UNIVERSITY OF NOTTINGHAM

An EEG investigation of learning and decision making in smokers.

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Abstract

To improve the efficacy of addiction treatments it is important to understand the learning and behavioural processes involved. The experimental work presented here aims to further our understanding of the behaviour and related brain activity of smokers, using a range of experimental paradigms and Electroencephalographic (EEG) techniques. A range of behavioural tasks adapted from the animal literature for use with humans, were utilised to explore the choices made by smokers and the effect of smoking-related cues on drug-seeking behaviour. Tasks included concurrent choice and variations of the Pavlovian to Instrumental Transfer (PIT) task. EEG data was recorded during these experiments, and analysed using Event Related Potential (ERP) and frequency measures, to identify a neural component related to these effects. Resting EEG data was also collected and analysed to investigate the relationship between EEG frequency measures and individual difference measures.

Behavioural results broadly replicated those found in both animal and human research; smoking related cues enhanced responding for smoking- related outcomes showing Pavlovian control of Instrumental behaviour. Extinction of the Pavlovian cues did not reduce instrumental responses in the transfer stage of a PIT task. However no ERP or frequency components were found that consistently correlated with these behavioural effects.

The resting EEG data showed higher beta levels (less desynchronisation) in those with longer histories of smoking (four years and over) suggestive of either sensitisation or the loss of inhibitory neural control in long term smokers.

In summary, the behavioural data adds support to a growing body of literature regarding the effects of cues on the behaviour of addicted individuals. More work and perhaps other techniques need to be utilised in order to explore the neural correlates of these behavioural effects and the resting data suggests a promising route for further research.

Declaration of Authorship

I declare that this is my own work, conducted during my time as a PhD student at the University of Nottingham. Half of the data presented in the concurrent choice chapter was collected during my Master's year and reported in my MSc thesis. It has since been significantly added to and totally re-analysed.

The behavioural data from Chapter 6 are in preperation for publication.

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Chapter 1

Introduction

To treat addiction we must understand the behavioural processes and learning that lead from first trying a drug, to the compulsive and harmful use seen in addicted individuals. The experiments discussed in this work will attempt to elucidate some of the learning mechanisms involved and also identify EEG components that have the potential to provide neural correlates of these behaviours. Robinson & Berridge (1993) proposed that addiction may develop due to a hypersensitivity to drug-related outcomes. A range of measures have been used to measure this, based on the idea that the amount of work an animal will do to obtain a reward, reflects their valuation of that outcome (Hursh & Silberberg, 2008). Although a number of different paradigms have been used to assess this, the purest measure would seem to be a simple choice between responses, with a comparison of drug-related and non-drug-related outcomes. A preference for the drug-related outcome is fairly well established in the animal literature (e.g. Deroche-Gamonet, Belin, & Piazza, 2004) but has received less attention in humans.

A recent paper by Lenoir et al. (2013) tested rats' preferences for heroin or cocaine versus a sucrose solution. In line with addiction rates in humans (e.g. Anthony, Warner & Kessler,1994), after extended use around 15% of rats chose cocaine over water. Interestingly the proportion choosing heroin over water was much higher (up to 51%). Similarly, Ahmed (2010) showed that only a small number of rats display a preference for cocaine over an alternative reward, a similar pattern to that shown in humans. This suggests that this type of simple preference task may well provide a useful measure of the preference for drug related outcomes in humans and therefore a marker of addicted individuals. Recent work with cocaine addicts has supported this, with choices in the task being associated with current and future drug use (Moeller et al., 2013) and addiction severity (Moeller et al., 2009).

The concurrent choice task can also help us to investigate the mechanisms involved in addiction related behaviour. For example, according to Hogarth (2011) impulsivity (a factor often implicated in addiction) may either lead to a hypersensitivity to drug reinforcement or it may be indicative of a propensity toward automatic control of drug seeking and taking behaviour. The study aimed to distinguish between these mechanisms using a concurrent choice or preference task in which participants chose one of two keyboard responses. One won them cigarettes and one chocolate. There was a 50% chance of the response winning, regardless of the key chosen, on each trial (in order to produce uncertainty in participants so that they sample both keys). Prior to this task participants completed impulsivity

and craving questionnaires and upon completing the choice task participants were sent outside to smoke as much as they liked for 10 minutes. Subjects recorded each puff consumed during this time. The results showed that impulsivity was not associated with higher rates of drug seeking. or taking, but individual differences in uptake and craving were, thus providing support for a dual-process theory of addiction vulnerability, in which the uptake is controlled by a hyper-valuation of the drug as a goal and later becomes mediated by automatic or habitual processes. In a subsequent paper Hogarth (2012) showed that Nicotine Replacement Therapy (NRT) nasal spray affected goal-directed behaviour but not the effect of cues on instrumental responding in a Pavlovian to Instrumental Transfer (PIT) task. This dissociation further suggests that drug seeking and taking behaviours are independently affected by outcome value and probability.

A paper by Hogarth & Chase (2011) presented further evidence for the dual process theory; that both goal-directed and habitual behaviours are present in addiction, with goal-directed choices displayed in free-choice situations and habitual control shown in cued paradigms such as the PIT task. The latter paradigm allows us to investigate the relationship between drug associated cues and drug-seeking behaviour and a number of variations on this task will be presented in this thesis. The PIT task is essentially a type of cue-reactivity paradigm; it measures the effects of presenting a cue to a participant. In addiction research a range of cue-reactivity procedures have been used including physiological measures, such as heart rate, sweat-gland activity and skin temperature, craving and

attentional measures such as eye-tracking. For a review of these see Carter & Tiffany (1999). The advantage of the PIT model of cue control is that it has been used extensively in animal research and therefore the behavioural mechanisms involved are fairly well understood. It also allows us to distinguish between goal-directed behaviour, in which the participant is guided by a representation of the outcome of an action, and habit based behaviour in which a stimulus comes to elicit an automatic response without representation of the outcome. This could have important implications for the research and treatment of addiction.

The general structure of the PIT task that we will be using is as follows; participants first receive Pavlovian training which involves the presentation of a cue (S+), followed by an outcome (O); either drug or non-drug related. For the second instrumental training stage participants are required to select a key (either d or h on the keyboard) to try to win a drug or non-drug-related reward. Responses will be rewarded 50% of the time, to increase switching between responses and therefore the number of all trials. Finally during the transfer stage participants make the instrumental responses in the presence of the Pavlovian S+s (as well as a control). If specific transfer has taken place then the frequency of responding for a drug-related outcome should increase in the presence of a previously conditioned drug-related S+. For example, this task was used by Hogarth, Dickinson, Wright, Kouvaraki, & Duka (2007) with tobacco and money outcomes. In the PIT test, conditioned stimuli were found to increase the number of instrumental responses for

their respective outcomes, suggesting that drug seeking was controlled by an expectation of the drug outcome, rather than a habitual response to a drug-related cue. This is mediated by goal-directed learning since the response and the stimulus are never contingently reinforced. This highlights the main advantage of the PIT paradigm; it allows us to discriminate between the types of learning implicated in addiction, in this case showing that drug seeking can be goal-directed rather than habitual. It also informs us about the effect drug-related cues can have on drug seeking behaviour, potentially leading to relapse in addicted individuals.

The behavioural PIT effect has been shown in both animals (e.g. Corbit & Balleine, 2011) and humans (e.g. Hogarth & Chase, 2011) but the neural correlates of the PIT effect have only recently begun to be investigated and so far have only utilised fMRI techniques. For example Bray, Rangel, Shimojo, Balleine, & ODoherty (2008) used food rewards and found that blood oxygenation level-dependent (BOLD) activation in the ventrolateral putamen was mediated by whether the cue and chosen action were consistent. Similarly, Talmi, Seymour, Dayan, & Dolan (2008) used monetary rewards and found that BOLD signal in the nucleus accumbens and amygdala correlated with the strength of the PIT effect. There have not been, to our knowledge, any previous EEG studies of the PIT effect but there is evidence that we might see differences in the ERP and frequency components described below. It is worth noting that neuroimaging studies to date have identified areas such as the orbitofrontal cortex (OFC) and sub cortical structures as mediators of the PIT effect (e.g. Bray et al., 2008; Prvost, Liljeholm, Tyszka, & ODoherty,

2012; Talmi et al., 2008). These areas are not easily accessible with EEG, which measures neural activity on the scalp, due to their location (in the case of the OFC, which is close to the nasal cavity and therefore leads to signal drop-out when imaged) and depth respecitvely. However activity of the OFC and deeper structures is likely to affect potentials on the scalp and there is some suggestion that some ERP components may be linked to activity in these areas (e.g. Potts, 2004a). This research will be discussed below. Alternatively, investigation of EEG signals may reveal different neural activity that is related to the PIT effect. The discovery of EEG correlates of addiction could provide a more economical method for the investigation, and potentially identification and treatment, of addicted individuals.

1.0.1 EEG Introduction

EEG is a measure of the electrical potentials generated by the synchronous activity of neurons within the cortex, detected using electrodes placed on the scalp. Recording this signal over time allows investigation of ongoing cortical activity with precise temporal resolution. In the following section we will review the Event Related Potential (ERP) and frequency components which we might expect to be modulated by our behavioural measures. ERP techniques are based on the assumption that averaging across a set of epochs around the same type of event will produce a discrete ERP signature, whilst averaging out the noise contained within any EEG data.

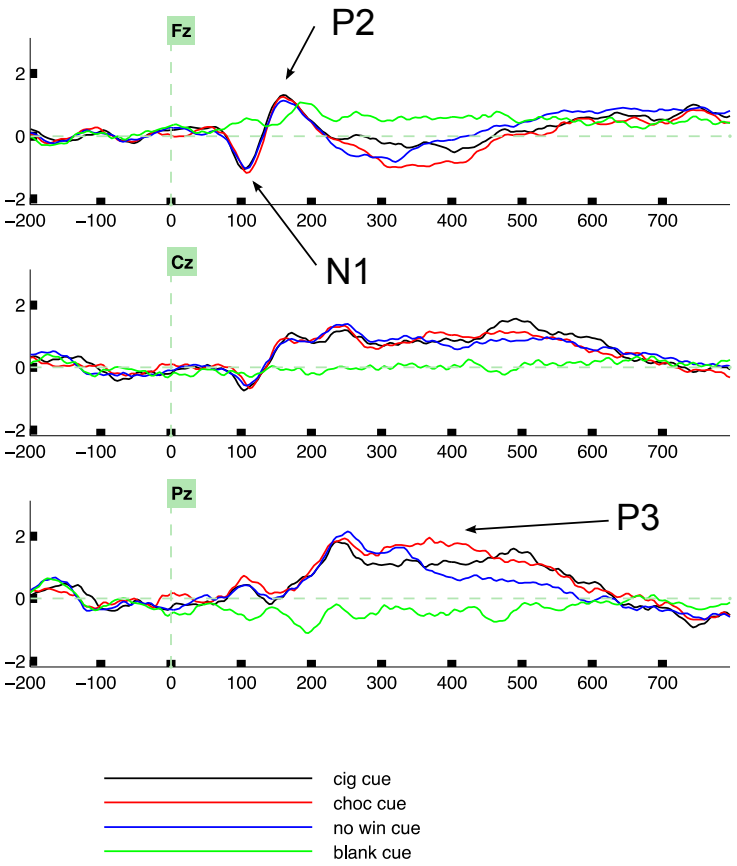


FIGURE 1.1: The main ERP components that will be analysed in the following experiments, the N1, P2 and P3. As we would expect the N1 and P2 are maximal at frontal electrodes, whilst the P3 is seen at parietal locations. The Y axis shows amplitude in microvolts.

N1

The N1 is usually the first negative deflection in the ERP wave, occurring between 150-200 milliseconds post stimulus (see figure 1). It can be seen at many cortical sites, dependent on the stask used. It is elicited by visual stimuli and its amplitude can be influenced by attention (Luck, Woodman, & Vogel, 2000), stimulus properties such

as colour and location (Anllo-Vento & Hillyard, 1996) and emotion (Schupp et al., 2007). With regard to emotion, the N1 seems to be modulated by the saliency of emotional stimuli where positive emotional words produce larger N1s than negative ones (Bernat, Bunce, & Shevrin, 2001), as do highly salient stimuli such as pain-related words in patients with chronic pain (Flor, Knost, & Birbaumer, 1997).

In a recent study Mason, OSullivan, Blackburn, Bentall, & El-Deredy (2012) utilised a choice task in which participants chose between immediate and delayed rewards. The study used vulnerability to hypomania as a model of impulsivity to examine the neural correlates of reward processing and delay discounting. The hypomania-prone group made significantly more immediate choices than controls. They also showed greater differentiation between delayed and immediate outcomes in the N1. Proneness to hypomania was also associated with greater general N1 amplitude, suggestive of an attentional bias to immediate rewards, which may drive subsequent cognitive appraisal of outcomes, measured by the FRN. This result highlights the early influence of attention on reward processing and supports reward dysregulation accounts of bipolar disorder.

The N1 has also been implicated in addiction with reduced amplitudes and prolonged latencies in heavy smokers during an auditory oddball task (Guney, Genc, Kutlu, & Ilhan, 2009), which may reflect delayed information processing. The oddball task involves presenting subjects with a train of stimuli (either visual or auditory) in which an oddball different stimulus occurs at unpredictable intervals. Neiman, Noldy, el-Nesr, McDonough, & Carlen (1991) looked

at the auditory evoked N1-P2 components which was reduced in alcoholics after one day of abstinence compared to controls. Those alcoholics with a history of seizures showed larger N1-P2 components than those without seizures. The increased size of the component reduced to near control levels after five days. Similarly Noldy, Neiman, el-Nesr, & Carlen (1990) suggested that the amplitude of the N1-P2, and the recovery of this component, provide a rapid and reliable measure of changes in brain function following diazepam intake. Following drug administration the amplitude of N1-P2 was reduced indicating a decrease in central nervous system excitability.

P2

The P2 is a positive potential usually observed around 200 milliseconds after the presentation of a stimulus and largest at frontal locations (see figure 1). The P2 can be modulated by a diverse range of tasks but is thought to provide an index of high level perceptual processing (Kranczioch, Debener, & Engel, 2003), perhaps integrating motivational and perceptual information (Potts, 2004b) and may provide a measure of saliency.

The P2 has also been linked to reward processing and impulsivity, two key factors involved in addiction. Martin & Potts (2004) demonstrated that impulsive individuals choose immediate small rewards over delayed larger rewards, indicative of reward hypersensitivity. Single unit and neuroimaging studies have shown that the orbitofrontal ventral tegmental area responds to reward and the anterior P2a has been proposed as an index of reward-related orbitofrontal activity. In a reward prediction experiment, participants

who scored highly on impulsive scales demonstrated the P2a, localized to the OFC, as largest to non-predicted rewards and smallest in the absence of predicted rewards. An interesting study by Potts, 2004b suggested that the P2 may index reward-related frontal activity and the dopamine (DA) reward system with connections to perceptual and motor areas.

A number of studies have used visual oddball paradigms to elicit the P2 (e.g. Goldstein, Cottone, et al., 2006; Wu & Zhou, 2009a; Yeung, Holroyd, & Cohen, 2005a). All these studies show the P2 was present following task-relevant stimuli but was not sensitive to whether responses were overt or covert, suggesting that the P2 reflects stimulus evaluation, rather than response production. P2a has been associated with the integration of motivational information, especially reward information (provided by the DA system), and perceptual information in the identification of task-relevant cues. This has obvious implications/usefulness for a limited capacity system, in deciding to which stimuli it should direct attention and resources.

Potts (2004) reasoned that if the P2a and the Medial Frontal Negativity (MFN) (these components appear to be related with similar medial frontal scalp topographies, latencies between 200 and 300 ms and localize to the medial frontal cortex (MFC)) index the DA reward system, then the ERP response of these components should be similar to that of the ventral tegmental area (VTA) DA neurons, with positive deflections following unpredicted reward, and negative in response to a predicted reward not being rewarded. The author thus suggests that the P2a and MFN may provide an index of the DA systems response to better-than-predicted, or worse-than-predicted

outcomes. The MFC is ideally located with projections to perceptual and motor areas of the cortex, thus allowing integration of DA reward system information with analysis of the perceptual qualities of a stimulus and the subsequent motor response.

More recently Franken, Van den Berg, & Van Strien (2010) utilised a passive gambling task in which participants viewed stimuli which predicted either rewarding or non-rewarding outcomes. It was predicted that alcohol-drinking frequency would be associated with ERP components thought to index reward processing. Results showed that the P2 and the medial frontal negativity (MFN) were larger following unpredicted rewards. The MFN to unpredicted rewards correlated with drinking frequency, although this association was not present for the P2.

The P2 has also been implicated in response selection on the basis of relevant stimulus information (Kuhn, Gevers, & Brass, 2009) and higher amplitudes in choice, than no-choice conditions (Peterson, Lotz, Halgren, Sejnowski, & Poizner, 2011). Franken et al. (2010) also suggest that the frontal P2 may be a reward-related component and provide an index of orbitofrontal reward processing and associated reward hypersensitivity.

P3

The P3 is a positive deflection of the ERP around 300 ms post stimulus presentation, first reported by Chapman & Bragdon (1964; see figure 1). It is most commonly studied using odd-ball paradigms in which participants are exposed to a stream of auditory or visual

stimuli, a rare or unexpected stimulus amonst them elicits a larger P3 than the common stimuli (e.g. Donchin, 1978). The P3 has since also been implicated in the allocation of attentional resources (Polich, 2007). A unified explanation of the P3 has proven difficult as the component is seen following any stimulus discrimination (Polich, 2007), however the discrimination of P3a and P3b waveforms has helped clarify its role. The P3a is maximal at central and parietal sites and has a relatively short peak latency (Polich & Criado, 2006). It is usually measured following an infrequent stimulus presented amongst more frequent stimuli and can be elicited simply by cues, independent of task. The P3b is considered to be task-dependent and related to memory processing. Polich (2007) suggests that the P3a is produced by early frontal processes which lead to the generation of the context dependent P3b at parietal sites.

Franken et al. (in press) compared P3s following the presentation of abstract stimuli, which had been pre-trained and associated with emotional events, and found that the P3 was enhanced for emotional compared to neutral stimuli. The same lab had previously compared the ERPs of smokers, ex-smokers and never-smokers following the presentation of smoking-related and neutral stimuli (Littel, Franken, & Van Strien, 2009). The P3 and slow positive wave (SPW) components were larger following smoking-related pictures, than neutral pictures, in the currently smoking group. Similarly Dan Lubman's lab compared the P3s of heroin addicts and healthy controls following presentation of either drug-related, affective or neutral cues (Lubman et al., 2009; Lubman, Allen, Peters, & Deakin, 2008a, 2007). The P3 in heroin addicts was greater following drug-related

stimuli than the affective or neutral stimuli. If the P3 is considered a measure of cognitive processing then these results suggest that current smokers show a drug-related bias that is not shown by ex-smokers or never-smokers. Indeed Lubman, Allen, Peters, & Deakin, 2008b) go further by suggesting that the P3 may even index the subjective value of a stimulus to an individual. Similarly Warren & McDonough (1999) found a P412, a P3-like potential, which they suggest may be an addiction specific measure of cue-reactivity (in smokers) and act as part of an automatic, perceptual categorization system.

Hajcak, Holroyd, Moser, & Simons (2005) suggest that as the P3 has been shown to be sensitive to the expectancies of an event (Courchesne, Hillyard, & Courchesne, 1977; Duncan-Johnson & Donchin, 1982) the P3 should be modulated by cues which provide information regarding the probability of an outcome. Their results supported this with larger P3 components to unexpected outcomes. The authors also predicted that on the basis of previous evidence the P3 would not be modulated by the (positive or negative) valence of the feedback (Yeung, Holroyd, & Cohen, 2005b; Yeung & Sanfey, 2004) but this was not the case with greater P3 amplitudes following positive feedback.

So the P3 seems to be involved in outcome and reward valence, but which aspects specifically, is controversial. Wu & Zhou (2009b) used a gambling task in which they manipulated the valence, magnitude and expectancies of the rewards, and looked at the effects these had on the P3. Results showed that the P3 was more positive for large

rewards, than small, and was also sensitive to the valence of the reward, although both effects could be reduced if the reward did not match the participants expectations for that trial. Similarly Goldstein, Cottone, et al. (2006) observed that the P3 amplitude was modulated by size of monetary reward, with graduated amplitudes dependent on the size of reward (45 cents >1 cent >0 cents). In contrast Yeung & Sanfey (2004) found that the P3 did code reward magnitude but not the valence (positive/negative) of outcomes in a gambling game.

Interestingly, the P3 has also been implicated in the impaired reward processing seen in addicted individuals. For example cocaine users have shown impaired sensitivity to monetary rewards compared to controls (Goldstein et al., 2008) and male alcoholics show reduced P3-like components and increased impulsivity and risk taking in a gambling task (Kamarajan et al., 2010). The decrease in amplitudes may be indicative of dysfunctional reward processing. Similarly there is a large body of literature demonstrating a reduced P3 component in a range of psychopathologies; for example a reduced P3 in depression (Foti & Hajcak, 2009; Joachim Rschke & Wagner, 2003), schizophrenia (J Rschke et al., 1996), cocaine addicts (Goldstein et al., 2008; Guney et al., 2009), alcoholics and those at risk of alcoholism (Polich & Ochoa, 2004; Porjesz & Begleiter, 1990; Ramsey & Finn, 1997) and smokers (Mobascher et al., 2010). In a large scale visual oddball study (n = 905 current smokers, 463 ex-smokers and 979 never smokers) Anokhin et al. (2000) found reduced P3 amplitudes in current smokers compared to never smokers. Ex-smokers did not significantly differ from never-smokers. The authors suggest

that this is either because long-term smoking leads to a reversible change in brain function, or reduced P3 is a marker for nicotine dependence. On the basis of this research it seems that the P3 may provide a marker for these behavioural abnormalities although it must be remembered that it may provide a proxy for some other causal factors. For example Nijs, Franken, & Smulders (2007) found correlations between P3 and the Behavioural Approach System (BAS: Carver & White, 1994) sensitivity. Reduced P3 amplitude has also been associated with treatment outcome; Wan, Baldridge, Colby, & Stanford (2010) found reduced P3 amplitude at Pz in those who did not complete treatment.

1.0.2 Time-frequency Introduction

Event related potential (ERP) techniques are based on the assumption that averaging across a set of epochs around the same type of event will produce a discrete ERP signature, whilst averaging out the noise contained within the EEG data. However this only provides part of the picture, the noise actually contains dynamic information thought to reflect ongoing neural processes which are reflected in the changes in levels of oscillatory activity. Frequency analysis can measure activity that is not phase locked but is still event-locked; this method allows examination of what happens within individual frequency bands in response to a particular event. Increases (also called event-related synchronization, ERS) and decreases (event-related desynchronization, ERD) within a frequency band in response to an event are thought to reflect an increase or decrease in the synchrony between neuronal populations (Pfurtscheller

& Lopes da Silva, 1999). Oscillatory activity measured by frequency analysis is thought to reflect the activity and communication between areas of the brain. It is too simplistic to assign particular processes to particular frequency bands but there are indications that certain frequencies are more prevalent at certain times. For example pre-stimulus alpha activity (approximately 10Hz) may represent temporal expectancy of an upcoming event (Min et al., 2008). More relevant to the current research are the data concerning oscillatory activity related to reward processing; Marco-Pallares et al. (2008) proposed that beta oscillatory activity (between 12 and 30Hz) during a gambling task, is associated with the processing of monetary gains (including the magnitude of these gains) and the activity of the multiple systems involved in reward processing. In the same task theta activity (4 - 7Hz) was associated with a medial frontal negativity (MFN) and negative feedback or monetary losses.

As previously discussed, frequency changes in EEG data may reflect communication between multiple cognitive systems. Event-related oscillations may reflect sensory and cognitive functions (Basar, Basar-Eroglu, Karakas, & Schrmann, 2001) whilst resting-sate oscillations may provide a window into the communication between brain areas and also into differences between populations (e.g. levels of addiction). Analysis of spontaneous fluctuations in brain activity using functional magnetic resonance imaging (fMRI) have revealed insight into the functional architecture of the brain, variability in behaviour and potential physiological correlates of neurological and psychiatric disease (Fox & Raichle, 2007). More specifically increased EEG beta

power has been suggested as a marker for the risk of developing alcoholism in the offspring of alcoholics (Rangaswamy et al., 2004) whilst the distribution of power between frequency bands (mainly alpha and beta) can differentiate between heroin abusers and healthy controls (Polunina & Davydov, 2004).

To analyse the mean power changes following the presentation of a cue we calculate the event-related spectral perturbation (ERSP), a measure of the mean (across trials) event-related changes over time. EEGLAB provides a number of options for calculating this including the Fourier transform, wavelet transform or a Slepian multitaper decomposition. In the current work we use only the first two, for the event-related frequency data we use a complex Morelet wavelet decomposition, in which the number of cycles increases with the frequency. This type of transform begins with a mother wavelet such as the Morelet which is scaled (widened or tightened) and translated (moved in time). The scaling represents the frequency information; the translational factor contains the time information. As the wavelet is moved across the EEG data it is compared to the actual data, if the scale matches the data then it produces a large value at that time point. To visualise the data we subtract the mean baseline log power from the spectral estimate and plot it as in figure two. For the resting data we use a Fast Fourier Transform (FFT) as we are not interested in the time course of the frequency bands, only average power, and this type of analysis does not consider the time-course (Akin, 2002). In FFT decomposition the EEG signal is divided into its sinusoidal (frequency) components. According to Delorme & Makeig (2004) these decompositions provide similar

results and this has been borne out in our own data using both methods.

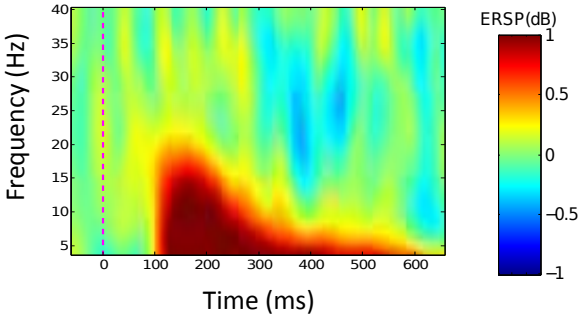


FIGURE 1.2: An example Time-frequency plot, with the mean baseline values subtracted from the power values post cue (zero ms). We see a general increase (shown in red) in the ERSP across theta, alpha and low beta frequencies between 100 and 300 ms. We then compare the mean power values for a particular frequency following different types of cue.

Oscillations within the brain may provide a way of understanding the way in which neurons within the brain interact during cognitive processes (Basar, Basar-Eroglu, Karakas, & Schrmann, 2001; Freeman, 1998). Frequency analysis may therefore provide a useful method of examining the neural basis of PIT as a range of brain regions have been implicated in the mediation of pavlovian and instrumental behaviours.

A range of frequency bands have been implicated in cue-processing with greater alpha at frontal locations following appetitive (food-related) pictures (Gable & Harmon-Jones, 2008), beta modulation following monetary rewards (Marco-Pallares et al., 2008) and according to the behavioural relevance of a cue (Williams, 2003).

Alpha band activity has traditionally been thought of as the idling rhythm (Miller, 2007) and there has been some research showing

that it may relate to the default mode network identified in fMRI research (Knyazev, Slobodskoj-Plusnin, Bocharov, & Pylkova, 2011). Desynchronization of alpha is usually seen following stimuli presentation and is thought to signal engagement. There is also evidence that alpha may play a role in a number of processes including memory, sensory responses and motor processes (Basar, Schürmann, Basar-Eroglu, & Karakaş, 1997)

Frequency measures may provide a useful measures of a number of problems related to addiction. Firstly alpha has been suggested as a marker for disorders such as depression (Allen & Cohen, 2010) and addiction (e.g. Knott, 2001). Beta has also been implicated in the genetic basis of addiction (e.g. Ehlers & Schuckit, 1990)and there is also a range of evidence linking frequency measures, addiction and individual differences such as impulsivity (e.g. OGorman & Lloyd, 1987) and craving (Davidson, 2004). Finally there is a possible link between resting EEG and reward or cue processing, as addicted individuals are thought to over-value drug-related cues and rewards, an EEG marker for this would be of great interest. These areas of research will be discussed in more detail in the relevant chapters.

1.0.3 Plan

Artifact detection comparison

Initially we will investigate a number of methods for the detection and removal of artifacts from our EEG data. These types of data are inherently noisy, with artifacts caused by external sources, blinking, muscle movements and a variety of other sources. As with most

neuroscience techniques prevention of artifacts during the recording of data is better than later removal but some level of noise is inevitable.

Concurrent choice To investigate the preferences of smokers we will use a concurrent choice task in which participants choose between two instrumental responses to win either cigarette or chocolate outcomes. It is hoped that this paradigm, in conjunction with EEG, will provide a measure of the hypothesised hyper-valuation of drug-related rewards seen in addicted individuals.

Pavlovian to Instrumental Transfer The PIT task will be used to investigate the effect of Pavlovian cues on an instrumental behaviour. This task will allow us to separate the mechanisms involved in drug-seeking behaviour and understand the important role played by external cues in the maintenance of addictive behaviour. We will attempt to identify an EEG component, which codes the magnitude of the PIT effect, and therefore a neural signal which could then be used in the development of therapies and identification of those at risk of addiction. A range of modifications to the PIT paradigm will be tested to see if the specific PIT effect is present with pictorial and arbitrary cues, and also whether the effect is susceptible to extinction.

Resting EEG Resting EEG data will be collected before and after each of the other experiments to see how the resting EEG oscillations of smokers relate to addiction level, individual differences and cue responsivity.

Chapter 2

The rejection of artifacts in EEG data

2.0.4 Abstract

EEG records the electrical activity of neurons in the brain using electrodes placed on the scalp. The indirect nature of this recording means that the data contains a large number of artifacts from a variety of sources, including eye blinks, muscle movements and outside sources. Separating the task-related signal from this noise is one of the key problems in the use of EEG techniques to probe neural responses. Traditionally fairly basic methods have been used in conjunction with the expectation that ERP methods will average out the non-task-related electrical activity. This assumption is not necessarily correct as some of the noise may be locked to experimental events of interest. For example a participant may blink at set points during a task, if we then average across trials using a window locked to an experimental event such as the presentation of a stimulus or a response; any artefact which regularly occurs along with

this event will be included in our average. To combat this problem and enable more sensitive analyses (such as single-trial analysis of EEG data) more complex artifact detection methods have been proposed. This chapter will discuss some of the options available and also the development of the processing pipeline used for the experiments presented in this thesis.

2.0.5 Introduction

The signal recorded in EEG experiments is extremely small and easily masked by artifactual noise; the challenge is to remove artifacts from the data without losing signal. EEG data contains artifacts from many sources such as eye movements, blinks, cardiac signals and external sources such as electricity supply and magnetic fields. The last two can be avoided or attenuated by band pass-filtering and careful shielding of the EEG recording room. However the artifacts produced by the participant, such as cardiac and movement artifacts, are more difficult to avoid and require some post-processing to separate the artifact from the signal of interest. This chapter will begin with a short review of some of the available methods for artefact detection and removal in EEG data before discussing the development of the methods used for the experiments presented in this thesis.

Traditionally EEG data is collected and analysed by extracting epochs of the EEG data which surround events of interest and averaging them to create ERPs. If we assume that the signal of interest will be locked to these events but the noise will not then the method should remove much of the noise. Unfortunately this assumption is not always correct, for example eye blinks and other artifacts can be locked to the events of interest and may be magnified by the averaging process. Stecker (2002) showed that the effects of averaging, to produce ERPs and remove noise, are sensitive to the type of noise. For example; short, infrequent, high-amplitude noise was shown to reduce the signal-to-noise ratio (SNR) significantly. One method for excluding this type of noise is to use a threshold, data which exceed

this threshold are then rejected. This allows automatic artifact rejection and therefore reduced processing time. However Stecker (2002) cautions that in certain situations this can bias the results so that the SNR is in fact lowered rather than improved. To alleviate this problem they suggest careful monitoring of the data rejection levels. Similarly Delorme, Sejnowski, & Makeig (2007) tested thresholding methods on semi-simulated data. They concluded that these types of method were most effective when used on ICA data, as opposed to raw data.In a comparisn of methods they found that conducting thresholding on ICA data was more sensitive than on the raw data. In addition simple thresholding may miss muscle artifacts or smaller eye blinks as it generally uses lower-order statistics such as minimum and maximum (Delorme et al., 2007).

Gratton, Coles, & Donchin (1983) describe two general strategies for the removal of eye artifacts; the first is to simply reject those trials in which there are artifacts, this leads to an unacceptable loss of data and potentially bias in the remaining data. The second is to correct for the artifacts using one of the many available procedures. Gratton et al. (1983) review correction by subtraction in the frequency and time domains but perhaps of more relevance here are the methods that model the artifactual components within the EEG data. These can also be divided into two types: those that attempt to localise the generators of the artifacts and those that use decomposition methods to separate the artifacts from the EEG signal (Joyce, Gorodnitsky, & Kutas, 2004). Those that use localisation techniques are hampered by the fact that there is no unique solution to the inverse problem (the problem of identifying the brain sources

that give rise to a particular scalp potential) and that EEG has very poor spatial acuity. The second group of techniques decomposes the data without reference to a particular source model and so avoids the pitfall of the localisation methods. The two main decomposition methods are Principal Component Analysis (PCA) and Independent Component Analysis (ICA; Bell & Sejnowski, 1995). PCA attempts to orthogonally translate the data into its uncorrelated principle components. The components are ordered such that the first component accounts for as much variation in the data as possible. The problem is that the components may not be orthogonal; for example a blink component and a frontal EEG signal source may be highly correlated (Joyce et al., 2004). These methods have been gaining favour as they offer the chance to remove artifacts without removing large swathes of data. ICA is often explained with reference to the cocktail party analogy where a person attempts to separate the voice of someone they are speaking to from the surrounding noise. ICA seeks to separate the EEG data into maximally independent components, similar to the individual voice of the person at a party. Some of these components will represent artifactual activity caused by muscular movements, eye blinks, line noise etc. which we wish to eliminate from the dataset.

