University of Lethbridge Research Repository

OPUS **http://opus.uleth.ca**

Theses Arts and Science, Faculty of

2010

Electrophysiological indices of feedback processing

Christie, Gregory J

Lethbridge, Alta. : University of Lethbridge, Dept. of Neuroscience, 2010

http://hdl.handle.net/10133/2551

Downloaded from University of Lethbridge Research Repository, OPUS

ELECTROPHYSIOLOGICAL INDICES OF FEEDBACK PROCESSING

by

GREGORY J. CHRISTIE

B.F.A., University of Lethbridge, 2005

A Thesis

Submitted to the School of Graduate Studies

of the University of Lethbridge

in Partial Fulfilment of the

Requirements for the Degree

MASTER OF SCIENCE, NEUROSCIENCE

Department of Neuroscience

University of Lethbridge

LETHBRIDGE, ALBERTA, CANADA

© Gregory J. Christie, 2010

Abstract

All sentient organisms use contextual information to assess the amount of reward associated with a particular behavior. Human beings have arguably evolved the most sophisticated of these mechanisms and are capable of integrating information over a long duration of time to accurately assess the expected outcome of a chosen action. This thesis used electroencephalography (EEG) to measure how the human brain processes rewarding and punishing feedback in a gambling-type game with variable risk and reward. Experiment 1 determined that phase-locked (evoked) and non-phase-locked (induced) electroencephalographic activity share only partially overlapping generators in human mediofrontal cortex. Experiment 2 determined that the magnitude of certain evoked EEG components during reward processing tracked subsequent changes in bets placed in the next round. These results extend the body of literature by assessing the overlap between induced and evoked EEG components and the role of evoked activity in affecting future decision making.

Acknowledgements

The page you're reading is the fourth in this thesis, but in reality is it's the *very last* page I wrote. I did this deliberately, both as a reward for finishing and as a reminder of the invaluable support I've received along the way, the absence of which this endeavor would certainly have failed.

To my supervisors, Matt Tata and Deb Saucier. I'm very fortunate to have two mentors to guide my research, ignite my curiosity, help bail me out whenever I got stuck, and to provide a swift kick in the ass whenever I tried to settle for "good enough". I couldn't have asked for a better introduction to grad school.

To the funding agencies that enabled this research: the Natural Sciences and Engineering Research Council, the Alberta Gaming Research Institute, the Canada Research Chairs program and the Canada Foundation for Innovation.

To the fantastic group of RAs, undergraduate, and graduate students I've worked with over the past three years: Andrew Butcher, Jarrod Dowdall, Karla Ponjavic, Scott Oberg, Brian Ward, Jodi Saucier, Matt Kalynchuk, Erin Zelinski and Wendy Maynes-Anderson. Collectively, you helped me record EEG from nearly *seventy-five hundred* electrodes in the two experiments in this thesis alone. To borrow from Matt's thesis, I wish you all the lowest of impedances for the rest of your years.

To my parents, Jim and Terri, for their support and encouragement, and for being far better cooks than me.

Finally, to two people near and dear to me. To Katy Hally, my trusted friend. I have a knack for getting myself into trouble; you have a gift for keeping me out of it. Finally, to David Thompson at UBC Hospital, for inspiring a young, frustrated artist to become a scientist.

To all of you, a heartfelt Thank You. I couldn't have done this without you.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ACC	Anterior Cingulate Cortex
ADHD	Attention-Deficit/Hyperactivity Disorder
ANOVA	Analysis of Variance
CPGI	Canadian Pathological Gambling Index
DA	Dopamine
EEG	Electroencephalography / electroencephalogram
EOG	Electrooculogram
EGI	Electrical Geodesics Incorporated
ERP	Event-Related Potential
FRN	Feedback-Related Negativity
HEOG	Horizontal EOG
HPC	Hippocampus
IGT	Iowa Gambling Task
MRI/fMRI	Magnetic Resonance Imagining / functional Magnetic Resonance Imaging
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PG	Pathological Gambling
RV	Residual Variance
SD	Standard Deviation
SSS	Zuckerman Sensation-Seeking Scale
TF	Time-Frequency
TSE	Temporal-Spectral Evolution
VEOG	Vertical EOG

"Of several responses made to the same situation, those which are accompanied or closely followed by satisfaction to the animal will, other things being equal, be more firmly connected with the situation, so that, when it recurs, they will be more likely to recur; those which are accompanied or closely followed by discomfort to the animal will, other things being equal, have their connections with that situation weakened, so that, when it recurs, they will be less likely to occur."

Edward Thorndike, Animal Intelligence: Experimental studies; p.244

Chapter 1: Introduction

It is evolutionarily advantageous for organisms to possess mechanisms to adapt behavior based on the perceived reward of a given action. Every sentient organism makes use of this adaptive system to balance the associated costs of a behavior with its potential benefits – from a predator deciding to hunt a prey animal to an insect foraging for food. The mechanisms that control adaptive behaviors in animals can be estimated using mathematical formulae and implemented in software to facilitate machine learning using artificial intelligence (Sutton & Barto, 1998) and, potentially, to also help predict the movements of stock markets (Sanfey, Loewenstein, McClure, & Cohen, 2006). Our pursuit of understanding the biological mechanisms mediating adaptive behaviors thus bears substantial relevance far beyond the scientific pursuit of the unknown.

A fundamental necessity to engage in decision making is the ability to monitor the outcomes of decisions to identify the amount of reward (positive outcomes) or punishment (negative outcomes) associated with the action – a cognitive process called *feedback processing*. This thesis investigates the brain's electrical responses associated with this operation. Human beings have evolved sophisticated cognitive mechanisms to compute the expected outcome of an action and can adjust and improve this analysis through time, making us an ideal organism for psychological and neuroscientific investigation into feedback processing. In the laboratory various types of free-choice, gambling-like tasks with variable and uncertain risk and reward can be used to study how the human brain engages in action selection and action monitoring when faced with uncertain outcomes.

