and added a reward component with an expection of a better performance. This change in the task dynamic, which is different from the previous training tasks, might affect the core purpose of the training (Boendermaker et al., 2017). Although the main foundation for the training was based on the inhibitory principles, validation of inhibitory components in the game with healthy population would have added to the strength of the results. This process would have even helped us to test the general acceptability of the training.

In all the studies the training was conducted on the population with a problem alcohol use. In the study in India although the HC was included for the validation of the

assessment tasks, not training the healthy individuals limits the comparability of the training findings. The training in the HC might show a different change in the outcome measures than our findings.

The game had some limitations such as an inability to measure the SSRT. The game could only measure the proportion of errors but, due to the nature of game dynamics, SSRT couldn't be measured. Due to this, we missed an avenue to measure a real-time fluctuation of the SSRT, giving us a better picture of an inhibitory control change. Perhaps the SSRT might show some other variation on the day to day basis, from the pre-post assessment as the disinhibition have a fluctuating nature (Jones, Christiansen, et al., 2013). One of the other limitations in our game was that, although we organized an active control group who was trained to go for all the responses without an inhibition, which is better than a passive control group not getting any intervention, this game was not as competitive as the inhibition training game. The control game included a competitive scoring system, but many participants finished the game even before 2-week duration. Such participants were asked to gain 3 stars in all levels they played. While building the game it was assumed that this control game would be equally competitive but was not seen during the study process. This factor could influence the results, affecting an improvement in the performance and changes in the brain activity.

In Chapter 4 and 5, the term ‘heavy drinkers’ is used for the participants because these studies use community samples who are consuming more alcohol than the UK guidelines. This population would have more than 8 AUDIT score (increased risk). This can be seen by the AUDIT scores to be between 10-12 in these chapters. As per the DSM 5 (clinical criteria), heavy drinkers may classify as mild to moderate alcohol use disorder but might not come in the severe criteria. As per ICD 10 (clinical criteria), they might classify as the alcohol abuse with 1 or 2 positive criteria. But, the use of one of these clinical criteria would have been a better choice to avoid the dilemma.

The handedness was asked by the participants in all the studies in a form of a question as “Which hand do they use more for day to day activity?”. No structured questionnaires were used for handedness assessment. The study 1 had 3 left handed participants, whereas all the other participants in all the studies were right-handed. Although the EEG studies had participants with right-handed, this warrants the interpretation of EEG data in these studies with caution.

IX. Conclusion and direction for future studies

To conclude, inhibitory control can be trained in the alcohol use disorder subjects with a smart-phone game. The neuronal changes are evident with a shorter duration of training, but a behavioural change might only be evident after a longer duration. The near transfer effects noted on the game performance was evident but not on the computerized task based on a same training principle. We didn't find any far transfer effect, but the sample size and the duration of training would have majorly influenced the results. The use of smart-phone game has their own added advantages, the possibility of collecting a real-time data and an ability to increase the frequency and adherence for the intervention.

On assessing the brief mindfulness intervention effects, we noticed strong neuronal changes related to the inhibitory control. Due to time constraints, we couldn't explore the effects of mindfulness on the inhibitory control when practiced for a longer duration. Also, mindfulness might influence differentially in patients compared to the healthy subjects, considering the limited neuronal reserves patients have. This opens an important avenue for a further research, might be beneficial for the treatment-related outcomes in patients.

Future studies attempting cognitive training should plan with a bigger sample size and for a longer duration of the training. Confounders like the smoking status and the IQ should also be considered. On gamification of the tasks, its validity should be tested and an initial training should be assessed in the healthy population before testing its efficacy in the target patient population.

The game dynamics should incorporate the basic assessment components such as the SSRT calculation possibility in the SST training. This would help in calculating the real-time change in a behaviour. Also, this would help in validation of the game by comparing it with the standardised tasks.

Along with the active control intervention, the inclusion of a passive control group would be more helpful in knowing the changes noted over the course of time and not specific for the intervention. For example, a confounding effect of an anti-craving medication in a training in the alcohol-dependent subjects. The anti-craving agents and the other treatments in the ward may influence the outcomes measures. The inclusion of a passive control group would give an opportunity for the comparative effect of any change produced in the outcome measures without the intervention.

The smart-phone based cognitive training apps give us an advantage of delivering interventions to the study participants remotely in their natural environment on a day to day basis. Looking at the previous advantages of a motivational interviewing (Rubak, Sandbæk, Lauritzen, & Christensen, 2005), future studies should explore effects of combining a motivational interviewing with the cognitive training on treatment outcomes in the patients and the alcohol consumption in heavy drinkers having a probable alcohol use disorder. As the training shows modulation at the neuronal levels, studies could be planned to train the offspring of alcohol-dependent population. These subjects also had demonstrated deficits in an inhibitory control including other executive functions, considered as endophenotype (Nigg et al., 2006). Training in these population might open a new preventive strategy in them.

X. References

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XI. Appendix 1: Wave form figures for Chapter 5