ICA is the decomposition of a linear mixture of unknown sources within the brain (Hoffmann & Falkenstein, 2008a). The sources and mixture are unknown and so are estimated. ICA assumes that the sources are statistically independent but the mixture is not. An

assumption that is thought to be plausible as different cortical areas are spatially and functionally separated (Makeig, Debener, Onton, & Delorme, 2004). With regards to artifact correction, ICA is usually used to identify artifactual components which resemble eye blinks, movements etc. These components are then removed and the remaining components, which hopefully represent the signal of interest, are projected back onto the data. ICA has the advantages that it does not rely on any information about head geometry or electrode locations to produce sources of signal with different time courses and dipolar scalp maps, these components often resemble more traditional EEG signals but have the advantage of better spatial resolution and higher signal-to-noise ratio (Makeig et al., 2004).

ICA has been shown to be an efficient method for the removal of artifacts in a number of studies (see Delorme, Sejnowski, & Makeig, 2007 & Makeig, Bell, Jung, & Sejnowski, 1996). Recently ICA was shown to yield almost perfect correction of eye-blinks in comparison to an eye movement correction procedure (EMCP) although the authors note that the complexity of data processing required to use ICA is a disadvantage (Hoffmann & Falkenstein, 2008b). Also enough data must be available for the algorithm to work effectively. More recently researchers are beginning to combine ICA with other methods such as empirical mode decomposition (Lindsen & Bhattacharya, 2010a) to maximise the amount of data that can be retained whilst selectively removing artifacts. Another recent development is the use of toolboxes to enable automated detection of artifactual ICs which decrease the labour, and error, involved in manually selecting components for rejection. These will be discussed

in the following section.

2.0.6 Development of the pipeline used in this thesis

The data discussed here were initially analysed in Netstation, the proprietary software provided by EGI (Electrical Geodesics Inc.), however the built-in artifact detection algorithms proved to be unsatisfactory as they resulted in the loss of a great deal of data and many participants. We then experimented with a range of artefact correction methods. First using thresholding methods implemented in EEGLab (Delorme & Makeig, 2004) whereby epochs of data were removed if they exceeded certain thresholds. This method makes sense when we remember that most artifacts are of much larger amplitude than the actual EEG signal of interest. However the two main problems with this approach are that the thresholds used tend to be arbitrary in nature, either relying on previous studies, default values or examination of the data. None of these methods are ideal, and even if they were satisfactory the technique would still lead to rejection of whole epochs. Instead, a system whereby artifacts are removed without removing whole epochs or participants (unless necessary) is preferable. Independent Component Analysis (ICA) is one method which may allow such an approach. ICA was run using the Binica algorithm, implemented in EEGLAB to identify blink and muscle artefacts which were then rejected manually for each subject. Running ICA produced 128 components which were manually

checked and rejected. During the final stage of pre-processing unlikely data epochs were rejected based on the EEGLAB joint probability function (which rejects data based on standard deviation), the data were then average referenced, bad channels were identified and then replaced using an EEGLAB-based spherical spline interpolation algorithm (Perrin, Pernier, Bertrand, & Echallier, 1989).

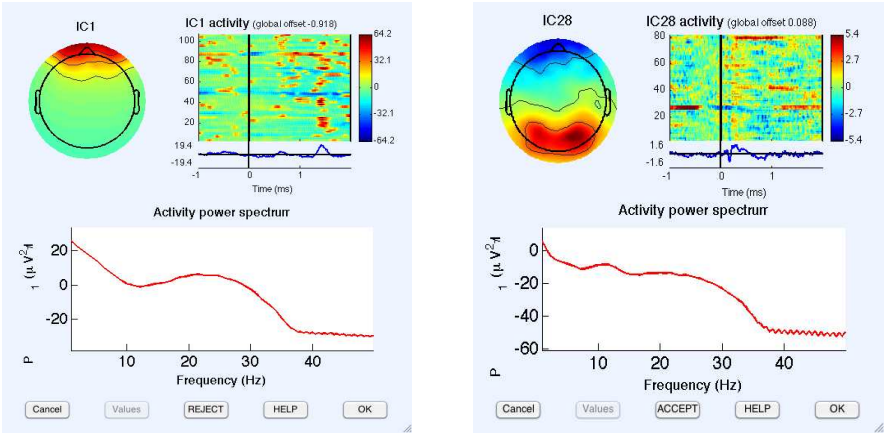
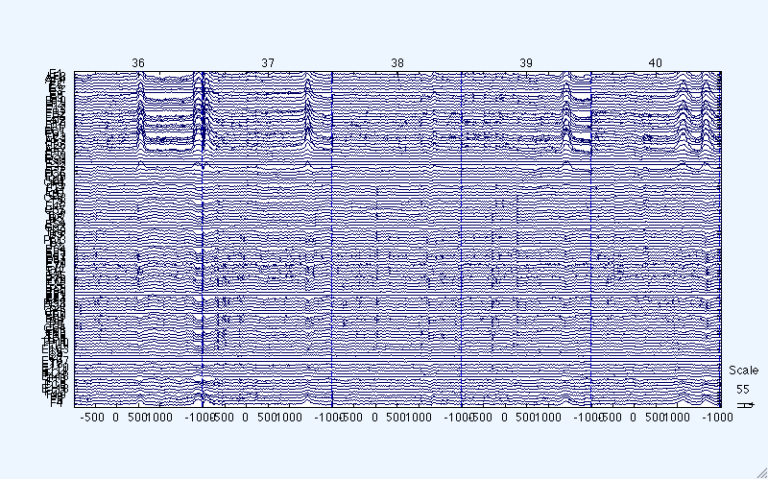


FIGURE 2.1: Example ICs from a single participant: IC1 (left) is a likely blink component with frontal activity shown on the topo plot, individual blinks can be seen on the activity spectrum. IC28 (right) is shown for interest only, it shows a component with activation mainly in parietal regions, an ERP which resembles a P1 followed by a P3 and similar activations across most trials indicative of a neural response.

Whilst this method allows us to keep much more of the data after artefact rejection, it required a great deal of time. For each subject all ICs were examined and those identified as artifacts were marked for rejection. This procedure also has the disadvantage that the identification of which ICs are artifactual is subjective and relies on experimenter experience. It was for these reasons that I finally adopted a plug-in for EEGLab produced by Hugh Nolan aptly named Fully Automated Statistical Thresholding for EEG

(FASTER). This set of functions has the advantage that identification of the artifactual ICs is conducted automatically based on z-scores. The values used for these thresholds were tested on both simulated and real data, using a variety of electrode arrays. The FASTER method was also compared to supervised artefact identification by experts and another method called Statistical Control for Dense Arrays of Sensors (SCADS). FASTER was found to outperform both methods on most measures with much better detection of contaminated data than SCADS and less variability than expert supervision of the data rejection.



To summarise the correction process used by FASTER; bad channels and epochs are rejected according to their deviation from the mean, variance and amplitude range. FASTER then uses Principle Component Analysis (PCA) to reduce the total number of components according to the quantity of data available. ICA is then used to identify the artifactual components, ICs are rejected if they are outliers (defined as having a z-score of +/- 3), these bad ICs are then subtracted from the data. Finally any rejected channels are interpolated.

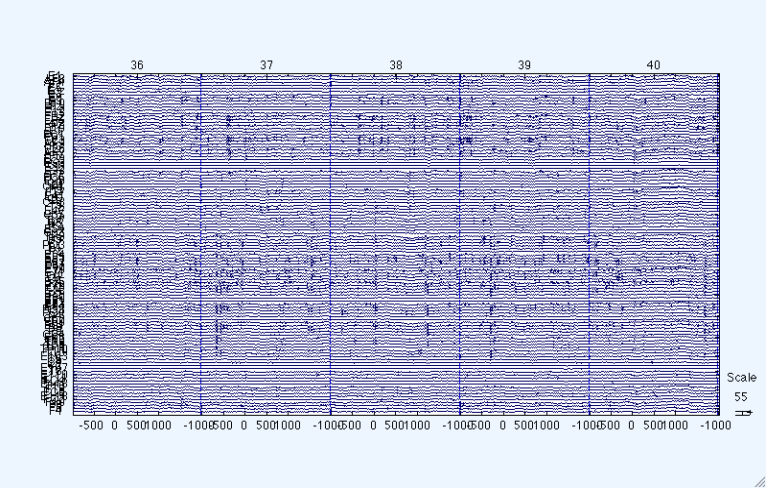


FIGURE 2.2: Epoched data prior to (top) and after (bottom) removal of artifactual ICs. Note that in the top panel there are six separate blinks, which have been removed in the bottom panel where the data is greatly improved.

Figure 2.2 demonstrates how by using ICA we can retain much more data than most common thresholding methods of artefact rejection. For example in Netstation all but one of the epochs would have been rejected due to the blink artifacts, which incidentally mainly affect a small number of electrodes; most of which would not be included in our analysis. By using ICA we may retain all of these epochs whilst removing the blink artifacts.

The pre-processing steps shown in figure 2.3 were initially implemented using my own custom scripts, however at a similar time Hugh Nolans lab developed FASTER. This allowed for the same pre-processing steps but with some extra options; previously artifactual ICs had been rejected by eye; a time-consuming and subjective process. The new toolbox allows batch processing with automatic rejection of ICs. Of the steps shown in figure 2.3; steps 2 to 5 can be automated using the FASTER toolbox. The initial processing of raw data and the frequency analyses were completed using custom

scripts incorporating EEGLab functions. The ERPs were initially computed using my own scripts but later using ERPLab (a toolbox designed by Steve Luck and Javier Lopez-Calderon at the University of California: Center for Mind and Brain).

2.0.7 Conclusion

The aims of this chapter were to introduce some of the methods for the detection and removal of artifacts from EEG data and outline the development of the processing pipeline used for the data presented in this thesis. The most effective method for improving the SNR is to minimise artifacts in the first place by using the best equipment, well shielded rooms and minimising movement, but however careful we are there will always be artifacts within EEG data. The challenge is to find the best possible method for removing the artifacts without removing the signal of interest. In order to do this we must balance the performance of the technique with the speed of computation (Delorme et al., 2007).

The methods used for the analysis of the data reported here are certainly much better, both in removal of artifactual noise and in the cost of computation, than the results of using proprietry software or more basic techniques. There are a number of studies demonstrating the effectiveness of ICA (e.g. Hoffmann & Falkenstein, 2008a; Jung et al., 2000; Makeig et al., 1996) and FASTER (Nolan et al., 2010b) but there is no doubt that they could be improved upon. For example even using methods such as ICA we are still likely to remove

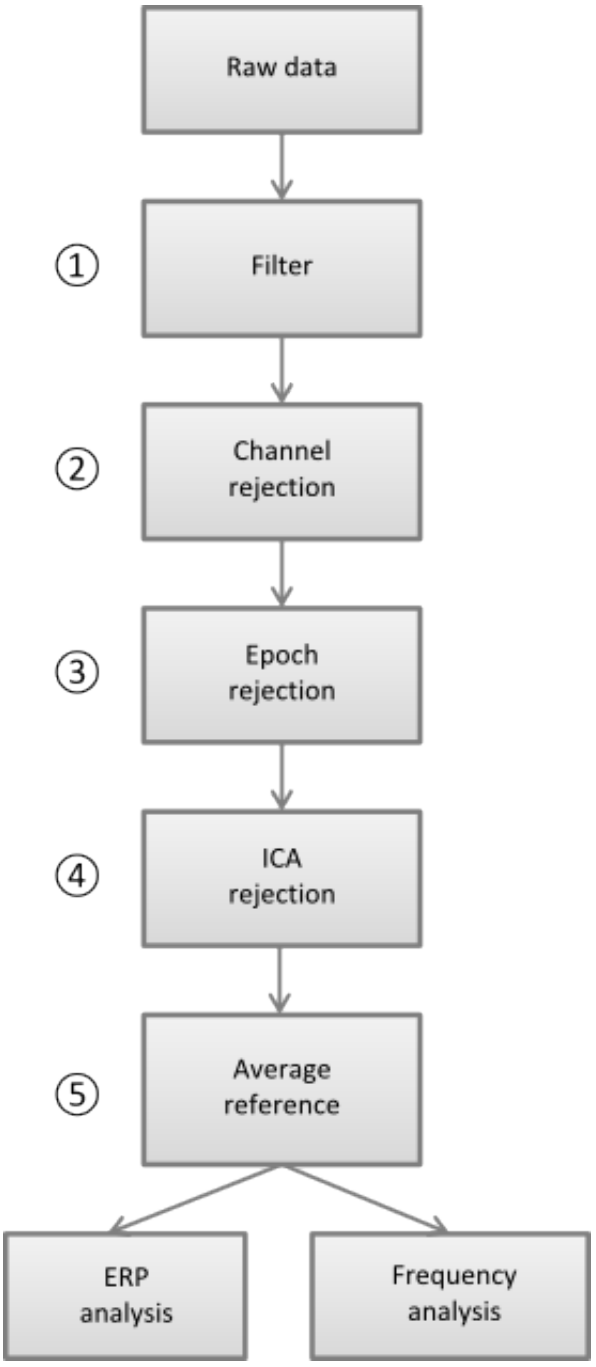


FIGURE 2.3: A flowchart showing the steps involved in preprocessing of the EEG data from raw data to statistical analysis. Steps 2-4 were performed using Nolan, Whelan, & Reilly, 2010b FASTER toolbox. The other stages of processing were completed using custom scripts and EEGLab functions.

some signal contained in the ICs marked as artifacts. New methods are being developed regularly, for example a couple of recent studies have demonstrated better SNR using other methods. Lindsen & Bhattacharya (2010b) combined ICA and Empirical Mode Decomposition (EMD) to maximise the SNR whilst removing eye blinks. EMD allowed the separation of the signal contained in predominantly artifactual ICs from the noise. Unlike Fourier or wavelet transforms of the data EMD is entirely data-driven and separates the oscillations based on their time scales. Secondly, Kierkels, Van Boxtel, & Vogten (2006) compared a number of algorithms designed to remove eye movement artifacts on simulated data produced using a realistic model of the human head and eye-tracking data. Their analysis showed that most methods including PCA and FastICA removed most of the artifact but other methods produced even better results. The authors recommended using the SOBI algorithm as it provided the best artifact rejection rate. This was however only concerned with eye movements so results may be different with other types of artifact.

In conclusion artifact rejection is evolving and we should continue to assess the available methods, compare them and use the most effective technique available. This may be dependent on the set-up used, the experimental design and the intended analysis. The methods chosen for the experiments presented here represent the best compromise between maximising SNR and automatizing the work involved. They are specific to the EEG set up and experiments used here.

Chapter 3

Identifying a neural measure of the value ascribed to drug rewards by smokers.

3.0.8 Abstract

Addicted individuals show a hyper-valuation of drug-related outcomes (Hogarth & Chase, 2011) which can be investigated using concurrent choice paradigms to measure the value assigned to drug related outcomes. By identifying differences across levels of addiction this approach may provide insight into the development of addiction. Our objective is to further understanding of the neural basis of the preference for drug-related outcomes in addicted individuals using EEG techniques; specifically the P3 ERP component and frequency measures, to index the reinforcement value of drug and non-drug outcomes. Daily and non-daily smokers completed a concurrent choice task which assessed their preference for either

cigarette or chocolate outcomes. EEG data were collected during the task. The P3 amplitude was larger to win than no-win outcomes, perhaps reflecting an element of outcome evaluation. Similarly low beta power was higher for chocolate win, than cigarette win outcomes. Further work is needed to reveal a signal which codes the value of an outcome, specifically the hypothesized hyper-valuation of drug outcomes by addicted individuals.

3.0.9 Introduction

To effectively treat addiction it is important to understand the behavioural processes and learning which lead from casual to compulsive drug use. Current addiction theory suggests two potential mediating processes; goal directed drug seeking where behaviour is mediated by a mental representation of the drug as an outcome, and habitual drug seeking where behaviour is elicited by drug paired cues, without representation of the outcome. It has been suggested that drug seeking is initially driven by knowledge about the desired outcome (the effects associated with the drug) but over time the behaviour becomes automatic and the initiation of drug seeking requires only the presence of drug-related stimuli (e.g. Tiffany, 1990). This is the point at which the drug-user loses control over drug seeking and is considered one of the key symptoms of addiction by the Diagnostic and Statistical Manual of Mental Disorders (DSM) -IV.

An individuals propensity to develop an addictive behaviour may be determined by the sensitivity of their reward systems to drugs, a so called reward hyper-sensitivity (Robinson & Berridge, 1993) whereby the drug reinforces and strengthens the link between drug-related stimuli (S), responses which gain drugs (R) and the drug effect (O). This results in a greater valuation of drug related Ss in comparison to non-drug related Ss in vulnerable individuals. Behavioural research has utilised the idea that the value of a drug reward is considered to be reflected in the amount of work or money an animal will expend to obtain it (Bickel, Hughes, Degrandpre, Higgins, & Rizzuto, 1992; Hursh & Silberberg, 2008; Skinner, 1932). This is thought to provide an indication of the value assigned to

a particular instrumental behaviour and its learned outcome. The difficulty has been in finding a pure measure of the value of a reinforcer; initially efforts focused on response rate but subsequent research demonstrated that this measure can be affected not only by the value of the reinforcer, but also by changes in reinforcement schedule (Hursh & Silberberg, 2008).

MacKillop et al. (2008) used a measure called the Cigarette Purchase Task (CPT) to assess the reinforcing effects of nicotine in smokers. As the price of cigarettes increased, consumption decreased, demonstrating cost affectation of the instrumental response. Previous work by Bickel et al. (1992) compared the reinforcing effects of cigarettes and coffee by changing the number of responses required to elicit the concurrently available outcomes (coffee and cigarettes). Coffee consumption decreased along with cigarette consumption when the price of cigarettes increased. However when the price of coffee increased, the consumption of coffee decreased, but consumption of cigarettes did not change. This research suggests that the value of a drug is less susceptible to devaluation in addicted individuals.

Herrnstein (1961) proposed a relative measure in which two or more reinforcers are compared in a simple choice condition and are then assessed in strength, relative to the strength of the other reinforcer. This approach has since been used to investigate the value of drug reinforcers, relative to non-drug reinforcers, in addicted individuals, and has shown that the choices made in concurrent choice tasks are correlated with dependence level. For example Perkins et al. (2002)

allowed participants to choose between two nasal sprays, one containing nicotine and the other a placebo. Their choice of the nicotine spray over the placebo predicted their likely withdrawal severity and how quickly they would subsequently relapse after quitting, suggesting that this type of measure may provide a clinically relevant measure of addiction severity. Further evidence was provided by a recent study which correlated cocaine addicts preference for viewing cocaine-related pictures, over neutral and unpleasant pictures, with level of recent cocaine use (Moeller et al., 2009).

A small number of studies have modelled addiction-like behaviour in rats by repeatedly administering cocaine over a period of time and then attempting to devalue that behaviour through simultaneous administration of punishment or aversive stimuli. Continued drug seeking in the face of punishment is thought to reflect the excessive value placed on the drug. Rats with an extended history of cocaine self-administration showed perseveration of the drug seeking behaviour in the presence of aversive stimuli (Vanderschuren & Everitt, 2004). This was not shown in rats with shorter histories of cocaine self-administration or in a control group of rats administered with sucrose solution for an extended period. Deroche-Gamonet, Belin, & Piazza (2004) found a similar effect; rats with an extended period of drug self-administration showed greater resistance to punishment (a foot shock), but this was only present in a sub population of the rats. More recently Pelloux, Everitt, & Dickinson (2007) found similar results with only a sub population of the rats who received extended administration of cocaine showing resistance to punishment. This provides a promising approach for human drug

addiction as it models the DSM-IVs criteria for addiction; compulsive drug seeking despite adverse consequences.

Whilst there seems to be strong evidence of a preference for drug-related outcomes between addicted and non-addicted groups, there has been less work investigating whether this preference exists between levels of dependence in humans. However there is evidence that the level of brain activity in cocaine addicts (measured by fMRI) when viewing cocaine-related stimuli is correlated with relapse rates (Kosten et al., 2006). Similarly McClernon, Kozink, & Rose (2008) found that nicotine dependence level was positively correlated with activation of regions which are commonly associated with dependence and reward, such as the OFC, when viewing smoking related pictures. Interestingly those participants who scored lower on dependence measures showed activation of different areas while viewing the same pictures, such as the fusiform gyrus and parahippocampul gyrus, areas which are implicated in face processing and attention but not the processing of rewards. The authors suggest that this disparity may mean that in less addicted individuals smoking-related pictures elicit smoking-related memories but do not necessarily guide behaviour towards consumption, as in the more highly addicted individuals.

The neural basis of the behavioural bias for drug-related stimuli shown by addicted individuals has also been investigated with EEG techniques, although the components focused upon differ between studies, probably due to the type of paradigm and stimuli used. Franken, Stam, Hendriks, & Van den Brink (2003) compared the slow positive wave (SPW) of abstinent heroin addicts and healthy

controls whilst viewing heroin-related and neutral pictures. The SPW of heroin addicts was larger to heroin-related than neutral pictures, and also correlated with reported craving. The SPW of the controls was the same for both types of picture. The heroin addicts showed different processing of drug-related stimuli to controls, as well as craving which suggests that the SPW component may reflect the motivational significance of the stimuli. A later study obtained similar findings in smokers (Littel & Franken, 2007). The event-related potentials (ERPs) of smokers, ex-smokers and never-smokers were compared when viewing smoking-related and neutral pictures. The P3 and SPW components were enhanced to smoking-related pictures in the smokers group but not in the other two groups, suggesting that a bias in the processing of smoking-related stimuli is only present in current smokers. This was also correlated with later craving in the smoking group.

The P3 is sensitive to the probability of an outcome and also the recent outcome history (Kopp & Wolff, 2000). It is also influenced by the motivational significance of a stimuli (Nieuwenhuis, Aston-Jones, & Cohen, 2005), so drug-related stimuli may elicit a larger P3 than non-drug related stimuli in addicted individuals. Lubman et al. (2009) found that heroin addicts showed less arousal and decreased P300 arousal when viewing pleasant stimuli but increased arousal and P3 (compared to controls) when viewing drug-related stimuli. Lubman et al. (2009) suggest two potential theoretical explanations, the first that drug-users develop higher reward thresholds for natural rewards following repeated exposure to a drug and its perceived rewards. The second is the incentive sensitization theory (Robinson &

Berridge, 1993) of addiction whereby the neural reward system becomes sensitized to drug cues which acquire incentive value through repeated pairing of stimulus and outcome.

Ramsey & Finn (1997) found a reduced P3 component in men with a family history of alcoholism in response to both reward and non-reward outcomes, whilst controls showed an increased P3 to the reward trials. This evidence suggests that the P3 may be sensitive to rewarding outcomes but is reduced in the offspring of those with alcoholism. Similarly Anokhin et al. (2000) tested a large sample of current, ex- and never-smokers on a visual oddball task; only the current smokers showed reduced P3, which was also associated with family history of alcoholism. The authors suggest that the reduced P3 may be attributed to either long-term smoking producing a reversible change in brain function or that the P3 may be a marker for risk of nicotine dependence. Interestingly the link between the risk for alcoholism and reduced P3 amplitude may be moderated by smoking status (Polich & Ochoa, 2004). More recently Goldstein et al. (2008) demonstrated reduced P3 to monetary reward in cocaine addicts, suggesting that the P3 may serve as a marker for addiction, and more generally a deficit in the processing of outcomes. Similarly Guney, Genc, Kutlu, & Ilhan (2009) found reduced P3 and N1 amplitude in smokers to an auditory oddball task suggestive of cognitive dysfunction.

This study aims to further our understanding of the neural basis of this preference for drug-related outcomes using ERPs and frequency measures to index the reinforcement value of drug and non-drug outcomes. The comparison of these measures following the outcome of

cigarette and chocolate seeking may allow differentiation of reward hypersensitivity from drug specific sensitivity, a distinction not possible unless two appetitive rewards are used, as well as a measure of drug seeking rather than Pavlovian responding, as seen in previous studies. The study utilises a concurrent choice paradigm where subjects respond for cigarette or chocolate outcomes presented on a fixed 50/50 reinforcement schedule to enable investigation of the processing of drug-related versus non-drug related outcomes. The concurrent choice design allows comparison to animal models of behavioural economics and reinforcement value. We aim to improve on previous work by contrasting reinforcement value across levels of dependence rather than comparing addicted individuals with controls; this will provide more information concerning the development of addiction.

As the time-frequency components related to this type of task have not been widely studied we will adopt an exploratory approach to the analysis. After examination of the spectral data, the theta, alpha and beta bands will be analysed for each type of trial. Alpha has been implicated during a large range of processes including memory, sensory processing and motor preparation (Basar, Basar-Eroglu, Karakas, & Schrmann, 2001) and is usually suppressed during the expectation of an event (Lima, Singer, & Neuenschwander, 2011). The latter study also found an enhancement within gamma power with the ratio between the two hypothesised to control information flow in the brain during memory tasks (Jokisch & Jensen, 2007). Similarly Knyazev & Slobodskoy-Plusnin (2009) found increased frontal theta and high frequency oscillations in those with

high scores on the behavioural approach system (BAS) scale, during expectation of reward. The reverse was found in low BAS scorers. The authors suggest that theta reflects the level of emotional arousal, and the high frequency oscillations reflect general cortical excitability. We predict that the amplitude of the P3 component in daily smokers will be lower than that of non-daily smokers to chocolate rewards and higher for cigarette rewards, demonstrating a sensitivity specific to drug-related rewards. It is anticipated that the P3 will correlate with measures of dependence, and therefore provide a diagnostic of dependence level. The behavioural data are predicted to show a corresponding preference, in daily smokers, for the cigarette key over the chocolate key.

3.0.10 Methods

Participants

32 participants (16 females, mean age = 22.8, sd = 3.17, mean number of years in education = 15.9, sd = 2.24) were recruited by email and poster adverts. Nine participants were excluded as they did not show contingency knowledge, the results below are for the remaining 23 participants. All were right-handed and had normal or corrected to normal vision, they received £15 inconvenience allowance. Participants were excluded from the study if they had consumed alcohol or drugs (within 12 hours), sleeping pills (within 48 hours) or antidepressants. Procedures were in accordance with the declaration of Helsinki and were approved by the University of Nottingham Ethics committee. All participants provided written and informed consent.

Apparatus

The experiment was programmed using E-prime software (E-Prime Psychology Software Tools Inc., Pittsburgh, USA) and displayed on a 15-inch monitor. Four metal containers were positioned in front of participants; one contained the cigarette rewards (10 Marlboro Lights Cigarettes; Tar 6mg, Nicotine 0.5mg), another the chocolate rewards (10 Cadbury Dairy Milk treat size bars; 15g with four chunks per bar). The two remaining tins were empty but labelled "Your cigarette box" and "Your chocolate box" respectively. The breath carbon monoxide levels of participants were measured at the commencement of the experiment using a Bedfont Smokerlyzer (Bedfont Scientific Ltd. UK).

Following the behavioural section of the experiment participants were questioned on their smoking history and then completed a battery of questionnaires which included the following measures; DSM-IV tobacco dependence criteria, the cigarette dependence scale (CDS-5; Heatherton, Herman, & Polivy, 1991), the Questionnaire of Smoking Urges (QSU-Brief; Cox, Tiffany, & Christen, 2001), Alcohol Use Questionnaire (AUQ; Townshend & Duka, 2002), the BIS-11 (Patton, Stanford, & Barratt, 1995), the Fagerstrm Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) and the Zuckerman sensation-seeking scale (Zuckerman, Kolin, Price, & Zoob, 1964). Please see the methods section of chapter seven for more detail on these measures.

Design and procedure

The participants were seated approximately one metre in front of a computer monitor. The experiment was presented using E-prime software (E-Prime Psychology Software Tools Inc., Pittsburgh, USA).

The EEG phase of the experiment began with a four-minute baseline period where participants were asked to sit with their eyes open until they heard a tone (administered through Sennheiser CX300 in-ear headphones) at which point they closed their eyes until they heard another tone. An identical baseline period followed the trials described below and will be analysed seperately.

The study utilised a concurrent choice paradigm in which participants were told that they are playing a game in which they should imagine winning cigarettes and chocolates. In each round 1/4 of a cigarette or 1/4 of a chocolate was available but they would not be told which. They should choose either the D or H key in each round to try and win the reward. The outcome associated with each key (either cigarettes or chocolate) was counterbalanced across participants. There was a 50% chance of each outcome and the trial type was replaced after selection.

On each trial participants fixated on a cross (2000 ms), followed by an instruction to select a key (instruction remains on the screen until a key is pressed), after selection there was a jittered interval of between 2000 and 4000 ms, before the outcome was displayed; either "you have won 1/4 of a cigarett" , "you have won 1/4 of chocolate" or "you have won nothing" (displayed for 1000ms). There was a random ITI of between 500 and 1000 ms.

There were 360 trials in total with 5 equal blocks of 72 trials. At the end of each block participants were provided with totals and asked to swap the number of chocolates and cigarettes that they had won into their tin. Participants were informed prior to the experiment that they would not keep their winnings in the game. At the end of the trask participants were asked "Which key won cigarettes?". If they answered incorrectly they were judged to not have contingency awareness and were removed from the analysis.

EEG methods and analysis

The EEG data was recorded from 128 sites at a 250Hz sampling rate using an (Electrical Geodesics Inc., Eugene, OR, USA) dense-array EEG system (GES 200 net) and a Net Amps 200 amplifier. Electrode impedences were kept below 50 k. The raw data was exported from Netstation to EEGLAB (a Matlab toolbox designed by Delorme & Makeig, 2004) for processing where all subsequent analysis was performed using purpose-written scripts that utilized EEGLAB functions. The data were low and high pass filtered (0.1-35Hz) and epochs were extracted according to trial type, with a 200ms pre-outcome baseline and a 2000ms post-outcome window. Outcome-locked ERPs were segmented to create the following trial types:

1. Cigarette win — cigarette trials where the cigarette key was selected.
2. Cigarette no win — cigarette trials where the chocolate key was selected.
3. Chocolate win – chocolate trials where the chocolate key was

selected.

4. Chocolate no win – chocolate trials where the cigarette key was selected.

Artifact correction was applied using the Fully Automated Statistical Thresholding for EEG artifact rejection (FASTER) plug-in for EEGlab (Nolan, Whelan, & Reilly, 2010). To summarise the process, bad channels and epochs are rejected according to their deviation from the mean, variance and amplitude range. FASTER then uses Principle component analysis to reduce the total number of components according to the quantity of data available. Independent component analysis (ICA) is then used to identify the artifactual components, which are rejected. Finally any rejected channels are interpolated.

ERP analysis. Individual subjects data were then averaged across a window of 250-550ms post cue for each event type and for frontal (Fz), central (Cz) and parietal (Pz) electrodes. For information on the corresponding electrode positions according to the 10-10 system please refer to Luu & Ferree (2000).

Frequency Analysis. Time-frequency analyses were conducted using the EEGLab function newtimef(). Event-related spectral perturbations were computed for epochs from -200 to 800 ms relative to cue presentation using wavelets (Makeig, 2004) and the following code: [ersp,times,freqs] = pop_newtimef(EEG, 1, 6, [-200 792], [1 0.5] , 'topovec', 6, 'elocs', EEG.chanlocs, 'chaninfo', EEG.chaninfo, 'baseline',[0],'freqs', [4 50], 'nfreqs', 47). Power was calculated in decibel (dB) change from baseline (-200 - 0 ms).

The spectral data were then manipulated in Matlab to produce average power values for each frequency band: delta (1-4Hz), theta (4-8Hz), alpha (8-13Hz) and beta (13-30Hz), for the electrode FCz.

3.0.11 Results

If any of the variables used in the following ANOVAs were found to violate the assumption of sphericity the results were corrected using the Greenhouse-Geisser correction. Results presented show the corrected values where applicable.

Questionnaire data

Participants smoked an average of 4.28 days per week (sd = 2.74), on which days they smoked 7.77 cigarettes (sd = 5.19), smoked their last cigarette 10.72 hours prior to the experiment (sd =30.97), started smoking at the age of 16.78 years (sd = 2.37), reported a DSM nicotine dependence score of 5 (sd = 1.21) (a score of over 3 on this scale is suggestive of nicotine dependence), a QSU-Brief, factor 1 craving score of 4.18 (sd = 1.61), QSU-Brief factor 2 craving score of 1.96 (sd = 1.24) (for the QSU measures of craving, any score above zero is indicative of craving), drank 18.73 units of alcohol per week (sd = 10.89) and had an alcohol binge score of 29.71 (sd = 16.72) (Together these measures provide a measure of how much is consumed (in units) and how often the subject drinks).

Behavioural results

Instrumental task. Nine participants were excluded from the analysis as they did not show contingency knowledge (based on a the question "Which key won cigarettes?" presented on screen at the end of the experiment). There was no preference for the tobacco over the chocolate key in the sample as a whole ($t(22) = 1.34$, $p = .2$, n.s.).

Behavioural correlations. The percentage of cigarette responses made in the task was correlated with individual difference measures. Due to the number of correlations tested we used a Bonferroni corrected alpha level of .005. None of the correlations met this criterion.

ERP results

Figure 3.1 shows the grand averaged ERP waveforms for a window 200ms prior to the presentation of the outcome, to 800ms post the onset of the outcome, for the four possible outcome types. The main component shown is the P3, which is consistent with previous research where P3 components are seen following the onset of an outcome in a similar area (e.g. Hajcak, Holroyd, Moser, & Simons, 2005).