The availability of modern functional neuroimaging systems provides a way to investigate the mechanisms by which the human brain registers positive and negative feedback. With few

exceptions these functional imaging techniques exploit one of two phenomena associated with neural activity. The first involves imaging changes in hemodynamic or metabolic activity within the brain in response to changes in neural activity. The two most common techniques used to visualize such changes are functional Magnetic Resonance Imaging (fMRI), which measures changes in blood oxygenation levels, and Positron Emission Tomography (PET), wherein a radioactive isotope is injected into the bloodstream to track metabolic changes in the brain. As a general rule, both PET and fMRI offer very good spatial resolution and the ability to detect changes in many subcortical regions, something that is not possible with other imaging techniques. However, this high spatial sensitivity comes at the expense of poor *temporal* resolution. For instance, changes in cerebral blood flow exhibit a lagged response of approximately 2-10 seconds after the onset of the increased neural activity. Thus, these types of functional imaging techniques are generally unsuited for identifying the specific timecourse of cerebral activity and can, at times, fail entirely at identifying brief cerebral responses (including some responses specific to feedback processing). In addition, metabolic imaging systems tend to be very expensive to purchase and operate and are generally stationary systems (although portable MRI/fMRI systems exist). They also do not directly measure brain electrical activity itself but rather the secondary increase in cerebral blood flow in response to increased brain electrical activity – leading to theoretical difficulty in extrapolating from fMRI results to brain mechanisms (see however, Lee et al., 2010).

The other common form of human functional neuroimaging directly measures the electrical activity of the brain at the scalp. These measurements are possible because of the laminar organization of neurons in the neocortex. Cortical pyramidal cell bodies are arranged parallel to each other with their dendrites pointing perpendicular to the surface of the cortex. The

movement of charged ions across the dendritic plasma membrane generates an electric field that individually is immeasurably small. However, the synchronous activity of many tens of thousands of pyramid cells generates a summed electric field that is sufficiently large to be measured many millimeters away. There are two scalp imaging techniques that directly measure this brain electrical activity: electroencephalography (EEG), which measures the differences in electrical potential energy between an electrode of interest and a reference electrode, and magnetoencephalography (MEG), which measures the orthogonal magnetic component of this electric field.

In practice, this means EEG is well suited for measuring neocortical activity from tissues arranged parallel to the skull whereas MEG is well-suited for measuring neocortical activity from tissues perpendicular to the skull. Modern EEG and MEG systems record from several dozen electrodes (EEG) or superconducting quantum interference devices (MEG) to provide whole-head recordings. Both modalities offer excellent temporal resolution (on the order of 1,000 samples per second) to determine the chronological sequence of cortical electrical activity.

Both techniques, however, are limited in their ability to accurately determine the cortical generators of the measured scalp activity – that is, both techniques have limited spatial resolution. The reasons for this are numerous. First, both systems are generally unable to record signals from non-laminar tissues and thus are unable to record from midbrain and brainstem regions. Second, both systems are sensitive to destructive interference, with the electric fields measured via EEG cancelled in horizontally opposed tissues and the magnetic fields measured via MEG cancelled in tissues aligned parallel with the skull. There is thus always some amount of electric/magnetic activity that is attenuated in each participant, and the amount of this attenuation varies with the gross morphology of each participant's cortical folding. Third,

and by extension from the previous point, there are an *infinite* number of configurations in which the neocortex can be electrically/magnetically active to generate the pattern of activity measured at the scalp – working backward from a scalp distribution of voltages to a source location in the cortex is known as the inverse problem (Luck, 2005). The inverse problem is a mathematically ill-posed problem, meaning there is no one unique correct solution. Source-localization techniques generally operate in a parsimonious fashion insofar as the simplest solution with the fewest assumptions is generally considered correct (Occam, ca. 1300).

Electroencephalography possesses additional limitations as compared to MEG. Electric fields, but not their magnetic counterparts, are sensitive to distortion by the differing electrical resistances of cortex, cerebrospinal fluid in the ventricles, meninges, pia, dura, skull, and scalp. Electric fields pass through these tissues by a process known as volume conduction, wherein the propagating fields bend and become distorted at the boundaries between regions of different electrical properties. This distortion tends to produce a diffuse pattern of electrical activity at the scalp (see Figure 2-2) and any attempt at source-localizing EEG activity must account for this distortion or accept a necessarily low spatial precision. In addition, EEG operates analogously to an electrician's voltmeter, requiring both a reference and a target voltage measurement. Most EEG systems use a single reference point (some use bilateral references at the earlobe or the mastoid processes behind the ear) against which all other electrodes of interest are compared. This makes EEG acquisition sensitive to erroneous and spurious electrical activity at the reference electrode. MEG is acquired in a reference-free montage that is not affected by this problem. Despite its limitations, however, the EEG technique is vastly more popular in research environments than MEG because the latter technique is, like MRI, expensive to purchase and operate, is immobile, and requires specialized personnel to maintain.

Both EEG and MEG are recorded continuously during an experiment (generally 30-60 minutes in duration, though some experiments last longer) but researchers are often interested in *event-related* neural activity during the moments before and after a particular cognitive operation. By segmenting the continuous EEG into discrete epochs at the event of interest, then averaging trials together for each participant, and then finally grand-averaging across participants, it is possible to minimize the random "background" neural activity recorded in the continuous EEG and measure the time-locked electric signal specific only to the cognitive task being studied. These grand-averaged EEG data are called Event-Related Potentials (ERP) and the experiments reported here make extensive use of this technique.

By recording from multiple electrodes and by generating ERPs at each electrode it is possible to create a topographic representation of scalp electrical activity (see Figure 2-2) that can offer some insight into the possible intracranial distribution of the neural generators of these voltages. The ERP associated with any instantaneous sensory or cognitive event is characterized by a series of negative and positive voltage deflections relative to a baseline time period prior to the event. These peaks, and often the differences between peaks, are called *components* of the ERP. With regards to feedback processing there are two ERP components of particular interest: the Feedback-Related Negativity (FRN), which is a positive-negative-positive waveform observed at fronto-central electrodes (often Fz or FCz; see Appendix B for standardized electrode locations on the scalp), and the P300, which is a positive-going deflection frequently observed at centro-posterior electrode sites (often Cz, CPz, or Pz). The FRN and P300 will be introduced in greater detail in the introduction to Experiment 1. Briefly, the FRN is likely generated from mediofrontal cortex, and possibly involves the Anterior Cingulate Cortex (ACC; Gehring & Willoughby, 2002). The FRN is sensitive both to the valence of feedback (i.e. reward or

punishment) and to the perceived riskiness of a choice (Holroyd, Larsen, & Cohen, 2004). The P300 reflects several overlapping components and lacks a single clear anatomical generator, but it is believed to be involved in registering and processing task-relevant novel stimuli (Yeung & Sanfey, 2004).