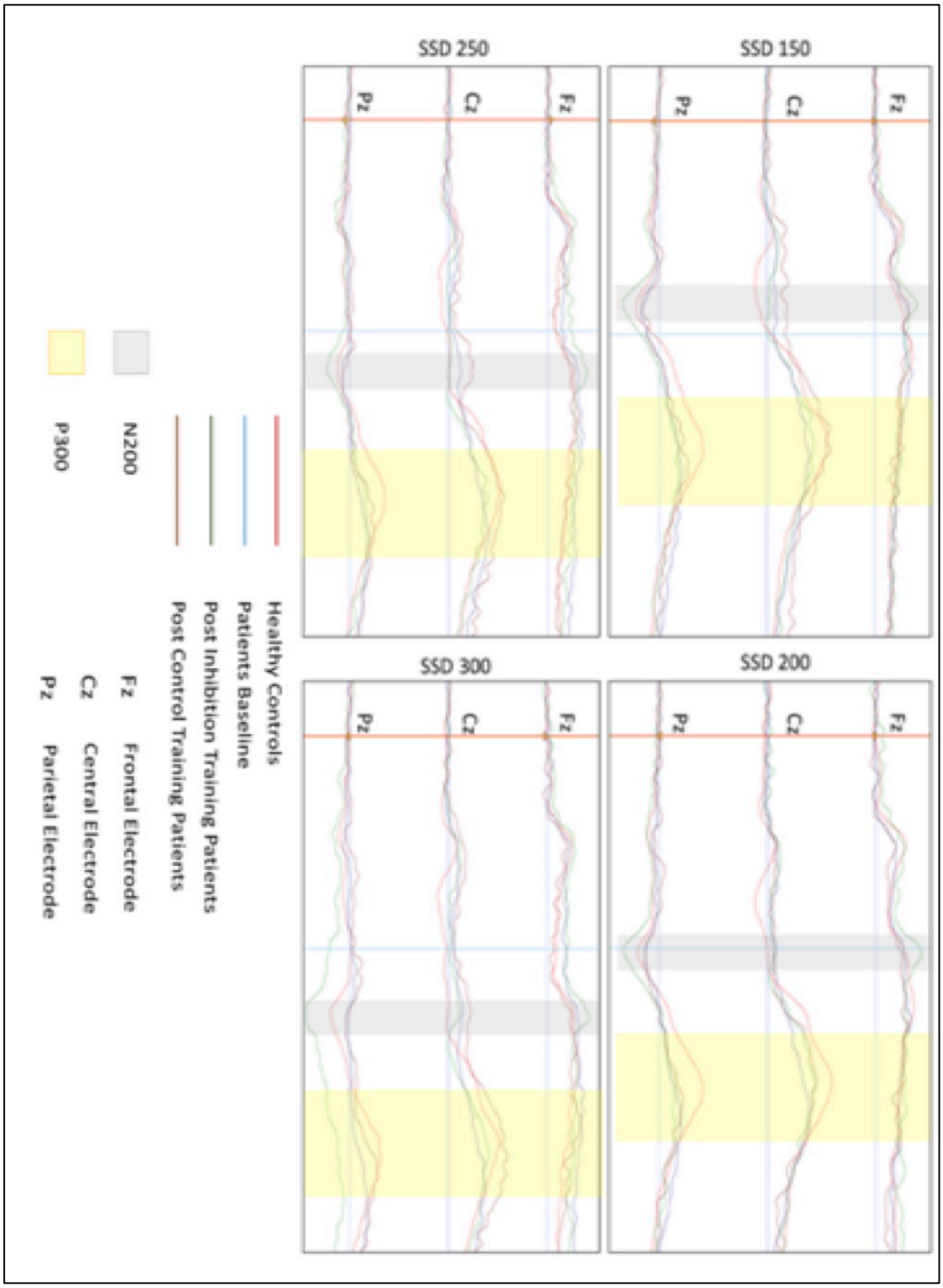


Figure 18 Event related potentials in stop-signal task

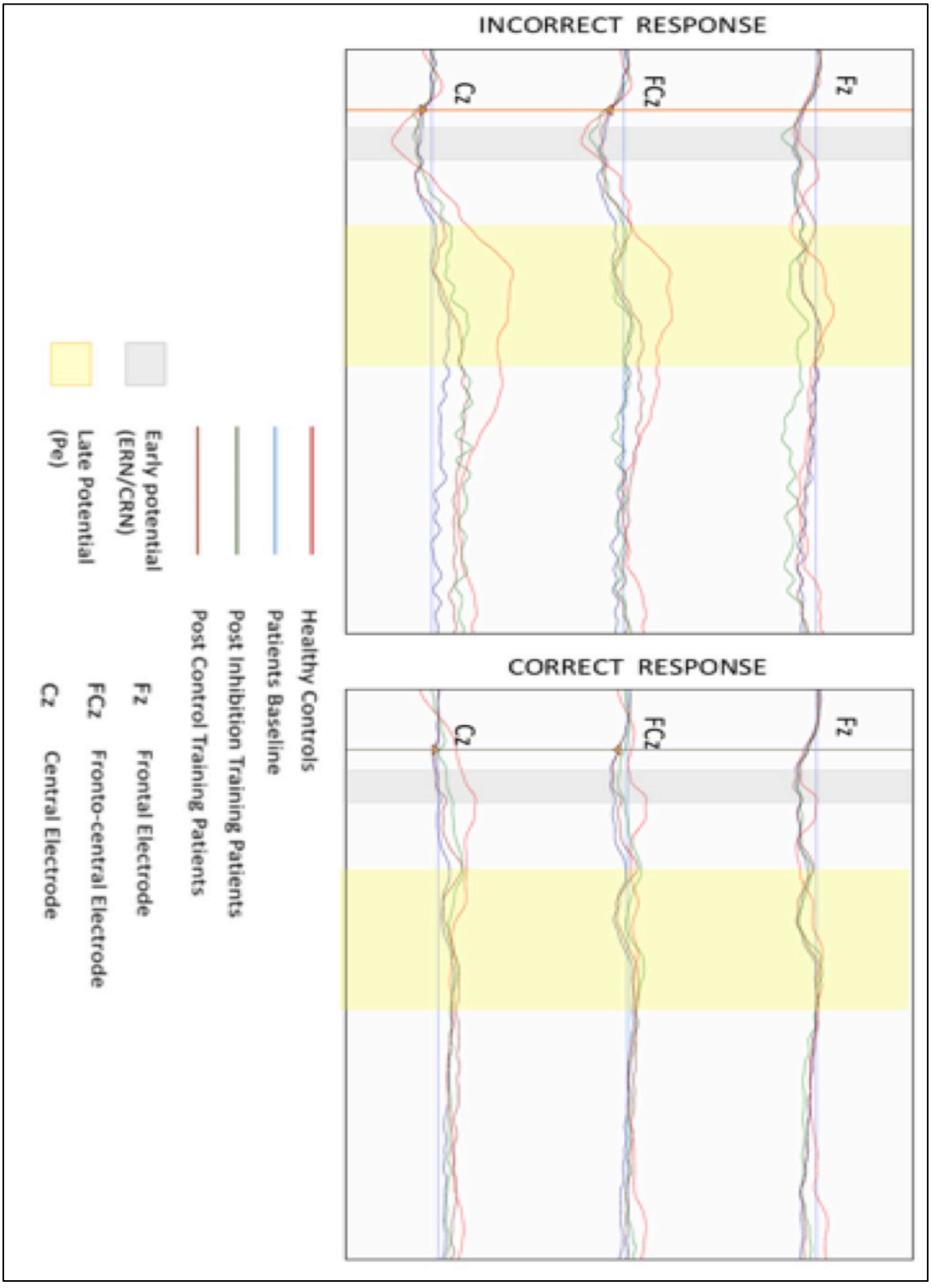


Figure 19 Event related potentials in Flanker task

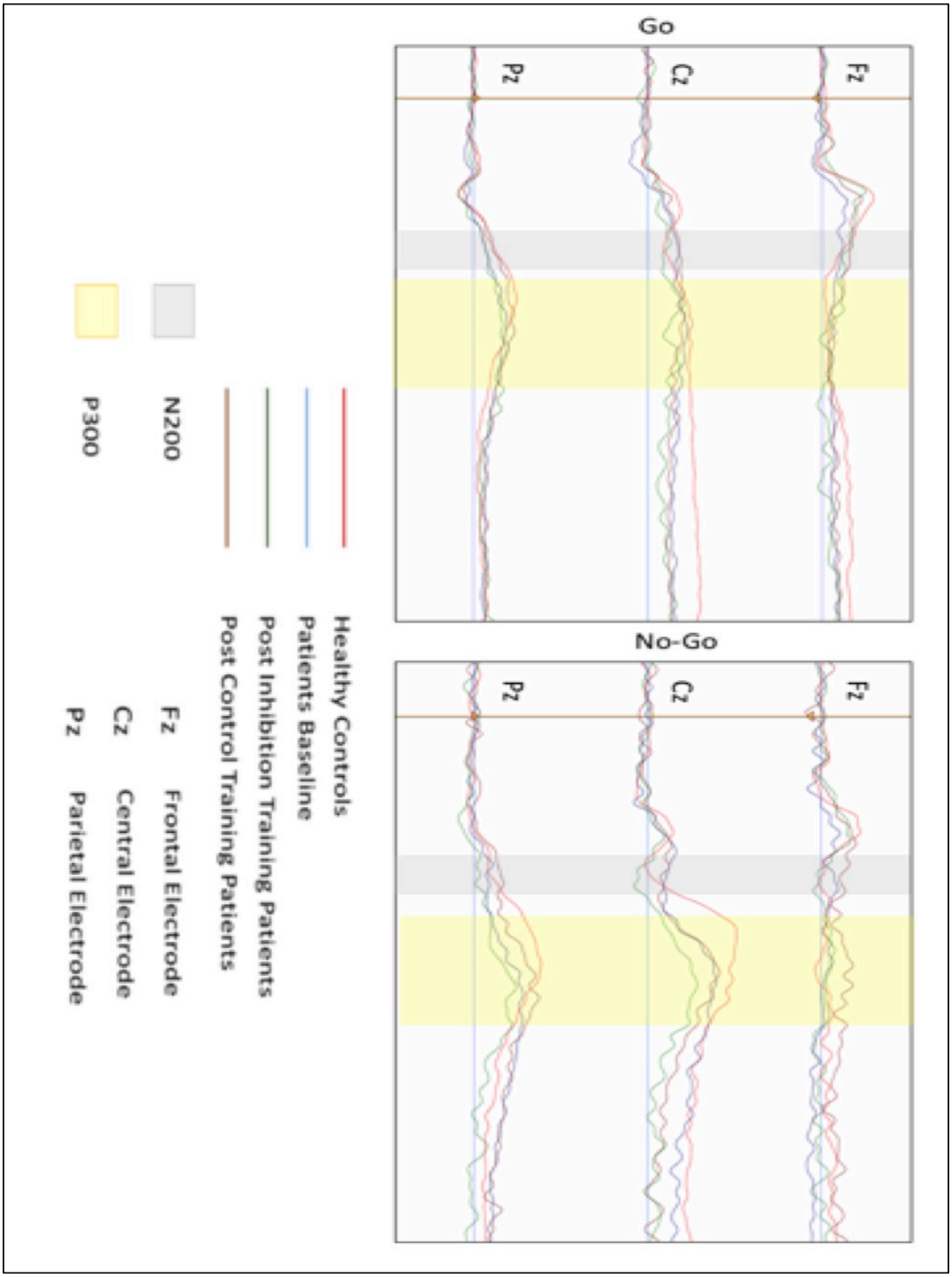


Figure 20 Event related potentials in go no-go task

XII. Appendix 2: Mindfulness instructions (Vinci et al., 2014)

“While sitting down in your chair, place your feet flat on the floor. Sit up straight. Relax your shoulders, relax your neck, and place your hands in your lap or on your knees. As you settle into a comfortable position, commit yourself to simply being fully awake, fully present for these next few moments. If you feel comfortable with it, gently close your eyes. Focus on tuning into the feeling of the breath moving in and out of your body. Focus on the sensation of the breath moving through your nose on each in breath and each outbreath. Allow yourself to just be here in this moment, following the breath as it comes in and as it goes out. Just breathe and let go. Breathe and let be.

Naturally your mind may wander off into thoughts of one kind or another. Take note of any thoughts as they come up. Note what's on your mind and how your body is feeling. Acknowledge these thoughts, whatever they are, without judging or evaluating them. And then just gently let them go. Bring your attention back to the breath, focusing on the feeling of the breath coming in and out of your nostrils.

And each time you notice that your mind has gone off somewhere else, wherever that may be, just bring your attention back to the feeling of the breath. And if the mind wanders off a thousand times, you simply bring it back a thousand times, intentionally cultivating an attitude of patience and gentleness towards yourself. This means choosing as best you can not to react to or judge any of your thoughts or feelings, impulses or perceptions, reminding yourself instead that absolutely anything that comes into the field of awareness is ok. We simply sit with it and breathe with it and observe it, staying open and awake in the present moment, right here, right now, a continual process of seeing and letting be, seeing and letting go, rejecting nothing, pursuing nothing, dwelling in stillness and in calmness as the breath moves in and out. If you'd like, commit yourself to bringing this attitude of attention and acceptance with you throughout your day, being fully aware in the present moment, noticing any thoughts or feelings that may arise, without judging them e just being right here and right now, accepting the present moment, and accepting yourself, no matter what happens. Remember that you can always bring your focus back to your breath, back to the sensations of the present moment, to cultivate this sense of attention and acceptance.”

XIII. Appendix 3: Chapter 3 Documents

A. Information Sheet

Version 1
December 2014

UNIVERSITY OF LIVERPOOL

Committee on Research Ethics

Participant Information Sheet

Study title: A smartphone based intervention to reduce alcohol consumption

You are being invited to participate in a research study. Before you decide whether to participate, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and feel free to ask us if you would like more information or if there is anything that you do not understand. Please also feel free to discuss this with your friends, relatives and GP if you wish. We would like to stress that you do not have to accept this invitation and should only agree to take part if you want to.

Purpose of this study.
The purpose of this study is to examine the effects of a smartphone administered computer task, designed to help people to reduce their drinking.

You are eligible to take part in this study if you;

- Are a fluent English speaker.
- Are aged between 21 and 60 years of age.
- Drink more than 14 units per week if you are Female, or 21 units per week if you are Male (see unit guidelines below and ask the experimenter if you are not sure).
- Are motivated to reduce your drinking ('cut down'), and willing to try to cut down for two weeks as you take part in this study.

You are NOT eligible to take part in this study if you;

- Have a current or previous diagnosis of alcohol abuse or alcohol dependence
- You have ever been diagnosed with Attention Deficit Disorder (ADD) or prescribed methylphenidate (Ritalin) for ADD or similar conditions.

Do I have to take part?

Version 1
December 2014

You are under no obligation to take part in this study; it is completely your choice. If you do decide to take part you will be able to retain this information sheet and a copy of the consent form. If you do decide to take part, you are free to withdraw at any time and without giving a reason.

What will happen if I take part?
If you would like to participate you should arrange an appointment with the researcher (Dr Mrunal Bandawar, email address mrunal.bandawar@liv.ac.uk). You will be required to come to the University for an initial session that will last approximately one and a half hours in total. In this session, we will check your eligibility for the study, and then ask you to complete some questionnaires about your alcohol consumption. You will then complete some exercises on the 'down your drink' website that will help you to think about your drinking, and will give you some helpful tips on cutting down. You will need to use your email address to create an account on the website (www.downyourdrink.org.uk) but we will not look at any of the information that you provide on the website. Afterwards you will complete some brief reaction time tests on a computer.

We have developed specialised applications (apps) that will run on a smartphone. The app includes a brief reaction time game, which is intended to 'train' you to improve your ability to control your behaviour. Some people will be allocated to a control group and we do not expect self-control to improve in these groups. The smartphone app will ask you questions about your alcohol consumption, craving for alcohol, and your mood. We will spend some time training you how to use the app on the smartphone, and you will then be asked to complete your first assessment.

We will then loan you a smartphone (plus charger) and ask you to keep this smartphone with you at all times over the next two weeks. We will ask you to access the 'app' twice per day, once at anytime between 8:00 am and 1:30 pm and once anytime between 2:00 pm and 7:30 pm. The app takes approximately 8 minutes to complete each time. You must complete the app in a quiet place, away from distractions and in a manner that will not cause any accidents. You should think carefully about whether or not you will be able to do this for two weeks, before deciding if you would like to take part in the study.

At the end of the first week you should come back to the University and bring the smartphone with you. We will download your results from the phone, check that you have completed enough of the assessments and ask you if you are happy to continue with the study. At the end of the second week, you should return the smartphone to us so that we can download your results again, and check that you have completed the assessments. We will ask you to complete the cognitive tests on the computer once more. Following this, you will be contacted by phone or email one and two weeks later and a researcher will ask about your alcohol consumption. Then your involvement in the study will be finished.

If you agree to take part in the study, we would ask that you pay attention to the following points regarding the smartphone that we will loan to you.

- Do not try to call/text/email anybody from the phone. The phone is on a 'pay and go' contract and does not contain any credit. Please do not add any credits to the phone.
- Do not download any apps or store any personal information on the phone (for example, telephone numbers)
- Treat the phone with care, as you would if it is was your own. Do not leave it unattended etc.
- The phone will have a protective case, which should not be removed.

Expenses/Payments
We understand that repeated testing over two weeks, several times per day, along with three visits to the University of Liverpool and two follow-ups requires a considerable time commitment from you. If you complete the study fully we will give you up to £80 (via bank transfer) as compensation for your time and commitment, but this is subject to the following:
1. You must come to the University for three scheduled appointments, and over the two weeks of the study you must complete the smartphone app twice per day. If you complete at

least 75% of the scheduled smartphone assessments, you will receive £60 at the end of the study. If you complete the smartphone app 100% of the time, you will receive £80. If you complete fewer than 75% of assessments during the first week of the study, we will have to withdraw you from the study and we will pay you £20. If you complete fewer than 75% of assessments during the second week of the study, we will pay you £50.
2. The smartphone **must be returned to the experimenter at the end of the study**. If you lose the smartphone, or damage it beyond repair, you will not receive any financial compensation.

Are there any risks in taking part?
We do not anticipate any direct risks to you if you take part in this study.

Are there any benefits from participation?
You will be taking part in an intervention which may help to reduce your alcohol consumption; you will also receive financial compensation.