A 3 x 2 x 2 ANOVA (area [Fz, Cz or Pz], choice [cigarette or chocolate key] and reward [win, no win]) conducted on the means shown in figure 3.1 revealed a main eect of reward ($F(1, 22) = 10.23$, $p < .05$) indicating that the P3 was greater when the response was won compared to lost. There was also an area x reward interaction ($F(1, 21) = 22.34$, $p < .001$). Further analysis showed that this

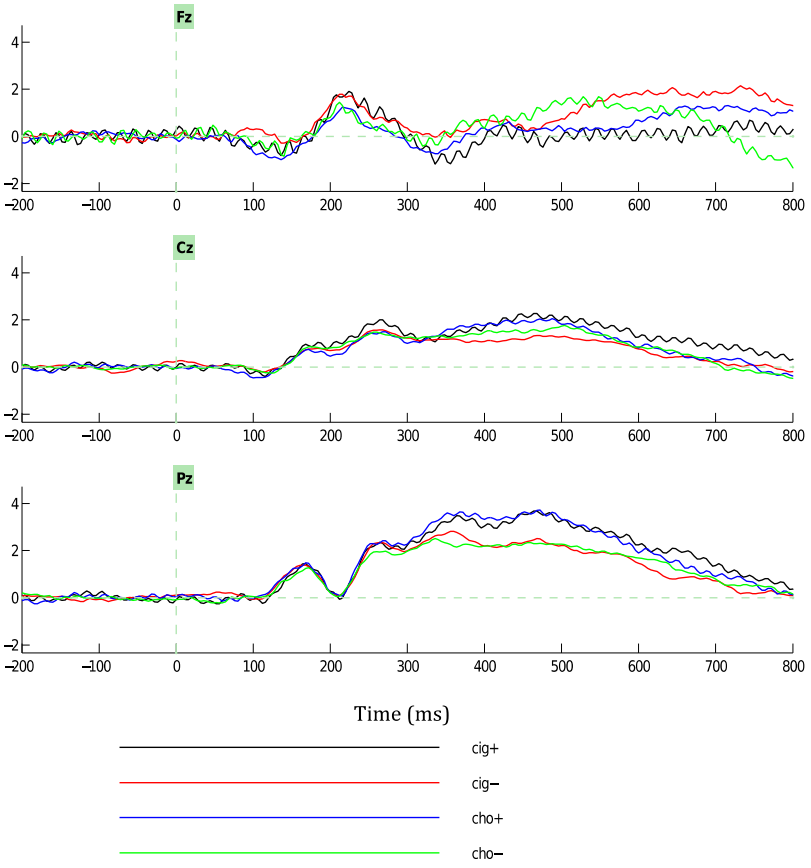


FIGURE 3.1: The ERP following cigarette win, cigarette no-win, chocolate win and chocolate no-win trials at frontal (Fz), central (Cz) and parietal (Pz) locations. Outcome onset at zero ms; represented by the dashed line). The Y-axis is the amplitude of the ERP in microvolts.

was driven by differences at Pz, with cigarette win cues producing a marginally greater P3 than cigarette no-wins ($t(22) = 2.01$, $p = .057$) and chocolate wins also produced greater P3s than chocolate no-win cues ($t(22) = 3.72$, $p < .001$). There was no difference between cig-win and choc-win cues ($t(22) = .05$, *n.s.*) or cig no-win and choc no-win cues ($t(22) = .60$, *n.s.*).

P3 and behavioural measures. As shown in table 3.1 there were no correlations between the differences in P3 between cigarette wins

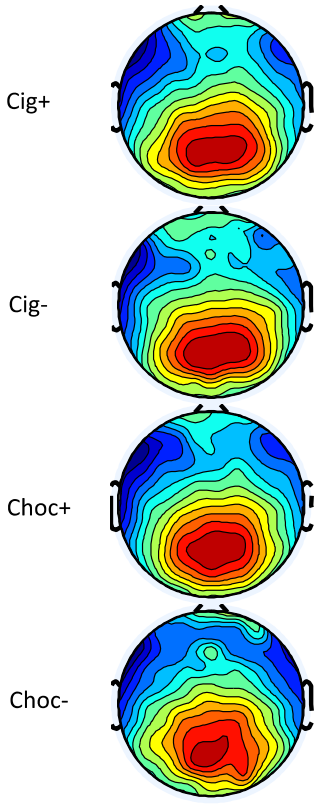


FIGURE 3.2: Topographical scalp plots of the mean ERP between 300 and 500 ms. Hot colours indicate increased activity in that area. We would expect increased activity at parietal regions during this period in line with a parietal P3.

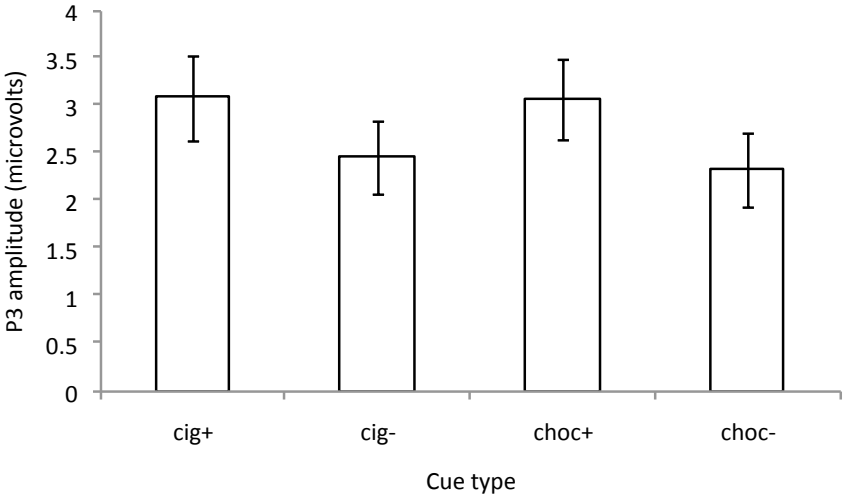


FIGURE 3.3: The mean ERP between 300 and 500 ms for each type of cue.

Questionnaire measure	Difference in ERP between cigarette wins and non-wins	Difference in ERP between chocolate wins and non-wins
CO	.06	-.06
CDS-5	-.07	-.28
Days smoking per week	-.06	-.39
Deprivation	.09	-.12
Number	.25	-.33
Years	.26	-.06
Onset	-.35	-.14
DSM IV	-.12	.05
AUQ units	.04	.18
AUQ binge	-.13	.20
ASMA	.11	-.24
QSU-1	-.19	-.33
QSU-2	-.34	-.29
% Cigarette Key	.24	-.07

TABLE 3.1: Spearmans correlations between the difference in P3 when winning and not winning cigarettes or chocolate, choice of key and dependence measures (* p <.05, ** p <.005).

and no-wins, or chocolate wins and no-wins, and measures of dependence. Similarly there were no correlations between P3 and behavioural/questionnaire measures (table 3.2).

Frequency analysis

Theta. An ANOVA of the mean power change at FCz for theta (100-400ms), showed no main effect of cue type ($F(1, 21) = .20$, *n.s.*), reward ($F(1, 21) = .13$, *n.s.*) or block ($F(4,84) = .41$, *n.s.*). There was however a cue by block interaction ($F(4, 84) = 4.81$, p <.005). Paired t-tests revealed that this interaction was driven by theta differences between cigarette no win and chocolate no win cues at block one ($t(21) = 2.98$, p <.05) and block three ($t(21) = 3.28$,

	P3 CIG WIN	P3 CIG NO-WIN	P3 CHOC WIN	P3 CHOC NO-WIN
NUMBER	.093	-.080	-.142	.074
DAYS	-.174	-.187	-.270	-.036
DEPRIVATION	.180	.329	.177	.324
YEARS	.245	.185	.044	.232
ONSET	-.199	.012	.010	.091
BAS_Drive	-.148	-.041	-.225	.128
BAS_FS	-.142	.002	-.272	.087
BAS_RR	.172	.047	-.050	.144
DSM	-.014	.061	.084	-.008
CDS5	-.013	-.042	-.169	-.017
QSU FACTOR 1	-.070	-.245	-.128	-.086
QSU FACTOR 2	-.144	.207	-.045	.091
AUQ UNITS	-.117	-.312	-.124	-.212
AUQ BINGE	.030	-.102	.066	-.083
BIS11 TOTAL	.109	.300	.160	.028
% CIGS KEY	.066	-.129	.147	.083

TABLE 3.2: Spearman's correlations between P3 amplitudes and behavioural/questionnaire measures. Due to the number of tests conducted a Bonferroni correction of 0.002 was used. None of the correlations met this criteria.

p <.005). There were no differences between cue type for cig and choc win or blocks 2, 4 or 5 for the no-win cues.

Alpha. An ANOVA of the mean power change at FCz for alpha (200-600ms), showed no main effect of cue type ($F(1, 21) = 1.01$, *n.s.*), reward ($F(1, 21) = .10$, *n.s.*) or block ($F(4,84) = 1.55$, *n.s.*). There was however a cue by block interaction ($F(4, 84) = 4.81$, p <.05). Paired t-tests revealed that this interaction was driven by alpha differences between cigarette and chocolate win cues at block five ($t(21) = -2.76$, p <.05).

Low beta. An ANOVA of the mean power change at FCz for low beta (200-600ms), showed no main effect of cue type ($F(1, 21) =$

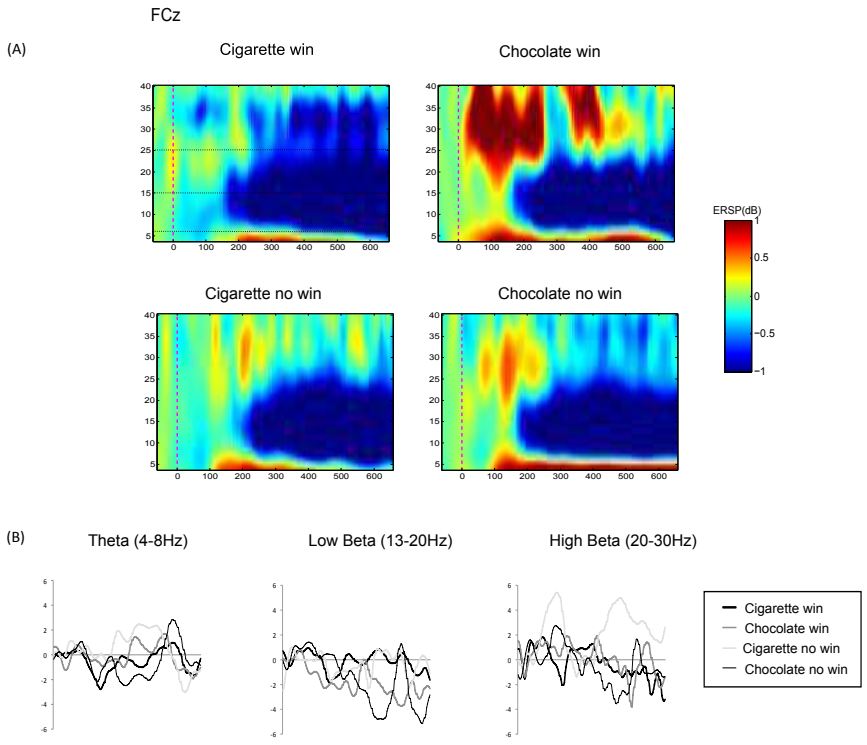


FIGURE 3.4: Changes in power from baseline for cigarette win, cigarette no win, chocolate win and chocolate no win trials at FCz. (B) The time course of selected frequencies (the dotted lines on A), theta, low beta and high beta for each type of trial. (C) Differences in power from baseline for theta, alpha and low beta frequencies by block.

1.84, *n.s.*), reward ($F(1, 21) = .26$, *n.s.*) or block ($F(4,84) = .24$, *n.s.*). There was however a cue by reward interaction ($F(1, 21) = 4.74$, $p < .05$) and a cue by block interaction ($F(4, 84) = 2.43$, $p = .05$). Paired t-tests revealed that the cue by block interaction was driven by low beta differences between cigarette and chocolate win cues at block five ($t(21) = -2.64$, $p < .05$) and cigarette and chocolate no win cues at block one ($t(21) = -2.28$, $p < .05$). The cue by reward interaction was driven by the difference in low beta amplitude between cigarette win and chocolate win cues ($t(21) = -2.28$, $p < .05$). Correlational analyses revealed no relationships between the difference in low beta power between cigarette and chocolate win

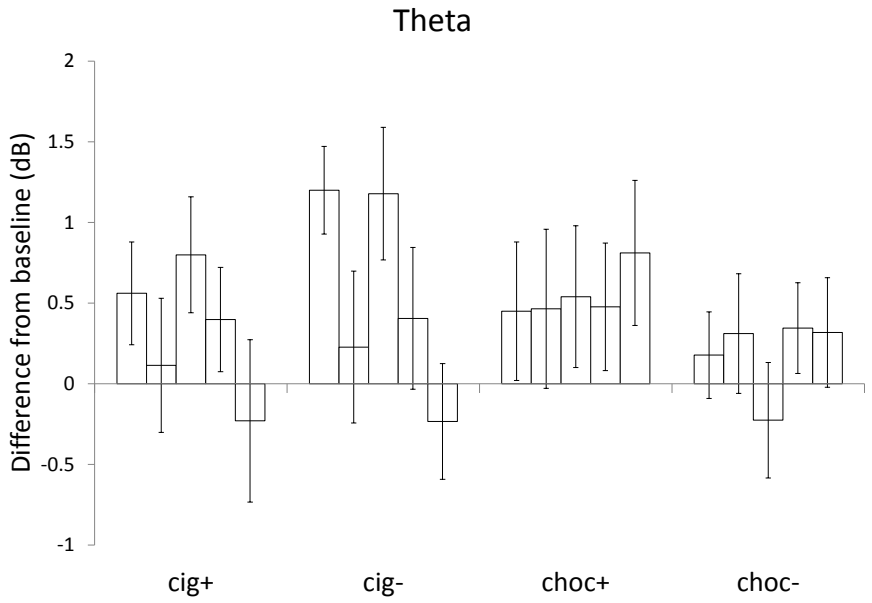


FIGURE 3.5: Theta power difference from baseline by block and for each cue.

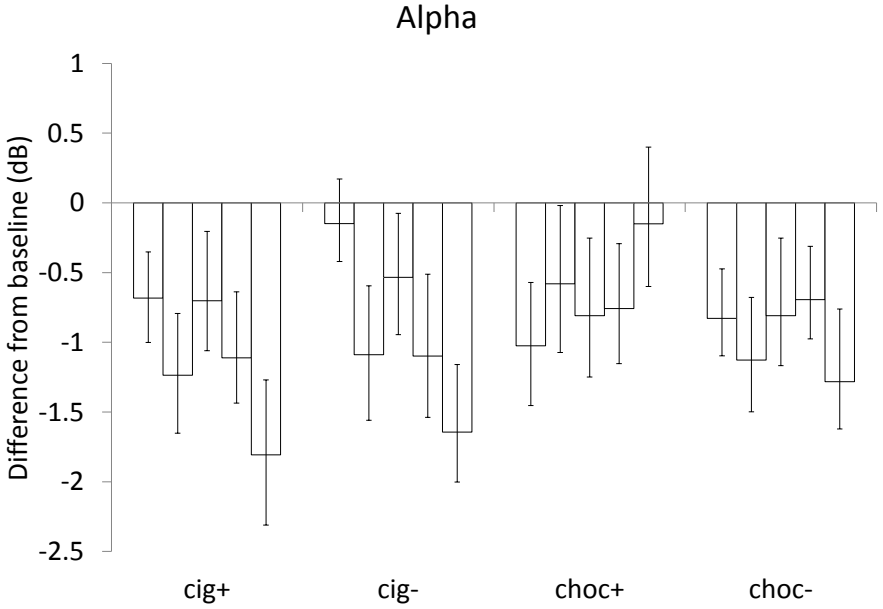


FIGURE 3.6: Alpha power difference from baseline by block and for each cue.

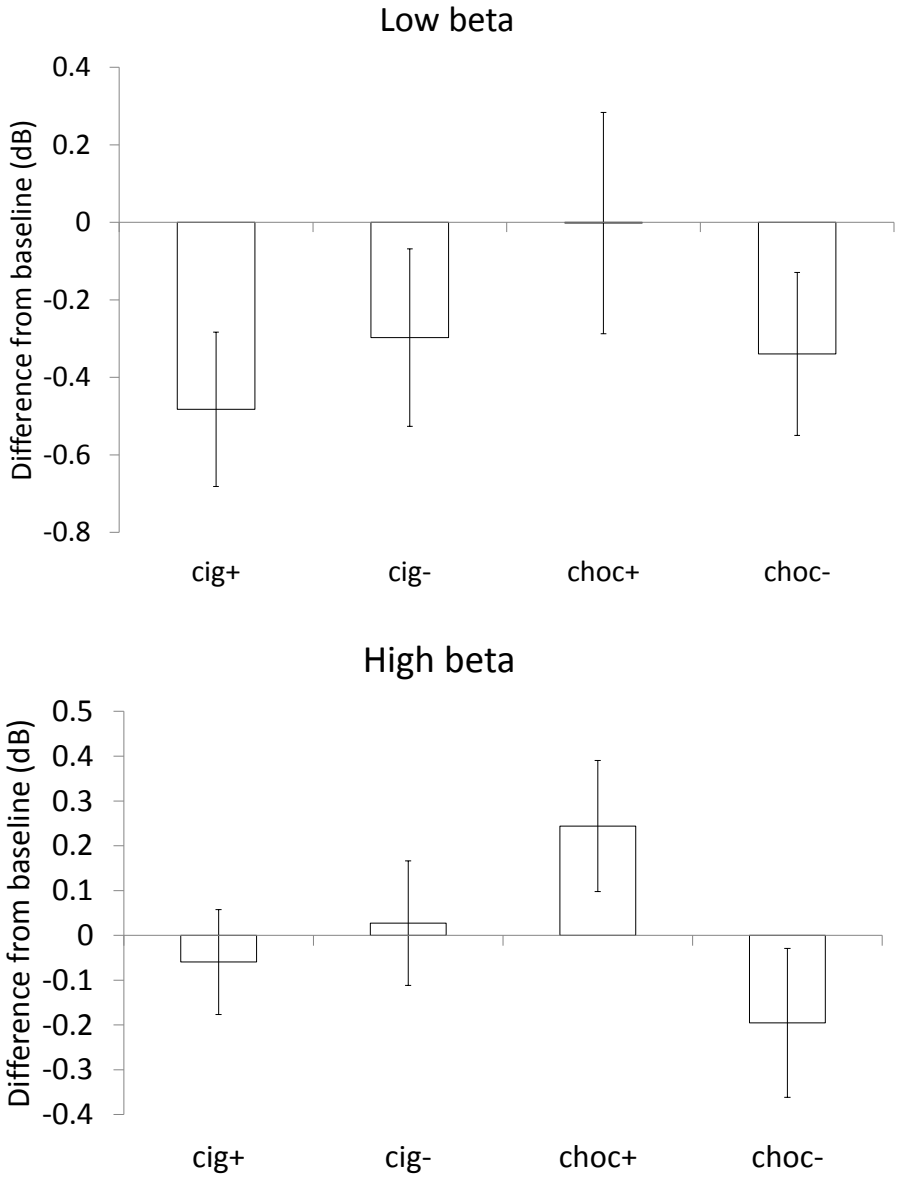


FIGURE 3.7: Low and high beta power difference from baseline by cue type. Blocks are collapsed as no main effect was observed.

trials, and addiction measures.

High beta. An ANOVA of the mean power change at FCz for high beta (50-250ms), showed no main effect of cue type ($F(1, 21) = .07$, *n.s.*), reward ($F(1, 21) = 1.07$, *n.s.*) or block ($F(4,84) = .54$, *n.s.*). There was however a cue by reward interaction ($F(1, 21) = 4.71$, $p < .05$). Further investigation of the cue by reward interaction, after

collapsing across blocks, revealed no difference in high beta power according to cue.

3.0.12 Discussion

In contrast to our prediction that smokers hyper-valuation of nicotine-related actions and outcomes would be reflected in their propensity to press the cigarette key over the chocolate key; the behavioural data did not show a preference for the cigarette key across participants. This is contrary to previous research showing a preference for drug-related behaviours and their associated outcomes in rats (e.g. Deroche-Gamonet et al., 2004; Pelloux et al., 2007; Vanderschuren & Everitt, 2004) and humans (e.g. Moeller et al., 2009; Perkins et al., 2002). The ERP results support previous findings suggesting that the P3 reflects outcome evaluation (Wu & Zhou, 2009). The P3 amplitude is larger for win than no-win outcomes. Previous results regarding the P3's role in reward processing have been mixed; Yeung & Sanfey (2004) reported a dissociation between the P3 and feedback negativity with P3 modulated by reward magnitude but not by valence (win or loss), whilst feedback negativity showed the opposite pattern. These results seem to be at odds with those of the current study, where the P3 was modulated by win vs. no-win, although there was no test of magnitude. However Yeung & Sanfey (2004) suggest that the P3 may be sensitive to valence in situations where high-level evaluation of the outcome is taking place (such as regret at having not won an outcome).

This is the first study to compare the ERPs across levels of smoker (as opposed to smokers and controls) on a concurrent choice paradigm. The P3 was recorded following the outcome of an instrumental response as opposed to passively viewing a Pavlovian cue (e.g. Littel & Franken, 2007), allowing investigation of drug seeking rather than response to drug cues. Another important difference from previous studies was that both the drug and non-drug rewards were appetitive in nature rather than comparing a drug cue to a neutral cue.

Previous research suggests that addicted individuals, or those at risk of addiction, may show reduced P3 amplitude in response to outcomes (Anokhin et al., 2000; Guney et al., 2009). As we did not have a control group of non-smokers we cannot compare directly to these findings but we found no correlations between the amplitude of the P3 and addiction levels. This may be due to the average addiction level of our participants; perhaps their relatively short smoking histories mean that any cumulative effects of the drug may not have taken effect.

We predicted that the P3 would correlate with behavioural preferences, this was not the case; the smokers showed no preference between cigarette and chocolate keys. This means that the P3 differences to outcomes cannot predict a participants preference for cigarette outcomes. There are a number of potential explanations for the lack of difference in cigarette preference between smokers, the paradigm randomly selected each outcome on a 50/50 basis which may have lead to participants using a winstay, loseshift (WSLS) strategy. The WSLS learning rule was formulated by (Thorndike & Bruce, 1911); successful responses are more likely to be repeated

whilst those which are unsuccessful are likely to lead to a change in behaviour. This approach may explain the results shown in the behavioural task used here. Indeed Posch (1999) demonstrated that it can be a successful tactic in repetitive games where a number of previous outcomes are incorporated into the strategy. Instead of responding for the outcome they wanted participants may have used the WSLS strategy in an effort to maximise their winnings. It is worth noting that the experiment was composed of five blocks of 72 trials; each block had a similar number of trials to that used for entire behavioural studies. The large number of trials necessary for EEG analysis may have caused the daily smokers to disengage from the task. Indeed research has demonstrated problems with reduced attention in smokers (Lawrence, Ross, & Stein, 2002). This effect may have been increased by the level at which participants were rewarded, over a single block they could earn up to 10 cigarettes. For many of the participants this reflected an entire days allowance and so may have caused further disengagement from the task. Another possibility is that because the participants knew in advance that the study would take two hours, the daily smokers may have smoked more than usual prior to starting the experiment. This may have caused a reduction in craving within this group, and therefore a reduction in preference for the cigarette key. In future participants should perhaps be asked to refrain from smoking for 24 hours prior to the experiment although this level of deprivation is also likely to affect the results.

Analysis of the frequency data revealed a mixed picture with some differences in theta, alpha and high beta according to cue type but

nothing consistent across blocks. However low beta showed differentiation between cigarette and chocolate win trials. This difference did not correlate with our questionnaire measures and so does not, according to this analysis, relate to addiction level. There was no difference between the cigarette and chocolate loss trials.

In summary, the present study has revealed that the P3 is sensitive to reward (vs. non-reward). It has not demonstrated any relationship between the P3 amplitude and addiction level and cannot therefore provide a measure of the hypothesised over-valuation of drug-related outcomes. The time-frequency analysis, and specifically low beta power, similarly showed differences according to the trial type but this did not relate to addiction level.

Chapter 4

Pavlovian control of an instrumental action - I

4.0.13 Abstract

A Pavlovian to Instrumental Transfer task (PIT) was utilized to investigate the influence of predictive Pavlovian cues on an instrumental behaviour in daily and non-daily smokers. Participants learned an instrumental discrimination in which keyboard responses were paired with either cigarette or chocolate outcomes on a 50% reinforcement schedule. In the transfer stage either cigarette, chocolate or blank pictorial cues were presented followed by a choice of the two keys. EEG data was collected during this phase and analyzed using ERP and frequency methods. In line with recent behavioural research, the cues elicited a bias to respond for the associated outcome. This outcome specific transfer effect suggests that the cues were controlling behaviour through a mental representation of the outcome, rather than a direct stimulus-response, or habit based

mechanism. None of the ERP components investigated differentiated between the types of cue. However the alpha frequency (8-13 Hz) differentiated between the types of pictorial cue with the highest amplitudes in response to cigarette, then chocolate and finally blank cues. Using a correlational analysis we found that the higher participants scored on the DSM-IV measure of addiction, the less difference there was in alpha power following cigarette and chocolate cues. These findings contribute to our understanding of the effect of cues in the progression from casual to compulsive drug use.

4.0.14 Introduction

To effectively treat addiction it is important to understand the behavioural processes and learning which lead from casual to compulsive drug use. Current addiction theory suggests two potential mediating processes: goal directed drug seeking where behaviour is mediated by a mental representation of the drug as an outcome, and habitual drug seeking where behaviour is elicited by drug-paired cues, without representation of the outcome. Pavlovian to Instrumental Transfer (PIT) paradigms provide a means of separating the two processes. In a traditional PIT study participants are trained on a Pavlovian set of cues which signal the presentation of specific outcomes. Next they learn an instrumental discrimination between a set of actions (such as a keyboard or lever press) and their associated outcomes. Finally in the test or transfer stage of the task the participants are asked to make the instrumental responses but in the presence of the Pavlovian cues. It is the effect of the previously unrelated cues on the participants responses that is termed the PIT effect. This effect takes two forms; the first is general PIT where Pavlovian stimuli are not associated with a specific outcome but instead produce a general appetitive arousal which increases instrumental responding. In outcome specific PIT the Pavlovian stimuli predict the same outcome as the instrumental responses with a particular cue increasing only responses for the associated outcome. For example Trick, Hogarth, & Duka (2011) trained participants on three stimuli which predicted an aversive noise with different levels of probability (90%, 50% or 10%). In the instrumental stage a key press cancelled the aversive noise in 50% of trials. Finally in the

test stage, the number of responses increased in line with the level of probability associated with the stimuli presented, suggesting that outcome prediction was mediating the PIT effect and more specifically that the higher the predictive value of the cue, the greater the subsequent transfer effect (Balleine & Ostlund, 2007).

Hogarth, Dickinson, Wright, Kouvaraki, & Duka (2007) used the PIT paradigm to investigate the effect of drug cues on behaviour. They trained smokers on arbitrary cues which had become associated with drug-related outcomes in training. The cues enhanced responding for the shared outcome, demonstrating the influence of drug-related cues on behaviour. More recently Hogarth & Chase (2011) used a devaluation-transfer procedure in which smokers were trained on a concurrent choice between keys to win either cigarettes or chocolate tokens. Next one of the outcomes was devalued using unpleasant statements or health warnings relating to the outcome. When subsequently tested in extinction, responses for the devalued outcome were reduced suggesting that the choice behaviour was controlled by a mental representation of the outcomes value. In the transfer stage of the experiment participants were asked to make the same choice but in the presence of a picture of a chocolate bar or cigarette cue, as expected these cues elicited increased responding for the associated outcome. However the magnitude of the transfer effect was not moderated by the devaluation. This suggests that whilst choice between the keys is controlled by a representation of the associated outcome, it is not sensitive to the current value of that outcome. In summary, research using the PIT paradigm in humans has demonstrated that both pictorial (Hogarth & Chase,

2011) and arbitrary (Hogarth et al., 2007) drug-related cues can enhance responding for drug related outcomes, suggesting that drug seeking behaviour is influenced by the presence of drug related cues, potentially leading to relapse in addicted individuals.

Whilst the PIT effect has been widely studied in both animals (e.g. Corbit & Balleine, 2005; Schoenbaum & Setlow, 2005) and humans (e.g. Hogarth & Chase, 2012), until recently, there has been no investigation of its neural correlates. The first study of this kind was conducted by Talmi, Seymour, Dayan, & Dolan (2008), who demonstrated PIT in humans using audiovisual cues which increased responses (squeezing a hand grip) to earn money. This enhancement correlated with the blood oxygenation level-dependent (BOLD) signal in the nucleus accumbens and amygdala. Bray, Rangel, Shimojo, Balleine, & ODoherty (2008) also investigated the neural correlates of the PIT effect in humans, this time with instrumental choices between liquid food rewards in the presence of pre-trained Pavlovian cues (associated with one of the rewards). Their analyses found that within the ventrolateral putamen BOLD differentiated between actions, which were consistent and inconsistent with the Pavlovian-predicted outcome.

The current study aims to further our knowledge about the neural basis of PIT using the temporal resolution of Electroencephalography (EEG) to see if we can identify an EEG signature that correlates with the behavioural effect or the addiction level of participants. There are a number of components, which based upon previous research; we might expect to show modulation according to cue type.

The background of the N1, P2 and P3 ERP components were reviewed in detail in the introduction but to summarise the N1 has been observed to be lower in tobacco smokers (Guney, Genc, Kutlu, & Ilhan, 2009) and also larger to rewarding stimuli (Mason, OSullivan, Blackburn, Bentall, & El-Deredy, 2012). The P2 is thought to reflect higher-level cue processing (Kranczioch, Debener, & Engel, 2003) and is associated with reward processing and impulsivity (Franken, Van den Berg, & Van Strien, 2010; Martin & Potts, n.d.); two key areas in addiction research. Similarly, the P3 is seen in many paradigms but has long been implicated in context updating (Pritchard, 1981) and allocation of resources; with salient, and more rewarding stimuli, attracting more attentional resources and producing larger P3s (Goldstein et al., 2006; Wu & Zhou, 2009; Yeung, Holroyd, & Cohen, 2005). The P3 has been observed to be reduced in, and may provide a marker for, alcoholism risk (Porjesz & Begleiter, 1990; Ramsey & Finn, 1997), general psychopathology (Nijs, Franken, & Smulders, 2007) and the effects of drug use, including cocaine (Goldstein et al., 2008) and tobacco use (Anokhin et al., 2000; Mobascher et al., 2010).

In addition, we will conduct frequency analysis on the EEG data to investigate the oscillatory activity following cue presentation during the transfer stage of the PIT task. Although the exact meaning of these fluctuations is yet to be determined, certain frequencies have been shown to be more prevalent during particular tasks, with theta during error processing and uncertainty (Cavanagh, Frank, Klein, & Allen, 2010), alpha (and beta) as a marker for addiction risk (Rangaswamy et al., 2004) and beta during the processing of

gains or rewards (Marco-Pallares et al., 2008).

The current study seeks to investigate the effect of drug-related cues on an instrumental response, to gain drug-related outcomes, using the PIT paradigm in conjunction with EEG techniques. Cigarette cues will be compared to chocolate control cues and the absence of a cue. Picture stimuli will be used as it is assumed that these cues will have been encountered regularly in the natural environment and will therefore be pre-trained. Behaviourally we expect to replicate the outcome-specific PIT effect in smokers with cigarette-related pictures enhancing responses for cigarette rewards. We will investigate both ERP and frequency data following presentation of the cues, and how these relate to the behavioural and individual difference measures. It is hypothesized that the P3 will distinguish between the cues, with greater enhancement following cigarette-related cues than chocolate cues, suggesting a cognitive bias for drug-related stimuli. Within the oscillatory data the beta band seems the most likely frequency to be modulated by cue type based on the literature discussed above, with greater beta power following cigarette cues than chocolate cues due to the saliency of the drug-related cue.

4.0.15 Method

Participants

30 participants (15 females, mean age 20 years (sd = 1.3), mean number of years in education 15.4 (sd = 1.54)) were recruited by email and poster adverts. Six participants were excluded as they did not show contingency knowledge, the results below are for the

remaining 24 participants. All were right-handed and had normal or corrected to normal vision, they received £10 inconvenience allowance and were asked to refrain from smoking for two hours prior to the experiment. Participants were excluded from the study if they had consumed alcohol or drugs (within 12 hours), sleeping pills (within 48 hours) or anti-depressants. Procedures were in accordance with the declaration of Helsinki and were approved by the University of Nottingham Ethics committee. All participants provided written and informed consent.

Apparatus

The experiment was programmed using E-prime software (E-Prime Psychology Software Tools Inc., Pittsburgh, USA) and displayed on a 15-inch monitor. Four metal containers were positioned in front of participants; one contained the cigarette rewards (10 Marlboro Lights Cigarettes; Tar 6mg, Nicotine 0.5mg), another the chocolate rewards (10 Cadbury Dairy Milk treat size bars; 15g with four chunks per bar). The two remaining tins were empty but labelled "Your cigarette box" and "Your chocolate box" respectively. The breath carbon monoxide levels of participants were measured at the commencement of the experiment using a Bedfont Smokerlyzer (Bedfont Scientific Ltd. UK).

Following the behavioural section of the experiment participants were questioned on their smoking history and then completed a battery of questionnaires which included the following measures; DSM-IV tobacco dependence criteria, the cigarette dependence scale (CDS-5; Heatherton, Herman, & Polivy, 1991), the Questionnaire

of Smoking Urges (QSU-Brief; Cox, Tiffany, & Christen, 2001), Alcohol Use Questionnaire (AUQ; Townshend & Duka, 2002), the BIS-11 (Patton, Stanford, & Barratt, 1995), the Fagerstrm Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) and the Zuckerman sensation-seeking scale (Zuckerman, Kolin, Price, & Zoob, 1964). Please see the methods section of chapter seven for more detail on these measures.

Design and procedure

The participants were seated approximately one metre in front of a computer monitor. The experiment was presented using E-prime software (E-Prime Psychology Software Tools Inc., Pittsburgh, USA). The EEG phase of the experiment began with a four-minute baseline period where participants were asked to sit with their eyes open until they heard a tone (administered through Sennheiser CX300 in-ear headphones) at which point they closed their eyes until they heard another tone. An identical baseline period followed the trials described below. This data is analysed and discussed in chapter six.

Instrumental stage. During the instrumental stage of training, participants were told that they were playing a game in which they should imagine winning cigarettes and chocolates. In each round 1/4 of a cigarette or 1/4 of a chocolate was available but they would not be told which. They should choose either the D or H key in each round to try and win the reward. The outcome associated with each key (either cigarettes or chocolate) was counterbalanced across participants. There was a 50% chance of winning each outcome on each trial and the trial type was replaced after selection.