By necessity the EEG activity represented in the grand-averaged ERP is phase-locked across trials. That is, the peaks and troughs of the ERP on successive trials would be aligned in time if overlaid onto each other. Any activity that is not phase-locked across trials is attenuated or removed entirely by the averaging process that creates the ERP. This occurs because of the wave-like nature of EEG activity. Like all waves, the recorded EEG signal has independent values for wavelength (i.e. its frequency), for amplitude (i.e. its power) and for phase (the discrete location within a particular wavelength). Waves interact through constructive and destructive interference: averaging in-phase waves sums their amplitudes (constructive interference), and averaging out-of-phase waves cancels them out (destructive interference). In fact, constructive interference permits cortical pyramidal electric fields to sum sufficiently to be detected by scalp electrodes. Although phase-locked EEG activity represents a substantial component of the observed trial-by-trial activity, it is known that power changes in non-phase-locked ongoing oscillations are also implicated in cognition. By convention the phase-locked activity represented in the ERP is called *evoked* activity, and the non-phase-locked changes in oscillatory activity are called *induced* activity. Both kinds of EEG signals are informative with respect to feedback processing and both are reported in the following chapters.

Computing grand-average changes in induced activity is not as straightforward as the construction of an ERP. Rather than simply averaging EEG activity across trials, the EEG must be demodulated by an algorithm to compute the discrete power level at each particular

frequency – that is, the discrete power at 1Hz, at 2Hz, at 3Hz, and so forth must be independently computed. These segregated power levels can then be grand-averaged and represented as a Temporal-Spectral Evolution (TSE) plot. These plots are three-dimensional, representing a percent change in power relative to a baseline (referred to as a 1° change), at a particular time latency (a 2° change), and at a specific frequency (a 3° change).

Neuroscientists have divided the possible EEG frequency spectra into discrete bands based on their functional importance. The conventional definitions are as follows: Delta, 0-4Hz; Theta, 4-7 Hz; Alpha, 8-11 Hz; Beta, 12-30 Hz; and Gamma, 30-100Hz. Frequencies above 100 Hz are for most practical purposes immeasurably weak and frequencies below approximately 0.1 Hz tend to be filtered out during most EEG acquisitions. Although each of these frequency bands may be involved in various forms of cognitive control, theta oscillations are of particular interest to cognitive neuroscientists. Theta oscillations are extremely robust, being among the most powerful oscillations generated by the human brain (only delta oscillations are of greater amplitude) and among the easiest to acquire. In turn, this means that event-related theta oscillations can be obtained by averaging over a limited number of trials (approximately 15). Theta rhythms have been implicated in a number of cognitive operations including feedback processing (Cohen, Elger, & Ranganath, 2007; Luu, Tucker, Derryberry, Reed, & Poulsen, 2003; Marco-Pallares et al., 2008), memory (Jensen & Tesche, 2002) and linguistic (Hagoort, Hald, Bastiaansen, & Petersson, 2004) tasks.

1.1 Research Goals

This thesis presents two studies aimed at elucidating the functional and anatomical properties of brain electrical activity during feedback processing. First, a number of EEG investigations

have identified characteristic changes in low-frequency EEG activity during feedback processing separate from the phase-locked ERP, but the generators of this activity were previously unknown. Experiment 1 thus used an advanced source localization technique, Beamformer spatial filtering, to identify the cortical generators of feedback-induced low-frequency activity, and the extent to which these generators overlap anatomically with the generators of evoked feedback responses. Second, the amplitude of certain ERPs are known to positively correlate with learning speed and negatively correlate with error avoidance. Experiment 2 thus tested the hypothesis that larger FRN and P300 amplitudes are associated with subsequent bet changes on a trial-by-trial basis.

Chapter 2: Experiment One. Right-Frontal Cortex Generates Reward-Related Theta-Band Oscillatory Activity

2.1 Abstract

When participants in a gambling game are given feedback as to whether they won or lost the previous bet, a series of stereotypical brain electrical responses can be observed in the electroencephalogram (EEG) and the stimulus-locked Event-Related Potential (ERP). These include the Feedback-Related Negativity (FRN), a posterior P300, and a feedback-induced increase in power at the theta (4 to 8 Hz) band over frontal scalp. Although the generators of the FRN and P300 have been studied previously, little is known about the generator of feedback-induced theta. To investigate these feedback-related responses, participants played a gambling game and chose either high-risk/high-reward or low-risk/low-reward bets. The FRN was not modulated by the riskiness of the bet, but both P300 and feedback-induced theta were of greater amplitude following high- relative to low-risk bets. Using a bilateral multi-source Beamformer approach, I localized the induced theta-band responses following wins and losses to partially overlapping regions in the right medial frontal cortex, possibly including Anterior Cingulate Cortex (ACC). Using a dipole-fitting approach, I found that the generators of feedback-induced theta were anatomically distinct from those of the FRN and P300.

2.2 Introduction

Humans can identify positive and negative outcomes of their actions and make predictions about future outcomes. Broadly construed, these mechanisms probably serve two functions: first, to guide our current actions by keeping us engaged in beneficial behaviors and causing us

---

This chapter is adapted from Christie, G.J., & Tata, M.S., 2009. Right frontal cortex generates reward-related theta-band oscillatory activity. *Neuroimage* 48, 415-422.

to disengage from detrimental behaviors, and second, to guide learning processes that influence future behaviors. The functional neurobiology of these reward processing systems can be investigated in the laboratory using neuroimaging techniques in conjunction with gambling or guessing games that provide feedback about good or bad choices.