What if I am unhappy, or there is a problem?
If you are unhappy, or if there is a problem, please feel free to let us know by contacting Prof. Matt Field on 0151 794 1124 and we will try to help. If you remain unhappy or have a complaint which you feel you cannot come to us with then you should contact the Research Governance Officer on 0151 794 8290 (ethics@liv.ac.uk). When contacting the Research Governance Officer, please provide details of the name or description of the study (A smartphone based intervention to reduce alcohol consumption), the researcher(s) involved, and the details of the complaint you wish to make.

What if I want advice about drinking, or help with giving up?
We are not qualified to offer advice ourselves, but if you are concerned about your drinking and would like help giving up, we advise you to seek information and advice from your GP, by calling Drinkline on 0800 917 82 82 or consult one of the following websites:
www.downyourdrink.org.uk
www.howsyourdrink.org.uk

Will my participation be kept confidential?
Data is collected and stored using a participant number. The data you provide will not be identifiable by name. The electronic data will be stored in password-protected files on University of Liverpool computers. Following completion of the study we anticipate the results will be published in a scientific journal. Reports in scientific journals will contain a summary of results from all of the participants who take part; you will not be identified by name.

Will my taking part be covered by an insurance scheme?
Participants taking part in a University of Liverpool ethically approved study will have cover.

Who can I contact if I have further questions?
If you have any questions then please contact the principal investigator:

Prof Matt Field
School of Psychology, University of Liverpool, L69 7ZA, UK
Telephone: 0151 7941124
Email: mfield@liv.ac.uk.

B. Consent form

UNIVERSITY OF LIVERPOOL

Committee on Research Ethics

PARTICIPANT CONSENT FORM

Title of Research Project:	A smartphone based intervention to reduce alcohol consumption
Researcher(s):	Prof. M Field and Dr M. Bandawar

Please initial box

1. I confirm that I have read and have understood the information sheet dated December 2014 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that in order to take part in the study, I should meet the following inclusion criteria: ☐
   - Aged between 21 and 60 years of age.
   - Fluent English speaker
   - Drink over 14 units of alcohol per week if female, 21 if male.
   - I am interested in reducing my alcohol consumption, and am willing to try to cut down for two weeks as I take part in the study.

   I understand that I cannot take part in the study if I meet any of the following exclusion criteria:
   - A current or previous diagnosis of alcohol abuse or dependence
   - Ever been diagnosed with Attention Deficit Disorder (ADD) or prescribed methylphenidate (Ritalin) for ADD or similar conditions.
3. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my rights being affected. In addition, should I not wish to answer any particular question or questions, I am free to decline. ☐

- I understand that my responses will be kept strictly confidential. I give permission for members of the research team to have access to my anonymised responses. I understand that my name will not be linked with the research materials, and I will not be identified or identifiable in the report or reports that result from the research. ☐

4. I agree to take part in the above study. ☐

Participant Name	Date	Signature
Name of Person taking consent	Date	Signature
Researcher	Date	Signature

Principle Investigator: Professor Matt Field, Department of Psychological Sciences, University of Liverpool, Liverpool, L69 7ZA. Telephone: 0151 7941124. Email: mfield@liv.ac.uk

C. Debriefing Sheet

UNIVERSITY OF LIVERPOOL

PARTICIPANT DEBRIEFING INFORMATION

Study Title: A smartphone based intervention to reduce alcohol consumption

Thank you for taking part in this research study.

We are interested in the psychological process of (dis)inhibition (also called inhibitory control), which is linked to heavy drinking in people who are trying to reduce their alcohol consumption. At the University of Liverpool we have recently demonstrated that training individuals to improve their inhibition reduced immediate alcohol-consumption in the laboratory, but did not affect consumption over the following week outside of the laboratory.

In this study we examined whether repeated training of inhibitory control on a smartphone could lead to improvements in inhibitory control over time, and whether these improvements would lead to reduced alcohol consumption outside of the laboratory. During your involvement in this research you were randomly allocated to one of two groups (the active intervention group, or a control group). Based on previous research we expect that, over the course of the study, inhibitory control will improve in the active intervention group, but not the control group.

We hypothesise that everybody who takes part in the research will show a reduction in alcohol consumption, due to the non-specific effects of the 'down your drink' intervention. We also hypothesize that the individuals in the active intervention group will show a larger reduction in alcohol consumption compared to the control group. We also measured your performance on other neuropsychological tests at the beginning and end of the study, so that we could see if the smartphone training led to other improvements in cognitive function.

The findings from this research will have important implications for our understanding of why people sometimes drink more than they should when they are trying to cut down. We hope that the findings from this study will lead to the development of new treatments for people who want help to reduce their drinking.

What if I want advice about drinking, or help with giving up?

We are not qualified to offer advice ourselves, but if you are concerned about your drinking and would like help to give up or reduce your drinking, we advise you to seek information and advice from your GP, by calling Drinkline on 0800 917 82 82:

Alternatively, you have already registered on www.downyourdrink.org.uk and completed the brief (one hour) exercises on the site. If you return to the website, you will see that additional help is available, including more extended programmes that will help you to think about your drinking, and give you the skills that you need to cut down. The website has been shown to be effective at helping people to reduce their drinking, so we highly recommend that you revisit the site if you are concerned about your drinking.

Who can I contact if I have further questions?

If you have any questions then please contact the principal investigator:

Prof Matt Field
School of Psychology, University of Liverpool, Liverpool, L69 7ZA
Tel: 0151 794 1124
Email: m.field@liverpool.ac.uk

D. Training Game Handout

Game play instuctions

The 'Pento Plaza' contains 5 shops along with apartments.
The 5 shops are:
1. Flower Shop 2. Fruit Shop 3. Bottle Shop 4. Balloons Shop 5. Cafe
In the Plaza live 4 mischievous kids who are just playing around but causing a mess. The owner of the Plaza is worried and asks you to help him.

Objective

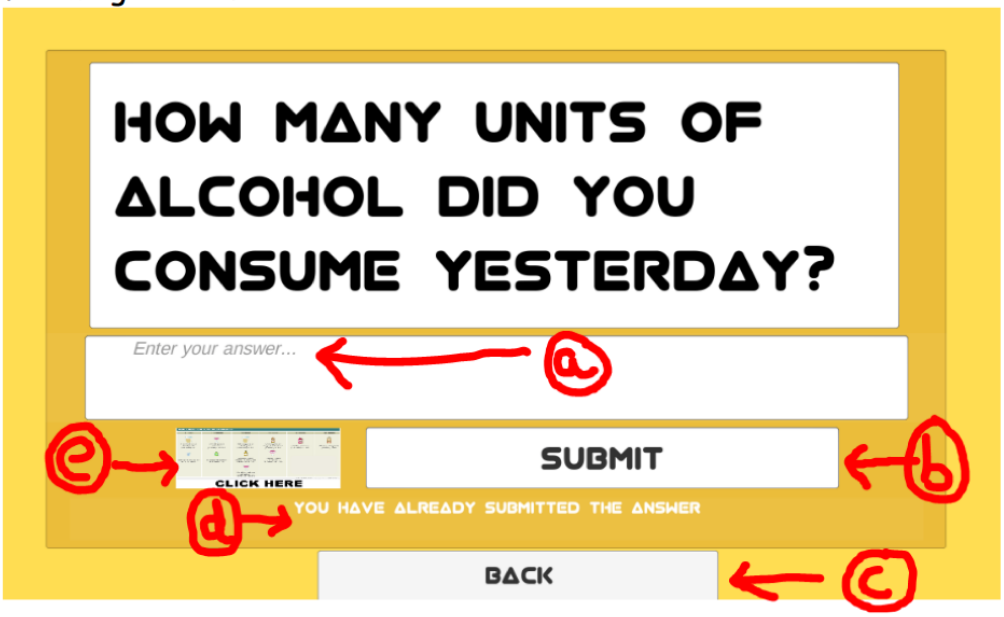
You are supposed to help the owner of the Plaza keep the place running. The kids are at the roof throwing stuff down. Your job is to collect the ones needed for the shop and leave the rest. The owner will explain each stage as we progress through the game.

The Game

The Game will mainly have 4 screens. They are:

Home Screen :

The screen will contain 3 buttons:
Play – This will take you to the Stage Screen.
Sound – On/Off
Alcohol meter- To note your alcohol consumption (labeled as 1).
At the start of first session of the day you 1st need to answer the alcohol meter question. Once you tap on alcohol meter button it will lead you to the following screen.



Once you are here you need to follow the following steps.

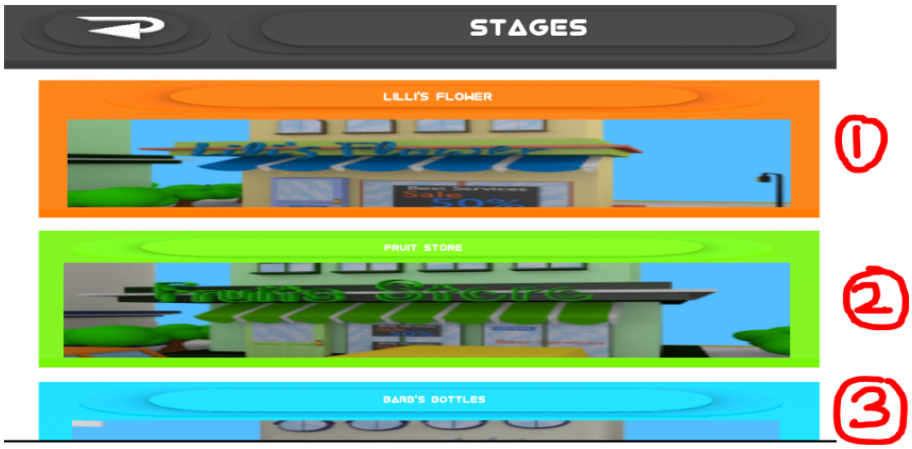
a. Tap to answer the question in the area a. and enter your answer.
b. Once over with step a, tap on submit button (b) and it will display "your answer for today is submitted" (d)
c. After step b, you need to tap on back button (c) which will take you to main screen.
d. If in case you need help for knowing the number of units different drinks may contain, you can tap on the button (e) which will take you to the screen bellow.

Note that you may not be able to zoom in this screen.

Once you are at the main screen your play button will be unlocked and you can proceed to the next screen.

Note: The answer to the question has to be enter in the number of units and not the number of drinks.

Stage Screen:

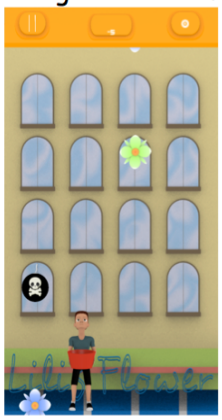


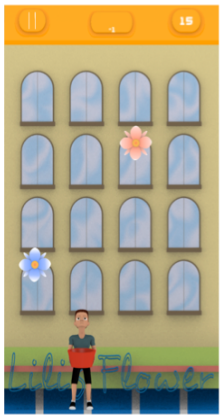
The game will contain 5 stages, each shop in the Plaza will be a stage. Each stage will have 9 levels.

You need to start from level 1 of each stage and need to proceed from stage 1 to 5 after crossing 9 levels of each stage.
You are not allowed to skip any stage or level.

Stage 1: Flower Shop.

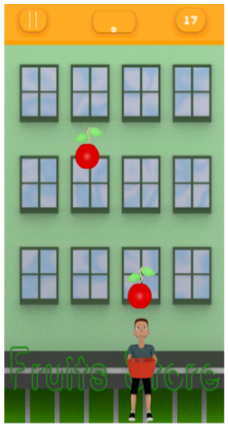
Things to collect: 1. Flower.
Things to avoid: 1. Bomb.

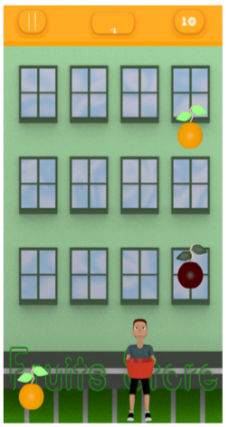




Stage 2: Fruit Shop.