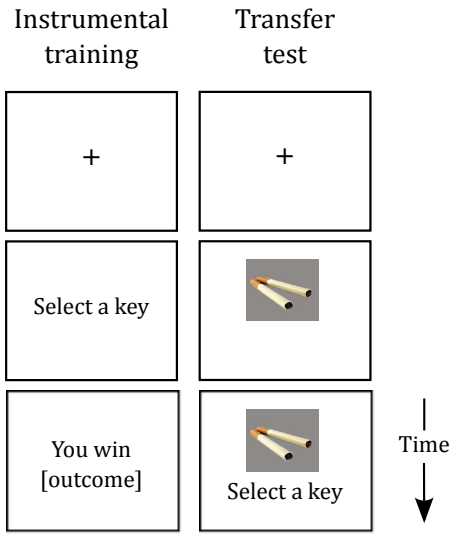


FIGURE 4.1: The experimental procedure

On each trial participants fixated on a cross (500 ms), followed by an instruction to select a key (instruction remains on the screen until a key is pressed), following the response the outcome was displayed; "You win 1/4 of a cigarette", "You win 1/4 of chocolate" or "You win nothing" (displayed for 1000 ms). There was a random ITI of between 500 and 1000 ms. There were 32 trials with totals presented at the end, participants were then asked to swap the number of chocolates and cigarettes that they had won into their tin. Participants were informed prior to the experiment that they would not keep their winnings in the game.

Transfer stage. In the transfer stage the fixation cross (500 ms) was followed by either a picture of cigarettes, a chocolate bar or a blank screen (see figure 4.1). After 800 ms participants were asked to select a key as in the instrumental stage of the experiment. The screen went blank for a jittered interval (1000-1500 ms) following their response before a jittered inter-trial interval (ITI) of between 500 and 1000 ms. EEG data was recorded only during the baseline and PIT

FIGURE 4.2: The stimuli used in the transfer stage of the experiment

stages of the experiment. Importantly the transfer test is conducted in a state of extinction where no rewards are presented, hopefully limiting any further learning taking place. Finally the participants were asked which key ("d" or "h") had produced cigarettes in the task. This assessed whether the information gained in the instrumental stage was maintained through the testing phase (when no reinforcement was provided).

Contingency knowledge test. Finally to test the participants knowledge of the contingencies between the keys and the associated outcomes they were also asked which key ("d" or "h") had produced cigarettes in the task. This test demonstrated whether the knowledge gained during training had been maintained throughout the PIT stage in which no outcomes were presented.

4.0.16 EEG methods and analysis

The EEG data was recorded from 128 sites at a 250Hz sampling rate using an EGI (Electrical Geodesics Inc., Eugene, OR, USA) dense-array EEG system (GES 200 net) and a Net Amps 200 amplifier.

Electrode impedances were kept below 50 k. The raw data was exported from Netstation to EEGLAB (a Matlab toolbox designed by Delorme & Makeig, 2004) for processing where all subsequent analysis was performed using purpose-written scripts that utilized EEGLAB and ERPLab (a plug-in for EEGLab designed by Luck, S.) functions. The data was low and high pass filtered (0.1-35Hz) and epochs were extracted according to trial type, with a 200ms pre-outcome baseline and a 800ms post-outcome window.

Artifact correction was applied using the Fully Automated Statistical Thresholding for EEG artifact rejection (FASTER) plug-in for EEGLab (Nolan, Whelan, & Reilly, 2010). To summarise the process, bad channels and epochs are rejected according to their deviation from the mean, variance and amplitude range. FASTER then uses Principle Component Analysis to reduce the total number of components according to the quantity of data available. Independent Component Analysis (ICA) is then used to identify the artifactual components, which are rejected. Finally any rejected channels are interpolated.

ERP analysis. Individual subjects data was then averaged across the following two windows 150-250 ms (P2) and 250-550 ms (P3) post cue for each event type and for frontal (Fz), central (Cz) and parietal (Pz) electrodes. For information on the corresponding electrode positions according to the 10-10 system please refer to Luu & Ferree, 2000).

Frequency analysis. Time-frequency analyses were conducted using the EEGLab function newtimef(). Event-related spectral perturbations were computed for epochs from -200 to 800 ms relative to

cue presentation using wavelet decomposition (Makeig, 2004) and the following code: [ersp,times,freqs] = pop_newtimef(EEG, 1, 6, [-200 792], [1 0.5] , 'topovec', 6, 'elocs', EEG.chanlocs, 'chaninfo', EEG.chaninfo, 'baseline',[0],'freqs', [4 50], 'nfreqs', 47). Power was calculated in decibel (dB) change from baseline (-200 - 0 ms).

The spectral data was then manipulated in Matlab to produce average power values for each frequency band: delta (1-4Hz), theta (4-8Hz), alpha (8-13Hz) and beta (13-30Hz), for the electrode FCz.

4.0.17 Results

If any of the variables used in the following ANOVAs were found to violate the assumption of sphericity the results were corrected using the Greenhouse-Geisser correction. Results presented show the corrected values where applicable.

Questionnaire data

Participants smoked an average of 5.4 days per week (sd = 2.31), on which days they smoked 6.3 cigarettes (sd = 3.33), smoked their last cigarette 19.4 hours prior to the experiment (sd = 31.14), started smoking at the age of 16.4 years (sd = 1.84), reported a DSM nicotine dependence score of 5.13 (sd = 1.19) (a score of over 3 on this scale is suggestive of nicotine dependence), a QSU-Brief, factor 1 craving score of 5.21 (sd = 1.53), QSU-Brief factor 2 craving score of 2 (sd = 1.01) (for the QSU measures of craving, any score above zero is indicative of craving), drank 32.38 units of alcohol per week (sd = 17.8), had an alcohol binge score of 68.07 (sd = 109.74) and

a habit score of 8.53 (sd = 1.41) (Together these measures provide a measure of how much is consumed (in units) and how often the subject drinks).

Behavioural results

Instrumental stage. There was a significant preference for the cigarette over the chocolate key across participants ($t(29) = 4.68$, $p < .001$). Six subjects were excluded, as they did not show instrumental knowledge in the final test.

Transfer stage. Figure 4.3 shows the effect of presenting cigarette, chocolate and blank cues on instrumental responding. An ANOVA yielded a main effect of cue type ($F(1.41, 26.75) = 20.11$, $p < .001$). Further analysis using paired t-tests revealed that the percentage of cigarette responses was significantly greater when a cigarette cue was presented than a chocolate cue ($t(23) = 4.91$, $p < .001$) or a blank cue ($t(23) = 3.11$, $p < .05$) and there were fewer cigarette responses following a chocolate cue than a blank cue ($t(23) = -4.36$, $p < .001$).

Behavioural correlations. The percentage of cigarette responses following each type of cue was correlated with individual difference measures (see table 4.1). Due to the large number of correlations tested we used a Bonferroni corrected alpha level of .004. Only the percentage of cigarette responses when chocolate cues were presented correlated with the number of cigarettes smoked per day (Spearmans rho = .69, $p = .001$).

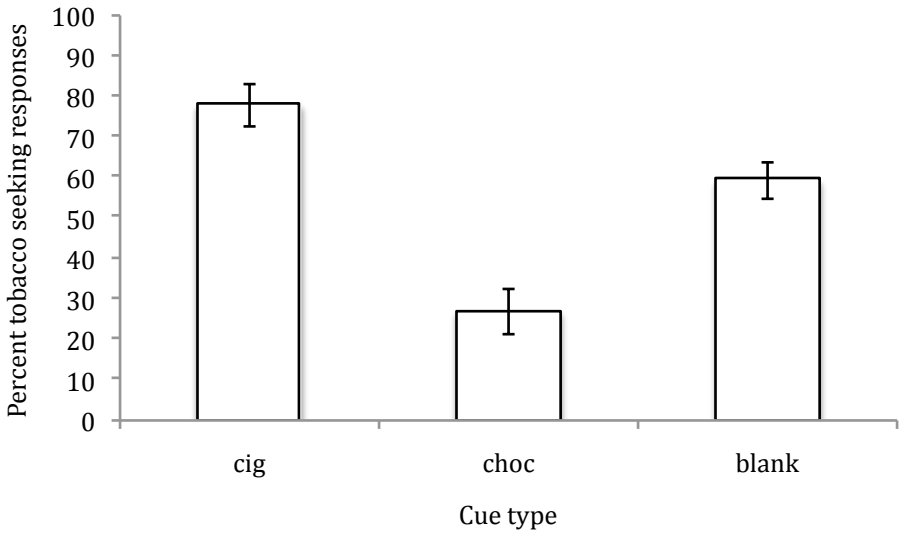


FIGURE 4.3: The percentage of tobacco seeking responses according to the cue presented in the transfer stage.

	% CIG CHOICE WITH CIG CUE	% CIG CHOICE WITH CHOC CUE
NUMBER	.238	.69**
DAYS	.374	0.543
DEPRIVATION	-.171	-0.47
CDS_5	.314	0.469
QSU_1	.099	0.565
QSU_2	.222	.274
FAGERSTROM	.171	.272
BIS - 11 TOTAL	.031	.084
DSM_IV	.205	.026
AUQ UNITS	.366	.071
AUQ BINGE	.078	.026

TABLE 4.1: Spearman's correlations between the percentage of cigarette responses and behavioural/questionnaire measures (** $p < .001$

ERP results

Figure 4.5 shows the grand average ERP waveforms for a window of 200ms prior to the presentation of the cue, to 800ms post the onset of the cue, for the three different cue types.

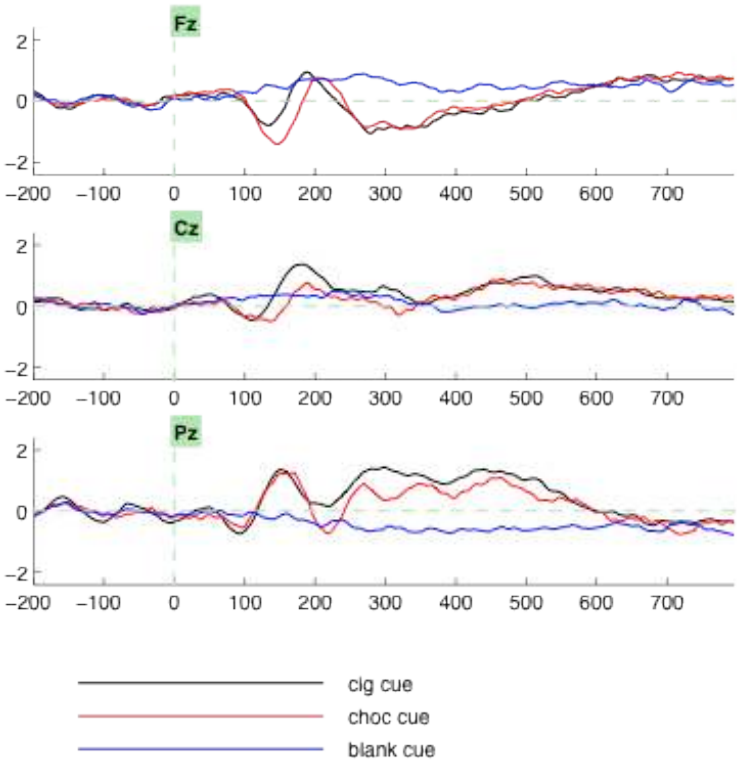


FIGURE 4.4: The ERP following cigarette, chocolate and blank cues at frontal (Fz), central (Cz) and parietal (Pz) electrodes. Cue onset at 0ms (represented by dashed line). The Y-axis shows amplitude of the ERP in microvolts.

P2. The average P2 amplitudes can be seen in figure 4.7. A 3 x 2 ANOVA (area [Fz, Cz or Pz] and cue [cigarette, chocolate or blank]) revealed a main eect of cue ($F(2, 46) = 4.5$, $p < .05$) and an area x cue interaction ($F(2,46) = 10.33$, $p < .001$). Further analysis showed that this was driven by differences at Fz, with a larger P2 following

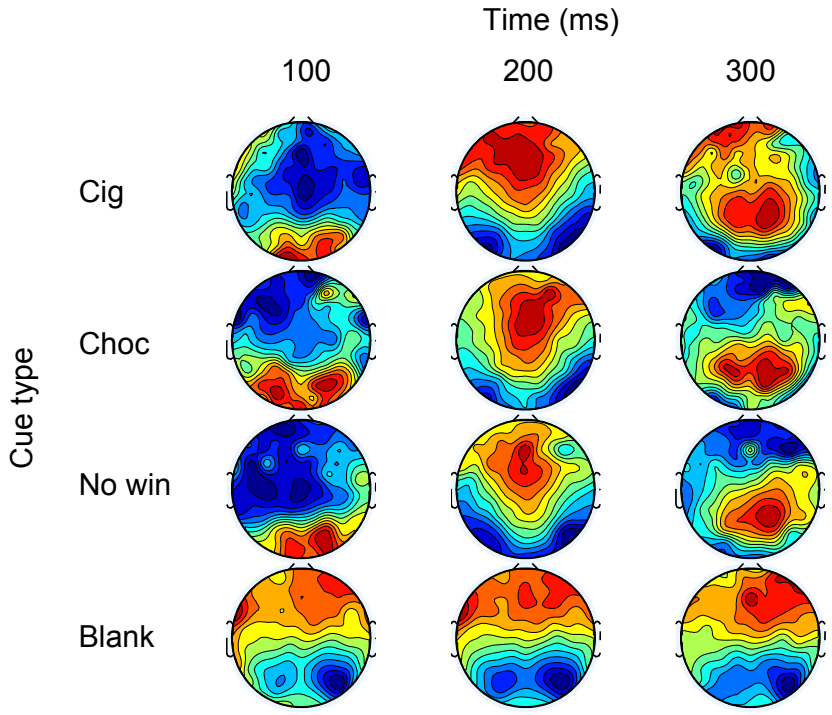


FIGURE 4.5: ERP scalp plots for each cue type (Cigarette, chocolate & blank) at three time points (100, 200 & 300 ms). Hot colours indicate greater activation.

cigarette than chocolate cues ($t(23) = 2.67$, $p < .05$) but not blank cues ($t(23) = .77$, *n.s.*). The P2 was reduced following chocolate cues compared to blank trials ($t(23) = -2.17$, $p < .05$).

Peak-to-peak analysis. The difference observed in P2 amplitude by cue type at Fz might simply be due to the offset latencies of the peaks for cigarette and chocolate cues. To investigate this we analysed the data using a peak-to peak measurement; the amplitude difference between the first negative peak (between 100 and 150ms) and the positive peak (between 150 and 200 ms). Results showed that there was no difference in the peak-to-peak measurement ($t(23) = 1.14$, *n.s.*) indicating that there may be a difference in processing between the cigarette and chocolate cues but it is not the P2 component that best describes this difference.

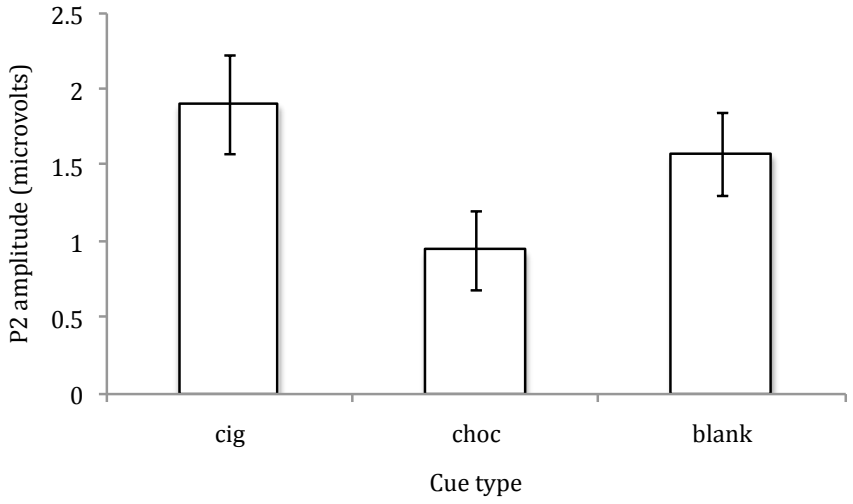


FIGURE 4.6: Mean P2 amplitude (175-225ms) following cigarette, chocolate and blanks cues at Pz.

P3. A 3 x 2 ANOVA (area [Fz, Cz or Pz] and cue [cigarette, chocolate or blank]) revealed a main eect of cue ($F(1.24, 28.58) = 34.56$, $p < .001$) and an area x cue interaction ($F(1.24, 28.58) = 40.48$, $p < .001$). Further analysis showed that this was driven by differences at Pz, with a larger P3s following both cigarette ($t(23) = 6.67$, $p < .001$) and chocolate cues ($t(23) = 7.11$, $p < .001$) was larger than following a blank screen. There was no difference in the P3 component between a cigarette or a chocolate cue ($t(23) = -.11$, *n.s.*). This suggests that the P3 signal may encode the saliency or relevance of the cue.

Correlations As shown in tables 4.2 and 4.3 there were no correlations between the P2 or P3 and behaviour/questionnaire measures. Due to the number of tests conducted a Bonferroni correction of 0.002 was used. None of the correlations met this criteria.

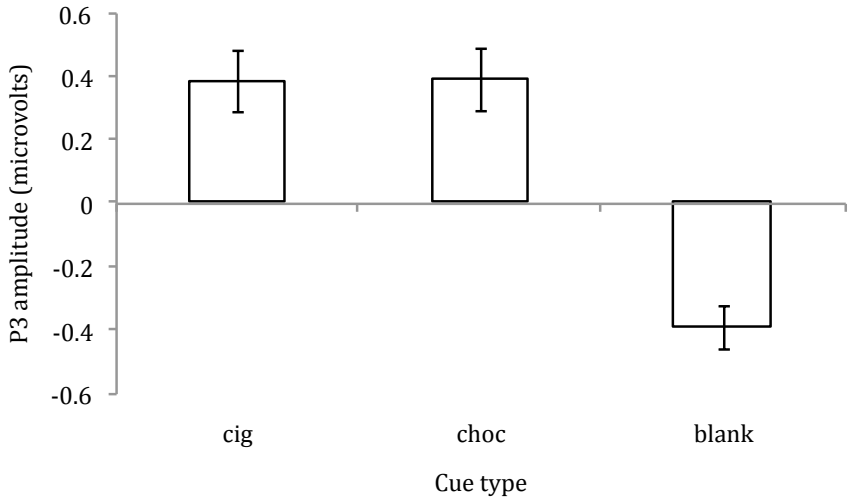


FIGURE 4.7: The mean P3 amplitude (250-550ms) following cigarette, chocolate and blank cues at Pz

	P2 CIG	P2 CHOC
NUMBER	0.463	-.035
DAYS	0.404	-.164
DEPRIVATION	-.263	.218
YEARS	.274	.140
ONSET	.044	.167
CDS_5	.167	-.265
QSU_1	.009	-.293
QSU_2	-.030	-.366
FAGERSTROM	.237	-.279
BIS11 TOTAL	-.248	-.207
DSM IV	-.057	-.134
AUQ UNITS	-.127	-0.555
AUQ BINGE	-.058	-.379
% CIGS KEY	.168	-.281

TABLE 4.2: Spearman's correlations between the P2 ERP amplitude at Fz and behavioural/questionnaire measures.

	P3 CIG	P3 CHOC
NUMBER	0.35	-.042
DAYS	0.41	-.050
DEPRIVATION	-.420	.318
YEARS	.310	.040
ONSET	.075	.617
CDS_5	.217	-.315
QSU_1	.015	-.412
QSU_2	-.110	-.486
FAGERSTROM	.457	-.359
BIS11 TOTAL	-.428	-.717
DSM IV	-.107	-.054
AUQ UNITS	-.347	-0.125
AUQ BINGE	-.218	-.229
% CIGS KEY	.728	-.641

TABLE 4.3: Spearman's correlations between the P3 ERP amplitude at Pz and behavioural/questionnaire measures.

Frequency analysis

Time-frequency analysis of the three trial types indicated an enhancement in theta, alpha and beta frequencies following cigarette and chocolate cues but not a blank screen. Each frequency was analysed separately using a 3 x 2 (cue type [cigarette, chocolate, blank], block [1, 2]) ANOVA.

Theta. An ANOVA of the mean power change at FCz for theta (100-400ms), showed a main effect of cue type ($F(2, 46) = 11.7$, $p < .001$) with no effect of block ($F(1, 23) = .01$, *n.s.*). Further analysis showed that theta was greater following cigarette cues ($t(23) = 4.46$, $p < .001$) and chocolate cues ($t(23) = 3.21$, $p < .005$) than blank cues. There was no difference in theta between cigarette and chocolate cues ($t(23) = 1.44$, *n.s.*).

Alpha. An ANOVA of the mean power change at FCz for alpha (120-220ms), showed a main effect of cue type ($F(2, 46) = 8.87$, p

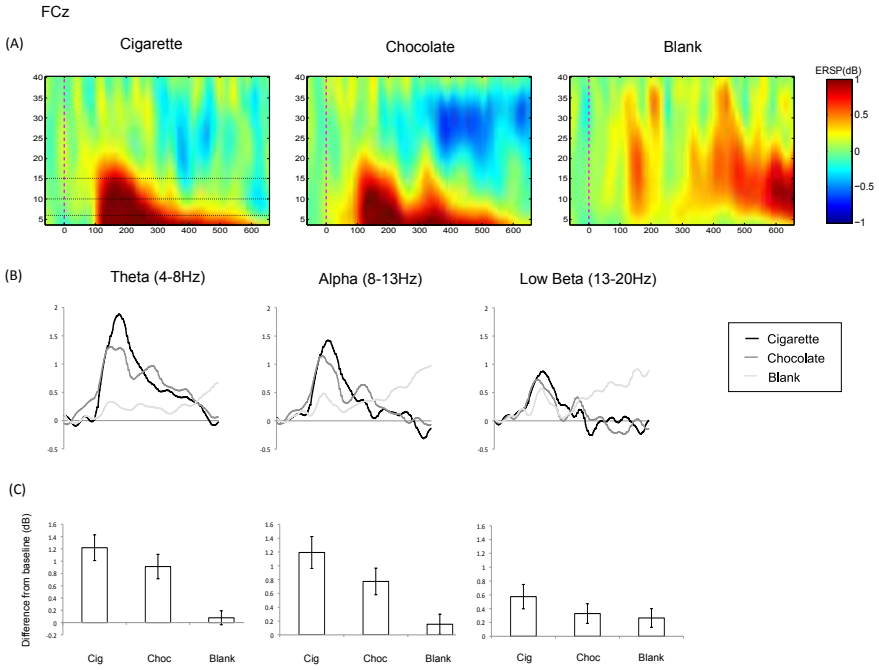


FIGURE 4.8: Changes in power from baseline for cigarette, chocolate and blank cues at FCz. (B) The time course of selected frequencies (the dotted lines on A), theta, alpha and low beta for each type of trial. (C) Differences in power from baseline for theta, alpha and low beta frequencies by block.

<.001) with no effect of block ($F(1, 23) = .04$, *n.s.*). Further analysis showed that alpha was greater following cigarette cues ($t(23) = 3.7$, p <.001) and chocolate cues ($t(23) = 2.4$, p <.05) than blank cues. There was also a significant difference in alpha between cigarette and chocolate cues ($t(23) = 2.12$, $p = .05$).

Alpha correlations. If we correlate the differences in alpha power according to cue, with measures of dependence, using a Bonferroni corrected alpha level of .008, the DSM-IV negatively correlates with the difference in alpha following cigarette minus chocolate cues (Spearmans rho = -.55, n = 24, p <.005). There were no correlations between alpha power and the behavioural (PIT) effects.

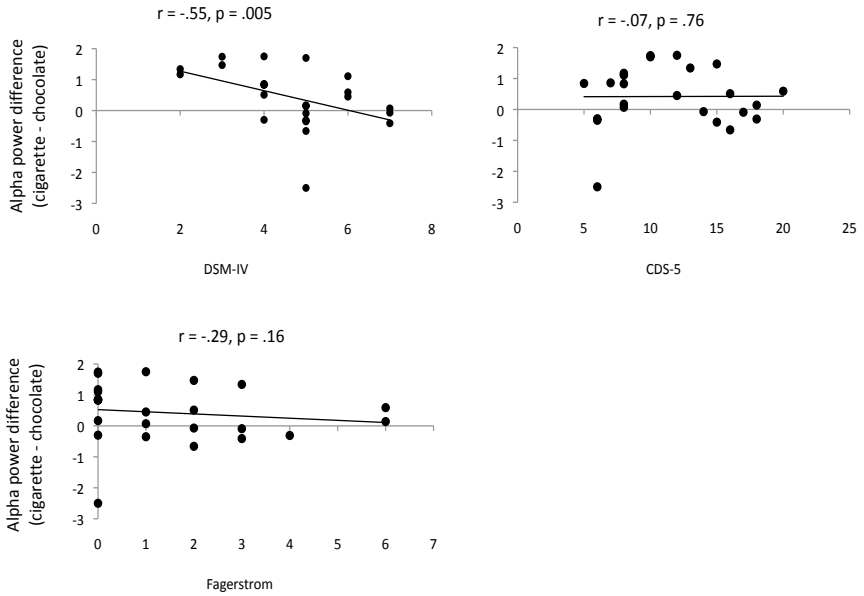


FIGURE 4.9: Correlations relating to the difference in alpha power following cigarette minus chocolate cues, and measures of dependence.

Low beta. An ANOVA of the mean power change at FCz for beta (120-220ms), showed no main effects of cue type ($F(2, 46) = 1.23$, *n.s.*) or block ($F(1, 23) = .16$, *n.s.*).

4.0.18 Discussion

The PIT paradigm is an important tool in understanding the way in which drug-related cues can influence drug seeking. The behavioural results show a specific PIT effect with significantly more cigarette responses in the presence of cigarette cues and the same pattern with chocolate responses following chocolate cues. This suggests that the drug-seeking behaviour, as measured by the number of instrumental responses, was guided by an expectancy of the outcome and was therefore goal-directed in nature (S-R-O). The alternative would be

a habit based mechanism in which a drug outcome reinforces an S-R association but then plays no further role in the relationship with the S automatically eliciting the R, without any conscious awareness or expectation of the drug outcome. A variation on the S-R mechanism, based upon the animal literature, has been proposed by Balleine & Ostlund (2007) who suggest that during instrumental training two outcome associations are formed; a response-outcome (R-O) and an outcome-response (O-R) association. Thus during the transfer stage an S-O-R association controls action selection in which the presentation of a pavlovian S triggers an expectation of the associated O, which in turn influences the instrumental R. Regardless of the learning mechanism taking place this result supports previous literature utilising the PIT effect to investigate drug-seeking, with drug-related cues enhancing instrumental responding for the drug-related outcome (Hogarth & Chase, 2011; Hogarth et al., 2007; Trick et al., 2011) and therefore, potentially leading to relapse in addicted individuals.

Correlational analyses of the behavioural data and individual difference measures revealed a moderate relationship between the preference to press the cigarette key when no cue is presented and the number of cigarettes smoked per week. This behavioural variable may be considered a general measure of the preference of the participants to select the cigarette-associated key in the absence of a cue, although it could be influenced by the previous trials. As we might expect the preference for the cigarette response correlated positively

with the number of cigarettes smoked per week, presumably a measure of addiction. This result is in accordance with previous literature suggesting that a bias for drug-related responses correlates with dependence level (e.g. Moeller et al., 2009; Perkins et al., 2002) and may be indicative of the value placed on drug related cues and behaviour. It is difficult to explain why we didn*t* see any other correlations with measures of dependence; for example Hogarth & Chase (2011) found correlations between the preference for tobacco, over chocolate outcomes, and a variety of measures, including tobacco use, dependence and craving.

With regard to the ERP data, we predicted that the type of cue presented would modulate the N1, P2 or P3. Although the P2 showed this effect initially, further analysis using a peak-to-peak measure, revealed that the early ERP components following cigarette and chocolate cues were the same amplitude, just slightly offset in latency. Although research suggests that we might expect differences in amplitude of the N1 component based on smoking status (Guney et al., 2009) and saliency of the stimuli (Mason et al., 2012), in the P2 according to cue (Kranczioch et al., 2003) and outcome processing, as well as impulsivity (Franken et al., 2010) and in the P3 according to addiction status (Anokhin et al., 2000), expectancy (Hajcak, Holroyd, Moser, & Simons, 2005) and reward processing (Goldstein et al., 2008), none of these components were modulated by cue type. The PIT task has not previously been investigated using EEG techniques, so our predictions were based upon previous research looking at the ERPs following various types of cued task and markers of addiction. The lack of effects in the ERP data may

be due to the averaging used, perhaps the large number of trials inherent in this type of analysis, meant that any effects were diluted. However this seems unlikely as including block as a variable in the analysis did not show any effects.

Analysis of the oscillatory data revealed that alpha power differentiated between cue types with the greatest amplitudes following cigarette related cues. This result is surprising, as reduced alpha power is usually understood to indicate greater cortical activity, we might therefore have expected to see the least alpha following drug-related cues, indicative of a bias for these types of cue. When we correlate dependence measures with the difference in alpha power following cigarette minus chocolate cues, we see a moderate negative correlation with the DSM-IV. The DSM-IV is a a manual providing classification of mental disorders. For a classification of addiction, a number of criteria must be met. The DSM-IV addiction measure rates participants on their level of addiction. The correlation here suggests that the higher participants score on the DSM-IV, and presumably the greater their level of addiction, the less difference there is in alpha power following cigarette and chocolate cues. Once again the opposite of what we might expect. Theta showed the same trend as alpha power but there was no difference between cigarette and chocolate cues, whilst low beta failed to differentiate cued from blank trials. Interpretation of the alpha result is difficult as we might expect to see alpha de-synchronization following a stimulus presentation indicating engagement with the task. However, there is some suggestion that alpha activity may reflect a functional signal, with a widespread spatial distribution in response to a number of events,

such as auditory and visual stimulation, cognitive targets, movements and memory (Basar, Basar-Eroglu, Karakas, & Schrmann, 2001; Baar, Schrmann, Baar-Eroglu, & Karaka, 1997). A replication of this result in subsequent experiments would improve our understanding of this affect and allow us to draw further conclusions regarding the role of alpha power during learning.

The use of naturalistic pictorial cues meant that we did not include a Pavlovian training stage in the experiment, as we assumed that participants would have a large amount of experience of the stimuli, cigarettes and chocolate. However this meant that prior exposure to the cues could not be assessed or balanced across participants. For this reason follow-up experiments should see if we replicate the findings using abstract cues, with which we can control exposure and ensure that all participants have the same level of training.

To conclude, the experiment presented here used the PIT paradigm to investigate the effect of drug-related cues on drug-seeking behaviour, demonstrating that cigarette-related cues selectively enhanced instrumental responses for cigarette related outcomes. This outcome specific transfer effect suggests that the cues were controlling behaviour through a mental representation of the outcome, rather than a direct stimulus-response, or habit based mechanism. The alpha frequency differentiated between the types of pictorial cue with the highest amplitudes following drug-related cues. The difference in alpha power following cigarette minus chocolate cues correlated negatively with the DSM-IV measure of drug dependence.

Chapter 5

Pavlovian control of an instrumental action - II

5.0.19 Abstract

A PIT paradigm was used to further investigate the influence of Pavlovian cues on instrumental responses. Chapter four demonstrated a specific transfer effect using stimulus-relevant pictorial cues. The current experiment used arbitrary patterns as the Pavlovian cues instead of pictures. This allowed control of participants exposure to the cues, and therefore the amount of learning that took place prior to the transfer phase. The experiment began with a Pavlovian stage where participants learnt which cues signaled either cigarette, chocolate or no-win outcomes. In the second stage they learnt an instrumental discrimination between two keyboard responses to win either cigarette or chocolate outcomes on a 50% reinforcement schedule. Finally in the transfer test, participants selected a response in the presence of one of the cues. EEG data was collected during this phase and analyzed using ERP and frequency

methods. As with pictorial cues we saw a strong specific PIT effect with cues enhancing responding for the shared outcome. Again suggesting that behaviour during the task was guided by a representation of the outcome of that action and therefore goal-oriented in nature. None of the ERP or frequency components investigated differentiated between cue types, thus we failed to replicate the alpha finding from chapter three. We conclude that the P3 is not modulated by the associative qualities of the cue but is simply a response to the presentation of the cue.

5.0.20 Introduction

Goal directed behaviours are often initiated by the presence of an associated cue, this might take the form of hunger leading to a search for food (Holmes, Marchand, & Coutureau, 2010) or in the case of addicted individuals, cues which are associated with drug-taking may trigger craving and potentially relapse (Holmes et al., 2010). For example there are a number of studies which suggest that drug-associated cues can lead to recollection of the effects of the drug, produce craving and subsequent relapse in addicted populations (e.g. OBrien et al., 1998; Childress et al., 1999). Pavlovian to instrumental transfer (PIT) provides an assay of the interaction between cues and goal directed behaviours to gain an associated outcome. The previous experiment demonstrated that the cigarette and chocolate seeking responses within the PIT paradigm were goal directed, in that the responses for each outcome increased in the presence of the associated pictorial cue. For example the presence of a cigarette cue selectively enhanced responding for cigarettes. The use of pictorial cues in the last chapter meant that we could not control for the participants level of previous exposure to the cues or the level of arousal that these cues cause in individuals. In the current experiment arbitrary patterns were used as the Pavlovian cues (as used by Hogarth, Dickinson, Wright, Kouvaraki, & Duka, 2007), which were trained over a limited number of trials, thus controlling for exposure in all participants.

The specific PIT effect has been demonstrated in smokers, with both pictorial (Hogarth & Chase, 2011) and abstract cues (Hogarth et al., 2007). In both cases the expectation of the drug-related

outcome controlled participants responses, with drug-related cues enhancing responding for the shared outcome. This demonstrates a goal-directed action rather than a habit based mechanism as defined by Dickinson & Balleine (1994), with contingency knowledge of the response-outcome (R-O) relationship and representation of the outcome (O) as a goal.

The PIT study discussed in the previous chapter showed a strong specific PIT effect using pictorial cues. There were no ERP components which differentiated between the type of cue presented, only between the presentation of a cue and a blank screen. Time-frequency analysis revealed that alpha power was higher following cigarette cues than chocolate cues and both were higher than on blank trials suggesting that alpha might code some difference in the brains response to cigarette and chocolate cues in a sample of young smokers.

The current study aims to replicate the behavioural and EEG findings of the previous study, using abstract cues to allow us to control for participants pre-exposure (and thus potential learning) to the cues. The presentation of pre-trained cigarette or chocolate cues is expected to enhance responding for the associated outcome in comparison to no-win cues. We tentatively hypothesize that alpha power will differentiate between the stimuli, showing the largest enhancement following drug-related cues, suggesting that alpha provides a measure of the predicted value or saliency of the associated outcome.