In a gambling game, feedback typically indicates either win or a loss to the player, resulting in a stereotypical series of deflections evoked in the ERP. Two components have been of particular interest: the FRN (possibly related to the feedback Error-Related Negativity) and the feedback-related P300. The FRN is a fronto-central negative difference in the ERP following losses or negative feedback that is generated from mediofrontal cortex, possibly within ACC (Gehring & Willoughby, 2002) . The FRN is associated with reward-based learning (Bellebaum & Daum, 2008) and adaptive decision-making (Cohen et al., 2007). The FRN reflects more than the simple registration of "win" or "lose": its magnitude is modulated by expectancy. Small wins generate an FRN if the alternative outcome was a bigger win (Holroyd, Larsen, & Cohen, 2004). There is a correlation between FRN amplitude and response switching (Yasuda, Sato, Miyawaki, Kumano, & Kuboki, 2004), FRN amplitude decreases as participants improve in a learning task (Krigolson, Pierce, Holroyd, & Tanaka, 2008), and FRN-like activity can be elicited by unexpected positive feedback (Holroyd, Pakzad-Vaezi, & Krigolson, 2008; Oliveira, McDonald, & Goodman, 2007). There is also evidence suggesting the evaluative properties of the FRN are affected by the motivational significance of a given task (Donkers, Nieuwenhuis, & van Boxtel, 2005; Yeung, Holroyd, & Cohen, 2005). Together, these results suggest the FRN reflects reward prediction errors and thus may represent the function of a neural system mediating reinforcement learning (Holroyd et al., 2004).

The feedback-related P300 is a posterior potential that has been found following feedback about wins and losses in gambling games (Yeung et al., 2005; Yeung & Sanfey, 2004) and in a learning task with a monetary reward (Bellebaum & Daum, 2008). Unlike the FRN, the P300 seems to be related to the probability or risk associated with a particular outcome and not to the valence (winning or losing) of that outcome (Yeung & Sanfey, 2004). Unlike the FRN, the anatomical generators of the P300 remain poorly identified.

In addition to the feedback-evoked FRN and P300, recent investigations have identified an induced oscillatory response in the theta band (4 – 8 Hz) during feedback processing (Cohen et al., 2007; Gehring & Willoughby, 2004; Marco-Pallares et al., 2008). This induced theta response is greater in power and phase coherence following losses relative to wins. Induced responses to wins, however, are modulated more by reward probability than are responses to losses, and are greatest in power and phase coherence when there is a low probability of winning (Cohen et al., 2007). It has been suggested that theta oscillatory activity represents the functional coupling of several mediofrontal brain structures involved in feedback processing. However, the neuroanatomical generators of this induced theta-band power have yet to be identified.

Despite substantial work to investigate reward processing mechanisms in non-human animals (see e.g. Everitt, Dickinson, & Robbins, 2001; Schultz, 2007), the functional anatomy of these circuits in humans remains poorly understood. Studies using functional MRI have implicated a distributed network of sub-cortical and frontal cortical structures mediating reward processing (Delgado, Nystrom, Fissell, Noll, & Fiez, 2000; McClure, Berns, & Montague, 2003; McClure, York, & Montague, 2004; O'Doherty et al., 2004; O'Doherty, Deichmann, Critchley, & Dolan, 2002; Pagnoni, Zink, Montague, & Berns, 2002; Schonberg, Daw, Joel, & O'Doherty, 2007). This network includes the ventral striatum and medial orbitofrontal cortex in reward processing

and the lateral orbitofrontal cortex and ACC in loss processing (Liu et al., 2007). Although the components of a frontal reward processing network have thus been identified based on metabolic activity, the electrical activity within this network has not yet been fully characterized.

One study using intra-cranial electrodes in a neurosurgical patient found feedback-related ERP responses in the alpha band within paracingulate cortex (Oya et al., 2005). Electrical Source Imaging of the FRN (Donkers et al., 2005; Gehring & Willoughby, 2002; Holroyd, Hajcak, & Larsen, 2006; Holroyd et al., 2004; Marco-Pallares et al., 2008; Miltner, Braun, & Coles, 1997; Nieuwenhuis, Holroyd, Mol, & Coles, 2004; Nieuwenhuis, Yeung, Holroyd, Schurger, & Cohen, 2004; Yeung et al., 2005; Yeung & Sanfey, 2004) has consistently found one or more generator(s) on the anterior medial wall of the frontal lobe, possibly in ACC, suggesting this structure contributes to reward processing. However, using a dipole analysis constrained by fMRI data, Nieuwenhuis et al. (2005) found evidence for a more distributed network involving rostral anterior cingulate, posterior cingulate, and right superior frontal gyrus.

It is unclear whether generators within ACC or elsewhere account for the feedback-induced theta-band power observed in other studies. The peak of the FRN and the peak increase in induced theta-band power are at similar latencies (approximately 250 ms post-stimulus), and both components appear to originate in right-hemisphere mediofrontal cortex (see Results section). Using a gambling paradigm, Cohen et al. (2007) observed enhanced theta-band activity during the window of the FRN. Taken together, this suggests a functional relationship between the FRN and increases in theta-band activity. The FRN may originate due to transient phase-locking of induced oscillatory theta-band activity. Conversely, the observed increase in theta-band power may be the result of the neural activity generating the evoked FRN. To date, no study has determined the relationship, if any, between these two components. A study by Luu et

al. (2003) used a dipole-fitting approach on filtered ERP data to examine feedback-evoked theta power and found possible generators in rostral ACC and in dorsal medial frontal cortex. Here I report evidence based on a Beamforming approach that feedback-induced theta power is indeed generated primarily in the right mediofrontal cortex.

The present study used a gambling game similar to the Iowa Gambling Task to investigate the functional anatomy of feedback-induced neural activity. All test participants were undergraduate students who received only a fixed, non-monetary reward of 2% bonus course credit. Gambling-game experiments frequently use a variable monetary reward, and subjects are motivated by financial gain to perform well on the experimental task. In this experiment, the amount of reward is not based on performance; thus, test subjects had no direct, salient incentive to learn based on the magnitude of the bets they placed or the feedback they received on these bets. Nevertheless, I hypothesized that feedback-related P300 and FRN effects would be modulated by risk and valence as reported in other literature.

I also extended the data collection to address three questions regarding the mechanisms of feedback processing. First, what are the anatomical generators of the observed theta-band signal, and does this activity arises from within ACC? Second, is the neural activity of this theta-band generator modulated by the riskiness of the bet that led to the reward? Finally, what relationship, if any, exists between the FRN, the P300 and the increase in induced theta-band activity? I used a three-stage process to analyze the data. First, to ensure the use of fixed reward engaged normal feedback processing, I replicated the results of previous studies with respect to FRN, P300, and oscillatory theta-band activity. Subsequently, I used the Beamformer spatial filtering technique to localize cortical sources of feedback-induced theta-band activity (Green & McDonald, 2008; Green & McDonald, 2010, in press; Gross et al., 2001; Van Veen, van

Drongelen, Yuchtman, & Suzuki, 1997), and concluded by implementing a dipole-fitting method, constrained by the Beamformer results, to identify the extent to which cortical regions associated with theta-band activity were also implicated in generating the FRN.