Things to collect: 1. Ripe Fruit.
Things to avoid: 1. Bomb. 2. Rotten Fruit.

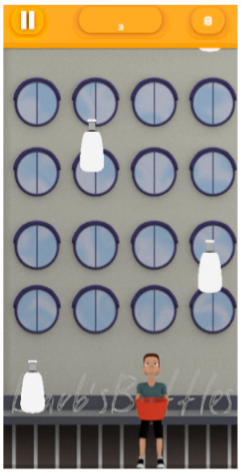


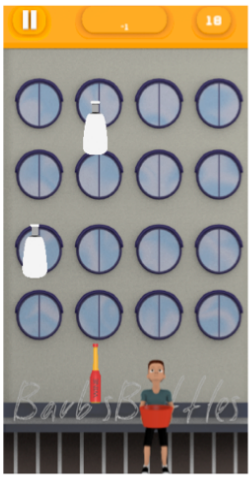


Stage 3: Bottle Shop.

Things to collect: 1. Milk Bottles.

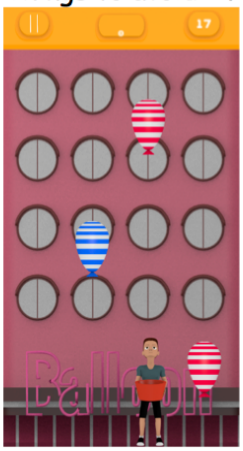
Things to avoid: 1. Bomb. 2. Alcohol Bottles.

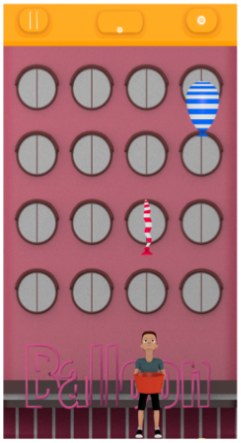




Stage 4: Balloon Shop.

Things to collect: 1. Red Balloon. 2. Blue Balloon.
Things to avoid: 1. Bomb. 2. Alcohol Bottles. 3. Deflated balloon

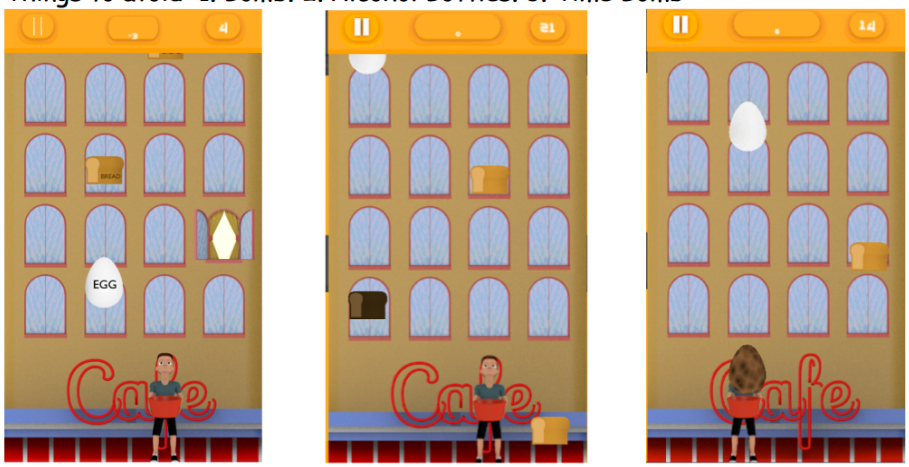




Stage 5: Cafe.

Things to collect: 1. Bread. 2. Eggs.

Things to avoid: 1. Bomb. 2. Alcohol Bottles. 3. Time Bomb



Game Play

The game will start with 30 seconds on the clock. The items will fall from the top to the bottom of the screen. The player has to click on the canopy just as soon as the item falling reaches the bottom.

Each item collected will reward the player with some points and the total points are displayed. Each item collected will also reward the player with some time increments +1 second. Each item miss or wrong hit will take away -3 seconds. The same count goes with the points. The stars are rewarded by the points. You need 2 stars or above to move to the next level.

Rewards

When you complete a level or if you tap the pause button you will go to this screen. If you have sufficient score and stars for the next level the button (a) will unlock (locked in the given picture) and by tapping it you can go to next level. If the score and stars are insufficient, you can tap on the button (b) to replay the level.

Note: Once you are done with the 9 levels in the stage, you can tap on the main menu button and go the stages screen to select the next stage for play.

E. Control Game Handout

Game play instuctions

The 'Pento Plaza' contains 5 shops along with apartments.
The 5 shops are:
1. Flower Shop 2. Fruit Shop 3. Bottle Shop 4. Balloons Shop 5. Cafe
In the Plaza live 4 mischievous kids who are just playing around but causing a mess. The owner of the Plaza is worried and asks you to help him.

Objective

You are supposed to help the owner of the Plaza keep the place running. The kids are at the roof throwing stuff down. Your job is to collect the ones needed for the shop. The owner will explain each stage as we progress through the game.

The Game

The Game will mainly have 4 screens. They are:

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Play – This will take you to the Stage Screen.
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Alcohol meter- To note your alcohol consumption (labeled as 1).
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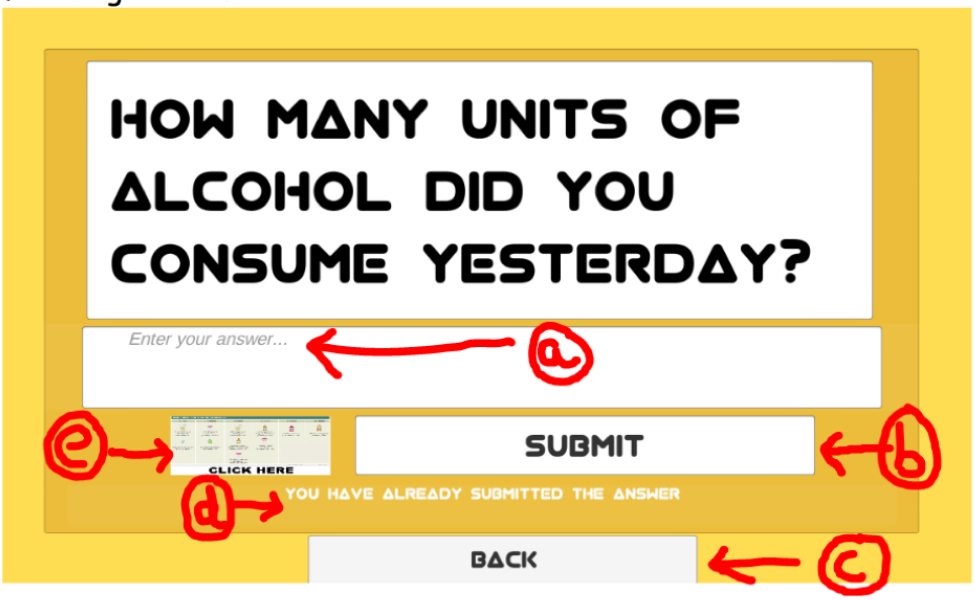

Once you are here you need to follow the following steps.

a. Tap to answer the question in the area a. and enter your answer.
b. Once over with step a, tap on submit button (b) and it will display "your answer for today is submitted" (d)
c. After step b, you need to tap on back button (c) which will take you to main screen.
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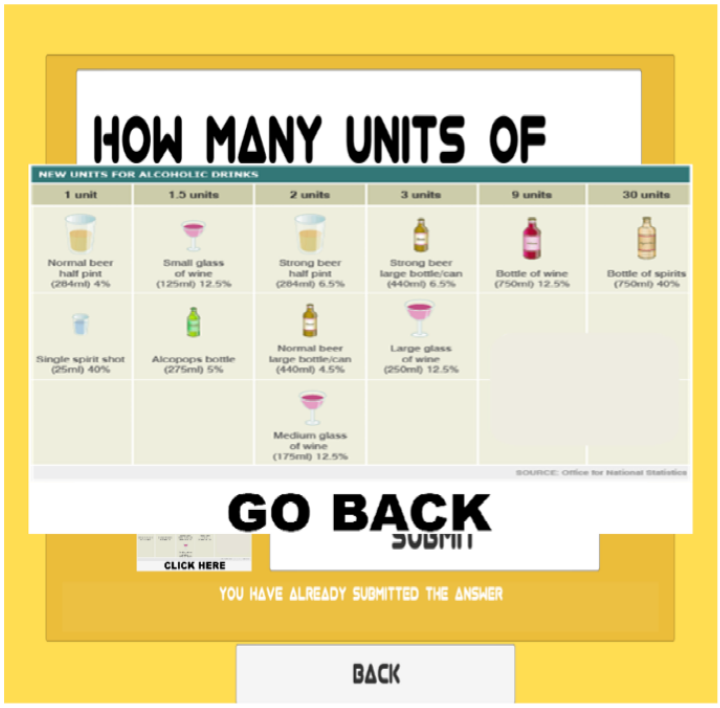
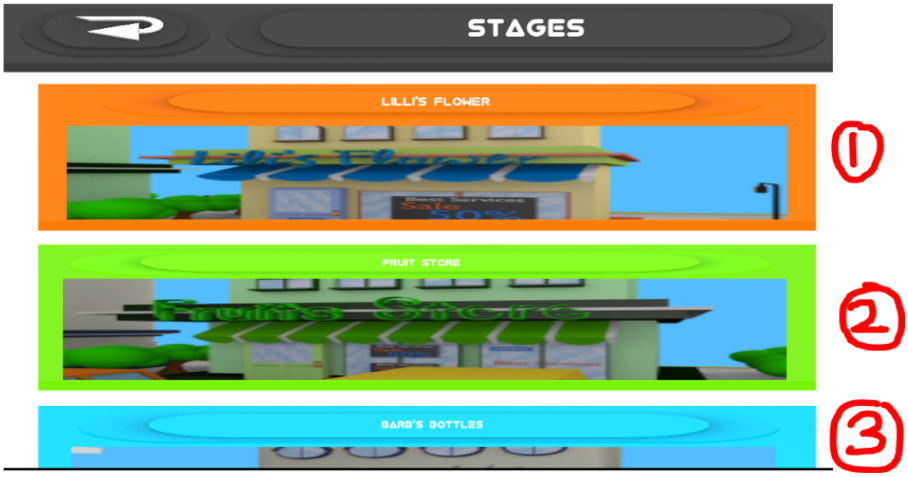


Note that you may not be able to zoom in this screen.

Once you are at the main screen your play button will be unlocked and you can proceed to the next screen.

Note: The answer to the question has to be enter in the number of units and not the number of drinks.

Stage Screen:



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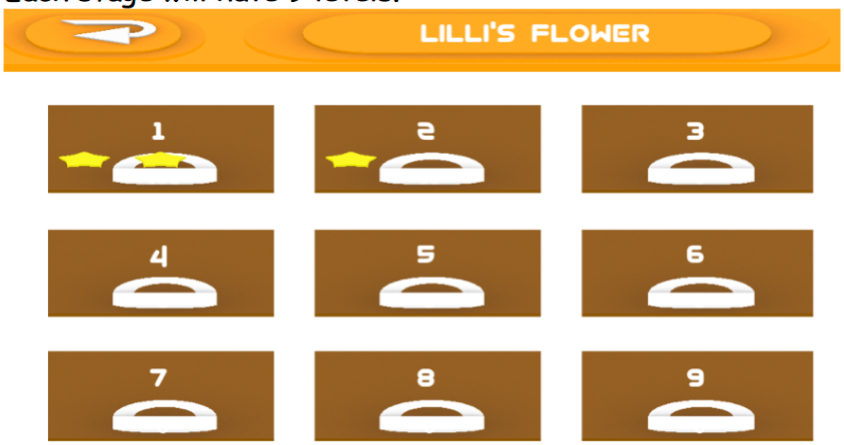
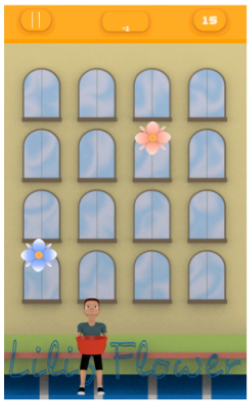
Each stage will have 9 levels.