5.0.21 Method

Participants

The study recruited 37 student smokers (17 females, mean age 20.6, mean number of years in education 15.9), recruited by email and poster adverts. Five participants were excluded as they did not show contingency knowledge, the results below are for the remaining 32 participants. All were right-handed and had normal or corrected to normal vision, they received £15 inconvenience allowance and were asked to refrain from smoking for two hours prior to the experiment. Participants were excluded from the study if they had consumed alcohol or drugs (within 12 hours), sleeping pills (within 48 hours) or anti-depressants. Procedures were in accordance with the declaration of Helsinki and were approved by the University of Nottingham Ethics committee. All participants provided written and informed consent.

Apparatus

The experiment was programmed using E-prime software (E-Prime Psychology Software Tools Inc., Pittsburgh, USA) and displayed on a 15-inch monitor. Four metal containers were positioned in front of participants; one contained the cigarette rewards (10 Marlboro Lights Cigarettes; Tar 6mg, Nicotine 0.5mg), another the chocolate rewards (10 Cadbury Dairy Milk treat size bars; 15g with four chunks per bar). The two remaining tins were empty but labelled "Your cigarette box" and "Your chocolate box" respectively. The breath carbon monoxide levels of participants were measured at

the commencement of the experiment using a Bedfont Smokerlyzer (Bedfont Scientific Ltd. UK).

Following the behavioural section of the experiment participants were questioned on their smoking history and then completed a battery of questionnaires which included the following measures; DSM-IV tobacco dependence criteria, the cigarette dependence scale (CDS-5; Heatherton, Herman, & Polivy, 1991), the Questionnaire of Smoking Urges (QSU-Brief; Cox, Tiffany, & Christen, 2001), Alcohol Use Questionnaire (AUQ; Townshend & Duka, 2002), the BIS-11 (Patton, Stanford, & Barratt, 1995), the Fagerstrm Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) and the Zuckerman sensation-seeking scale (Zuckerman, Kolin, Price, & Zoob, 1964). Please see the methods section of chapter seven for more detail on these measures.

Design and procedure

The participants were seated approximately one metre in front of a computer monitor. The experiment was presented using E-prime software (E-Prime Psychology Software Tools Inc., Pittsburgh, USA). The EEG phase of the experiment began with a four-minute baseline period where participants were asked to sit with their eyes open until they heard a tone (administered through Sennheiser CX300 in-ear headphones) at which point they closed their eyes until they heard another tone. An identical baseline period followed the trials described below.

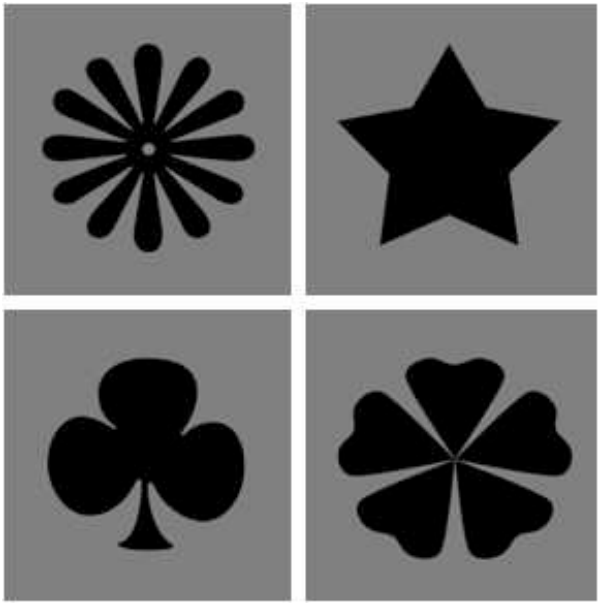


FIGURE 5.1: The stimuli used in the Pavlovian training stage of the experiment. The four stimuli were counterbalanced across participants.

Pavlovian stage. During the initial Pavlovian training component of the PIT paradigm a fixation cross was displayed (for 500 ms) followed by one of four arbitrary cues (Figure 5.1), each had an assigned outcome; either a quarter of a cigarette, a quarter of a chocolate or no win (participants were trained on two no-win cues). These were fully counterbalanced across subjects and displayed for 1000 ms. They were then asked "What do you think you will win?". Responses were categorical and made using the keyboard numbers 1-4 which corresponded to the answers "Don*t* know, "Nothing", "Cigarette" and "Chocolate". The outcome of the trial was then displayed for 1000 ms. It is important to note that the outcomes were not contingent on the responses of the subjects, only the type of stimuli presented, the responses allowed later analysis of whether participants had learnt the contingency knowledge. During the 32

trials each stimulus was presented an equal number of times to allow participants chance to learn which outcomes were contingent on which stimuli. There was a random ITI of between 500 and 1000 ms.

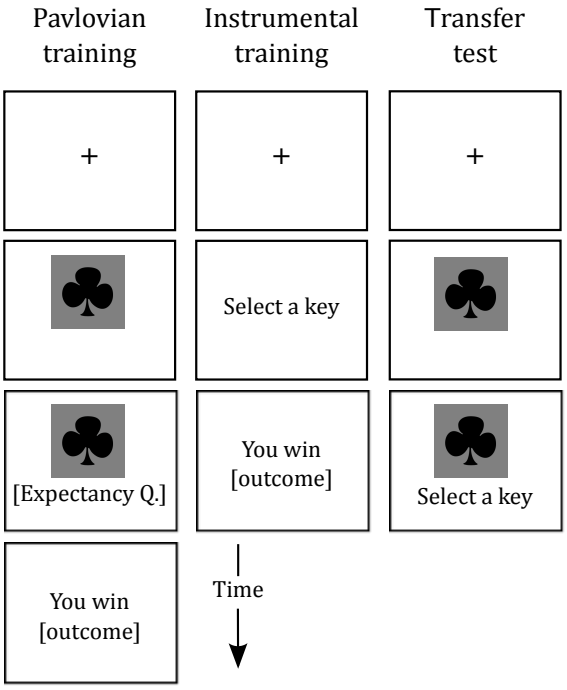


FIGURE 5.2: The experimental procedure.

Instrumental stage. During the second, instrumental stage of training, participants were told that they were playing a game in which they should imagine winning cigarettes and chocolates. In each round a quarter of a cigarette or a quarter of a chocolate was available but they would not be told which. They should choose either the D or H key in each round to try and win the reward. The outcome associated with each key (either cigarettes or chocolate) was counterbalanced across participants. There was a 50% chance of each outcome and the trial type was replaced after selection. On each trial participants fixated on a cross (500 ms), followed by an instruction to select a key (instruction remains on the screen until

a key is pressed), following the response the outcome was displayed; "You win 1/4 of a cigarette", "You win 1/4 of chocolate" or "You win nothing" (displayed for 1000 ms). There was a random ITI of between 500 and 1000 ms. There were 32 trials with totals presented at the end, participants were then asked to swap the number of chocolates and cigarettes that they had won into their tin. Participants were informed prior to the experiment that they would not keep their winnings in the game.

Transfer stage. In the transfer stage the fixation cross (500 ms) was followed by one of the Pavlovian cues or a blank screen. After 800 ms participants were asked to select a key as in the instrumental stage of the experiment. The screen went blank for a jittered interval (1000-1500 ms) following their response before a jittered ITI period of between 500 and 1000 ms. EEG data was recorded only during the PIT stage of the experiment. No outcome screens were displayed in this part of the experiment, as it is important to conduct the testing stage in extinction to limit further learning.

Contingency knowledge test. Finally the participants knowledge of the contingencies between the Pavlovian cues and outcomes was explicitly tested with a short block of 8 trials, identical to the initial Pavlovian training block. They were also asked which key ("d" or "h") had produced cigarettes in the task. These tests demonstrated whether the knowledge gained during training had been maintained throughout the PIT stage in which no outcomes were presented.

EEG methods and analysis

The EEG data was recorded from 128 sites at a 250Hz sampling rate using an EGI (Electrical Geodesics Inc., Eugene, OR, USA) dense-array EEG system (GES 200 net) and a Net Amps 200 amplifier. Electrode impedances were kept below 50 k. The raw data was exported from Netstation to EEGLAB (a Matlab toolbox designed by Delorme & Makeig, 2004) for processing where all subsequent analysis was performed using purpose-written scripts that utilized EEGLAB and ERPLab (a plug-in for EEGLab designed by Luck, S.) functions. The data was low and high pass filtered (0.1-35Hz) and epochs were extracted according to trial type, with a 200ms pre-outcome baseline and a 800ms post-outcome window.

Artifact correction was applied using the Fully Automated Statistical Thresholding for EEG artifact rejection (FASTER) plug-in for EEGLab (Nolan, Whelan, & Reilly, 2010). To summarise the process, bad channels and epochs are rejected according to their deviation from the mean, variance and amplitude range. FASTER then uses Principle Component Analysis to reduce the total number of components according to the quantity of data available. Independent Component Analysis (ICA) is then used to identify the artifactual components, which are rejected. Finally any rejected channels are interpolated.

ERP analysis. Individual subjects data was then averaged across a window of 250-550ms post cue for each event type and for frontal (Fz), central (Cz) and parietal (Pz) electrodes. For information on

the corresponding electrode positions according to the 10-10 system please refer to Luu & Ferree (2000).

Frequency analysis. Time-frequency analyses were conducted using the EEGLab function newtimef(). Event-related spectral perturbations were computed for epochs from -200 to 800 ms relative to cue presentation using wavelet decomposition (Makeig, 2004) and the following code: [ersp,times,freqs] = pop_newtimef(EEG, 1, 6, [-200 792], [1 0.5] , 'topovec', 6, 'elocs', EEG.chanlocs, 'chaninfo', EEG.chaninfo, 'baseline',[0],'freqs', [4 50], 'nfreqs', 47). Power was calculated in decibel (dB) change from baseline (-200 - 0 ms).

The spectral data was then manipulated in Matlab to produce average power values for each frequency band: delta (1-4Hz), theta (4-8Hz), alpha (8-13Hz) and beta (13-30Hz), for the electrodes equivalent to FCz.

5.0.22 Results

If any of the variables used in the following ANOVAs were found to violate the assumption of sphericity the results were corrected using the Greenhouse-Geisser correction. Results presented show the corrected values where applicable.

Questionnaire data

Table 5.1 shows a summary of the demographic and questionnaire results for the aware and unaware participants. Participants were termed aware if they correctly responded to at least two out of three

on each of the Pavlovian cues presented in the final test of contingency knowledge. 16 participants were classed as aware; 16 were unaware. As the variables were not normally distributed between groups non-parametric Mann-Whitney tests were used to reduce the impact of outliers. The aware and unaware groups did not differ on any of the measures.

Measure	Aware median	Unaware median	*U*
Hours since last cigarette	12.75	9.5	.72
Age	20	22.5	.48
Years of education	15	17	.15
Cigarettes per day	4.5	4.5	.72
CO	2.5	4	.07
Years of smoking	3	5	.48
Age of smoking onset	16	16	1
CDS-5	10.5	11	1
QSU-1	4.8	4.7	.72
QSU-2	2	1.67	.72
Fagerstrom	1	0	.72
BIS-11	63.5	66.5	.47
DSM-IV	5	5	.46
AUQ units	15.15	16.53	1
AUQ binge	17.5	24.5	.72
Zuckerman	43.5	53.5	.08
Habit	8	8	.72

TABLE 5.1: The median values for aware and unaware groups on demographic and questionnaire measures. The Mann-Whitney U test statistic is reported in the final column.

Behavioural results

Pavlovian stage. During the initial training phase of the experiment participants provided expectancy responses eight times for each type of stimulus. The mean responses for each stimulus are provided in figure 5.3. The accuracy of their responses increased over the trials. There were no significant differences in acquisition between the cue types.

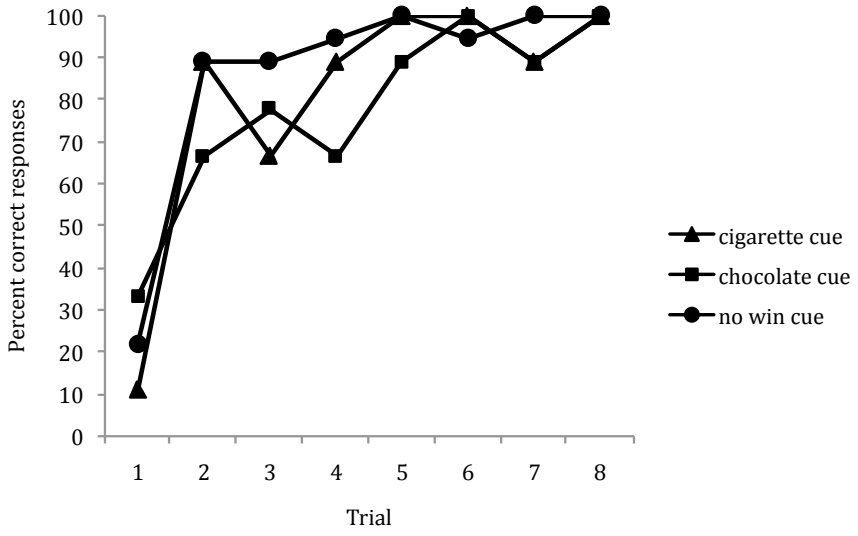


FIGURE 5.3: The percentage of correct responses across trials in Pavlovian training.

Instrumental stage. Five of the original 37 participants did not demonstrate instrumental knowledge in the subsequent test and were removed from the analysis. In the remaining 32 participants there was a significant preference for the cigarette over the chocolate key ($t(31) = 4.29$, $p < .001$).

Transfer stage.

The percentage of responses for cigarette outcomes in the presence of each of the cue types was averaged across the transfer phase of the experiment. A score of 50% would indicate no preference between the keys. Figure 5.4 shows that aware subjects selected the cigarette key over the chocolate key on the cigarette trials but not on the chocolate trials, indicative of the PIT effect. A 4 x 2 ANOVA (cue type [cigarette, chocolate, no-win or blank] and group [aware, unaware]) conducted on the percent tobacco seeking responses shown in figure four found a main effect of cue ($F(1.7, 50.9) = 15.19$, $p < .001$) and a cue x group interaction ($F(1.7, 50.9) = 3.23$, $p < .05$).

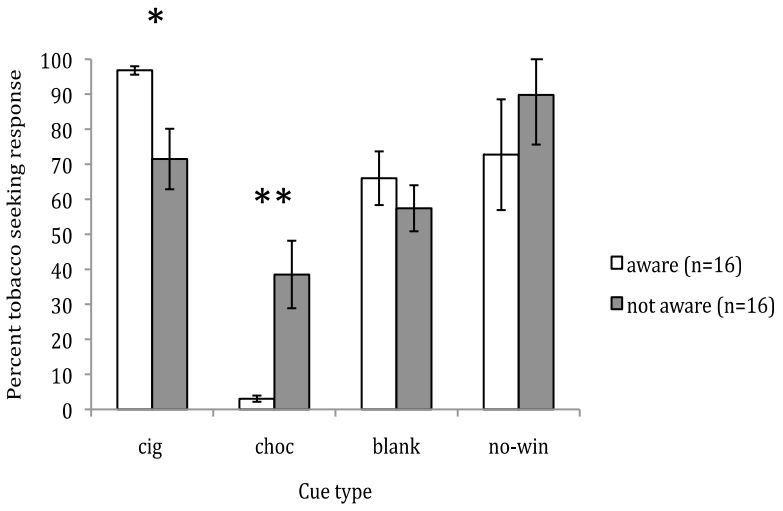


FIGURE 5.4: The mean percentage of tobacco versus chocolate seeking responses on cigarette, chocolate, blank and no-win trials in the transfer test. ** p <.005, * p <.05.

Further analysis revealed group differences in the percentage of tobacco seeking responses following cigarette ($F(1, 31) = 8.45$, $p = .007$) and chocolate ($F(1, 31) = 13.47$, $p = .001$) cues. There were no group differences following blank ($F(1, 31) = .72$, $p = .40$, *n.s.*) or no-win cues ($F(1, 31) = .64$, $p = .43$, *n.s.*).

To check the outcome-specific PIT effect we used t-tests to compare the percentage of each type of response to a no-preference level of 50%. The aware participants showed a preference for cigarettes in the presence of a cigarette cue ($t(15) = 38.93$, p <.001) and blank cues ($t(15) = 2.09$, $p = .05$), and a preference for the chocolate response in the presence of a chocolate cue ($t(15) = -53.14$, p <.001). There was no difference in responding in the presence of no-win cues ($t(15) = 1.44$, $p = .17$). The unaware participants responded more for cigarettes following cigarette ($t(15) = 2.49$, p <.05) and no-win cues ($t(15) = 2.8$, p <.05), but showed no preference during

chocolate ($t(31) = 4.29$, $p < .001$) or blank cues ($t(15) = 1.13$, $p = .28$).

	% CIG WITH CIG CUE	% CIG WITH CHOC CUE	% CIG WITH BLANK CUE	% CIG WITH NO-WIN CUE
NUMBER	.009	-.174	.263	.089
DAYS	.099	-.094	0.374	-.060
DEPRIVATION	-.052	.158	-.239	-.293
YEARS	.079	-.051	-.045	-.051
ONSET	-0.352	.138	-.196	.133
CDS_5	-.194	-.210	.241	.173
QSU_1	-.013	.032	.048	.104
QSU_2	.061	-.032	.070	.228
FAGERSTROM	-.085	-.172	0.341	.117
BIS11 TOTAL	-.327	.238	.186	.145
DSM IV	-.080	-.102	.098	.213
AUQ UNITS	-.042	-.165	.108	.120
AUQ BINGE	.083	-.162	.019	.251

TABLE 5.2: Spearman's correlations between the subjects behaviour in te transfer test and questionnaire measures.

Behavioural correlations. Correlational analyses were conducted to explore the relationships between participants behaviour in the transfer test and questionnaire measures. Due to the large number of comparisons we used a Bonferroni corrected alpha level of .003. None of the correlations met this criterion.

ERP results

Figures 5.5 and 5.6 show the grand average ERP waveforms for a window 200ms prior to the presentation of the cue, to 800ms post the onset of the cue, for the three different cue types.

Figure 5.7 shows the ERP topographical plots across time for each of the cues. As with the ERP data presented above there were few

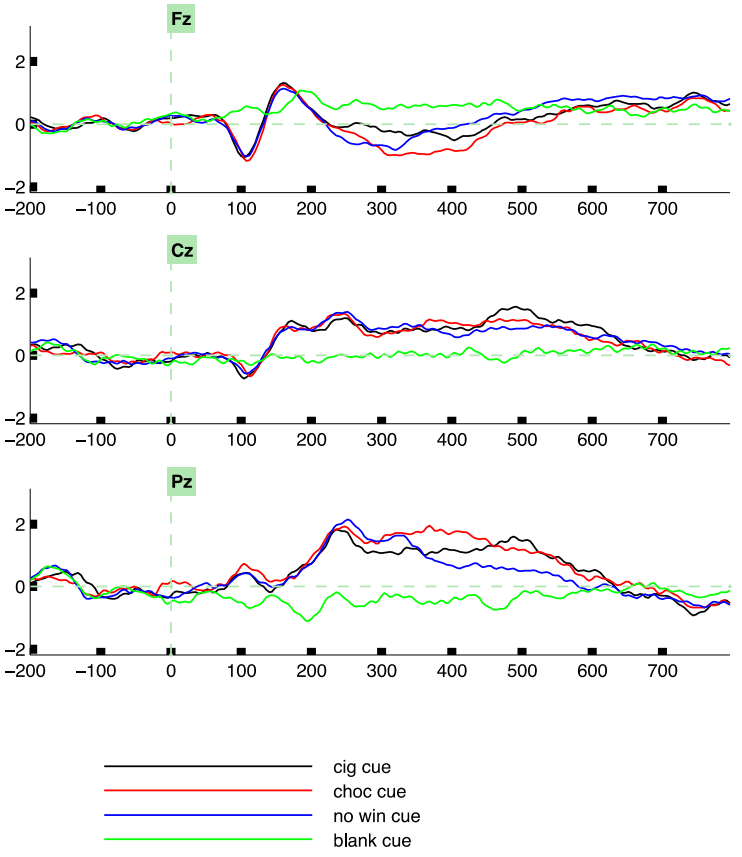


FIGURE 5.5: The ERP of aware participants following cigarette, chocolate, no-win and blank cues at frontal (Fz), central (Cz) and parietal (Pz) electrodes. Cue onset at 0 ms (represented by the dashed line). The y-axis is the amplitude in microvolts.

differences between cues, but a large difference between trials on which a cue was presented and a blank screen.

P3. A 3 x 4 x 2 ANOVA (area [Fz, Cz or Pz], P3 following each cue type [cigarette, chocolate, no win or blank] and group [aware, unaware]) shows a main effect of cue ($F(1.4, 26.64) = 19.53$, $p < .001$) and an area x cue interaction ($F(1.88, 35.72) = 32.66$, $p < .001$) but no group effect. Figure 5.8 suggests that these effects are driven by

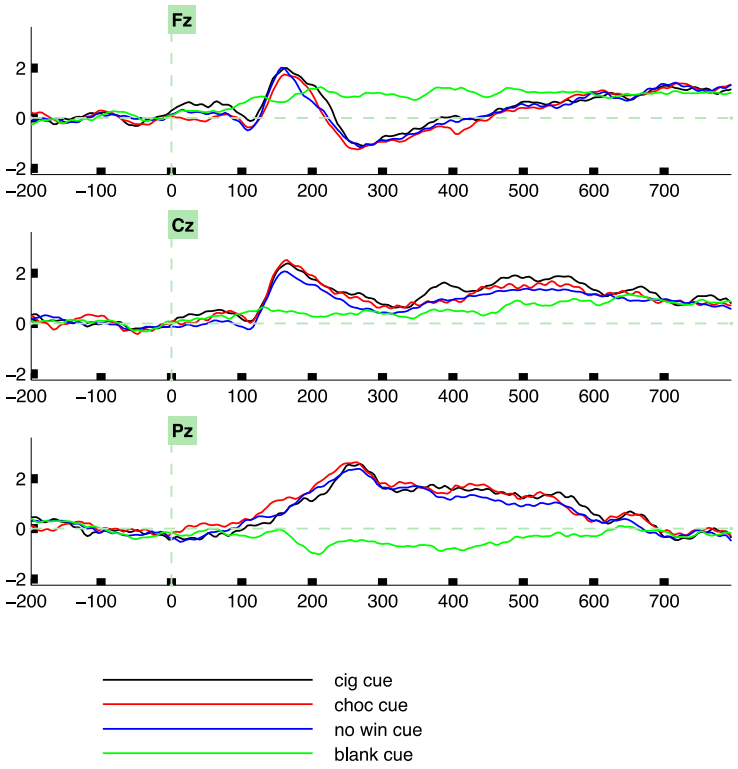


FIGURE 5.6: The ERP of unaware participants following cigarette, chocolate, no-win and blank cues at frontal (Fz), central (Cz) and parietal (Pz) electrodes. Cue onset at 0 ms (represented by the dashed line). The y-axis is the amplitude in microvolts.

the difference in P3 following cues versus a blank screen. Analysis confirmed this; there were no significant differences in P3 amplitude, in any of the clusters, between the types of cue, only between cued and blank trials.

Correlations As shown in table 5.2 there were no correlations between the P3 and behaviour/questionnaire measures. Due to the number of tests conducted a Bonferroni correction of 0.002 was used. None of the correlations met this criteria.

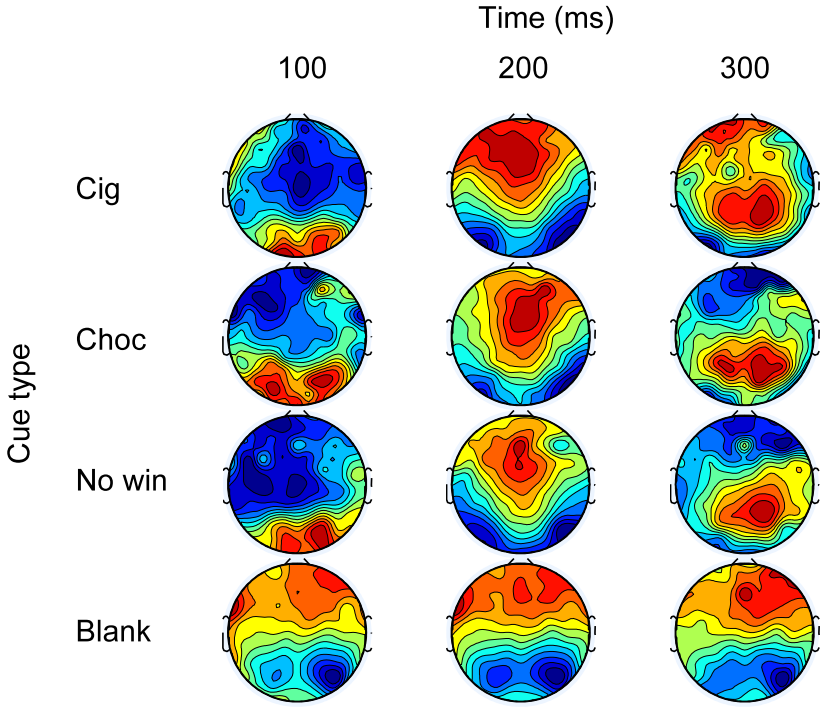


FIGURE 5.7: ERP scalp plots for each cue type (Cigarette, chocolate, no-win & blank) at three time points (100, 200 & 300ms). Hot colours indicate greater activation

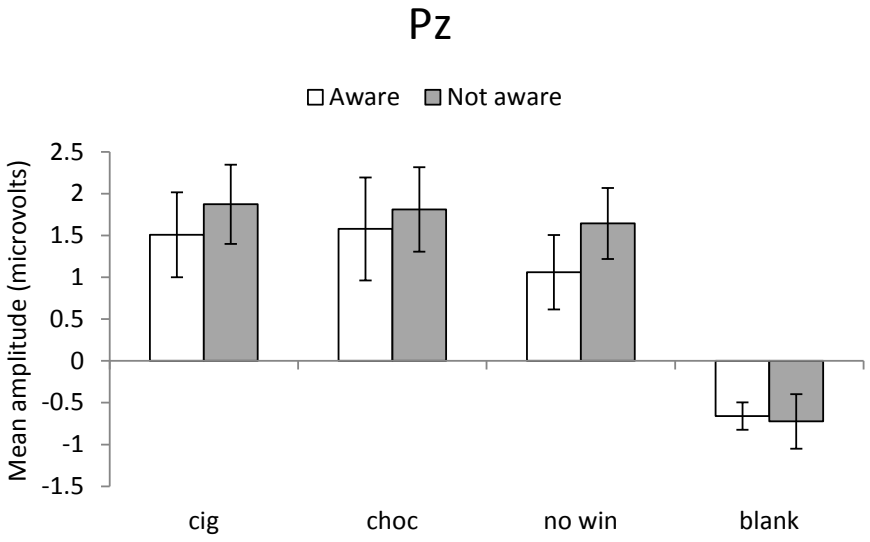


FIGURE 5.8: The mean P3 amplitude (250-550ms) following cigarette, chocolate, no-win and blank cues at Pz.

	P3 CIG	P3 CHOC	P3 BLANK	P3 NO-WIN
NUMBER	.235	-.125	-.025	.225
DAYS	.056	-.134	.007	-.060
DEPRIVATION	-.086	.084	-.001	.063
YEARS	.208	-.031	.138	.111
ONSET	-.098	.002	-.089	-.128
CDS_5	.075	-.345*	.262	.005
QSU_1	.140	-.022	.183	.040
QSU_2	-.099	-.112	.152	-.076
FAGERSTROM	.004	-.227	.067	-.022
BIS11 TOTAL	-.161	-.061	.284	-.157
DSM IV	-.132	-.231	.327	.006
AUQ UNITS	.150	.061	.166	.065
AUQ BINGE	.153	.190	-.033	.033
% CIGS KEY	-.087	.184	-.050	.145

TABLE 5.3: Spearman's correlations between the P3 ERP amplitude at Pz and behavioural/questionnaire measures.

Frequency analysis

Time-frequency analysis of the three trial types indicated an enhancement in theta, alpha and low beta frequencies following cigarette, chocolate and no-win cues but not a blank screen. Each frequency was analysed separately using a 3 x 2 x 2 (cue type [cigarette, chocolate, blank], block [1, 2], group [aware, unaware]) ANOVA.

Theta. An ANOVA of the mean power change at FCz for theta (100-400ms), showed a main effect of cue type ($F(3, 54) = 5.18$, $p < .005$) with no effect of block ($F(1, 18) = .04$, *n.s.*). Further analysis showed that theta was greater following cigarette cues ($t(19) = 2.98$, $p < .05$) and chocolate cues ($t(19) = 2.85$, $p < .05$) than blank cues. There was no difference in theta between cigarette and chocolate cues ($t(23) = .35$, *n.s.*).

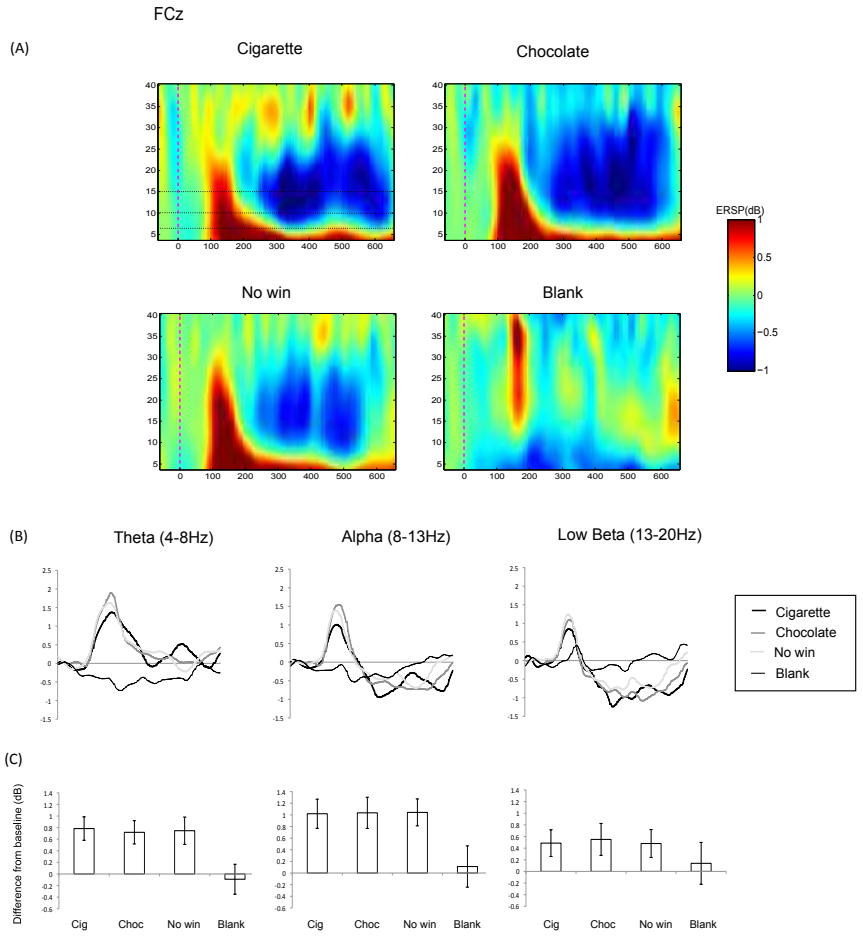


FIGURE 5.9: Aware participants only. Changes in power from baseline for cigarette, chocolate, no-win and blank cues at FCz. (B) The time course of selected frequencies (the dotted lines on A), theta, alpha and low beta for each type of trial. (C) Differences in power from baseline for theta, alpha and low beta frequencies.

Alpha. An ANOVA of the mean power change at FCz for alpha (120-220ms), showed a main effect of cue type ($F(2.03, 36.28) = 3.74$, $p < .05$) with no effect of block ($F(1, 18) = .05$, *n.s.*). Further analysis showed that theta was greater following cigarette cues ($t(19) = 2.26$, $p < .05$) and chocolate cues ($t(19) = 2.1$, $p = .05$) than blank cues. There was no difference in alpha between cigarette and chocolate

cues ($t(19)$ = -.05, *n.s.*).

Low beta. An ANOVA of the mean power change at FCz for beta (120-220ms), showed no main effects of cue type ($F(1.65, 29.72)$ = .33, *n.s.*) or block ($F(1, 18)$ = .33, *n.s.*).

5.0.23 Discussion

The contingencies between arbitrary cues and outcomes learnt in the Pavlovian phase of the experiment selectively enhanced instrumental responding in the test phase, in which no outcome information was available, showing the specific PIT effect. This effect was present for both cigarette and chocolate cues in a subset of the participants who showed that they had learnt the contingencies between cue and outcome in initial training. Those without this knowledge did not show the PIT effect for chocolate cues. This adds to the previous evidence that explicit contingency knowledge is necessary for conditioned responses to be performed (see Hogarth & Duka, 2006; Lovibond & Shanks, 2002). The high number of participants who did not learn the contingencies is somewhat surprising we suggest that this result may be due to some participants answering incorrectly in the contingency awareness test, perhaps due to disengagement from the lengthy study. Alternatively the unaware group could have simply learnt the cigarette cues and none of the others, thus they would fail the contingency test but still show a PIT effect for the cigarette cues. We might therefore expect that this group would perhaps show some individual differences from the aware group, such as greater impulsivity or addiction level, but this was not seen in the group analysis

of questionnaire and demographic data. Another reason for this finding is that the task rewards were hypothetical, the participants were informed at the outset that they would not get the rewards, and this may have lead to disinterest, and a lack of engagement in the task.

The specific PIT effect seen here, adds to previous research showing that both pictorial (Hogarth & Chase, 2011) and abstract (Hogarth et al., 2007) cues can influence instrumental behaviour in smokers. These types of study help us to understand the behaviours involved in addiction such as drug seeking and the influence external stimuli can have on these behaviours. The specific PIT effect demonstrates that drug seeking can be controlled by a goal-directed mechanism in which a representation of the associated outcome, with a stimulus and a response, is maintained.

In the present study there were no correlations between behavioural response measures and questionnaire measures. In the previous chapter we identified a positive correlation between the percentage of cigarette responses on the blank trials and the number of cigarettes smoked per week. This relationship was not replicated here.