2.3 Materials and Methods

2.3.1 Participants

Twenty-five undergraduate students at the University of Lethbridge participated for course credit (but not monetary reward). Of these, data from two were excluded after debriefing because they indicated they had used a card-counting strategy to try to "beat" the game and thus had erratic behavioral performance. Data from four participants were excluded because of excessive eye-movement artifact (see below). Thus, data from 19 participants (12 female, mean age 22.0, two left-handed) were entered into the analysis. Participants were screened with the Canadian Problem Gambling Index to exclude frequent gamblers and none reached exclusion criteria (the mean CPGI score was 0.9). All procedures were in accordance with the Declaration of Helsinki and were approved by the University of Lethbridge Human Subject Research Committee; all participants gave written informed consent.

2.3.2 Gambling Task

Participants in gambling tasks form an implicit understanding of the risks and rewards of the various choice options and adjust their selections accordingly (Bechara, Damasio, Damasio, & Anderson, 1994; Cavedini, Riboldi, Keller, D'Annucci, & Bellodi, 2002; Goudriaan, Oosterlaan, de Beurs, & van den Brink, 2005). Thus, to facilitate the implicit learning required for the task, participants completed a training session in which they completed a computerized version of the

Iowa Gambling Task prior to EEG recording sessions. The task was as described in Bechara et al. (1994); briefly, participants were instructed to obtain as much reward as possible by selecting from four decks of cards, denoted as decks A, B, C and D. Decks A and B always paid $100 for each selection and decks C and D always paid $50. Each draw also had a pseudorandom chance of having a loss in addition to the gain, and the loss could exceed the gain. For example, if a participant selected deck B he or she would always win $100 but might also simultaneously lose $1250, for a net loss of $1150. The test lasted 100 draws, although participants were not instructed as to the length of the task nor were they informed as to the amount of time remaining. A characteristic property of the IGT is that the higher-reward decks, namely decks A and B, have the same net negative expected value of -$250 over ten draws, and decks C and D have the same net positive expected value of +$250 over ten draws. Thus, good performance in the IGT requires preferentially selecting the apparently lower-reward $50 decks (C and D) over the apparently higher-reward $100 decks (A and B).

Once the training sessions were complete, participants performed an adaptation of the IGT suitable for the ERP technique (similar also to previous tasks used to elicit the FRN) (Gehring & Willoughby, 2002; Hewig et al., 2006; Nieuwenhuis, Holroyd et al., 2004; Oya et al., 2005; Yacubian et al., 2006; Yeung et al., 2005). The paradigm consisted of a main screen with a horizontal bar (size) at the top, which displayed the subject's current winnings or losses. Two buttons at the center of the screen (size; how were they placed side by side or on top of each other) allowed the participant to specify either a small ($50) or large ($100) bet (betting screen) and to play the selected bet by clicking with a computer mouse. Upon selecting their choice (small or large), a central fixation cross appeared. A colored square, the feedback stimulus, then appeared after a random (but uniformly distributed) duration of 500 to 1500 ms . A green square

indicated a win and a red square indicate a loss for the current trial. This feedback stimulus remained visible for 1000 ms and then the betting screen reappeared. Participants either won or lost the value of their wager. The win/loss schedule was pseudorandom (randomized within runs of 10 trials) with a 0.6/0.4 win/lose probability for the $50 bet and a 0.4/0.6 win/lose probability with the $100 bet. Thus there were four possible outcomes: High-Risk Win (40% chance after betting "high"), High-Risk Loss (60% chance after betting "high"), Low-Risk Win (60% chance after betting "low"), and Low-Risk Loss (40% chance after betting "low"). Participants played the game for 45 minutes or until 400 trials had been completed, whichever came first.

2.3.3 EEG Recording and Analysis

The EEG was recorded from 128 sites at a 500 Hz sampling rate using Ag/AgCl electrodes in a geodesic net (Electrical Geodesics Inc., Eugene, OR, USA). Electrode placement was recorded with a Polhemus Fast-Trak (Polhemus, Colchester, VT, USA) for later registration with the EEG dataset. Impedances were maintained below 100 KΩ. The montage was initially referenced to the vertex and then digitally re-referenced to an average reference. Data were imported into the BESA software package (Megis Software, Grafelfing, Germany) for further analysis. The record was visually inspected for bad channels and the signal from a small number of electrodes was replaced with interpolated signal (approximately five per participant; ocular, reference, and channels of interest were not interpolated). Ocular artifacts were corrected using the adaptive artifact correction algorithm (Ille, Berg, & Scherg, 2002b). HEOG and VEOG threshold voltages were 150 μV and 250 μV respectively.

2.3.4 Analysis of Evoked Activity

The ERP was computed by averaging the EEG in a 1000 ms window, with a 200 ms pre-stimulus baseline, time-locked to the presentation of the feedback stimulus. Epochs with an amplitude greater than 120 μV were rejected during automatic artifact scanning. Epochs were averaged within the four conditions and the waveforms interpolated into a standard 81-electrode montage in the 10-20 system to minimize electrode placement errors across participants. The data were then grand-averaged and filtered with high-pass (0.6 Hz, 6 dB/octave) and low-pass (30 Hz, 12 dB/octave) zero-phase Butterworth filters.

The FRN was identified as the largest difference between the win and loss waveforms at an approximate latency of 246 ms post-stimulus. The mean amplitude of the FRN was computed inside a window spanning approximately 50 milliseconds on either side of this peak, from 200 to 300 ms post-stimulus. Similarly, the P300 was identified as the peak of the positive-going deflection in the waveform of each condition, identified at a latency of approximately 330 ms in all conditions. The amplitude of the P300 was measured as the mean amplitude in a window spanning twenty milliseconds on either side of this peak, from 310 and 350 ms post-stimulus. These windows are broadly consistent with previous studies (Holroyd & Coles, 2002) and appeared to capture the important differences between conditions. In the analysis to follow the FRN is defined as the *mean* difference between the peaks in this window, not the absolute amplitudes of these waves, as in the P300. For isopotential maps the difference wave was computed by subtracting High-Risk Loss from High-Risk Win waveforms and Low-Risk Loss from Low-Risk Win waveforms.