You need to start from level 1 of each stage and need to proceed from stage 1 to 5 after crossing 9 levels of each stage.
You are not allowed to skip any stage or level.

Stage 1: Flower Shop.

Things to collect: 1. Flower.



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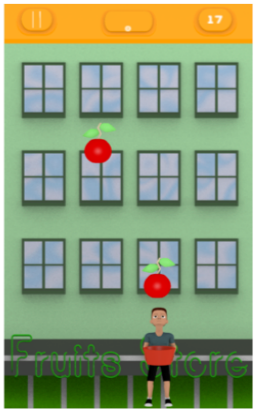
Things to collect: 1. Ripe Fruit.



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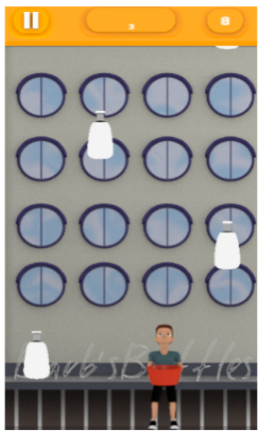
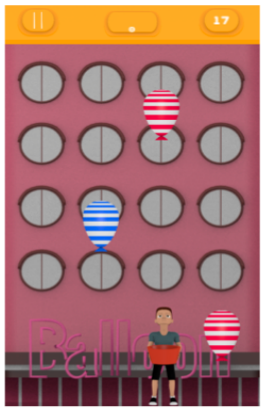


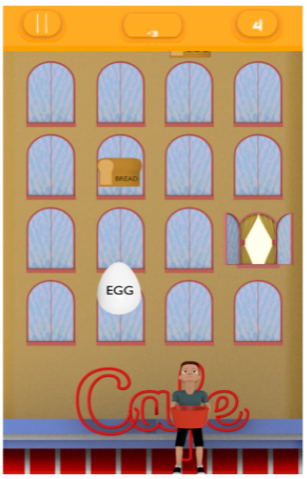
Stage 4: Balloon Shop.

Things to collect: 1. Red Balloon. 2. Blue Balloon.



Stage 5: Cafe.

Things to collect: 1. Bread. 2. Eggs.

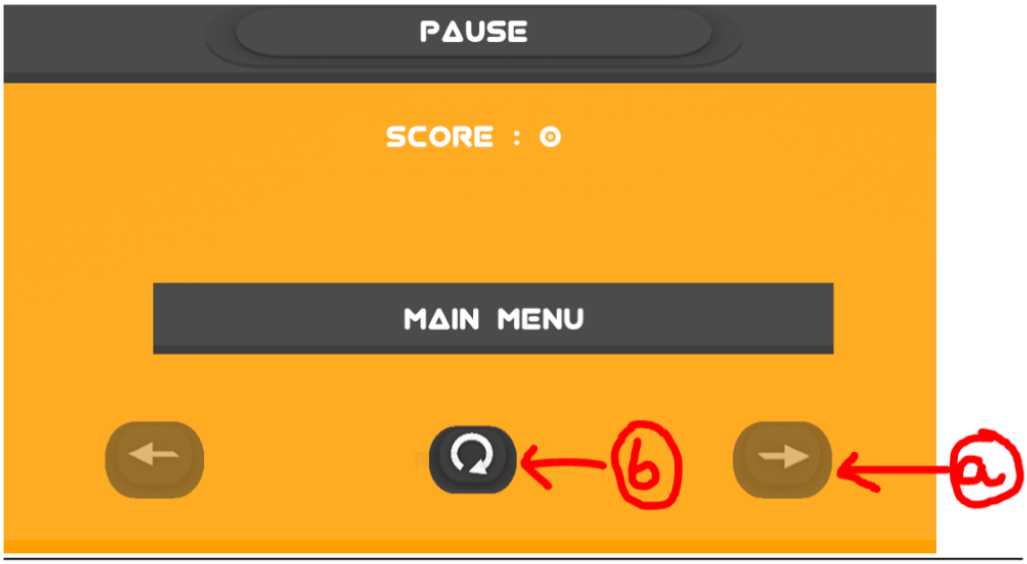


Game Play

The game will start with 30 seconds on the clock. The items will fall from the top to the bottom of the screen. The player has to click on the canopy just as soon as the item falling reaches the bottom.

Each item collected will reward the player with some points and the total points are displayed. Each item collected will also reward the player with some time increments +1 second. Each item miss will take away -3 seconds. The same count goes with the points. The stars are rewarded by the points. You need 2 stars or above to move to the next level.

Rewards



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Note: Once you are done with the 9 levels in the stage, you can tap on the main menu button and go the stages screen to select the next stage for play.

XIV. Appendix 8: Chapter 4 Documents

A. Information Sheet

Version 1 January 2015

UNIVERSITY OF LIVERPOOL

Participant Information sheet

STUDY TITLE: **Inhibition and EEG**

You are being invited to participate in a research study. Before you decide whether to participate, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and feel free to ask us if you would like more information or if there is anything that you do not understand. Please also feel free to discuss this with your friends, relatives and GP if you wish. We would like to stress that you do not have to accept this invitation and should only agree to take part if you want to.

What is the purpose of the study?

Previous research has shown that some people find it difficult to control their behaviour, and this may be a factor in why some people drink more than others. It may be possible to improve the ability to inhibit behaviour either by repeatedly performing a computer game that uses this ability, or by practicing 'mindfulness meditation' which involves being aware of your breathing, thoughts, and emotions. The purpose of this study is to investigate if behavioural inhibition training and mindfulness meditation help people to improve their inhibitory control, and if they produce short-term changes in brain activity during inhibition.

Why have I been chosen to take part?

We are looking for HEALTHY volunteers who:

- **Are between 18 and 35 years of age;**
- **Speak fluent English;**
- **Regularly consume alcoholic beverages over the UK government limits (a minimum of 14 units per week for females and 21units per week for males).** If you are not sure about your alcohol units please refer to the following web-page: www.nhs.uk/Livewell/alcohol/Pages/alcohol-units.aspx**;**
- **Have normal or corrected to normal vision (e.g. contact lenses or glasses).**

If you meet these criteria, then you are eligible to take part.

However, you **cannot take part if you have ever received treatment for an alcohol problem, or if you are currently seeking such treatment.**

Do I have to take part?

You are under no obligation to take part in this study; it is completely your choice. If you do decide to take part you will be able to retain this information sheet and a copy of the consent form. If you do decide to take part, you are free to withdraw at any time and without giving a reason. You can terminate the experiment at any time, for example in case of stress produced by viewing an unpleasant picture, or being in a confined space.

1

Version 1 January 2015

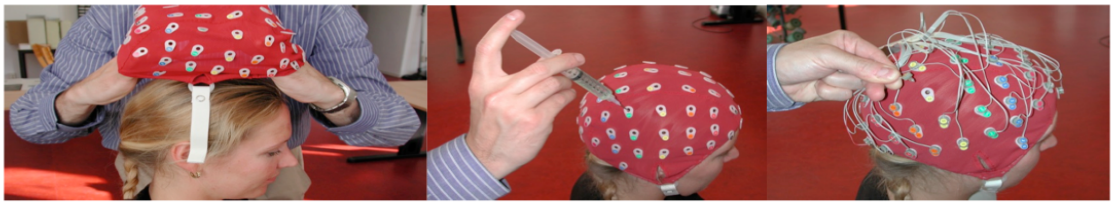
What will happen if I take part?

If you agree to take part in the study, we will ask you to participate in a single experimental session that will last no more than two hours and fifteen minutes in the EEG lab, on the ground floor of the Eleanor Rathbone building.

During the session, we will ask you to provide informed consent and a breath alcohol sample. You should not drink any alcohol on the day before you come to the laboratory. Any participants who provide a positive breath alcohol sample will not be allowed to take part in the study on that day, although they can reschedule.

After this, you will be asked to complete some tests on a smartphone. You will either play a computer game on the phone, or practice some minfulness meditation with the help of some audio instructions. After this you will complete a computer test that measures your ability to inhibit your behaviour. This will take around one hour and fifteen minutes in total, although you will be given lots of breaks to make it less boring.

Before you complete the computer tests, you will be connected to an EEG system (electroencephalograph) so that we can monitor your brain activity. This device requires that a headcap will be placed on your head. The electrode holders of the headcap will be filled with saline-based conductant gel and pin-type electrodes will be plugged in to electrode holders.



EEG will not cause you any pain or discomfort. The conducting gel should not cause any skin irritation but if it does, we will clean it off with warm water before ending the experiment. Our EEG system is not able to detect any abnormalities in the structure or function of your brain.

At the end of the computer task you will be asked to complete some questionnaires about your alcohol consumption. You will be then fully debriefed, and given the opportunity to wash your hair if you want to.

Expenses

You will receive a £20 shopping voucher in return for your participation in the study as reasonable compensation for your time and expense in taking part. Undergraduate psychology students will receive course credit (EPR points).

Are there any risks in taking part?

There are no anticipated risks to you if you take part in the study.

Are there any benefits to taking part?

Although there are no direct benefits from taking part, at the end of the study you will be thoroughly debriefed and this will include information about brain changes that are associated with response inhibition and implications for the study of alcohol problems.

What if I am unhappy or if there is a problem?

If you are unhappy at any point in the study, or if there is a problem, please tell the researcher or let us know by contacting the principle investigator Dr Matt Field at the address or phone number below. You can also contact the Research Governance Officer (RGO) at the University, on 0151 794 8290 or via email at ethics@liv.ac.uk. The RGO is in charge of making sure our research is done properly. Please tell the RGO what study you are taking part in (Inhibition and EEG) and the name of the principle investigator (Matt Field).

Will my participation be kept confidential?

All the information collected about you during the course of the research will be kept strictly confidential. Any information about you will not be disclosed to anyone.

What will happen to the results of the study?

We intend to publish the results from this study in a scientific journal. However, any information which you provide will be stored completely anonymously (with a random number), and you will not be identified in any publication.

What will happen if I want to stop taking part?

You will be free to withdraw from the study at any time, without explanation. Results up to the period of withdrawal may be used, if you are happy for this to be done. Otherwise you may request that they are destroyed and no further use is made of them.

What if I want advice about drinking, or help with reducing my drinking?

We are not qualified to offer advice ourselves, but if you are concerned about your drinking, and would like help giving up, we advise you to seek information and advice from your Doctor, by calling Drinkline on 0800 917 82 82, or from one of the following websites:

www.downyourdrink.org.uk
www.howsyourdrink.org.uk

Who can I contact if I have further questions?

If you have any questions then please contact the principle investigator:

Prof Matt Field

Dept. Psychological Sciences, University of Liverpool, Liverpool, L69 7ZA

Tel. 0151 794 1124

Email: m.field@liverpool.ac.uk

B. Consent form

UNIVERSITY OF LIVERPOOL

Committee on Research Ethics

PARTICIPANT CONSENT FORM

Title of Research Project: Inhibition and EEG

Researcher(s): Mrunal Bandawar and Matt Field

	Please initial box
1. I confirm that I have read and understood the information sheet dated January 2015 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my rights being affected. In addition, should I not wish to answer any particular question or questions, I am free to decline.	☐
3. I understand that confidentiality and anonymity will be maintained and it will not be possible to identify me in any publications. I understand and agree that once I submit my data it will become anonymised and I will therefore no longer be able to withdraw my data.	☐
4. I agree to take part in the above study.	☐

Participant Name	Date	Signature
Name of Person taking consent	Date	Signature
Researcher	Date	Signature

Principal Investigator:
Prof, Matt Field
Dept. Psychological Sciences
University of Liverpool
Liverpool, L69 7ZA
0151 7941124
mfield@liv.ac.uk

Student Researcher:
Mrunal Bandawar
Dept. Psychological Sciences
University of Liverpool
Liverpool, L69 7ZA
0151 7943715
drmrunal@liverpool.ac.uk

Version 1
January 2015

C. Debriefing sheet

UNIVERSITY OF LIVERPOOL

Study Title: Inhibition and EEG

Thank you for participating in this study

What was the study about?