As in the previous PIT experiment no ERP components were modulated by the type of cue presented, the only differences were between trials in which a cue was presented versus choices made in the presence of a blank screen. In other words, the P3 was the same for aware and unaware participants, and on all types of cue, but there was no P3 on blank trials. The similarity between the ERPs of aware and unaware participants strongly suggests that the EEG

data is not providing a measure of the associative qualities of the cue, but instead simply the electrophysiological response to the presentation of a pattern compared to a blank screen. This contrasts with suggestions that the P3 is larger following drug-related cues, reflecting greater cortical processing (Lubman et al., 2009; Lubman, Allen, Peters, & Deakin, 2008) and the motivational significance (Nieuwenhuis, Aston-Jones, & Cohen, 2005) of these types of cues. These differences may be due to the use of different, or more addicted populations. For example Lubman et al. (2009) are using participants with alcohol addiction recruited from a clinical setting.

The time-frequency analysis revealed no modulation by cue-type; the only differences were between the blank and cued trials. We did not replicate the finding of the previous chapter in which alpha differentiated between the types of cue. This could be due to a variety of reasons; perhaps alpha is sensitive to the perceptual qualities of pictorial cues but not those of single colour abstract patterns. Alternatively it could be due to controlling for exposure to the cues in the current study. In contrast to the pictorial cues used in the previous experiment, participants all received the same number of presentations of each cue and it is presumed would not have had significant exposure to the Pavlovian cues previously.

To summarise, we have replicated the specific PIT effect seen with pictorial cues in the previous chapter, this time with abstract cues. This effect was evident even in those who failed the contingency knowledge test, presumably as they had only learnt about the drug-related cues. We did not identify an EEG component which was

modulated by cue type, specifically failing to replicate the alpha finding of the previous study.

Chapter 6

The Effect of Extinction on Pavlovian to Instrumental Transfer in Smokers

6.0.24 Abstract

A Pavlovian to Instrumental Transfer (PIT) task was utilized to investigate the influence of Pavlovian cues on an instrumental behaviour in daily and non-daily smokers. Participants were trained on four arbitrary Pavlovian cues, of which two predicted cigarette and two predicted chocolate outcomes. Subsequently one chocolate and one cigarette cue were extinguished. Participants then learned an instrumental discrimination in which keyboard responses were paired with either cigarette or chocolate outcomes on a 50% reinforcement schedule. In the final transfer stage the cues were presented followed by a choice between the two keys. The cues elicited a bias for the response that had earned the same outcome as the current cue. This outcome specific transfer effect was not sensitive to extinction of either the cigarette or chocolate cues. ERPs were recorded during

this transfer stage. The P3 was modulated by cigarette and chocolate maintained cues but not for extinguished cues. There was no correlation between behaviour in the transfer task and the P3 measure. These findings add to previous animal work, suggesting that extinction does not reduce cue elicited responding in the PIT task, and have implications for treatments involving cue exposure.

6.0.25 Introduction

Separating the complex interactions between the cues and behaviors involved in addiction has been the focus of much recent work within the addiction field. A cue can be any stimuli or event that becomes associated with an addictive behaviour; in the case of smoking the cue might be an advertisement or a drink of alcohol, which through repeated pairings has become associated with smoking. Eventually the presence of just the cue can initiate craving (see Drummond, 2000) and potentially relapse (see Everitt, Dickinson, & Robbins, 2001) in addicted individuals. Paradigms such as the Pavlovian to Instrumental Transfer (PIT) task can provide a way of separating the processes involved in the progression from casual to compulsive drug use. In a PIT study participants are trained on a Pavlovian set of cues which signal the presentation of specific outcomes. Next they learn an instrumental discrimination between a set of actions (such as a keyboard or lever press) and their associated outcomes. Finally in the transfer stage participants are asked to make the instrumental choice between responses in the presence of the Pavlovian cues. It is the effect of the previously unrelated cues on the participants responses that is termed the PIT effect.

According to associative theory, learning involves three components; a stimulus (S), a response (R) and an outcome (O). The relationships between these elements can be investigated to better understand the learning processes involved within a learning situation. In the Pavlovian stage of a PIT task participants learn the contingencies between stimuli and outcomes. In the instrumental stage they learn the relationship between a response and an outcome. Extinction is the

disruption of the contingency between either two stimuli or a stimuli and a response (Mowrer, 2001), and it may offer a way of weakening the S-O association. However animal work has not supported this idea. For example Rescorla (1992) found that the original S-O associations of rats during an instrumental training task were unaffected by a subsequent change in the contingencies; either additional training, pairing of the S with a different O or non-reinforcement of the O following an S. Similarly in a series of experiments utilizing the PIT task in rats (Delamater, 1996) demonstrated that S-O associations, were insensitive to extinction via omitted outcomes, alternative outcomes or negative reinforcement. This despite the rats showing normal acquisition and extinction of Pavlovian cues in training, which the author suggests is due to a separate inhibitory S-R response learnt during extinction.

More recently the insensitivity of the S-O association to extinction has been investigated in humans. Gamez & Rosas (2005) and Rosas, Paredes-Olay, Garca-Gutirrez, Espinosa, & Abad (2010) used similar PIT extinction tasks but found quite different results. The first study showed extinction of the PIT effect (suggesting that the S-O relationship had been affected by extinction) but the second did not. In the latter study, extinction did not affect the transfer stage, regardless of the number of extinction trials used, which is consistent with the animal literature described above. The authors suggested that methodological differences between the studies may have lead to the conflicting results. In the first set of experiments (Gamez & Rosas, 2005) the extinguished responses were the same as the non-extinguished responses (key selection on a normal keyboard),

perhaps leading to generalization between the responses and a generalized suppression of PIT. In the later experiments this would not have been likely as generalization would have to occur between a keyboard response and a predictive judgment (Rosas et al., 2010). These studies suggest that more research is needed into the extinction of an S-O association in humans.

In a series of studies by Van Gucht, Vansteenwegen, Van den Bergh, & Beckers (2008) approach tendencies were measured following the repeated pairing of a neutral stimulus with chocolate consumption. The approach tendencies and the expectancy of chocolate were sensitive to extinction and renewal but the cue induced craving was not (Van Gucht, Vansteenwegen, Beckers, & Van den Bergh, 2008; Van Gucht, Vansteenwegen, Van den Bergh, et al., 2008). These findings are highly relevant for addiction research, particularly for those addiction treatment strategies, which utilize extinction and cue exposure. In a subsequent paper Van Gucht, Baeyens, Vansteenwegen, Hermans, & Beckers (2010) replicated the finding that cue-induced craving was not easily reduced by extinction or cue-exposure. However counter conditioning; the pairing of a Pavlovian cue with an aversive stimulus instead of the expected outcome, showed greater efficacy, with a reduction in the reported expectancy of chocolate consumption and cue-elicited consumption.

Research using the PIT paradigm in humans has demonstrated that both pictorial (Hogarth & Chase, 2011) and arbitrary (Hogarth, Dickinson, Wright, Kouvaraki, & Duka, 2007) drug-related cues can enhance responding for drug related outcomes This suggests that drug seeking behaviour may be influenced by the presence of drug

related cues, potentially leading to relapse in addicted individuals. For example a recent paper by Hogarth & Chase (2012) trained participants on a concurrent choice task, where keyboard responses won either cigarette or chocolate outcomes before the tobacco outcome was systematically reduced from 50 to zero percent probability of winning (in 10% intervals). This gradual extinction was used to allow for increased sensitivity to group differences (between daily and non-daily smokers) in perseveration of tobacco-seeking responses. In the transfer test, participants were asked to select a key but this time a picture of either cigarettes, chocolates or a blank screen were presented at the same time. There were no group differences in tobacco choice within the transfer phase or in the sensitivity to extinction.

Although we have found a robust specific PIT effect, using both pictorial and abstract cues, in the preceding chapters, the EEG signals relating to the task have been less consistent. With pictorial stimuli the alpha frequency differentiated between smoking and chocolate cues, whilst no ERP components differentiated between the types of cue. In the second PIT study we added a Pavlovian training stage in which participants learnt the contingencies between abstract pattern stimuli and drug or no drug outcomes. With these stimuli none of the ERP or frequency components investigated were modulated by the type of cue presented. Although the PIT task and EEG have not previously been combined, we had hypothesized that the P3 ERP component or beta power might reflect a cognitive bias for drug-related stimuli, reflected in greater amplitudes to these types of stimuli. The main aim of the current experiment is to investigate the effect of extinction on the PIT effect but we will also investigate

the ERP and frequency components following presentation of maintained and extinguished, smoking and chocolate associated stimuli.

The current study is similar to that of Hogarth & Chase (2012) described above. In the instrumental stage participants were trained on two keys, one won tobacco and the other chocolate rewards. In the Pavlovian stage they learnt to discriminate between four cues: A+/+, B+/0, C+/+ and D+/0 two of which won tobacco rewards and two won chocolate rewards, before one of each type of cue was extinguished (B+/0 and D+/0). The superscripted annotation denotes the outcomes that followed the stimulus, with + = winning either cigarettes or chocolate (depending on the cue) and 0 = you win nothing. The slash (/) indicates the boundary between acquisition and extinction. In the final transfer phase of the experiment the cues were presented whilst participants chose between the keyboard responses. No outcome information was provided in the transfer stage in order that no further learning could take place.

We expect that the presence of a Pavlovian cue will increase responses with the key that shares the outcome with that cue; the traditional PIT effect. If extinction has no impact on the relationship between the Pavlovian cues and the associated outcomes, then there should be no difference in instrumental responding in the presence of extinguished or non-extinguished cues.

6.0.26 Method

Participants

The study recruited 44 participants by email and poster adverts. All were right-handed and had normal or corrected to normal vision, they received 15 inconvenience allowance and were asked to refrain from smoking for two hours prior to the experiment. Twelve participants were excluded as they did not show contingency knowledge, the results below are for the remaining 32 participants. Participants were excluded from the study if they had consumed alcohol or drugs (within 12 hours), sleeping pills (within 48 hours) or antidepressants. Procedures were in accordance with the declaration of Helsinki and were approved by the University of Nottingham Ethics committee. All participants provided written and informed consent.

Apparatus

The experiment was programmed using E-prime software (E-Prime Psychology Software Tools Inc., Pittsburgh, USA) and displayed on a 15-inch monitor. Four metal containers were positioned in front of participants; one contained the cigarette rewards (10 Marlboro Lights Cigarettes; Tar 6mg, Nicotine 0.5mg), another the chocolate rewards (10 Cadbury Dairy Milk treat size bars; 15g with four chunks per bar). The two remaining tins were empty but labelled "Your cigarette box" and "Your chocolate box" respectively. The breath carbon monoxide levels of participants were measured at the commencement of the experiment using a Bedfont Smokerlyzer (Bedfont Scientific Ltd. UK).

Following the behavioural section of the experiment participants were questioned on their smoking history and then completed a battery of questionnaires which included the following measures; DSM-IV tobacco dependence criteria, the cigarette dependence scale (CDS-5; Heatherton, Herman, & Polivy, 1991), the Questionnaire of Smoking Urges (QSU-Brief; Cox, Tiffany, & Christen, 2001), Alcohol Use Questionnaire (AUQ; Townshend & Duka, 2002), the BIS-11 (Patton, Stanford, & Barratt, 1995), the Fagerstrm Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) and the Zuckerman sensation-seeking scale (Zuckerman, Kolin, Price, & Zoob, 1964). Please see the methods section of chapter seven for more detail on these measures.

Design and procedure

Concurrent choice training. The first stage of training began with the instructions, "This is a game in which you imagine winning cigarettes and chocolates. In each round either of a cigarette or of a chocolate will be available but you will not be told which. Choose either the D or H key in each round to try and win the reward. Use separate hands for each key. You will only win if you select the correct key. Press any key to begin". The outcome associated with each key (either cigarettes or chocolate) was counterbalanced across participants. There was a 50% chance of each outcome and the trial type was replaced after selection. On each trial participants fixated on a cross (500 ms), followed by an instruction to select a key (instruction remained on the screen until a key was selected), after 1000ms the outcome was displayed; "You win 1/4 of a cigarette",

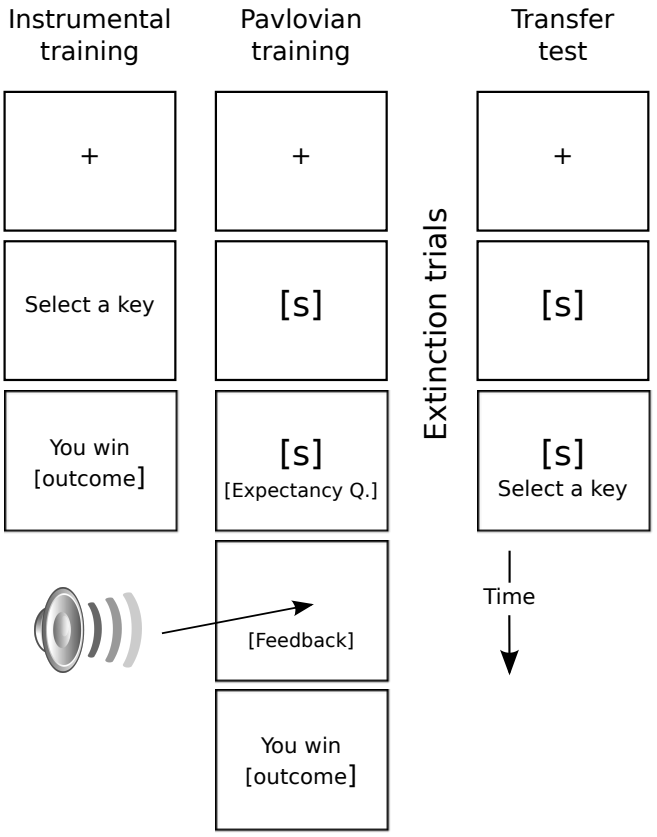


FIGURE 6.1: The experimental procedure. In instrumental training the "outcome" refers to either "You win 1/4 of a cigarette" or "You win 1/4 of a chocolate". The s refers to the stimulus presentation. The feedback slide is either "correct" or "incorrect" presented with a high-pitched beep or aversive noise respectively.

"You win 1/4 of chocolate" or "You win nothing" (displayed for 1000 ms). There was a random ITI of between 500 and 1000 ms. There were 48 trials with totals presented at the end, participants were then asked to swap the number of chocolates and cigarettes that they had won into their tin. Participants were informed prior to the experiment that they would not keep their winnings in the game.

Pavlovian training. Began with the instructions: "This is a game in which you imagine winning cigarettes and chocolates. In each round, you will be presented with a letter and asked if you expect

to win a cigarette reward, a chocolate reward or nothing. You should try to learn which letters predict which rewards. Press any key to see the letters". Upon pressing a key the stimuli were presented followed by "Here are the four letters you will see during the task. Remember certain letters predict certain rewards. Press any key to begin". Each trial was initiated by a fixation cross (displayed for 500 ms), followed by one of four letter cues ("a", "b", "c" or "d"). Two of the cues signalled that participants would win of a cigarette, whilst the other two cues won of a chocolate. The assignment of cue and outcome was fully counterbalanced across subjects. The cues were displayed for 1000ms. Participants were then asked "What do you think you will win?". Responses were categorical and made using the keyboard numbers 1-4 which corresponded to the responses "Don*t* know", "Nothing", "Cigarette" or "Chocolate'. Feedback was provided, initially with an on-screen display of either "correct" or "incorrect" (displayed for 1000ms), accompanied by a sound; either a high pitched beep (500ms) signalling a correct response or an aversive noise (500ms) for incorrect responses, followed by the outcome of the trial; either "You win 1/4 of a cigarette" or "You win 1/4 of chocolate" (2000ms). It is important to note that the outcomes were not contingent on the responses of the participants, only the type of stimuli presented, the responses allowed us to assess participants contingency knowledge. The four stimuli A+/+, B+/0, C+/+ and D+/0 were each presented 12 times in random order. There was a random ITI of between 500 and 1000 ms.

Extinction. This phase followed immediately after the Pavlovian training, with no indication to participants that they had entered a

new stage of the experiment. The 48 trials were identical to Pavlovian training except that the cues B+/0 and D+/0 were now followed by the outcome "You win nothing". The cues A+/+ and C+/+ continued to win their respective outcomes (1/4 of a cigarette or 1/4 of a chocolate). The end of training was marked by a short participant-terminated break.

Transfer test. The final transfer stage of the experiment began with the instructions "In the next section of the experiment you will continue to earn cigarettes and chocolate by pressing the D and H keys, as you did earlier in the study. You will only be told how many you have earned at the end of the task. Sometimes the letters you saw earlier will be presented. Press any key to begin". The fixation cross (500 ms) was followed by one of the Pavlovian cues or a blank screen. After 1000 ms participants were asked to select a key as in the instrumental stage of the experiment (instruction and cue remained on screen until a button was selected). Following the response the screen went blank for a jittered interval (1000-1500 ms) before a jittered ITI period of between 500 and 1000 ms. No outcome screens were displayed in this part of the experiment to avoid further learning taking place. There were two blocks of the transfer task, each with 200 trials, separated by a short break.

Contingency knowledge. Finally the participants knowledge of the contingencies between the Pavlovian cues and outcomes was explicitly tested with a short block of 12 trials, identical to the initial Pavlovian training block. They were also asked which key ("d" or "h") had produced cigarettes in the task. These tests demonstrated

whether the knowledge gained during training had been maintained throughout the PIT stage in which no outcomes were presented.

EEG methods and analysis

The EEG data was recorded from 128 sites at a 250Hz sampling rate using an EGI (Electrical Geodesics Inc., Eugene, OR, USA) dense-array EEG system (GES 200 net) and a Net Amps 200 amplifier. Electrode impedances were kept below 50 k. The raw data was exported from Netstation to EEGLAB (a Matlab toolbox designed by Delorme & Makeig, 2004) for processing where all subsequent analysis was performed using purpose-written scripts that utilized EEGLAB and ERPLab (a plug-in for EEGLab designed by Luck, S.) functions. The data was low and high pass filtered (0.1-35Hz) and epochs were extracted according to trial type, with a 200ms pre-outcome baseline and a 800ms post-outcome window.

Artifact correction was applied using the Fully Automated Statistical Thresholding for EEG artifact rejection (FASTER) plug-in for EEGLab (Nolan, Whelan, & Reilly, 2010). To summarise the process, bad channels and epochs are rejected according to their deviation from the mean, variance and amplitude range. FASTER then uses Principle Component Analysis to reduce the total number of components according to the quantity of data available. Independent Component Analysis (ICA) is then used to identify the artifactual components, which are rejected. Finally any rejected channels are interpolated.

ERP analysis. Individual subjects data was then averaged across a window of 250-550ms post cue for each event type and for frontal (Fz), central (Cz) and parietal (Pz) electrodes. For information on the corresponding electrode positions according to the 10-10 system please refer to Luu & Ferree (2000).

Frequency analysis. Time-frequency analyses were conducted using the EEGLab function newtimef(). Event-related spectral perturbations were computed for epochs from -200 to 800 ms relative to cue presentation using wavelet decomposition (Makeig, 2004) and the following code: [ersp,times,freqs] = pop_newtimef(EEG, 1, 6, [-200 792], [1 0.5] , 'topovec', 6, 'elocs', EEG.chanlocs, 'chaninfo', EEG.chaninfo, 'baseline',[0],'freqs', [4 50], 'nfreqs', 47). Power was calculated in decibel (dB) change from baseline (-200 - 0 ms).

The spectral data was then manipulated in Matlab to produce average power values for each frequency band: delta (1-4Hz), theta (4-8Hz), alpha1 (8.5-10Hz), alpha2 (10.5-12Hz), total alpha (8-13Hz) and beta (13-30Hz), for the electrodes equivalent to FCz.

6.0.27 Results

If any of the variables used in the following ANOVAs were found to violate the assumption of sphericity the results were corrected using the Greenhouse-Geisser correction. Results presented show the corrected values where applicable.

Participants

Of the 44 participants recruited, 32 learnt the contingencies (contingency knowledge was categorised as two out of three correct expectancy responses in the final three trials of both Pavlovian training and extinction). Participants were recruited with a broad range of variance in tobacco use and dependence level.

Questionnaire data

Participants had an average age of 20 (standard deviation sd = 1.9), 15 years of education (sd = 1.6), smoked 5.6 days per week ((sd = 1.9), on which days they smoked 6.4 cigarettes (sd = 3.7), smoked their last cigarette 20.4 hours prior to the experiment (sd = 28.5), started smoking at the age of 17.6 years (sd = 1.5), reported a DSM nicotine dependence score of 5 (sd = 1.5) (a score of over 3 on this scale is suggestive of nicotine dependence), a QSU1 craving score of 5.2 (sd = 1.8), QSU2 craving score of 2.6 (sd = 1.5) (for the QSU measures of craving, any score above zero is indicative of craving), drank 22.4 units of alcohol per week (sd = 17.3), had an alcohol binge score of 24.4 (sd = 20.5), a habit intention score of 8.5 (sd = 2) and habit score of 8.7 (sd = 1.4) (Together these measures provide a measure of how much is consumed (in units) and how often the subject drinks).

Behavioural results

Pavlovian stage. The responses of participants are shown in figure 2. The percentage of correct responses for each cue rapidly increased

across the Pavlovian trials. In extinction the number of responses remained high for A+/+ and C+/+ cues but quickly declined for the non-rewarded cues; B+/0 and D+/0. The apparent difference in figure 6.2, at the start of extinction, between trail types was not significant (paired t-tests for all trial types).

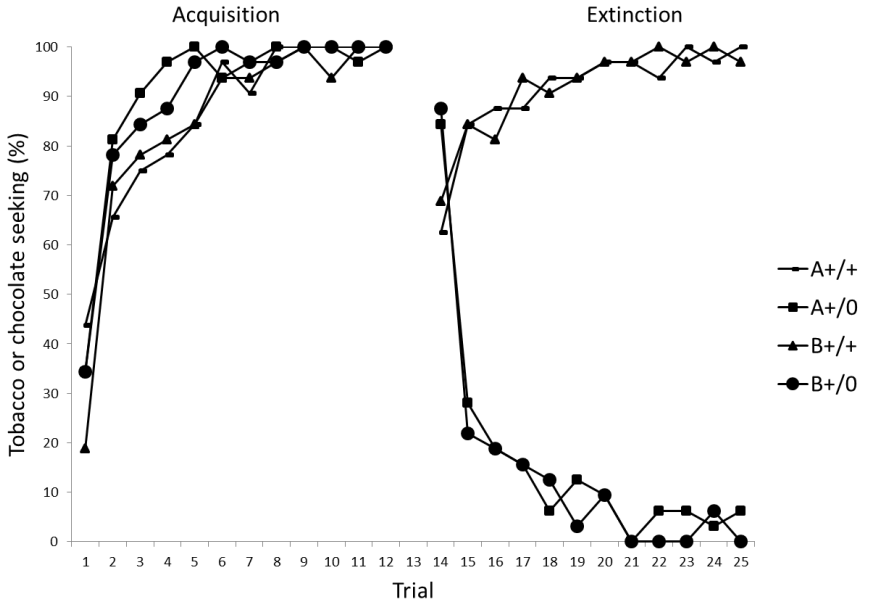


FIGURE 6.2: The percentage tobacco seeking during acquisition (trials 1-12) and extinction (trials 13-25). The sign notion following each stimulus indicates the outcome of tobacco or chocolate seeking in the presence of that cue (+: "You win 1/4 of a cigarette/chocolate". 0: "You win nothing"). The slash symbol (/) indicates the division between the acquisition and extinction phases of the experiment.

Instrumental stage. In instrumental training there was a significant preference for the cigarette key over the chocolate key across participants ($t(31) = 6.15$, $p < .001$).

Transfer stage. Figure 6.3 shows the percentage of cigarette, compared to chocolate, responses in the presence of each type of cue, in the transfer test. A score of 50% would indicate indifference whilst a score above or below this level would indicate a bias for a particular

response. An ANOVA on these data revealed a main effect of cue, $F(1, 31) = 31$, $p < .001$, but no effect of block, $F(1, 31) = 1.34$, $p = .25$, or interaction between cue and block, $F < 1$. It is clear that the cue type modulated the responses made in the presence of the associated cue and that extinction did not affect responding. All of the cues increased responding for the associated outcome relative to blank trials (A+/+ (tobacco cue) = $F(1,31) = 8.46$, $p = .007$; B+/0 (extinguished tobacco cue) = $F(1,31) = 6.41$, $p = .017$; C+/+ (chocolate cue) = $F(1,31) = 39.16$, $p < .001$); D+/0 (extinguished chocolate cue) = $F(1,31) = 25.84$, $p < .001$) and there was no difference in responding between the maintained and extinguished cues, $F < 1$.

Behavioural correlations. Correlational analysis was undertaken to investigate the relationship between individual difference measures and behaviour in the transfer test. Due to the lage number of correlations conducted, a Bonferroni correction of 0.002 was used. None of the correlations met this criteria.

ERP results

Figure 6.4 shows the grand averaged ERP waveforms for a window 200ms prior to the presentation of the outcome; to 800 ms post the onset of the outcome, for the five possible outcome types.

P3. A 3 x 5 x 2 ANOVA (area [Fz, Cz or Pz], cue [cigarette, chocolate, cigarette no win, chocolate no win, blank]) and block conducted on the means from figure 6.4 revealed a main eect of cue ($F(4, 124) = 11.84$, $p < .001$), no effect of block ($F(1, 31) = .23$, *n.s.*) but

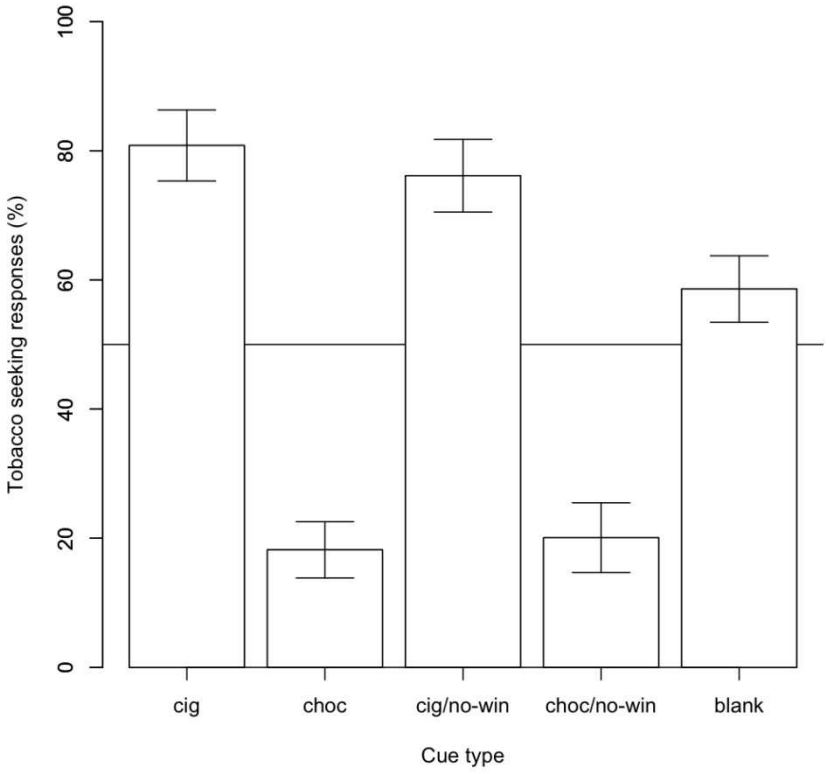


FIGURE 6.3: The mean percentage of tobacco seeking responses relative to chocolate seeking responses in the presence of cigarette, chocolate, extinguished-cigarette, extinguished-chocolate and blank trials, in the transfer test.

an area x cue interaction ($F(4,\ 124) = 14.64,\ p < .001$). Further analysis showed that the P3 following cigarette win cues was larger than following chocolate win cues ($t(31) = 3.16,\ p < .005$). There was no difference between extinguished cigarette and extinguished chocolate cues ($t(31) = -.66,\ p = .52,\ n.s.$) or between maintained and extinguished cues for cigarette outcomes ($t(31) = .94,\ p = .35,\ n.s.$) or chocolate outcomes ($t(31) = -1.27,\ p = .21,\ n.s.$). Correlational analysis revealed no relationships between the P3 difference for cigarette and chocolate cues, and behavioural or addiction measures.

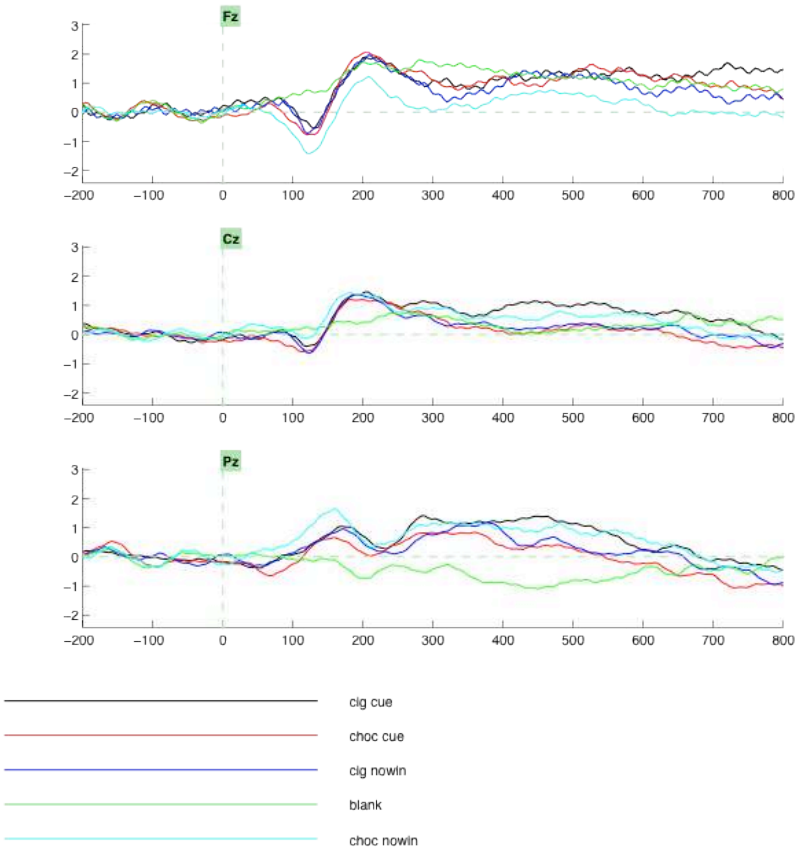


FIGURE 6.4: The ERP data following cigarette, chocolate, cigarette no-win, blank and chocolate no-win trials at frontal (Fz), central (Cz) and parietal (Pz) electrodes. Cue onset at zero ms (represented by the dashed line). The y-axis is the amplitude of the ERP in microvolts.

Correlations As shown in table 6.1 there were no correlations between the P3 and behaviour/questionnaire measures. Due to the number of tests conducted a Bonferroni correction of 0.002 was used. None of the correlations met this criteria.

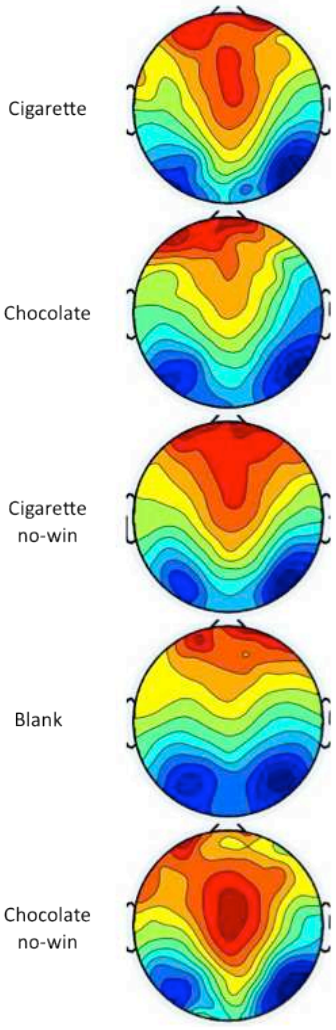


FIGURE 6.5: ERP scalp plots for each type of cue (cigarette, chocolate, cigarette no-win, blank and chocolate no-win) averaged between 175 and 225 ms. Hot colours indicate greater activation

Frequency analysis

Theta. An ANOVA of the mean power change at FCz for theta (100-400ms), showed a main effect of cue type ($F(3.04, 94.15)$ 7.79, $p < .001$) with no effect of block ($F(1, 31) = .41$, *n.s.*). Further analysis showed that these effects were driven by the theta differences between cue and blank trials with greater theta following cigarette win ($t(31) = 5.08$, $p < .001$), cigarette no-win ($t(31) = 4.13$, $p < .001$),

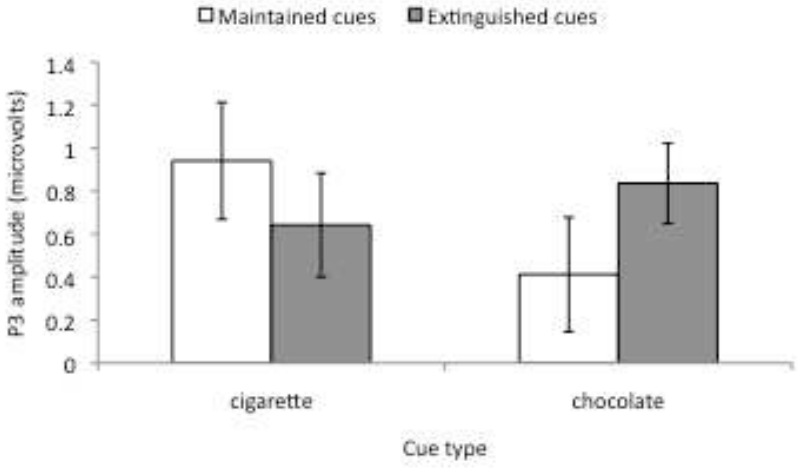


FIGURE 6.6: Mean P3 amplitude following maintained and extinguished trials for cigarettes and chocolate.