A repeated-measures ANOVA (Fisher, 1918) with two levels of the factor risk (high/low) and two levels of the factor valence (win/lose) was performed on the mean amplitude of the evoked

activity. For the FRN the ANOVA was performed at electrode FCz between 200 and 300 ms and for the P300 the ANOVA was performed at CPz between 310 and 350 ms.

2.3.5 Time-Frequency Analysis

Time-Frequency (TF) plots were calculated using BESA for each participant's four conditions within a frequency range of 4.0 to 50.0 Hz with a 2.0 Hz / 25 ms sampling resolution. These values were selected to provide a maximal tradeoff in accuracy between frequency and time resolution. The Fieldtrip (F.C. Donders Centre, Nijmegen, Netherlands) toolbox for Matlab (The Mathworks, Natick, MA, USA) was used to create averaged TF plots across all participants for each of the four conditions. An ANOVA with two levels of the factor risk (high/low) and two levels of the factor valence (win/lose) was performed on the theta-band amplitude during the 150 – 350 ms post-stimulus interval.

A bilateral multi-source Beamformer technique (Hoechstetter et al., 2004) was used to image the intracranial signal sources of induced theta-band power subsequent to both wins and losses. Beamformer images were generated using BESA within a 150 – 350 ms post-stimulus interval (-200 to 0 baseline) for signal between 4 and 8 Hz, using a four-shell ellipsoid head model and the original 128-channel montage. The Beamforming approach results in four (one per condition) 3D volumetric datasets for each participant in which the parameter Q, a measure of signal strength in the epoch of interest relative to baseline, is computed for each voxel. These volume maps were imported into the BrainVoyager QX software package (Brain Innovation B.V., Maastricht, Netherlands). Rather than average across participants, I identified voxels that were most likely to have exhibited increased theta signal relative to baseline. For each voxel, a one-tailed t-test (Gossett, 1908) was used to compare the mean Q value to zero. As is commonly

done in fMRI work, the resulting volume map of t-scores was thresholded at $p<.001$ (uncorrected for multiple comparisons).

2.3.6 Dipole-Fitting Analysis

I tested the hypothesis that the FRN and/or the P300 might reflect a transient phase-locking of theta by considering whether the computed theta sources could account for the grand-average FRN and/or P300 ERP components in a multiple dipole model of brain electrical activity. Electrical source analysis (BESA) was applied to the 20 ms window centered on the peak of the FRN, which I have described as the difference wave between wins and losses at a given bet magnitude. A multi-source dipole-fitting solution was computed inside the BESA program for the 240 – 260 ms post-stimulus window. The same analysis was repeated on the 320 – 340 ms post-stimulus window of the P300 for the High-Risk Win and High-Risk Loss waveforms. Because of well-known spatial limitations of the dipole-fitting technique (Green, Conder, & McDonald, 2008) this procedure is best attempted using dipole locations constrained by a priori knowledge of the underlying functional anatomy. In this analysis, dipoles were placed at the two foci of increased theta activity obtained from the Beamformer analysis of High-Risk Wins and High-Risk Losses. Dipoles were fixed at the Talairach coordinates of the focus for High-Risk Loss (19, 33, 12) and the maximum focus for High-Risk Win (25, 17, 28). I also modeled a three-dipole solution for the same difference wave with an additional dipole placed at a second focus of theta activity in the Beamformed High-Risk Win condition (31, 25, 7). Finally, to determine the extent to which the FRN and P300 components are generated by *bilateral* theta generators, I repeated these analyses using four- and six-dipole models, with additional dipoles mirrored into the left hemisphere at Talairach coordinates -25, 17, 28; -19, 33, 12; and -31, 25, 7. For the FRN

component, a forward solution was computed for the High-Risk Losses – High-Risk Wins difference wave, and for the P300 component, forward solutions were computed using the High-Risk Win and High-Risk Loss waveforms.

2.4 Results

2.4.1 Behavioural Results

Participants registered an average of 342 wagers (±90.2). Of these, the Low-Risk $50 bet was selected 69.7 % of the time and the High-Risk $100 bet was selected 30.3% of the time (± 12.6%). The absolute outcomes of the four experimental conditions were thus: 12.1% for High-Risk Wins, 18.2% for High-Risk Losses, 41.8% for Low-Risk Wins, and 27.9% for Low-Risk Losses (note that the subsequent electrophysiological results consider the smaller subset of trials that were accepted as artifact-free).

2.4.2 EEG Results

Participants in this gambling task demonstrated both FRN (Figure 2-1A, 2-3A) and P300 effects (Figure 2-1B, 2-3B) consistent with previous literature. The FRN had slightly right-lateralized frontal scalp distribution (Figures 2-2A and 2-2B). Differences in P300 scalp distributions were midline and posterior (Figures 2-2C and 2-2D).