Several recent studies have shown that heavy drinkers can be directly 'trained' to improve their inhibitory control, and this helps them to reduce their alcohol consumption. Mindfulness meditation may also be helpful and there is some suggestion that it may work through a similar mechanism. However, very little is known about the brain mechanisms that underlie these effects.

In the present study, we measured your inhibitory control and accompanying brain activity after you had received either inhibition training (the smartphone game) or had practiced mindfulness meditation. You may have been allocated to a control group who performed an easy version of the game that will not lead to improvements in inhibitory control. What we expect to find is that both the inhibition training and the mindfulness meditation will lead to short-term improvements in inhibitory control and these will be accompanied by changes in brain activity.

We hope that the findings of this study will tell us more about the changes in brain activity that occur as a result of mindfulness meditation and cognitive training.

What if I want advice about drinking, or help with reducing my drinking?

We are not qualified to offer advice ourselves, but if you are concerned about your drinking, and would like help giving up, we advise you to seek information and advice from your Doctor, by calling Drinkline on 0800 917 82 82, or from one of the following websites:

www.downyourdrink.org.uk
www.howsyourdrink.org.uk

Who can I contact if I have further questions?

If you have any questions then please contact the principle investigator:
Prof. Matt Field
Dept. Psychological Sciences, University of Liverpool, Liverpool, L69 7ZA.

Tel. 0151 794 1124
Email: m.field@liverpool.ac.uk

XV. Appendix-9: Chapter 5 Documents

A. Consent form English

CONSENT FORM

TITLE OF THE STUDY

"Inhibition training and electrophysiology in Alcohol Use Disorder"

INFORMATION

The study involves group of people with alcohol dependence syndrome and healthy controls. Patient participants will be randomly divided into two. One group will receive structured inhibition training with the help of a smart phone game and the other group will receive placebo gaming. ***Total duration of the study is of 2 weeks with total 28 sessions, each 10 minutes in duration***. It will be delivered in the form of smart phone games. A smart phone will be loaned to you for playing the game which is to be returned to the investigator. ***The games are designed for improving cognition related to response prevention with successive sessions.*** Placebo game will be similar to cognitive training game but successive sessions will not be of increasing intensity of complication. Before and after the therapy neuropsychology and electrophysiology assessments will be done. Before undergoing this procedure, it will be demonstrated. During the procedure both you and the doctor can speak to each other. I would like your permission to do such a study using electroencephalography (EEG). I will also be assessing you clinically using some rating scales. The results of these examinations may not be of direct relevance to you or your current treatment, but is expected to advance our understanding of alcohol dependence syndrome and the functional abnormalities in specific brain regions in alcohol dependence syndrome. It will also help in understanding effect of cognitive training. **The group receiving the placebo intervention will receive structured cognitive enhancement therapy if the study shows positive results. For healthy controls, only initial baseline EEG recording with questionnaire shall be done and no training shall be provided. This is for the comparison between healthy controls and alcohol dependent participants.**

Undertaking by the Investigator:

You are free to withdraw from the study without any reason if you desire so and this will not in any way affect your / relative's treatment. In such an event, you / relative will still receive the best possible treatment without prejudice. If you have any doubts, please feel free to clarify the same. Even during the study you are free to contact any of the investigators for clarification if you so desire (Dr. Mrunal Bandawar – 09611233206, Dr.

Vivek Benegal– 08026995360) at any time. All the information/data collected from you will be kept strictly confidential.

CONSENT FORM

I have been informed about the process of the study. I have understood that I have the right to refuse consent or withdraw at any time during the study without adversely affecting my /relative's treatment. I am aware that by subjecting to this study process, I will have to give more time for assessments by the investigating team and that these assessments do not interfere with the benefits.

I, ……, the undersigned, give my consent to be a participant of this study program.

SIGNATURE OF SUBJECT: SIGNATURE OF WITNESS:

NAME: NAME:

ADDRESS AND PHONE NUMBER: ADDRESS:

SIGNATURE OF THE DOCTOR:

NAME:

DESIGNATION:

B. Consent form Hindi

निमहांस , बंगलौर में विषयों के लिए सहमति फॉर्म

अध्ययन का शीर्षक

"सामाजिक रूप से अधिक शराब पीने वालों ~~और शराबियों के बच्चों~~ में आवेगशीलता और प्रतिक्रिया अवरोध पर संज्ञानात्मक संवर्धन के प्रभाव: घटना संबंधित संभावित अध्ययन."

जानकारी

इस अध्ययन में लोगों का एक समूह शामिल है- पिता का शराब निर्भरता सिंड्रोम और उम्र के साथ मिलान नियंत्रकों के परिवार के इतिहास में नकारात्मक शराब निर्भरता सिंड्रोम. बच्चों के पहले समूह को बेतरतीब ढंग से दो समूहों में विभाजित किया जायेगा. एक समूह संरचित संज्ञानात्मक वृद्धि चिकित्सा और अन्य समूह प्लेसबो गेमिंग प्राप्त करेगा. अध्ययन की अवधि में ~~1~~2 हफ़्तों में कुल 48 सत्र होंगे, प्रत्येक 20 से 30 मिनट की अवधि के होंगे. इसे स्मार्ट फोन खेल के रूप में वितरित किया जाएगा. प्लेसबो खेल संज्ञानात्मक प्रशिक्षण खेल के समान होगा, लेकिन बाकी के सत्रों में जटिलता की बढ़ती तीव्रता नहीं होगी. नियंत्रण समूह संरचित संज्ञानात्मक संवर्धन चिकित्सा प्राप्त करेगा. चिकित्सा के पहले और बाद में तंत्रिका मनोविज्ञान और इलेक्ट्रोफिजियोलॉजी आकलन किये जायेंगे. इस प्रक्रिया से पहले, इसका प्रदर्शन किया जायेगा. प्रक्रिया के दौरान आप और आपके डॉक्टर दोनों एक दूसरे से बात कर सकते हैं. मैं इस अध्ययन के लिए आपके मस्तिष्क पर इलेक्ट्रोएनसीफैलोग्राफी (ईईजी) का उपयोग करने की अनुमति चाहता हूँ. मैं आपका/आपके बेटे का चिकित्सकीय आकलन कुछ रेटिंग स्केल का उपयोग करके करूँगा. इन परीक्षाओं के परिणाम आप या आपके मौजूदा उपचार के लिए प्रत्यक्ष रूप से प्रासंगिक नहीं हो सकते हैं, लेकिन शराब पर निर्भरता सिंड्रोम के साथ माता - पिता की संतानों में विशिष्ट मस्तिष्क क्षेत्रों में शराब पर निर्भरता सिंड्रोम और कार्यात्मक असामान्यताएं के बारे में हमारी समझ बढ़ने की उम्मीद है. इससे संज्ञानात्मक प्रशिक्षण के प्रभाव को समझने में मदद भी मिलेगी.

जांचकर्ता द्वारा उपक्रम:

यदि आप चाहें आप इस अध्ययन से बिना कारण बताये अपनी सहमति वापस ले सकते हैं, इससे आपके/आपके रिश्तेदार के उपचार पर कोई प्रतिकूल प्रभाव नहीं पड़ेगा. ऐसा होने पर भी, आपको/आपके रिश्तेदार को बिना किसी पूर्वाग्रह के सबसे अच्छा संभव उपचार प्राप्त होगा. अध्ययन के बारे में किसी भी प्रकार का शक होने पर, कृपया उसे स्पष्ट करने में स्वतंत्र महसूस करें. अध्ययन के दौरान भी आप किसी भी समय जांचकर्ता से स्पष्टीकरण के लिए

1

संपर्क कर सकते हैं (डॉ. मृणाल बंदवर– 09611233206, डॉ. विवेक बेनेगल– 08026995360) आपसे एकत्रित सभी जानकारी/डेटा को गोपनीय रखा जाएगा.

सहमति फॉर्म

मुझे अध्ययन की प्रक्रिया के बारे में सूचित किया गया है. मैं जानता/जानती हूँ कि अध्ययन के दौरान किसी भी समय, मेरे/मेरे रिश्तेदार के उपचार पर किसी प्रकार का प्रतिकूल प्रभाव पड़े बिना, मैं अपनी सहमति को मना या वापस ले सकता हूँ. मैं यह भी जानता हूँ कि इस अध्ययन प्रक्रिया के लिए स्वीकृति देने पर, मुझे जांचकर्ता के द्वारा किये गए आकलन के लिए अधिक समय देना पड़ेगा और यह आकलन लाभ के साथ हस्तक्षेप नहीं करेंगे|

मैं, अधोहस्ताक्षरी, इस अध्ययन कार्यक्रम में भाग लेने के लिए अपनी सहमति देता हूँ_____

विषय/माता-पिता का हस्ताक्षर: गवाह के हस्ताक्षर:

नाम: नाम:

पता और फ़ोन नंबर: पता:

डॉक्टर के हस्ताक्षर:

नाम:

पद:

एसेंट

विषय का हस्ताक्षर: गवाह के हस्ताक्षर:

नाम: नाम:

पता और फ़ोन नंबर: पता:

2

C. Consent form Kannada

ರೋಗಿಗಳಿಗೆ ಒಪ್ಪಿಗೆ ಪತ್ರ

ನಿಂಹಾನ್ಸ್, ಬೆಂಗಳೂರು

ಅಧ್ಯಯನದ ಶೀರ್ಷಿಕೆ

"Effect Of cognitive enhancement on impulsivity and response inhibition in heavy social drinkers and ~~offspring of~~ alcoholics: Event related potential study".

ಮಾಹಿತಿ:

ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಮದ್ಯವ್ಯಸನಿ ತಂದೆಯ ಮಕ್ಕಳು ಮತ್ತು ಮದ್ಯವ್ಯಸನವಿಲ್ಲದ ಕುಟುಂಬದ ಸಮಾನ ವಯಸ್ಕ ಮಕ್ಕಳು ಸೇರಿರುತ್ತಾರೆ. ಮೊದಲ ಗುಂಪನ್ನು ಯಾದೃಚ್ಛಿಕವಾಗಿ ಎರಡು ತಂಡಗಳಾಗಿ ವಿಭಜಿಸಲಾಗುವುದು. ಒಂದು ತಂಡಕ್ಕೆ ಗ್ರಹಿಕೆ ಸುಧಾರಣೆ ಚಿಕಿತ್ಸೆ ನೀಡಲಾಗುತ್ತದೆ ಮತ್ತು ಇನ್ನೊಂದು ತಂಡಕ್ಕೆ ಹುಸಿ ಮದ್ದಿನ ಆಟ ನೀಡಲಾಗುವುದು. ಅಧ್ಯಯನದ ಒಟ್ಟು ಅವಧಿ 12 ವಾರಗಳಾಗಿದ್ದು ಅದರಲ್ಲಿ 20-30 ನಿಮಿಷಗಳ ಅವಧಿಯ 48 ಸಮಾಲೋಚನೆಗಳಿರುತ್ತವೆ. ಇವುಗಳನ್ನು ಸ್ಮಾರ್ಟ್ ಫೋನ್ ಆಟಗಳ ರೂಪದಲ್ಲಿ ನೀಡಲಾಗುವುದು. ಹುಸಿ ಮದ್ದು ಆಟವೂ ಗ್ರಹಿಕೆ ತರಬೇತಿ ಆಟದ ತರಹ ಇದ್ದರೂ ಮುಂದುವರೆದ ಆಟಗಳಲ್ಲಿ ತೀವ್ರತರದ ಕ್ಲಿಷ್ಟತೆಗಳಿರುವುದಿಲ್ಲ. ನಿಯಂತ್ರಿತ ಗುಂಪಿಗೆ ನಿಗದಿತ ಗ್ರಹಿಕೆ ಸುಧಾರಣೆ ಚಿಕಿತ್ಸೆಯನ್ನು ನೀಡಲಾಗುವುದು. ಚಿಕಿತ್ಸೆಯ ಮುನ್ನ ಮತ್ತು ನಂತರ ನ್ಯೂರೋ ಮಾನಸಿಕ ಮತ್ತು ಎಲೆಕ್ಟ್ರೊಫಿಸಿಯಾಲಜಿ ಮಾಪನಗಳನ್ನು ನಡೆಸಲಾಗುವುದು. ಈ ಚಿಕಿತ್ಸೆಯನ್ನು ನೀಡುವ ಮುನ್ನ ಒಂದು ಪ್ರದರ್ಶನವನ್ನು ನೀಡಲಾಗುವುದು. ಚಿಕಿತ್ಸೆ ಅವಧಿಯಲ್ಲಿ ನೀವು ಮತ್ತು ವೈದ್ಯರು ಪರಸ್ಪರ ಮಾತಾಡಬಹುದು. ನಿಮ್ಮ ಮೆದುಳಿನ ಎಲೆಕ್ಟ್ರೊಎನ್ಸಿಫಾಲೋಗ್ರಫಿ(ಇಇಜಿ) ಬಳಸಿಕೊಂಡು ಈ ಅಧ್ಯಯನವನ್ನು ನಡೆಸಲು ನನಗೆ ನಿಮ್ಮ ಅನುಮತಿ ನೀಡಬೇಕೆಂದು ಕೋರುತ್ತೇನೆ. ಕೆಲವು ಮಾಪನ ಪ್ರಶ್ನಾವಳಿಗಳನ್ನು ಬಳಸಿಕೊಂಡು ನಾನು ನಿಮ್ಮ/ನಿಮ್ಮ ಮಗನ ಮಾಪನವನ್ನೂ ಮಾಡುತ್ತೇನೆ. ಈ ಪರೀಕ್ಷೆಯ ಫಲಿತಾಂಶಗಳು ನಿಮಗೆ ನೇರವಾಗಿ ಅಥವಾ ಈಗಿನ ಚಿಕಿತ್ಸೆಗೆ ಸಂಬಂಧಿಸಿಲ್ಲದಿರಬಹುದು, ಆದರೆ ಮದ್ಯವ್ಯಸನದ ಬಗ್ಗೆ ಹಾಗೂ ಮದ್ಯವ್ಯಸನಿಗಳ ಮಕ್ಕಳಲ್ಲಿನ ಮೆದುಳಿನ ನಿರ್ದಿಷ್ಟ ಭಾಗಗಳಲ್ಲಿ ಕಾರ್ಯಕ್ಷಮತೆ ಅಸಹಜತೆಗಳ ಬಗ್ಗೆ ನಮ್ಮ ಅರಿವನ್ನು ಹೆಚ್ಚಿಸುತ್ತದೆ ಎಂದು ನಿರೀಕ್ಷಿಸಲಾಗಿದೆ. ಗ್ರಹಿಕೆ ತರಬೇತಿಯ ಪರಿಣಾಮದ ಬಗ್ಗೆಯ ಅರಿವನ್ನೂ ಇದು ಹೆಚ್ಚಿಸುತ್ತದೆ.

ಪರಿಶೋಧಕರ ವಾಗ್ದಾನ:

ನೀವು ಇಚ್ಛಿಸಿದಲ್ಲಿ, ಯಾವುದೇ ಕಾರಣವನ್ನು ನೀಡದೆ ಅಧ್ಯಯನದಿಂದ ಹಿಂದೆಗೆಯುವ ಸಂಪೂರ್ಣ ಅಧಿಕಾರ ನಿಮಗಿದೆ ಮತ್ತು ಇದರಿಂದ ನಿಮ್ಮ/ನಿಮ್ಮ ಬಂಧುವಿನ ಚಿಕಿತ್ಸೆಗೆ ಯಾವ ರೀತಿಯಿಂದಲೂ ಬಾಧಕವಿಲ್ಲ. ನೀವು ಈ ಸಂಶೋಧನೆಯಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪದಿದ್ದರೂ ಸಹ ಯಾವರೀತಿಯ ಪಕ್ಷಪಾತವಿಲ್ಲದೆ ನಮ್ಮ ವೈದ್ಯಕೀಯ ಸೇವೆಯಲ್ಲಿ ಚ್ಯುತಿ ಬರುವುದಿಲ್ಲ. ಅಧ್ಯಯನದ ಬಗ್ಗೆ ನಿಮಗೆ ಯಾವುದೇ ಅನುಮಾನಗಳಿದ್ದರೆ ಹಿಂಜರಿಯದೆ ಪರಿಹರಿಸಿಕೊಳ್ಳಿ. ಇಚ್ಛಿಸಿದಲ್ಲಿ ಅಧ್ಯಯನಾವಧಿ ಜಾರಿಯಲ್ಲಿದ್ದಾಗ ಕೂಡ ನೀವು ಪರಿಶೋಧಕರಲ್ಲಿ ಯಾರನ್ನು ಬೇಕಾದರೂ ಮುಕ್ತವಾಗಿ ಕಾಣಬಹುದಾಗಿದೆ. (ಡಾ. ಮೃಣಾಲ್ ಬಂಡವಾರ ದೂರವಾಣಿ 09611233206, ಡಾ. ವಿವೇಕ್ ಬೆನೆಗಲ್ - 080 26995360) ನಿಮ್ಮಿಂದ ಸಂಗ್ರಹಿಸಲಾದ ಎಲ್ಲ ಮಾಹಿತಿ/ದಖಲೆಗಳನ್ನು ಕಟ್ಟುನಿಟ್ಟಾಗಿ ಗೋಪ್ಯವಾಗಿಡಲಾಗುತ್ತದೆ.

ಸಮ್ಮತಿ ಪತ್ರ

ಅಧ್ಯಯನದ ಪರಿಕ್ರಮದ ಬಗ್ಗೆ ನನಗೆ ತಿಳಿಯಪಡಿಸಲಾಗಿದೆ. ನನ್ನ ಸಂಬಂಧಿಯ ಚಿಕಿತ್ಸೆಗೆ ಯಾವುದೇ ನ್ಯೂನತೆ ಉಂಟಾಗದಂತೆ, ಯಾವಾಗ ಬೇಕಾದರೂ ಸಮ್ಮತಿಯನ್ನು ಹಿಂದೆಗೆದುಕೊಳ್ಳುವ ಅಥವಾ ಈ ಅಧ್ಯಯನದಿಂದ ಹೊರಬರುವ ಅಧಿಕಾರ ನನಗಿದೆ ಎಂದು ನನಗೆ ಮನವರಿಕೆಯಾಗಿದೆ. ನಾನು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವುದರಿಂದ ಪರಿಶೋಧನಾ ತಂಡದ ಮೌಲ್ಯಮಾಪನಗಳಿಗೆ ಹೆಚ್ಚಿನ ಸಮಯವನ್ನು ನೀಡಬೇಕೆಂದು ಮತ್ತು ಈ ಮೌಲ್ಯಮಾಪನಗಳು ಲಾಭಗಳಿಗೆ ಅಡ್ಡಿಪಡಿಸುವುದಿಲ್ಲವೆಂದು, ನಾನು ತಿಳಿದುಕೊಂಡಿದ್ದೇನೆ.

ಈ ಕೆಳಗೆ ಸಹಿ ಮಾಡಿರುವ ನಾನು, ... ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ನನ್ನ ಒಪ್ಪಿಗೆಯನ್ನು ನೀಡಿದ್ದೇನೆ.

ರೋಗಿ/ಪೋಷಕರ ಸಹಿ:	ಸಾಕ್ಷಿಯ ಸಹಿ:
ಹೆಸರು:	ಹೆಸರು:
ವಿಳಾಸ ಮತ್ತು ದೂರವಾಣಿ ಸಂಖ್ಯೆ:	ವಿಳಾಸ:

ವೈದ್ಯರ ಸಹಿ

ಹೆಸರು:

ಹುದ್ದೆ

ಒಪ್ಪಿಗೆ

ಪೋಷಕರ ಸಹಿ:	ಸಾಕ್ಷಿಯ ಸಹಿ:
ಹೆಸರು:	ಹೆಸರು:
ವಿಳಾಸ ಮತ್ತು ದೂರವಾಣಿ ಸಂಖ್ಯೆ:	ವಿಳಾಸ:

XVI. Appendix 10: Questionnaires

A. Timeline Follow back

To help me evaluate your drinking I need to get an idea of your alcohol consumption in the past fourteen days. Please fill out the table with the number of units of alcohol consumed on each day, being as accurate as possible. Please use the information given below to work out how many units you consumed on each day in the past week and fill in the number of units in the table. On days when you did not drink please write 0 (zero). I realise it isn't easy to recall things with 100% accuracy, but if you are not sure how many units you drank on a certain day please try to give it your best guess.

What is a unit of alcohol?

The list below shows the number of units of alcohol in common drinks:-

- A pint of ordinary strength lager (Carling Black Label, Fosters) - 2 units
- A pint of strong lager (Stella Artois, Kronenbourg 1664) - 3 units
- A pint of ordinary bitter (John Smith's, Boddingtons) - 2 units
- A pint of best bitter (Fuller's ESB, Young's Special) - 3 units
- A pint of ordinary strength cider (Woodpecker) - 2 units
- A pint of strong cider (Dry Blackthorn, Strongbow) - 3 units
- A 175ml glass of red or white wine - around 2 units
- A 750ml bottle of red or white wine – around 9 units
- A pub measure of spirits - 1 unit
- An alcopop (eg Smirnoff Ice, Bacardi Breezer, WKD, Reef) - around 1.5 units

Please now fill in the following table stating the total number of alcohol units you consumed for each day. Please start from whichever day it was yesterday and work backwards. For example if today is Monday start from Sunday and work backwards, with Monday being Monday a week ago. Once you have completed this please answer the statements below the table. Please double check that you have filled in the number of units for all fourteen days.

Last week:

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday

Previous week:

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday

B. Toronto Mindfulness Scale

	Instructions: We are interested in what you just experienced. Below is a list of things that people sometimes experience. Please read each statement. Next to each statement are five choices: "not at all," "a little," "moderately," "quite a bit," and "very much." Please indicate the extent to which you agree with each statement. In other words, how well does the statement describe what you just experienced, just now?	**Not at all**	**A little**	**Moderately**	**Quite a bit**	**Very much**
1.	I experienced myself as separate from my changing thoughts and feelings.	0	1	2	3	4
2.	I was more concerned with being open to my experiences than controlling or changing them.	0	1	2	3	4
3.	I was curious about what I might learn about myself by taking notice of how I react to certain thoughts, feelings or sensations.	0	1	2	3	4
4.	I experienced my thoughts more as events in my mind than as a necessarily accurate reflection of the way things 'really' are.	0	1	2	3	4
5.	I was curious to see what my mind was up to from moment to moment.	0	1	2	3	4
6.	I was curious about each of the thoughts and feelings that I was having.	0	1	2	3	4
7.	I was receptive to observing unpleasant thoughts and feelings without interfering with them	0	1	2	3	4
8.	I was more invested in just watching my experiences as they arose, than in figuring out what they could mean.	0	1	2	3	4
9.	I approached each experience by trying to accept it, no matter whether it was pleasant or unpleasant.	0	1	2	3	4
10.	I remained curious about the nature of each experience as it arose.	0	1	2	3	4
11.	I was aware of my thoughts and feelings without over identifying with them.	0	1	2	3	4
12.	I was curious about my reactions to things.	0	1	2	3	4
13.	I was curious about what I might learn about myself by just taking notice of what my attention gets drawn to.	0	1	2	3	4

C. Self-Control Scale

Using the scale provided, please indicate how much each of the following statements reflects how you typically are.