	P3 CIG	P3 CHOC	P3 CIG NO-WIN	P3 CHOC NO-WIN	P3 BLANK
NUMBER	.069	-.212	-.092	.032	.113
DAYS	.040	-0.362	-.224	0.413	.134
DEPRIVATION	-.199	.230	-.092	-.100	-.175
YEARS	-.144	.260	.174	-.153	-.088
ONSET	.100	-.132	.128	.167	-.180
CDS_5	.061	-.201	-.051	.220	.255
QSU_1	.013	-.248	.152	0.353	.129
QSU_2	-.012	-.055	-.009	.268	-.064
FAGERSTROM	-.259	-.291	-.090	.252	.122
BIS11 TOTAL	.028	-.044	-.050	.199	-.257
DSM IV	-.029	.014	-.130	.222	-.059
AUQ UNITS	.001	-.052	-.124	-.070	-.138
AUQ BINGE	.114	.137	.026	-.347	-.015
% CIGS KEY	.074	.130	.191	-.040	0.4

TABLE 6.1: Spearman's correlations between the P3 ERP amplitude at Pz and behavioural/questionnaire measures.

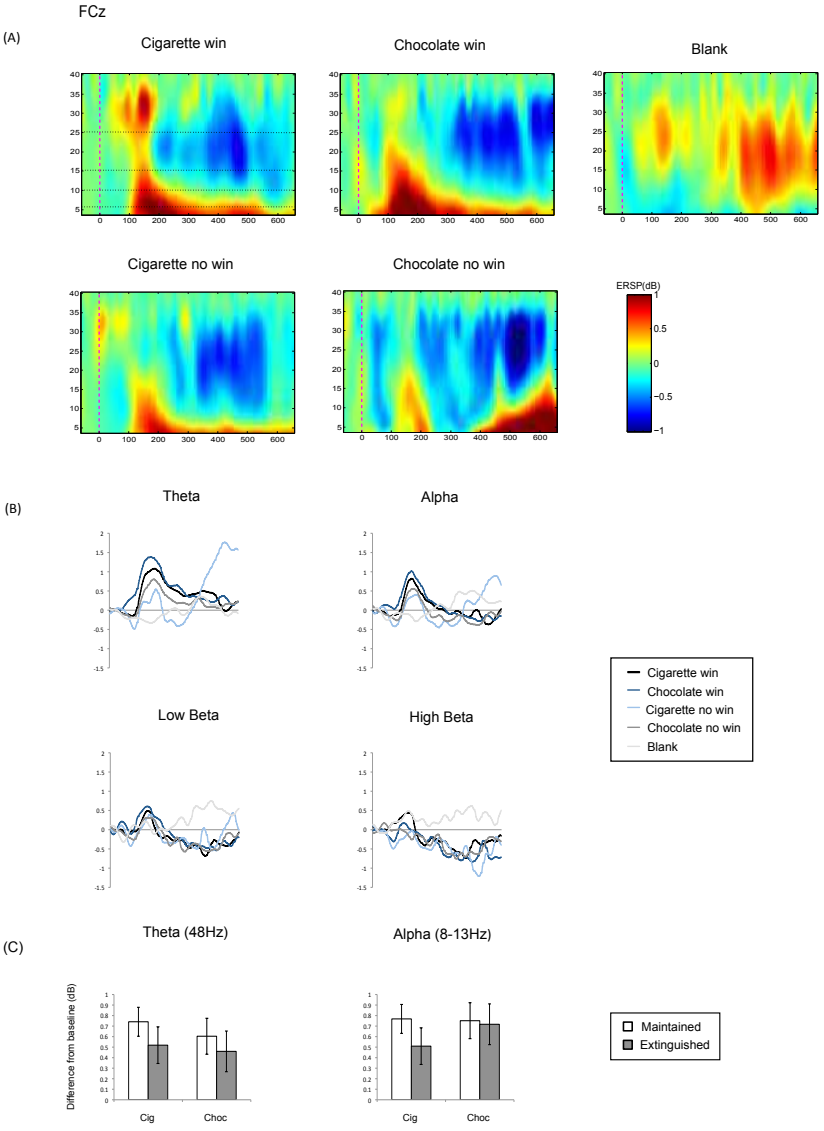


FIGURE 6.7: Changes in power from baseline for cigarette win, chocolate win, cigarette no-win, chocolate no-win and blank cues at FCz. (B) The time course of selected frequencies (the dotted lines on A), theta, alpha low and high beta for each type of trial. (C) Differences in power from baseline for theta and alpha frequencies.

chocolate win cues ($t(31) = 4.88$, $p < .01$) and chocolate no-win cues ($t(31) = 2.92$, $p < .05$) than blank cues. There were no differences in theta between the cue types or maintained/extinguished cues.

Alpha. An ANOVA of the mean power change at FCz for alpha (120-220ms), showed a main effect of cue type ($F(3.09, 95.68) = 7.62$, $p < .05$) with no effect of block ($F(1, 31) = .32$, *n.s.*). Further analysis showed that these effects were driven by the alpha differences between cue and blank trials with greater alpha following cigarette win ($t(31) = 4.63$, $p < .001$), cigarette no-win ($t(31) = 3.36$, $p < .005$), chocolate win cues ($t(31) = 5.0$, $p < .001$) and chocolate no-win cues ($t(31) = 4.14$, $p < .001$) than blank cues. There were no differences in alpha between the cue types or maintained/extinguished cues.

Low beta. An ANOVA of the mean power change at FCz for low beta (120-220ms at 13-20Hz), showed no main effects of cue type ($F(3.1, 96) = 1.22$, *n.s.*) or block ($F(1, 31) = .02$, *n.s.*).

High beta. An ANOVA of the mean power change at FCz for high beta (120-220ms at 20-30Hz), showed no main effects of cue type ($F(4,124) = 1.20$, *n.s.*) or block ($F(1, 31) = 1.41$, *n.s.*).

6.0.28 Discussion

In the transfer stage, Pavlovian cues enhanced responding for the instrumental response that shared the same outcome. This finding replicates previous results in human (e.g. Hogarth et al., 2007) and animal (e.g. Crombag, Galarce, & Holland, 2008) literature. Importantly extinction of the Pavlovian cues had no effect on the instrumental responses of participants in the transfer phase. Despite

showing normal acquisition and extinction in training, the cues continued to bias responses towards the original shared outcome. This result adds to the small body of literature suggesting that in both animals (Delamater, 1996; Rescorla, 1992) and humans (Hogarth & Chase, 2012; Rosas et al., 2010) extinction does not affect responding in the transfer stage of a PIT task. This suggests that the S-O association learnt in initial training is intact following extinction.

The learning which takes place during extinction has been the subject of much discussion (see Delamater (2012) for a review). The idea that the S-O association is weakened by extinction is not supported by the results presented here or previous literature. Both Rescorla (1996) and Delamater (1996) have tested the associative strengths of extinguished and non-extinguished conditioned stimuli (CS), finding no difference between them in their ability to enhance instrumental responding. Rescorla (1994) proposed that instead of weakening the S-O association, extinction may produce an inhibitory S-R association. This would be context dependent and rely on no further presentations of the original outcome. It would also leave the original association intact (Bouton, 2004) and therefore account for the above findings.

Hogarth & Chase (2011) used a devaluation-transfer procedure in which smokers were trained on a concurrent choice between keys to win either cigarette or chocolate tokens. Next, one of the outcomes was devalued using unpleasant statements or health warnings relating to the outcome. When subsequently tested in extinction responses for the devalued outcome were reduced suggesting that the choice behaviour was controlled by a mental representation of the

outcomes value. In the transfer stage of the experiment participants were asked to make the same choice but in the presence of a picture of either a chocolate bar or cigarette cue, as expected these cues elicited increased responding for the associated outcome. Baseline choice in the transfer test (the preference for a particular response) was sensitive to the devaluation procedure but the magnitude of the transfer effect was not moderated by the devaluation. This suggests that whilst the choice between the keys is controlled by a representation of the associated outcome, it is not sensitive to the current value of that outcome. This, Hogarth & Chase (2011) suggest, is due to an S-O-R relationship where presentation of the cue retrieves a representation of the outcome, which then triggers the subsequent response. As the outcome had been successfully devalued in training it seems likely that the outcome in this relationship does not code the absolute value, but instead automatically triggers the associated response (Hogarth & Chase, 2012).

Interestingly the preference for cigarette over chocolate outcomes, in the presence of cigarette cues, during the transfer test, correlated with some measures of dependence; the number of cigarettes smoked per day, length of smoking history and habit. Although the correlations were modest, they suggest those with a higher level of tobacco use show greater stimulus control of behaviour. This is consistent with the theory that addiction is in part due to excessive stimulus control of behaviour (e.g. Kosten et al., 2006). However we have not previously found any association between dependence and the magnitude of transfer (Hogarth & Chase, 2012) so we will avoid over analysing these correlations until they can be replicated.

The findings of this experiment contrast with those of Gámez & Rosas (2005) in which extinction suppressed responding in the transfer phase. Rosas et al. (2010) suggested that the result might be due to generalization between the extinguished and non-extinguished responses. The outcome specific PIT effect seen in the current experiment did not show any sign of generalisation between responses suggesting that the effect of extinction on transfer in Gámez & Rosas (2005) was either anomalous or has an alternative explanation.

Addiction treatments based on extinction research such as cue-exposure therapy have produced inconsistent results. In a meta-analysis Conklin & Tiffany (2002) suggest that further implementation of extinction research might improve the efficacy of such treatments. On the basis of this experiment and the previous literature it would seem that therapies based on extinction require further investigation but perhaps other methods such as the counter conditioning used by Van Gucht et al. (2010) may prove more effective at reducing craving and cue-elicited consumption.

In our two previous PIT experiments the EEG results had been mixed. We had expected to see differences, according to cue type, in the P3 ERP component and the beta frequency. With pictorial cues we found that the alpha frequency was modulated by cue type but this result was not replicated using arbitrary shapes as the Pavlovian stimuli. In the present experiment we see that the P3 component differentiated between cigarette and chocolate cues, which had not been extinguished. The same difference was not present for the extinguished cigarette-chocolate difference or between extinguished

and maintained cues for cigarette or chocolate trials. This suggests that the P3 is coding some difference between the maintained cigarette and chocolate cues and as with the behavioural data, this is not modulated by whether the cue has been maintained or extinguished. In isolation this result would suggest that that P3 may provide a measure of the specific PIT effect seen in the behavioural data, however correlational analyses revealed no relationship between the P3 difference for cigarette and chocolate cues, and either behavioural or addiction measures. It is interesting that although the cues used here were not abstract, they were not likely to have been previously associated with smoking and so are similar to the pattern cues used in chapter four, in which we found no difference in P3. As the results regarding an EEG measure of the specific PIT effect have been mixed in the three studies reported here, and the as the P3 does not seem to relate to our behavioural data or addiction measures, we will not speculate further.

Of the frequency bands investigated, theta and alpha were modulated by cue type, but further investigation revealed that the differences were between cued and blank trials. Neither low, or high, beta power showed an effect of cue type. None of the frequency bands showed differentiation between cigarette and chocolate, or extinguished and maintained cues.

In conclusion, both cigarette and chocolate cues enhanced responding for the response with a shared outcome, demonstrating the classic PIT effect. Although extinction proceeded as expected in training it did not reduce responding in the transfer phase. In the EEG

data, the P3 was larger following maintained cigarette than maintained chocolate cues. This component was not modulated by the maintained/extinguished nature of the cue.

Chapter 7

An investigation into the resting EEG of smokers

7.0.29 Abstract

Resting data was collected before and after a number of experiments in our lab to investigate how the resting EEG oscillations of smokers relate to addiction level, individual differences and cue responsivity. The data consisted of two minutes eyes open and two minutes eyes closed resting data. There were two important findings with regard to our hypotheses: (1) Those participants with shorter smoking histories (four or less years) showed lower beta levels than those with an extended smoking history (over four years) at frontal and central locations, suggestive of either sensitisation or the loss of inhibitory control in long term smokers. (2) Alpha asymmetry at Cz in the post experiment period correlated with both QSU-Brief measures of craving.

7.0.30 Introduction

Resting-state EEG oscillations may provide a window into the communication between brain areas and also into differences between populations (e.g. level of addiction). Using a large sample of resting data from young smokers, collected before and after other experiments run in our lab we hope to investigate whether resting oscillatory activity relates to (1) The length of a participants tobacco use, thus providing a potential marker for the risk of addiction or a measure of neurotoxicity. (2) Individual difference measures which are thought to play an important role in the development, maintenance or relapse of addictive behaviour. (3) The level of control a cue exerts over an instrumental behaviour in a subsequent task. We will start by reviewing the research relating to each of these areas, before investigating each using the current data.

1. Does resting state EEG reflect addiction status in young smokers?

A growing body of evidence suggests that power differences within the alpha frequency may provide a marker for disorders such as depression and addiction. For example a number of studies have linked alpha asymmetry with emotion regulation (Coan & Allen, 2004) and depression, specifically reduced left frontal activity as a risk marker (Allen & Cohen, 2010; Stewart, Bismark, Towers, Coan, & Allen, 2010). More relevant to the current study is the work of Knott et al. who have focused on whether smokers show a different EEG signature to that of non-smokers and how smoking affects the

EEG signal. Knott & Venables (1977) compared alpha levels prior to, and post smoking in deprived and non-deprived smokers to that of non-smokers. Results showed slower dominant alpha in deprived smokers than non-deprived smokers and non-smokers. Interestingly when the deprived smokers were allowed to smoke their alpha frequency returned to similar levels as the other two groups. There were no differences in alpha amplitude between the groups. The authors suggested that smoking acts as self-medication for smokers, perhaps returning them to a homeostasis with regard to alpha levels and related cognitive states. In this case use of drugs such as nicotine may be self-medicating for problems related to arousal and affective state (Knott, 2001).

In a subsequent experiment Knott & Venables (1979) examined the effects of alcohol and cigarettes on alpha frequency. Alcohol reduced the dominant alpha but tobacco smoking prior to or during alcohol consumption counteracted this effect, which was evident in both non-smokers and deprived smokers. More recently Knott & Harr (1997) looked at the effects of age and smoking history on EEG asymmetry. Resting EEG data were collected in young and old smokers and non-smokers. The smokers and non-smokers showed similar trends but differed in the ratio of alpha in frontal or posterior locations depending on age. Smoking altered the alpha ratio of both age groups. Similarly Fisher, Daniels, Jaworska, Knobelsdorf, & Knott (2012) found that nicotine administration resulted in greater left frontal alpha2 in smokers. This was not found in non-smokers suggesting that the finding was due to withdrawal.

Evidence linking alpha differences to drug use is not confined to

tobacco and alcohol use; Polunina & Davydov (2004) suggest that chronic heroin use may lead to frequency changes; specifically, pronounced desynchronization in withdrawal. These spectral changes tend to normalize after several weeks of abstinence. Gritz et al. (1975) compared alpha frequency in methadone maintained and abstinent heroin addicts, with normal subjects. It was possible to distinguish between these groups on the basis of the frequency of their alpha peak, which was at the lowest in the methadone group, followed by the abstinent group. Similarly Shufman et al. (1996) examined the spectral components of the EEG of heroin addicts, abstainers and controls. The addicts had a higher ratio of slow to fast alpha and the abstainers showed slowing of their alpha waves. The differences between abstainers and controls decreased with the length of abstinence.

There is some evidence of a genetic basis to the oscillations observed, specifically low alpha which showed complete concordance in monozygotic twins (Vogel, 1970). In line with this, reduced alpha and increased beta (occipital and frontal regions) have been shown in the offspring of alcoholics (Finn & Justus, 1999). Suggesting that low voltage alpha (LVA) may be a trait marker for risk of alcohol use disorders. Enoch et al. (1999) found that the LVA trait was more common in alcoholics with anxiety disorders suggesting a link between the LVA, anxiety and risk of alcoholism. More recently Enoch et al. (2008) suggested that resting EEG may reveal a phenotype for many behaviours in which arousal is implicated such as anxiety and alcoholism. The beta frequency also seems to be implicated in the genetic basis of addiction and it may serve as a marker for the

risk of developing alcoholism. Ehlers & Schuckit (1990) studied the beta frequency in the sons of alcoholics compared to those with no family history of alcohol abuse. The former group showed greater beta activity following ethanol consumption than the control group. Interestingly, in those without a family history of alcoholism, those who consumed moderate amounts of alcohol also showed greater beta following ethanol consumption than those who consumed low amounts. This difference was not present in the sons of alcoholics. This suggests that beta power may be modified by both genetic and behavioural factors. Further support is provided by Rangaswamy et al. (2004) who also showed higher beta in the offspring of alcoholics, although this was expressed at different frequencies within the beta range depending upon the participants gender. Bauer (2001) applied this research to test whether resting oscillations could predict relapse in abstinent alcoholics. Those who relapsed showed greater high frequency beta (19.5-39.8Hz) than those patients who maintained abstinence and those with no history of alcohol misuse. Fast beta power was found to be a good predictor of relapse, providing better results than factors such as severity of illness or depression score.

2. Resting EEG and individual differences

This part of the discussion will focus on the individual differences in impulsivity and craving, and their relation to the resting EEG of smokers. These two factors are highly important in understanding the aetiology and maintenance of drug addiction. In a study by Billieux, Van der Linden, & Ceschi (2007) the link between impulsivity

and craving were investigated, using the QSU-12 and the Impulsive behaviour scale (UPPS). The results showed a relationship between the urgency factor of the UPPS scale and tobacco cravings suggesting that these influential factors are linked.

Impulsivity. Although impulsivity has a wide range of definitions, for our purposes it can be defined as acting swiftly without conscious forethought of the outcome (Hinslie & Shatzky (1940) in Rogers, Moeller, Swann, & Clark (2010)). It has been implicated in a number of psychiatric disorders such as depression (Ruchsow et al., 2008), attention-deficit/hyperactivity (ADHD) (Scheres, Tontsch, Thoeny, & Kaczkurkin, 2010), obesity (Guerrieri, Nederkoorn, Schrooten, Martijn, & Jansen, 2009) and addictions including smoking, alcohol (Gran, Virtanen, Vahtera, Elovainio, & Kivimki, 2004) and gambling (Rogers et al., 2010). Impulsivity can be measured using behavioural tasks which generally require participants to withhold a response, such as in the Go/No Go (Newman, Widom, & Nathan, 1985), delay discounting (Reynolds, Ortengren, Richards, & De Wit, 2006) tasks, or self-report measures such as the Barratt Impulsiveness Scale (BIS-11 Barratt, 1959). The latter identified three key dimensions of impulsivity: the inability to maintain attention, motor impulsiveness acting without thinking, and non-planning impulsiveness, demonstrated by a lack of forethought. In general, questionnaire measures are intended to measure long-term characteristics and so are considered trait measures of impulsivity. In contrast, behavioural measures can be altered by experimental manipulations and are therefore regarded as state measures (Rogers et al., 2010). For this reason we will use the BIS measure of impulsivity in the

current study.

A number of studies have linked drug use with impulsivity, for example Moeller et al. (2002) identified a correlation between impulsivity, measured using the BIS-11, and cocaine use, even after controlling for aggression or antisocial personality disorder (ASPD). Although impulsiveness measured in a behavioural delayed reward task also correlated with cocaine use, this was not significant when ASPD was used as a covariate. Similarly Patkar et al. (2004) found higher BIS scores for cocaine patients than controls. Interestingly the levels of impulsivity predicted days of treatment attended and treatment dropout rate. ERP investigations of impulsivity have generally shown reduced P3 components (Chen et al., 2007; Ruchsow et al., 2008), consistent with the idea of reduced EEG activity in impulsive individuals, perhaps suggesting greater cortical activation in these individuals. Similarly Houston & Stanford (2005) found reduced frontal delta and theta, along with a different topographical pattern of beta, in an impulsive group when compared to controls. Using a visual-oddball task (Chen et al., 2007) found reduced frontal activity in alcoholic and impulsive participants. O'Gorman & Lloyd (1987) measured the spontaneous alpha activity whilst subjects opened and closed their eyes, as instructed. Impulsivity was measured using the Eysenck (1977) extraversion scale (EPQ). Alpha activity was lower in those with high scores on the narrow impulsiveness dimension, suggesting greater arousal in impulsive individuals. Parvaz, Alia-Klein, Woicik, Volkow, & Goldstein (2011) also found low beta frequencies in alcoholics suggestive of hyper-arousal. However, there is some evidence that highly impulsive participants show higher levels

of theta; an EEG signature that is consistent with lower arousal (Stenberg, 1992) and to confuse the issue further, there is also evidence of higher alpha activity in impulsive individuals but only if they showed high anxiety as well. Taken together, this evidence suggests that further investigation is warranted of the relationship between EEG activity and impulsivity, in relation to addiction.

Craving. Craving is thought to play a crucial role within addiction, both increasing the likelihood of consumption and relapse. It is usually conceptualised as either positively reinforcing the effects of drug taking (e.g. Robinson & Berridge, 1993) or as negatively reinforcing the effects of withdrawal (e.g. Shiffman, Paty, Gnys, Kassel, & Hickcox, 1996). Alternatively craving may not drive drug use at all; for example Tiffany (1990) proposes that craving is the result of an interruption in a habitual drug-taking sequence.

The brief questionnaire of smoking urges (QSU-brief) is analysed according to two factors identified using exploratory factor analysis (Cox, Tiffany, & Christen, 2001). Factor 1 reflects the desire and intention to smoke, in which smoking is inherently rewarding. Factor 2 also reflects a desire to smoke but in this case with an anticipated relief from negative effect. Affect-regulation theories of addiction propose that smoking may be driven by two processes; the enhancement of positive affect through the rewarding properties of nicotine, and by the reduction of negative affect such as that caused by withdrawal (Gilbert, 1979). Subsequently, alpha asymmetry has been proposed to index these affective states with greater left anterior activity during approach and positive states, and right frontal hyperactivity during negative, withdrawal-related states (Davidson,

2004). Jaworska et al. (2011) suggest that individual differences in alpha asymmetry may bias a persons affective style and potentially predispose them towards Major Depressive Disorder (MDD). As research suggests individual differences in alpha asymmetry within the addiction and specifically smoking, literature, the asymmetry scores may also reflect affective states within addiction or a predisposition toward habitual behaviours. Most research into EEG and craving has focused on the brains responses to cue-induced craving rather than resting EEG measures. It is interesting however that differences in alpha asymmetry have been observed following cigarette-cue exposure and subsequent reported cravings (Knott et al., 2008) and reduced alpha coinciding with reduced craving following virtual reality therapy (Lee et al., 2009). The current study aims to investigate whether we can observe any differences in resting EEG which relate to participants craving as measured by the QSU.

3. Is there a relationship between cue/reward processing and resting EEG?

Reward bias or sensitivity has been implicated in the progression towards addiction (e.g. Gladwin & Wiers, 2012) so a neural measure of this phenomenon would be of interest in the understanding and treatment of addiction. Pizzagalli, Sherwood, Henriques, & Davidson (2005) correlated resting alpha asymmetry with reward responsivity. The study utilised a verbal recognition task in which participants responded according to whether they had previously seen a word. A distracter task was used between the word presentation and the recognition stages. The task was completed under

three payoff contingencies; reward in which correct responses earned 10 cents, punishment where incorrect responses lost 10 cents and neutral trials in which feedback was provided but no monetary outcome. Higher alpha2 (10.5-12Hz) in left dorsolateral prefrontal and medial orbitofrontal regions correlated with the bias to respond in the presence of reward-related cues. Pizzagalli et al. (2005) suggest that this data adds to the literature suggesting that left frontal regions play a role in approach tendencies and appetitive behaviour.

To summarise this chapter aims to address three questions utilising resting EEG data and young smokers:

1. Does resting state EEG reflect addiction status in young smokers?

We expect to see differences within alpha and/or beta bands according to the length of participants smoking history and addiction level. Specifically, reduced frontal alpha in more highly addicted individuals or those with longer smoking histories. We would expect greater beta in this group.

2. Does resting EEG correlate with individual differences in smokers?

A correlational analysis will be used to examine the relationship between participants resting EEG and their scores on questionnaire measures assessing impulsivity and craving. We expect to see a positive correlation between alpha and impulsivity with lower alpha, suggestive of greater cortical activity, in those with high impulsivity scores.

3. Is there a relationship between cue/reward processing and resting EEG?

A correlational analysis will be used to see if alpha or beta bands reflect cue responsivity in the tasks administered between resting sessions.

7.0.31 Method

Participants

The data from the previously described experiments was combined to provide resting data for 146 participants, who had been recruited by email and poster adverts. All were right-handed and had normal or corrected to normal vision, they received £15 inconvenience allowance and were asked to refrain from smoking for two hours prior to the experiment. Participants were excluded from the study if they had consumed alcohol or drugs (within 12 hours), sleeping pills (within 48 hours) or anti-depressants. Procedures were in accordance with the declaration of Helsinki and were approved by the University of Nottingham Ethics committee. All participants provided written and informed consent.

Apparatus

The experiment was programmed using E-prime software (E-Prime Psychology Software Tools Inc., Pittsburgh, USA) and displayed on

a 15-inch monitor. The breath carbon monoxide levels of participants were measured at the commencement of the experiment using a Bedfont Smokerlyzer (Bedfont Scientific Ltd. UK).

The following questionnaire measures were used:

BIS The Barratt Impulsiveness scale (BIS) is used as a marker for dependence and other neuropsychiatric conditions. It contains three subscales of impulsivity (a key factor in addiction); 1. Motor impulsivity (e.g. I do things without thinking), (2) non-planning impulsivity (e.g. I do not plan tasks carefully) and (3) Attentional impulsivity (e.g. I struggle to maintain attention). Although there are many methods for measuring impulsivity, both behaviourally and in questionnaire format, the BIS has regularly been associated with drug addiction (Stanford et al., 2009).

The Zuckerman Sensation Seeking scale, developed by Zuckerman (1971), is intended to measure individual differences in levels of stimulation or arousal. The original study reviews evidence that sensation seeking is positively associated with impulsive traits, suggesting that it may be of use in the study of addiction.

BIS/BAS Gray (1981) argued that two general motivational systems underlie behavior. (1) A behavioral approach system (BAS) which is believed to regulate appetitive motives, in which the goal is to move toward something desired. (2) A behavioral avoidance (or inhibition) system (BIS) which is said to regulate aversive motives, in which the goal is to move away from something unpleasant or avoid punishment. Carver and White (1994) subsequently developed the BIS/BAS scales to assess individual differences in the sensitivity

of these systems. There is evidence that BAS scores may be higher in addicted individuals (Franken et al. 2006).

Fagerstrom: The Fagerstrom test for nicotine dependence was adapted from the Fagerstrom Tolerance Questionnaire (Fagerstrom, 1978) by Heatherton, Kozlowski, Frecker & Fagerstrom (1991). The latter assessment and revision concluded that the test provides a valid measure of heaviness of smoking. The scale has six items with an overall score ranging between zero and ten. High dependence is usually defined as a score of six or more (John, Meyer, Rumpf & Hapke, 2004; Fagerstrom et al., 1996).

CDS-5 The Cigarette Dependence Scale (CDS; Etter, Houezec & Perneger, 2003) was developed from qualitative surveys and then tested on a large sample (n = 3009) of smokers via the Internet. This study resulted in both a twelve and a five item version (CDS-5). It covers the main components of both the DSM-IV and ICD-10 definitions of addiction (compulsion, withdrawal symptoms, loss of control, neglect of other activities and persistence despite harm). Scores range from 5 (low dependence) to 25 (high dependence) (Etter, Houezec & Perneger, 2003).

QSU-brief The brief questionnaire of smoking urges (QSU-brief) was developed from the original QSU by Cox, Tiffany and Christen (2001) to provide a brief measure of craving in smokers. A factor analysis of the original QSU revealed two main factors: (1) a strong desire and intention to smoke and (2) the anticipation of relief from the negative effect caused by withdrawal. Craving may be a key factor in the relapse of addicted individuals and as suggested in the introduction may relate to resting EEG.

AUQ The Alcohol use questionnaire (AUQ) is used widely in alcohol research. It provides information about the quantity and frequency of a subjects alcohol intake, along with information about the types of alcohol consumed. Townshend and Duka (2002) compared it to a four week diary of alcohol consumption. They found that the questionnaire tended to lead to underestimation of consumption in heavy drinkers but the two measures showed fairly good correlation. We used this measure as it provides a quick and easy measure of alcohol consumption but this limitation should be born in mind when interpreting results.

These measures were used in all the experiments presented in this thesis and combined in this chapter in order that we might have a range of measures of addiction level and character traits, which we can then correlate with resting EEG activity.

Design and procedure

Following application of the EEG nets, participants were seated in a separate room from the experimenter. The participants were sat in front of a monitor, on which the instructions; "Please sit still with your eyes open, when you hear a tone, close your eyes. Keep them closed until you hear a second tone, signalling the end of this part of the experiment". The EEG phase of the experiment began with a four-minute baseline period where participants were asked to sit with their eyes open until they heard a tone (administered through Sennheiser CX300 in-ear headphones) at which point they closed their eyes until they heard another tone. This signalled the end of

the baseline period. During the baseline measurements the computer monitor remained blank with just a grey background. Participants then completed one of the behavioural experiments described earlier in this thesis, followed by an identical resting measure to finish the EEG stage of the study. Finally participants completed a battery of questionnaires.

EEG methods and analysis

The EEG data was recorded from 128 sites at a 250 Hz sampling rate using an EGI (Electrical Geodesics Inc., Eugene, OR, USA) dense-array EEG system (GES 200 net) and a Net Amps 200 amplifier. Electrode impedances were kept below 50 k. The raw data was exported from Netstation to EEGlab (a Matlab toolbox designed by Delorme & Makeig, 2004) for processing where all subsequent analysis was performed using purpose-written scripts that utilized EEGLab and the FASTER toolbox (Nolan, Whelan, & Reilly, 2010). The data was low and high pass filtered (0.5-35Hz) and two-minute epochs were extracted according to whether the participant was instructed to have their eyes open or closed, and whether the data was taken before or after the behavioural task. This provided four types of epoch: (1) Eyes open/pre-test, (2) Eyes closed/pre-test, (3) Eyes open/post-test and (4) Eyes closed/post-test.

Artifact correction was applied using the Fully Automated Statistical Thresholding for EEG artifact rejection (FASTER) plug-in for EEGLab (Nolan et al., 2010). To summarise the process, bad channels and epochs are rejected according to their deviation from the

mean, variance and amplitude range. FASTER then uses Principle component analysis to reduce the total number of components according to the quantity of data available. Independent component analysis (ICA) is then used to identify the artifactual components, which are rejected. Finally any rejected channels are interpolated.

The processed files were then submitted to frequency analysis in EEGLab using a Fast Fourier Transform (FFT) to compute the log spectral data for each channel and frequency. The EEGLab function spectopo() was used with two-second epochs which were overlapped by 50%, using Hamming windows (Harris, 1978) to reduce edge effects. The power density at each frequency was estimated using Welchs method (Welch, 1967).

The spectral data was then manipulated in Matlab to produce average power values for each frequency band: delta (1-4Hz), theta (4-8Hz), alpha1 (8.5-10Hz), alpha2 (10.5-12Hz), total alpha (8-13Hz) and beta (13-30Hz), for midline electrodes equivalent to Fz, Cz and Pz. For information on the corresponding electrode positions according to the 10-10 system please refer to Luu & Ferree (2000). Alpha and beta asymmetry was also calculated using: (L-R)/(L+R), the method suggested by Pivik et al. (1993) to be the most easily interpretable asymmetry index. Positive values indicate higher power in the left hemisphere.

7.0.32 Results

If any of the variables used in the following ANOVAs were found to violate the assumption of sphericity the results were corrected

using the Greenhouse-Geisser correction. Results presented show the corrected values where applicable.

Participants

Participants had an average age of 21.84 (sd = 3.6), 15.86 years of education (sd = 2.43), smoked 5.22 days per week (sd = 2.2), on which days they smoked 6.78 cigarettes (sd = 4.56), smoked their last cigarette 20.4 hours prior to the experiment (sd = 28.5), started smoking at the age of 17.5 years (sd = 3.10), reported a DSM nicotine dependence score of 4.85 (sd = 1.45) (a score of over 3 on this scale is suggestive of nicotine dependence), a QSU-Brief, factor 1 craving score of 4.79 (sd = 1.75), QSU-Brief factor 2 craving score of 2.28 (sd = 1.34) (for the QSU measures of craving, any score above zero is indicative of craving), drank 20.4 units of alcohol per week (sd = 15.65) and had an alcohol binge score of 30.46 (sd = 58.66) (Together these measures provide a measure of how much is consumed (in units) and how often the subject drinks).

Frequency analysis

Initially each frequency band was analysed separately to check for differences between the epoch types. If there were differences, then the epochs were treated separately in further analysis. Alternatively, if there were no differences between epoch types, the data were collapsed either across periods (before/after) or eye state (open/-closed), or both, before further analysis.

Delta. A 2 x 2 x 3 (period [pre-experiment/post-experiment]), eye state [eyes open/eyes closed], area [Fz, Cz, Pz]) ANOVA revealed main effects of eye state ($F(1, 137) = 28.07$, $p < .001$) and area ($F(1.33, 182.47) = 479.73$, $p < .001$). There were interactions between period and area ($F(1.62, 222.43) = 23.32$, $p < .001$), eyes and area ($F(1.14, 156.24) = 113.48$, $p < .001$).

Theta. A 2 x 2 x 3 (period [pre-experiment/post-experiment]), eye state [eyes open/eyes closed], area [Fz, Cz, Pz]) ANOVA revealed main effects of period ($F(1, 137) = 28.73$, $p < .001$,), eye state ($F(1, 137) = 63.08$, $p < .001$) and area ($F(1.74, 237.84) = 126.45$, $p < .001$). There were interactions between period and area ($F(1.70, 233.21) = 8.76$, $p < .001$), eyes and area ($F(1.35, 184.89) = 103.04$, $p < .001$) and period, eyes and area ($F(1.69, 231.76) = 8.12$, $p < .001$).

Alpha. As expected we see greater alpha during the eyes closed periods of the EEG measurement. A 2 x 2 x 3 (period [pre-experiment/post-experiment]), eye state [eyes open/eyes closed], area [Fz, Cz, Pz]) ANOVA revealed main effects of period ($F(1, 137) = 28.33$, $p < .001$), eye state ($F(1, 137) = 88.53$, $p < .001$) and area ($F(1.91, 261.97) = 135.60$, $p < .001$). There were interactions between period and eyes ($F(1, 137) = 4.30$, $p < .05$), period and area ($F(2, 274) = 8.86$, $p < .001$), eyes and area ($F(2, 274) = 36.16$, $p < .001$) and period, eyes and area ($F(2,274) = 3.22$, $p < .05$).