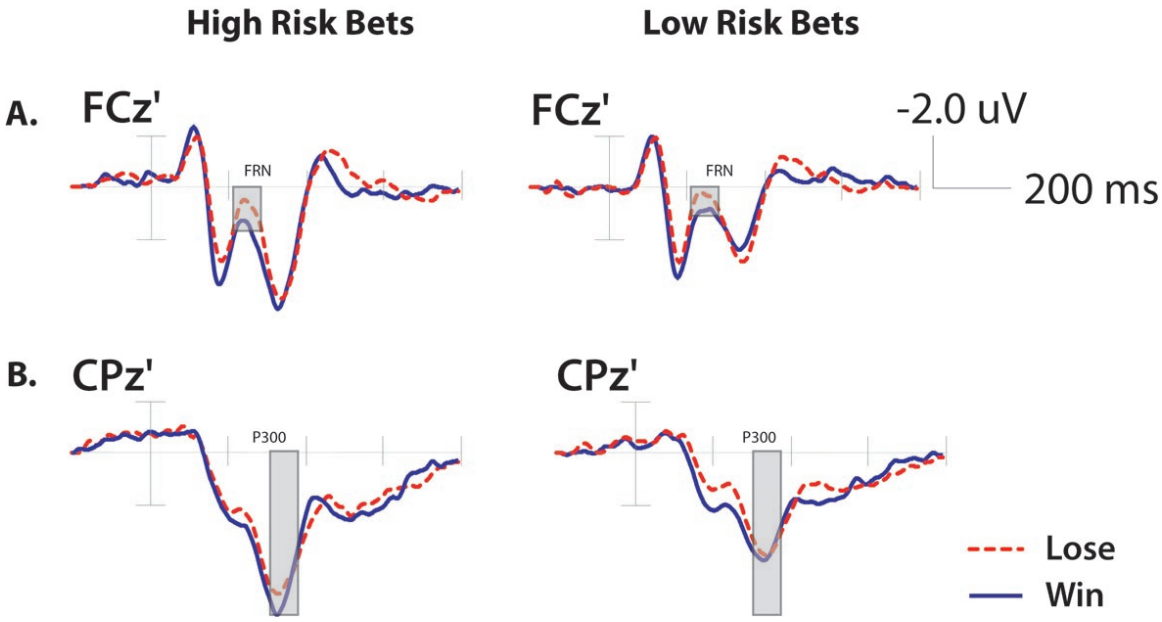


Figure 2-1: Grand-Averaged ERP waveforms showing FRN and P300 effects for wins and losses following feedback on high-risk/high-reward bets and low-risk/low-reward bets at selected sites. A) The Feedback-Related Negativity, indicated by shading, is the difference between Win and Lose waveforms at about 245 ms. B) The P300, indicated by shading, is the positive deflection at about 330 ms.

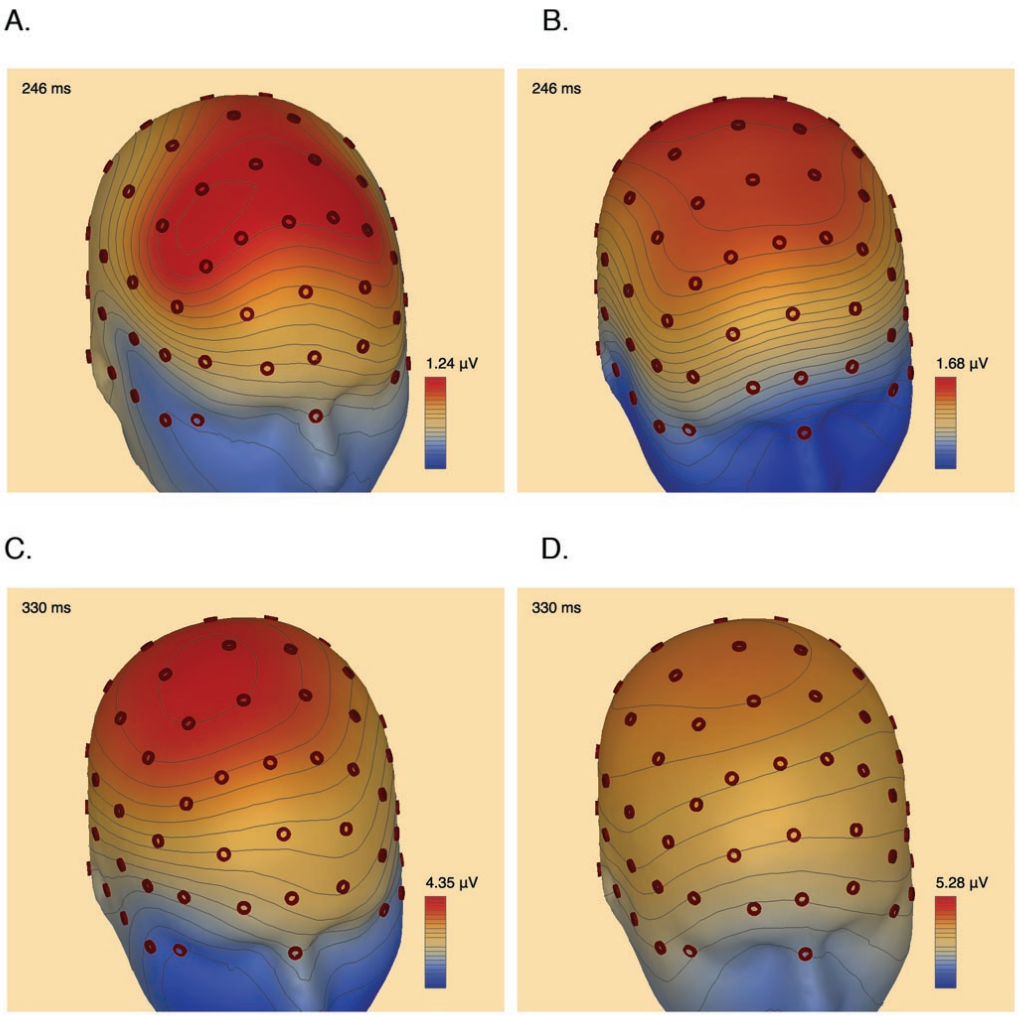


Figure 2-2: Grand-Averaged ERP waveforms showing FRN and P300 effects for wins and losses Distribution of scalp voltages during feedback processing, overlaid onto an average head model. Distribution of the Win – Loss FRN following feedback on A) high-risk/high-reward bets and B) low-risk/low-reward bets. Scalp distribution of P300 modulation due to risk (high minus low) on C) winning trials and D) losing trials.