Not at all ----------Very much

1. I am good at resisting temptation. 1———2———3———4———5
2. I have a hard time breaking bad habits. 1———2———3———4———5
3. I am lazy. 1———2———3———4———5
4. I say inappropriate things. 1———2———3———4———5
5. I never allow myself to lose control. 1———2———3———4———5
6. I do certain things that are bad for me, if they are fun.
   1———2———3———4———5
7. People can count on me to keep on schedule.
   1———2———3———4———5
8. Getting up in the morning is hard for me. 1———2———3———4———5
9. I have trouble saying no. 1———2———3———4———5
10. I change my mind fairly often. 1———2———3———4———5
11. I blurt out whatever is on my mind. 1———2———3———4———5
12. People would describe me as impulsive. 1———2———3———4———5
13. I refuse things that are bad for me. 1———2———3———4———5
14. I spend too much money. 1———2———3———4———5
15. I keep everything neat. 1———2———3———4———5
16. I am self-indulgent at times. 1———2———3———4———5
17. I wish I had more self-discipline. 1———2———3———4———5
18. I am reliable. 1———2———3———4———5
19. I get carried away by my feelings. 1———2———3———4———5
20. I do many things on the spur of the moment.
    1———2———3———4———5
21. I don't keep secrets very well. 1———2———3———4———5
22. People would say that I have iron self- discipline.
    1———2———3———4———5
23. I have worked or studied all night at the last minute.
    1———2———3———4———5
24. I'm not easily discouraged. 1———2———3———4———5
25. I'd be better off if I stopped to think before acting.
    1———2———3———4———5
26. I engage in healthy practices. 1———2———3———4———5
27. I eat healthy foods. 1———2———3———4———5
28. Pleasure and fun sometimes keep me from getting work done.
    1———2———3———4———5
29. I have trouble concentrating. 1———2———3———4———5

30. I am able to work effectively toward long-term goals.
1———2———3———4———5

31. Sometimes I can't stop myself from doing something, even if I know it is wrong.
1———2———3———4———5

32. I often act without thinking through all the alternatives.
1———2———3———4———5

33. I lose my temper too easily. 1———2———3———4———5
34. I often interrupt people. 1———2———3———4———5
35. I sometimes drink or use drugs to excess. 1———2———3———4———5
36. I am always on time. 1———2———3———4———5

D. Barratt Impulsivity Scale (BIS-11)

Directions: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and place a check in the appropriate box on the right side of the page. Do not spend too much time on any statement. Answer quickly and honestly.		**Rarely/Never**	**Occasionally**	Often	**Almost always/ Always**
1.	I plan tasks carefully				
2.	I do things without thinking				
3.	I am happy-go-lucky				
4.	I have "racing" thoughts				
5.	I plan trips well ahead of time				
6.	I am self-controlled				
7.	I concentrate easily				
8.	I save regularly				
9.	I find it hard to sit still for long periods of time				
10.	I am a careful thinker				
11.	I plan for job security				
12.	I say things without thinking				
13.	I like to think about complex problems				
14.	I change jobs				
15.	I act "on impulse"				
16.	I get easily bored when solving thought problems				
17.	I have regular medical/dental checkups				

18.	I act on the spur of the moment				
19.	I am a steady thinker				
20.	I change where I live				
21.	I buy things on impulse				
22.	I finish what I start				
23.	I walk and move fast				
24.	I solve problems by trial-and-error				
25.	I spend or charge more than I earn				
26.	I talk fast				
27.	I have outside thoughts when thinking				
28.	I am more interested in the present than the future				
29.	I am restless at lectures or talks				
30.	I plan for the future				

E. AUDIT

The Alcohol Use Disorders Identification Test: Self-Report Version

PATIENT: Because alcohol use can affect your health and can interfere with certain medications and treatments, it is important that we ask some questions about your use of alcohol. Your answers will remain confidential so please be honest. Place an X in one box that best describes your answer to each question.

Questions	0	1	2	3	4	
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week	
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more	
3. How often do you have six or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, during the last year	
10. Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year	
					Total	

The Alcohol Use Disorders Identification Test: Interview Version

Read questions as written. Record answers carefully. Begin the AUDIT by saying "Now I am going to ask you some questions about your use of alcoholic beverages during this past year." Explain what is meant by "alcoholic beverages" by using local examples of beer, wine, vodka, etc. Code answers in terms of "standard drinks". Place the correct answer number in the box at the right.

1. How often do you have a drink containing alcohol?
   (0) Never [Skip to Qs 9-10]
   (1) Monthly or less
   (2) 2 to 4 times a month
   (3) 2 to 3 times a week
   (4) 4 or more times a week

2. How many drinks containing alcohol do you have on a typical day when you are drinking?
   (0) 1 or 2
   (1) 3 or 4
   (2) 5 or 6
   (3) 7, 8, or 9
   (4) 10 or more

3. How often do you have six or more drinks on one occasion?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily
   Skip to Questions 9 and 10 if Total Score for Questions 2 and 3 = 0

4. How often during the last year have you found that you were not able to stop drinking once you had started?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

5. How often during the last year have you failed to do what was normally expected from you because of drinking?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

7. How often during the last year have you had a feeling of guilt or remorse after drinking?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

9. Have you or someone else been injured as a result of your drinking?
   (0) No
   (2) Yes, but not in the last year
   (4) Yes, during the last year

10. Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?
    (0) No
    (2) Yes, but not in the last year
    (4) Yes, during the last year

Record total of specific items here

If total is greater than recommended cut-off, consult User's Manual.

F. Alcohol Approach Avoidence Queastionnaire

This questionnaire relates to YOUR ATTITUDES toward alcohol RIGHT NOW. Please indicate how much you agree with the statements below by circling the number corresponding most closely to your general attitude RIGHT NOW. Your answers may range from AGREE NOT AT ALL (0) with the statement to AGREE VERY STRONGLY (8) with the statement.

		I AGREE WITH THIS STATEMENT…								
		Not At All								**Very Strongly**
1	I would like to have a drink or two.	0	1	2	3	4	5	6	7	8
2	I am avoiding people who are likely to offer me a drink.	0	1	2	3	4	5	6	7	8
3	If I were in a pub or club I would want a drink.	0	1	2	3	4	5	6	7	8
4	My desire to drink seems overwhelming.	0	1	2	3	4	5	6	7	8
5	I am planning to drink alcohol.	0	1	2	3	4	5	6	7	8
6	I am deliberately occupying myself so I will not drink alcohol.	0	1	2	3	4	5	6	7	8
7	I am thinking about the benefits of being sober.	0	1	2	3	4	5	6	7	8
8	I want to drink alcohol so much that if I start drinking now I will find it difficult to stop.	0	1	2	3	4	5	6	7	8
9	I would accept a drink now if one was offered to me.	0	1	2	3	4	5	6	7	8
1	I am avoiding places in which I might be tempted to drink alcohol.	0	1	2	3	4	5	6	7	8
1	I am thinking about alcohol a lot of the time.	0	1	2	3	4	5	6	7	8
1	I want to drink as soon as I have the chance.	0	1	2	3	4	5	6	7	8
1	The bad things that could happen if I drink alcohol are fresh in my mind.	0	1	2	3	4	5	6	7	8
1	If I were at a party now I would have a drink without thinking twice.	0	1	2	3	4	5	6	7	8

G. ICD-10 Checklist

ICD-10 CHECKLIST

Psychoactive Substance Use Syndromes Module

The following questions ask about symptoms associated with your heroin or other opioid use, for which you are currently being treated. The questions apply to the time period immediately before you started your current treatment.

[For the following items, substitute the name of the opioid used for 'substance', where applicable]

1.	Did you have a strong desire or sense of compulsion to use *substance*? ('craving')	Yes	No
2.	Did you find it difficult or impossible to control your use of *substance*?	Yes	No
3.	Did you experience withdrawal symptoms after going without *substance* for a while?	Yes	No
4.	Did you use *substance* to relieve or avoid withdrawal symptoms?	Yes	No
5.	Did you notice that you required more *substance* to achieve the same physical or mental effects? ('tolerance')	Yes	No
6.	Over time, did you tend not to vary your pattern of use of *substance*?	Yes	No
7.	Did you increasingly neglect other pleasures or interests in favour of using *substance*?	Yes	No
8.	Did you experience psychological or physical harm because of your *substance* use?	Yes	No
9.	Did you persist with using *substance*, despite clear evidence of harmful consequences?	Yes	No

10.	How long did you experience this pattern of problem drug use?		
	a. in years		
	b. in months		

Dependence indicated if **3 or more** of the symptoms 1, 2, 3, 5, 7 and 9 are present.

11.	a. ***Record whether opioid dependence syndrome (F11.2) is present***	Yes	No
	b. If "Yes", record specific opioid: _____		

H. Five Facet Mindfulness Questionnaire

Please rate each of the following statements using the scale provided. Write the number in the blank that best describes your own opinion of what is generally true for you

1	2	3	4	5
never or very rarely true	rarely true	sometimes true	often true	very often or always true

1. When I'm walking, I deliberately notice the sensations of my body moving.
2. I'm good at finding words to describe my feelings.
3. I criticize myself for having irrational or inappropriate emotions.
4. I perceive my feelings and emotions without having to react to them.
5. When I do things, my mind wanders off and I'm easily distracted.
6. When I take a shower or bath, I stay alert to the sensations of water on my body.
7. I can easily put my beliefs, opinions, and expectations into words.
8. I don't pay attention to what I'm doing because I'm daydreaming, worrying, or otherwise distracted.
9. I watch my feelings without getting lost in them.
10. I tell myself I shouldn't be feeling the way I'm feeling.
11. I notice how foods and drinks affect my thoughts, bodily sensations, and emotions.
12. It's hard for me to find the words to describe what I'm thinking.
13. I am easily distracted.
14. I believe some of my thoughts are abnormal or bad and I shouldn't think that way.

15. I pay attention to sensations, such as the wind in my hair or sun on my face.
16. I have trouble thinking of the right words to express how I feel about things.
17. I make judgments about whether my thoughts are good or bad.
18. I find it difficult to stay focused on what's happening in the present.
19. When I have distressing thoughts or images, I "step back" and am aware of the thought or image without getting taken over by it.
20. I pay attention to sounds, such as clocks ticking, birds chirping, or cars passing.
21. In difficult situations, I can pause without immediately reacting.
22. When I have a sensation in my body, it's difficult for me to describe it because I can't find the right words.
23. It seems I am "running on automatic" without much awareness of what I'm doing.
24. When I have distressing thoughts or images, I feel calm soon after.
25. I tell myself that I shouldn't be thinking the way I'm thinking.
26. I notice the smells and aromas of things.
27. Even when I'm feeling terribly upset, I can find a way to put it into words.
28. I rush through activities without being really attentive to them.
29. When I have distressing thoughts or images I am able just to notice them without reacting.
30. I think some of my emotions are bad or inappropriate and I shouldn't feel them.
31. I notice visual elements in art or nature, such as colors, shapes, textures, or patterns of light and shadow.
32. My natural tendency is to put my experiences into words.

33. When I have distressing thoughts or images, I just notice them and let them go.
34. I do jobs or tasks automatically without being aware of what I'm doing.
35. When I have distressing thoughts or images, I judge myself as good or bad, depending what the thought/image is about.
36. I pay attention to how my emotions affect my thoughts and behavior.
37. I can usually describe how I feel at the moment in considerable detail.
38. I find myself doing things without paying attention
39. I disapprove of myself when I have irrational idea