Alpha asymmetry. The data for overall alpha and the two levels of alpha were analysed separately. The overall alpha asymmetry was subjected to a 3 x 2 x 2 (area [Fz, Cz, Pz], eye state [eyes open/eyes closed], period [pre-experiment/post-experiment]) ANOVA which revealed no main effects but an interaction between area and period

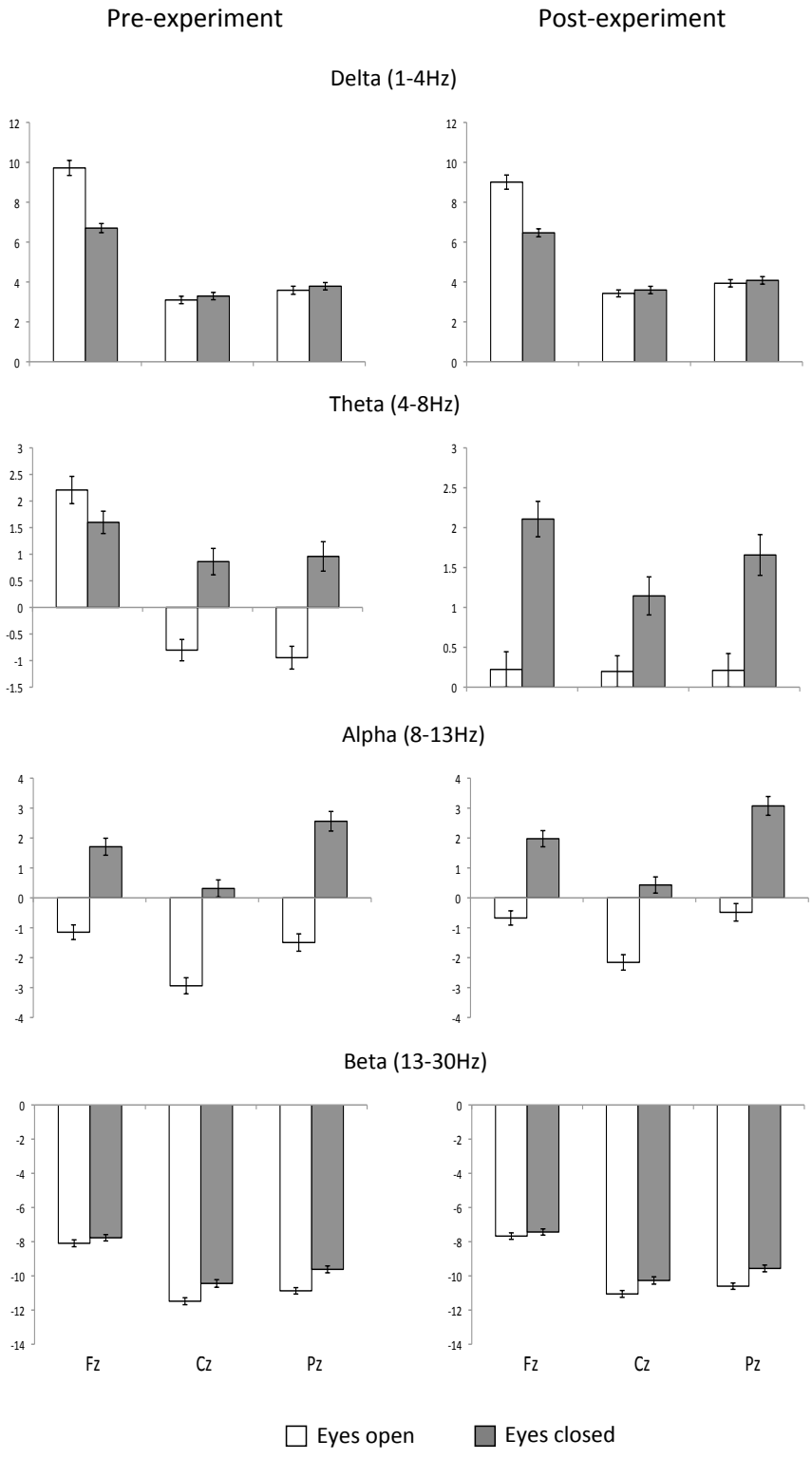


FIGURE 7.1: Power in Delta, theta and Beta frequency bands at frontal, central and parietal locations. The left-hand column shows the data pre-experiment, post experiment data is displayed on the right. The Y axis is mean power (dB) in the selected frequency range.

($F(1.4, 258) = 3.99$, $p < .05$). Further analysis of this interaction with t-tests showed that the interaction was driven by the difference in alpha asymmetry between the pre- and post-experiment conditions at parietal locations ($t(129) = -2.65$, $p < .05$), whereby alpha was greater in the right parietal location prior to the experiment but showed greater left alpha post experiment. The differences at frontal ($t(129) = .718$, $p = .47$, ns) and central ($t(129) = -1.47$, $p = .14$, ns) locations were not significant.

Alpha asymmetry was also split into the two levels for a separate 3 x 2 x 4 (area [Fz, Cz, Pz], Alpha [alpha1, alpha2], recording period [pre-open, pre-closed, post-open, post-closed]) ANOVA, but this revealed no main effects or interactions.

Beta. A 2 x 2 x 3 (period [pre-experiment/post-experiment]), eye state [eyes open/eyes closed], area [Fz, Cz, Pz]) ANOVA revealed main effects of period ($F(1, 137) = 15.29$, $p < .001$), eye state ($F(1, 137) = 96.22$, $p < .001$) and area ($F(1.86, 255.23) = 336.65$, $p < .001$). There was an interaction between eyes and area ($F(1.95, 267.32) = 46.47$, $p < .001$).

Beta asymmetry. A 3 x 2 x 2 (area [Frontal, Central, Parietal], eye state [eyes open/eyes closed], period [pre-experiment/post-experiment]) ANOVA of beta asymmetry revealed no main effects or interactions.

1. Does resting state EEG reflect addiction status in young smokers?

Alpha. The alpha frequency was analysed according to a median split of the number of years participants had been smoking for. A 2 x

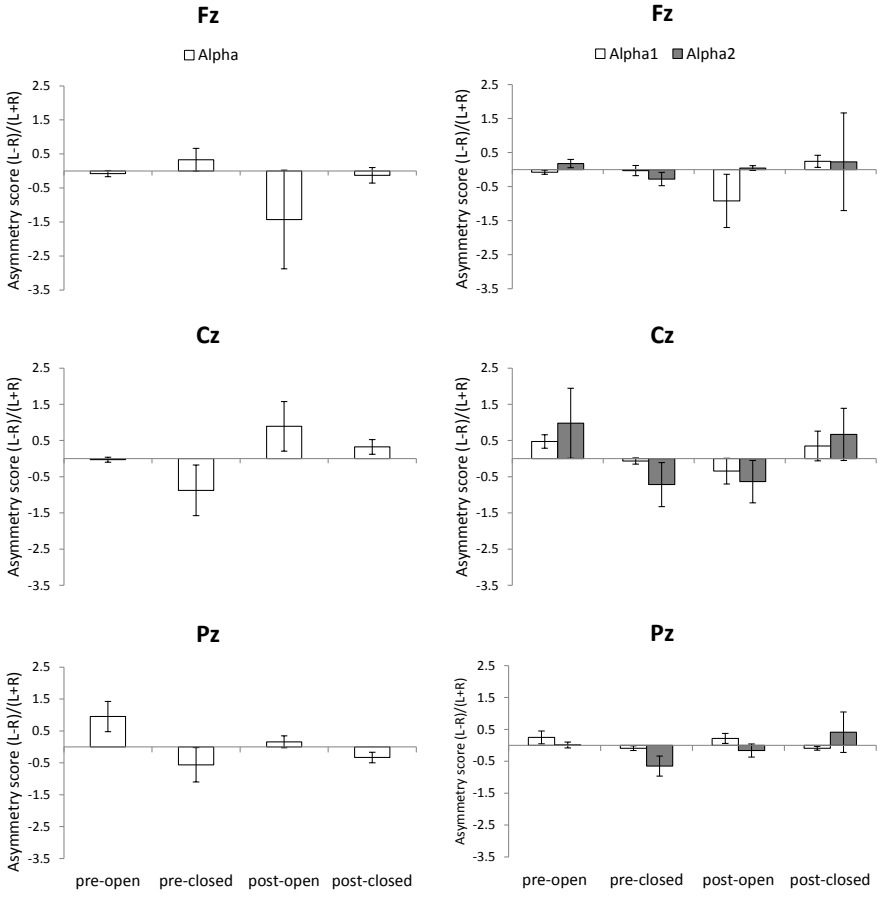


FIGURE 7.2: Alpha asymmetry scores. The left column is overall alpha (8-13Hz). The right-hand column shows the values for alpha1 (8.5-10Hz) and alpha2 (10.5-12Hz). Positive scores reflect greater left than right hemisphere alpha activity.

2 x 3 x 2 (period [pre-experiment/post-experiment]), eye state [eyes open/eyes closed], area [Fz, Cz, Pz], group [1-4 years, 4+ years]) ANOVA revealed no main effects or interactions with the number of years smoking history variable.

Beta. We analysed the beta frequency according to a median split of the number of years participants had been smoking for. A 2 x 2 x 3 x 2 (period [pre-experiment/post-experiment]), eye state [eyes open/eyes closed], area [Fz, Cz, Pz], group [1-4 years, 4+ years]) ANOVA revealed main effects of period ($F(1, 136) = 14.86$, $p < .001$), eye state ($F(1, 136) = 99.40$, $p < .001$) and area ($F(1.87,$

254.44) = 334.78, p <.001). There were interactions between area and group (F(2, 272) = 3.56, p <.05), and eye state and area (F(2, 272) = 45.84, p <.001).

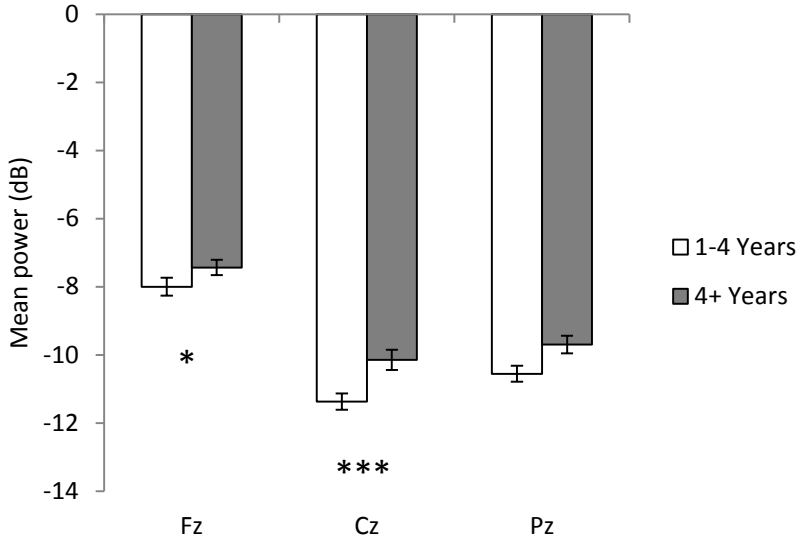


FIGURE 7.3: Beta power at frontal (Fz), central (Cz) and parietal (Pz) electrodes, split by the median number of years of smoking history (* p <.05, *** p <.001).

Further analysis of the group differences at each area revealed differences between the groups at Fz (F(1, 137) = 5.96, p <.05) and at Cz (F(1, 137) = 10.7, p <.001), with those participants with shorter smoking histories (four or less years) showing lower beta levels than those with an extended smoking history (over four years) at frontal and central locations.

2. Resting EEG and individual differences

Questionnaire measures of addiction, impulsivity and craving were correlated with resting frequency data using Spearmans rho, as some of the measures were not normally distributed. Separate analyses

were conducted for each frequency. As there were a large number of comparisons, the results were only reported if they met the Bonferroni adjusted significance level of $p < .003$. There were no correlations that met this level for delta, theta, alpha or beta. However there were positive correlations between alpha asymmetry at Cz in the post experiment period and the QSU-Brief factor 1 (Spearmans rho = .29, n = 145, $p < .001$) and the QSU-brief factor 2 (Spearmans rho = .27, n = 145, $p < .001$) measures of craving, whereby increased left, central alpha was related to increased levels of craving.

Reward bias

The preference for the cigarette key over the chocolate key on cigarette trials was correlated with alpha, alpha asymmetry, beta and beta asymmetry. A Bonferroni multiple comparisons corrected significance level of .004 was used. Only beta asymmetry at Pz, during the post-experiment eyes closed trials met this criteria, positively correlating with the preference for the cigarette key over the chocolate key in the presence of the cigarette cue (Spearmans rho = .25, n = 106, $p = .004$).

7.0.33 Discussion

1. Does resting state EEG reflect addiction status in young smokers?

Based upon previous research in the area, we expected to see reduced alpha (e.g. Knott, 2001b) and increased beta power (e.g. Ehlers &

Schuckit, 1990) in participants with lengthy smoking histories. In line with our predictions, those participants with more than four years smoking history showed less beta de-synchronization at frontal and central sites, relative to those with shorter smoking histories. There were however, no differences in alpha using the same grouping variable.

Previous evidence has found increased beta in the offspring of alcoholics (Rangaswamy et al., 2004), greater beta power following ethanol consumption (Ehlers & Schuckit, 1990) and that beta levels can predict relapse in abstinent alcoholics (Bauer, 2001). This study suggests that beta levels in smokers reflect the length of smoking history, with those who have been smoking over four years showing increased beta levels, compared to those with shorter smoking histories. We did not investigate the smoking or addiction status of the participant's relatives so cannot determine whether the beta differences reflect a possible genetic trait or predisposition to addiction, or are as a result of the smoking behaviour, perhaps a neurotoxic effect of smoking for a number of years.

An intriguing difference between the current results and those of previous studies is that we see overall reduced beta during the resting state, most other studies see small (in relation to other frequencies such as alpha) increases (e.g. Bauer, 2001; Ehlers & Schuckit, 1990; Jaworska et al., 2012). The reason for this difference is unclear but if beta activity is indicative of cortical processing (e.g. Marco-Pallares et al., 2008) we might expect to see decreases in beta power during a resting state, and increases in alpha rythms indicative of relaxation.

This does not explain why others have not seen the overall beta decrease and thus requires further investigation.

Based mainly upon the work of V.J. Knott and colleagues we expected to see reduced alpha levels in those with a longer smoking history. Differences in alpha have been found in chronic heroin use (Polunina & Davydov, 2004) and more generally with arousal and anxiety-related behaviours (Enoch et al., 2008). There was no indication of a difference in the alpha frequency band for the current participants, based upon the length of their smoking history. If such differences are neurotoxic in nature this may be explained by the fact that the smoking histories were not lengthy enough for the differences to appear

2. Does resting EEG correlate with individual differences in smokers?

We predicted that alpha power would correlate with impulsivity; specifically that lower alpha, suggestive of greater cortical activity, would be found in those with high impulsivity. There were no correlations between any of the frequency bands and the BIS-11 measure of impulsivity. However the results did show a relationship between alpha asymmetry and craving. Specifically, alpha asymmetry at Cz in the post experiment period correlated with both factors of the QSU-Brief suggesting that greater left central alpha was related to higher levels of craving. Factor 1 of the QSU-Brief reflects the positive and rewarding aspects of smoking such as the desire and intention to smoke, whilst factor 2 represent the anticipation of relief from the negative aspects (Cox et al., 2001). Interestingly alpha

asymmetry at Cz during the post experiment period correlated with both factors. We had expected any differences to occur at Frontal locations but Jaworska et al. (2011) found that in the short term at least, nicotine administration lead to differences in alpha asymmetry at central locations. In their study nicotine modulated alpha activity in a similar manner to the alpha modulation seen during positive affective states (Jaworska et al., 2011).

The complexity of craving as a clinical construct is reflected in the multidimensional nature of the scales used to assess it. It is thought to play a role in drug seeking and relapse. Multiple brain structures have been shown activation during craving including the OFC and the limbic system which have been shown to be involved in reward processing and decision making which both play key roles in addiction (Lee et al., 2009).

The lack of correlation between any of the frequency bands and impulsivity is surprising in the light of a number of studies suggesting a link between alpha, impulsivity and treatment outcome (Moeller et al., 2001; Patkar et al., 2004). This might be due to the levels of impulsivity within our sample. The average BIS-11 score for all subjects was 68.73 (s.d. = 11.08). It is difficult to assess whether this is particularly high as most studies compare the impulsivity by splitting high/low impulsives according to the mean score for their sample. However Li & Chen (2007) suggest average BIS-11 scores of between 64 and 72 for western samples. This would suggest that our sample is fairly average in terms of impulsivity and may well explain why we don't see the expected relationship between impulsivity and

EEG measures. Alternatively it could be due to the use of the BIS-11 to measure impulsivity rather than a behavioural paradigm; a study by Reynolds et al. (2006) found a poor correlation between self-report personality measures such as the BIS and behavioural measures of impulsivity. However the latter explanation seems unlikely, as both studies cited above (Moeller et al., 2001; Patkar et al., 2004) used the BIS among other measures of impulsivity. It was unclear whether the relationship between alpha power and impulsivity indicated a predisposition to addiction or where a result of it. As the BIS is thought to provide a measure of the trait like aspects of impulsivity rather than the current state of the participant as measured by behavioural tasks, this relationship is worthy of further research.

3. Is there a relationship between cue/reward processing and resting EEG?

Alpha and beta band power were correlated with the preference for the cigarette response in the presence of a cigarette cue. Parietal beta during the post-experiment eyes closed period correlated with the preference for the cigarette key over the chocolate key in the presence of cigarette cues during the behavioural tasks administered between resting sessions. Although the correlation met the Bonferroni correction for multiple comparisons, we treat this result with caution, as we would not expect the correlation to be limited to the eyes closed, post-experiment condition, or for it to be at parietal locations.

A small body of literature suggests a link between frontal alpha asymmetry and various measures of individual differences such as approach tendencies (Harmon-Jones & Allen, 1997), emotional reactivity (Wheeler et al., 1993), positive and negative affect (Tomarken et al., 1992) and reward responsivity (Pizzagalli et al., 2005). In the current study there were no significant correlations between mean alpha power or alpha asymmetry, and the preference for the cigarette key in the presence of the cigarette cue.

Summary

The current study was intended to investigate the resting EEG data of young smokers with a range of addiction levels and drug histories. It was exploratory in nature but has demonstrated two key findings; 1. Resting beta power, at frontal and central sites, is greater in participants with smoking histories exceeding four years, suggesting that beta power may provide a measure of either the neurotoxic effects of a lengthy smoking history or a predisposition toward a lengthy history and presumably a higher chance, or level, of addiction. 2. Alpha asymmetry at Cz, in the post-experiment condition correlated with both QSU-Brief measures of craving. So, greater left frontal activity correlated with both the rewarding aspects of smoking (factor 1) and the expected relief from negative affect (factor 2).

There was also a correlation between beta power at Pz and the behavioural preference for the cigarette key in the presence of the cigarette key. This may support theories of cue control in addicted individuals, but as the finding was limited to the post experiment,

eyes closed period, the result needs replication before we can draw further conclusions.

Chapter 8

Conclusion

In this thesis I have presented a number of studies that aim to increase understanding of the learning and decision making of addicted individuals using behavioural and EEG techniques. The behavioural PIT evidence broadly supports previous work in this area demonstrating the effect of Pavlovian cues on instrumental responses. However the EEG data, whilst interesting, are inconclusive with regard to an EEG correlate of the hypothesised hypervaluation of drug-related stimuli. I have attempted to apply rigorous standards to the analysis of the data with corrections for multiple comparisons and seeking to replicate results across studies. These results are discussed, chapter by chapter, along with their implications, limitations and finally suggestions for future research in this area.

8.0.34 Summary of results

Chapter 3: Concurrent choice.

Smokers completed a concurrent choice task which assessed their preference for either cigarette or chocolate outcomes. Behaviourally there was no preference for either key across subjects. The P3 was sensitive to reward (vs. non-reward) and also to the frequency of an outcome. It did not demonstrate any relationship between the P3 amplitude and addiction level and cannot therefore provide a measure of the hypothesised over-valuation of drug-related outcomes. The time-frequency analysis, and specifically low beta power, similarly showed differences according to the trial type but this did not relate to addiction level.

Chapter 4: PIT with pictorial cues.

A PIT was utilized to investigate the influence of predictive Pavlovian cues on an instrumental behaviour in daily and non-daily smokers. The cues elicited a bias to respond for the associated outcome. This outcome-specific transfer effect suggests that the cues were controlling behaviour through a mental representation of the outcome, rather than a direct stimulus-response, or habit based mechanism. None of the ERP components investigated differentiated between the types of cue. However the alpha frequency (8-13 Hz) differentiated between the types of pictorial cue with the highest amplitudes in response to cigarette, then chocolate and finally blank cues. Using a correlational analysis we found that the higher participants score on the DSM-IV measure of addiction, the less difference there is in alpha power following cigarette and chocolate cues.

Chapter 5: PIT with arbitrary cues

A PIT paradigm was used to further investigate the influence of Pavlovian cues on instrumental responses but this time using arbitrary patterns as the Pavlovian cues instead of pictures, thus allowing control over the extent of participants exposure to the cues. As with pictorial cues we saw a specific PIT effect with cues enhancing responding for the shared outcome. None of the ERP or frequency components investigated differentiated between cue types.

Chapter 6: PIT with extinction

The PIT task was modified to include an extinction phase in which one cigarette and one chocolate cue were extinguished by omitting rewards for these cues. Both of the maintained cigarette and chocolate cues enhanced responding for the shared outcome, demonstrating the classic PIT effect. Although extinction proceeded as expected in training it did not reduce responding in the transfer phase. In the EEG data, the P3 was larger following maintained cigarette than maintained chocolate cues. This component was not modulated by the maintained/extinguished nature of the cue.

Chapter 7: Resting data

Resting data was collected before and after a number of experiments in our lab to investigate how the resting EEG oscillations of smokers relate to addiction level, individual differences and cue responsivity. The data consisted of two minutes eyes open and two minutes eyes closed resting data. There were two important findings with regard to our hypotheses: (1) Those participants with shorter smoking histories (four or less years) showed lower beta levels than those with

an extended smoking history (over four years) at frontal and central locations, suggestive of either sensitisation or the loss of inhibitory control in long term smokers. (2) Alpha asymmetry at Cz in the post experiment period correlated with both QSU-Brief measures of craving, suggesting that greater left frontal activity is associated with both the rewarding aspects of smoking (factor 1) and the expected relief from negative affect (factor 2).

8.0.35 Summary of contributions

Surprisingly, in the concurrent choice task, we did not replicate previous research showing a preference for drug-related behaviours in rats (Deroche-Gamonet, Belin, & Piazza, 2004; Pelloux, Everitt, & Dickinson, 2007; Vanderschuren & Everitt, 2004) and humans (Moeller et al., 2009; Perkins et al., 2002). This preference is often taken as evidence for a hyper valuation of drug related behaviours and related cues (Robinson & Berridge, 2008). The lack of such a finding suggests that perhaps the levels, and length, of addiction seen amongst our group of smokers was perhaps too low for this preference to be expressed. However within the instrumental stages of all the individual PIT tasks we consistently saw a strong preference for the cigarette key over the chocolate key supporting the idea that drug-users place a higher valuation on drug-related actions and outcomes than other, non-drug related behaviour. A possible explanation for the disparity between the concurrent choice and PIT results is that the preferences shown in the PIT tasks are over a relatively low number of trials, perhaps the effect is diluted by the number of trials included in the concurrent choice task.

The PIT results here both support and extend previous work showing a robust PIT effect with both pictorial and abstract stimuli, suggesting that the outcome representation is similar regardless of whether the cue is abstract or explicitly drug-related in nature. This demonstration of a strong specific PIT effect with both abstract patterns and drug related cues provides evidence that drug cues influence behaviour through a mental representation of the association between the cue and the outcome, not by a habit based mechanism in which the cue would automatically trigger a response. This replicates previous work which has also shown the effect of drug cues on drug-seeking (Hogarth & Chase, 2011; Hogarth, Dickinson, Wright, Kouvaraki, & Duka, 2007; Trick, Hogarth, & Duka, 2011) but is only the second demonstration in humans, of the outcome-specific control of drug seeking by drug-associated stimuli (Hogarth, Balleine, Corbit, & Killcross, 2013).

Interestingly the PIT effect was not affected by extinction, suggesting that the S-O relationship remains intact and supporting previous research with animals (Delamater, 1996; Rescorla, 1992) and humans (Hogarth & Chase, 2011; Rosas, Paredes-Olay, Garca-Gutirrez, Espinosa, & Abad, 2010). However there is some indication that other methods of extinction may be more effective. Recent data from our lab suggests that the type of extinction used may dictate whether it affects the transfer phase. Whilst responding is not reduced by Pavlovian extinction as used here, discriminative extinction does seem to reduce responding (data in preparation).

Regarding the EEG findings, there do not appear to be any consistent ERP or frequency components which code the hyper-valuation

of drug-related cues in addicted populations. Reasons for this will be discussed below. In the preference task the P3 differentiated between reward versus non-reward trials and was sensitive to the frequency of an outcome, which is in line with other research (e.g. Friedman, Cycowicz, & Gaeta, 2001). For the PIT experiments, the most interesting EEG result was that alpha power was modulated by the type of cue presented (with the highest amplitudes in response to cigarette, then chocolate and finally blank cues), and that the difference in alpha power following cigarette to chocolate cues was smaller in more addicted individuals (as measured by the DSM-IV). This was not however replicated for arbitrary cues or letter cues in the later studies suggesting that the effect was specific to pictorial cues rather than cues with learned associations.

Using a fairly large sample of participants, collected across all of the studies presented here, we examined the resting data of smokers. The first question of interest was whether resting EEG could provide a measure of nicotine addiction status. Although we did not see the expected differences in alpha power there was less beta de-synchronization in those with longer smoking histories. Previous evidence of beta differences in resting EEG with drug-using populations has shown increases in the offspring of alcoholics (Rangaswamy et al., 2004), greater beta following ethanol administration (Ehlers & Schuckit, 1990) and that beta power can be used to predict relapse in alcoholics (Bauer, 2001). As we did not investigate the participants relatives or look at their smoking behaviour longitudinally we cannot make any claims about these areas. However it does suggest that beta power may be implicated in addiction and therefore be

worthy of further investigation.

We also investigated the relationship between measures of individual differences in smokers and their resting EEG. There was a correlation between alpha asymmetry and craving at central electrode sights which is consistent with a recent paper by Hayashi, Ko, Strafella, & Dagher (2013) in which de-activation of the left dorsolateral prefrontal cortex (DPFC) using TMS produced reductions in reported craving. Further support for the involvement of alpha comes from the findings of Jaworska et al. (2011), who demonstrated modulation of alpha by administration of nicotine.

Finally we looked at whether there was any relationship between cue or reward processing and the resting EEG data. Although there was a correlation between beta power at parietal locations and the preference for the cigarette key in the presence of the cigarette cue, we treat the result with caution as it was limited to the post experiment, eyes closed period.

8.0.36 Limitations

A problem inherent in neuroscience research (particularly fMRI experiments) is that if a large number of statistical tests are computed we stand a chance of a false positive result. Although it is not a problem associated with traditional EEG methods, some more recent techniques and research such as that presented here, where the effects of interest are not well-known, mean that it must be a consideration. For this reason I have tried to base my analyses on precise hypotheses and apply rigorous standards to the analyses (such as

correction for multiple comparisons). Within the EEG literature there is little discussion of false positives, even in the face of often inconsistent results. More rigorous investigation of the likelihood of false discoveries and analysis methods which minimize them is needed. For example Singh & Phillips (2010) discuss (and test) the false discovery rate in EEG phase synchrony research and suggest a method for minimizing the chances of false positive (or Type one) errors, using the False Discovery Rate control, which controls the ratio of false-detections to total number of significant results. Similarly Simmons, Nelson, & Simonsohn (2011) highlight how easy it is to find false-positive results in this type of research.

Within the animal literature the orbitofrontal cortex (OFC) has regularly been implicated in PIT processes; for example lesions of the OFC disrupt the coding of an outcome during Pavlovian but not instrumental learning (Ostlund & Balleine, 2007a). Similarly Ostlund & Balleine (2007b) found that lesions of the OFC disrupt PIT but not the devaluation of an outcome suggesting that the OFC is involved in the S-O relationship but not in O-R associations. Other areas have also been implicated, such as the ventral striatum and the amygdala, in the processing of PIT cues (Balleine, Leung, & Ostlund, 2011), the nucleus accumbens (NAC) core and shell in general and specific PIT effects (Corbit & Balleine, 2011), the basolateral complex (BLA) and mediodorsal thalamus (MD) in instrumental choices (Ostlund & Balleine, 2008) and the BLA appears to mediate specific PIT, whilst the central nucleus (CN) has a more general role in the motivational aspects of reward-related events (Corbit & Balleine, 2005) . In the last few years a small

number of labs have begun to investigate the human neural correlates of PIT. Bray, Rangel, Shimojo, Balleine, & ODoherty (2008) found that the BOLD activation in the ventrolateral putamen was modulated according to whether subjects choices were consistent, or inconsistent with the Pavlovian predictive cue. They suggested that this may be indicative of the inhibition of a possible but non-selected choice. Talmi, Seymour, Dayan, & Dolan (2008) implicated the NAC and amygdala in the motivatory aspects of a Pavlovian cue. Similarly Prvost, Liljeholm, Tyszka, & ODoherty (2012) identified specific regions of the amygdala involved in specific and general PIT; with the ventral amygdala and ventrolateral putamen involved in specific PIT and a region of the dorsal amygdala involved in the general PIT effect. This work corroborates the animal research discussed above. However it also demonstrates why EEG may not be a good method for identifying neural correlates of PIT and learning; most of the areas implicated are either the OFC or subcortical areas which are unlikely to be measured using EEG techniques. Accessing these areas with fMRI has its own inherent problems but seems to provide a better technique for establishing the neural basis of this behavioural effect.

There are a number of other limitations of this work which should be considered; (1) Due to te effort involved in collecting EEG data the sample sizes are relatively small by behavioural research standards (Incidentally the sample sizes for EEG research are quite normal). This may have limited the power of our analyses. (2) Although we took some rough chocolate and cigarette liking scales, these were not incorperated in the analysis and may therefore have allowed the

use of subjects who would always choose cigarettes purely because they really disliked chocolate. (3) We used hypothetical rewards in our tasks and indeed subjects were informed in the initial information sheet that they would not get to keep the rewards. This was due to ethical restrictions in giving cigarettes as rewards but could be addressed by deceiving subjects and then providing alternative rewards. (4) The smokers used in these tasks were mainly students who had quite limited smoking histories and are therefore less likely to show any drug-related toxic effects due to prolonged drug use. in future studies it would be interesting to incorperate subjects with addictions to other drugs and with longer drug-taking histories.

8.0.37 Future directions

The experimental work discussed here has attempted to elucidate the neural mechanisms underpinning learning in smokers. Although there are some mixed findings, both in the work presented here and in the general literature, the investigation of neural activity during complex learning paradigms is a promising and under-researched area. As previously discussed fMRI may offer a better tool for this type of research if the neural correlates are inaccessible using EEG. However the use of combined methods such as EEG and fMRI in which the temporal capabilities of EEG are combined usefully with the spatial resolution of fMRI may provide the ideal tool. Ideally these methods will be combined with recent analysis techniques, such as ICA, single trial analysis and modeling, to get the most complete picture of decision making and learning in addicted populations, including the areas involved and the timing/order of events.

Recent work such as that of Philiastides, Auksztulewicz, Heekeren, & Blankenburg (2011) using TMS to probe the flow of decision making could also be usefully applied to addicted populations to identify the causal factors involved in the maladaptive decision making and learning of addicted individuals. With regard to the behavioural results, although extinction was effective at reducing responding during the Pavlovian extinction phase, it did not affect responding in the PIT phase. This is consistent with research showing that extinction training, in which cues are presented without reinforcement, is not an effective treatment for addiction. In a meta-analysis of cue-exposure treatments Conklin & Tiffany (2002) found that these types of addiction treatment do not show any impact on abstinence rates. However they do suggest that the failure of these treatments may be due to the poor application of current animal extinction theory. Further research, and application of current behavioural theory, is required to improve addiction treatments utilizing extinction. For example An alternative would be to use either a different method of extinction or multi-context extinction in which as the name suggests the association is extinguished in multiple settings thus potentially reducing the chance of renewal when a new context is encountered. this approach has shown some success in rats (Gunther, Denniston & Miller, 1998; Chelonis, Calton, Hart, and Schactman, 1999) but has been less successful in humans (MacKillop & Lisman, 2008).

A devaluation procedure would provide the most direct test of the idea that addiction is characterised by a hyper-valuation of drug-related outcomes or rewards. In such a task a subject is trained on two instrumental responses for particular rewards. One of the

rewards is subsequently devalued by providing it to the subject i.e. in the case of food they might be fed to satiety. This would be reflected in reduced responses for the devalued outcome. Hogarth and Chase (2011) used a combined devaluation and PIT task in a sample of smokers. Interestingly devaluation did not affect the size of the PIT effect suggesting that, at least in the initial stages of drug use, hyper valuation of the drug-related outcome is likely to guide behaviour. It would be very interestign to understand the neural correlates and networks involved in this finding.

Although we did not see the expected preference for cigarette actions in the concurrent choice task, we did see it in the instrumental training stages of the PIT tasks. We suggest that this shows a preference for drug related actions, relative to non-drug actions. To understand the importance of this preference it would be important to see if this preference is only shown in addicted individuals compared to controls.

The lack of differences in the behavioural and EEG results dependent on addiction level may be due to a number of factors. The smokers tested may not have had long enough smoking histories for differences to have emerged. Alternatively, differences in addiction level in smokers may not translate to differences in behavioural and neural activity. We might find stronger effects in users of other, perhaps more addictive, substances. Such research would however come with its own caveats, such as increased poly-drug use making it difficult to narrow down the effects of a single drug.

To conclude, this work has combined EEG with established behavioural paradigms adapted from the animal and human literature to investigate the neural mechanisms underlying drug seeking. Based upon the research reviewed in the interdiction we had hoped to find EEG components that correlated with the behavioural effects of interest (e.g. preference and PIT). However the use of EEG did not identify neural markers for some of the behavior we see in addicted individuals, indicating the need for further work in this area that utilises more recent developments in data collection and analysis methods.

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