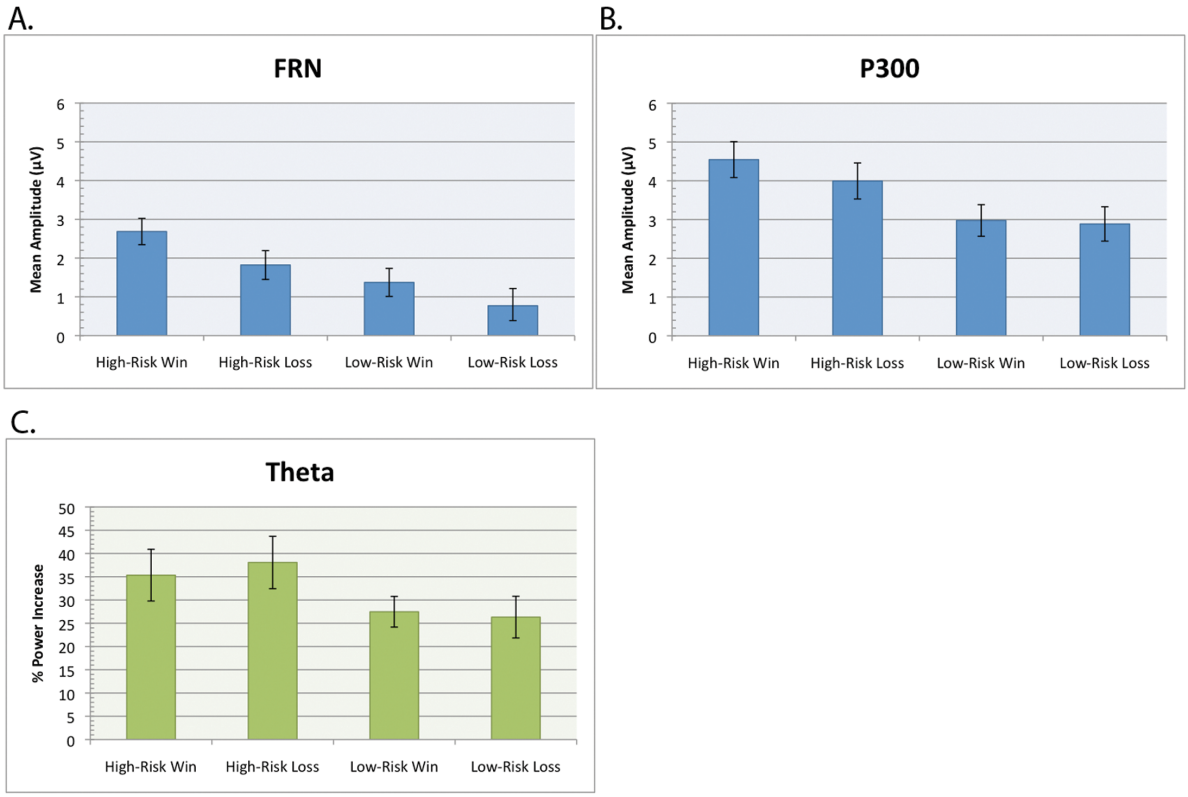


Figure 2-3: Mean amplitudes (in μV) of feedback-evoked potentials A) during the FRN window: 200 – 300 ms; B) during the P300 window: 310 – 350 ms. C) Power changes (in percent) in induced theta-band oscillatory window: 150 – 350 ms. Frequency range (theta activity): 4 – 8 Hz. Error bars depict standard error of the mean.

An FRN was present during the feedback window from 200 to 300 milliseconds, as evidenced by a significant main effect of valence (win vs. loss), $F_{1,18}$=7.135; p=.016. I also found a significant main effect of risk (high vs. low), $F_{1,18}$=30.494; p<.001, however the interaction was not significant, $F_{1,18}$ = 1.497; p = .237 (Figure 2-1). Since the FRN is usually taken to be the difference between wins and losses (i.e. the effect of valence), I thus conclude that the FRN was not modulated by risk in this paradigm (non-significant interaction). To rule out deviations from expectancy I compared two outcomes with identical expected probabilities: High-Risk Wins and

Low-Risk Losses (both have an EP of 40%). A post-hoc comparison was made between the mean amplitudes of the High-Risk Win and Low-Risk Loss waveforms during the 200 – 300 ms window; the mean amplitudes of the two waveforms differed significantly, t_{18} = 5.002; p<.001.

During the 310 to 350 ms interval the P300 was larger in High- relative to Low-Risk bets, but its amplitude was not affected by valence. There was a significant main effect of risk, $F_{1,18}$=28.898; p<.001, but not of valence, $F_{1,18}$=1.701; p=.209, and the interaction between risk and valence was only marginally significant, $F_{1,18}$=2.844; p=.109.

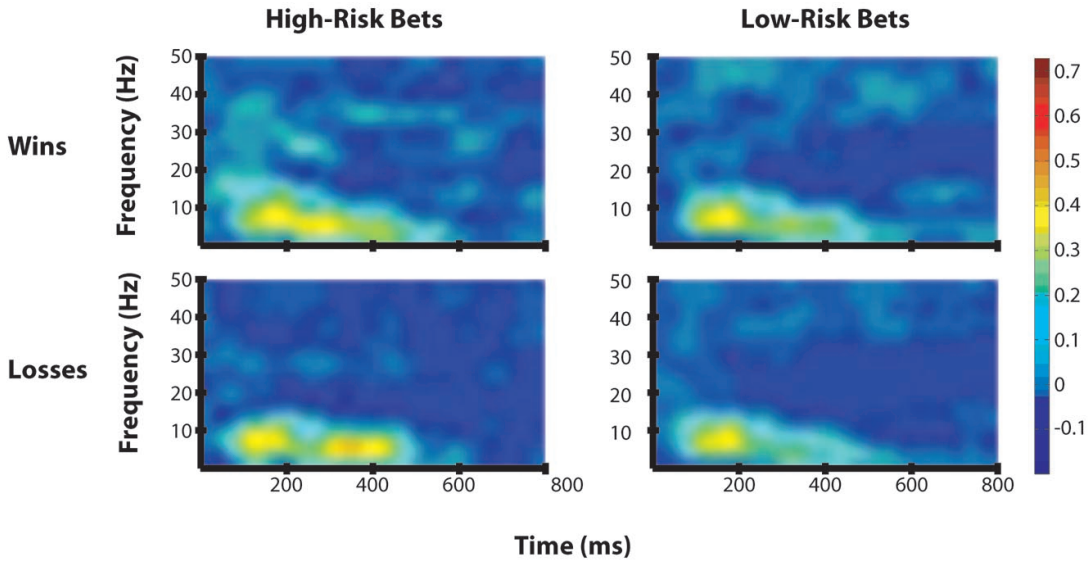


Figure 2-4: Time-Frequency plots showing induced theta (4 – 8 Hz) at FCz for each condition at a time and frequency sampling resolution of 2.0 Hz / 25 ms.

Feedback-induced increases in theta-band (4 – 8 Hz) amplitude over baseline were modulated by risk (Figure 1-3), $F_{1,18}$=10.004; p=.005, but did not differ significantly with valence, $F_{1,18}$=0.058; p=.812, nor was the interaction between risk and valence significant, $F_{1,18}$=0.402; ; p=.534. Beamformer analysis revealed regions of voxels significant at the p<.001 level in the

High-Risk Loss and High-Risk Win conditions (Figure 2-5) but were not observed in either of the Low-Risk conditions. These regions were only partially overlapping, with High-Risk Loss activity focused at Talairach coordinates 19, 33, 12, and High-Risk Win activity at two foci: 25, 17, 28 and 31, 25, 7.

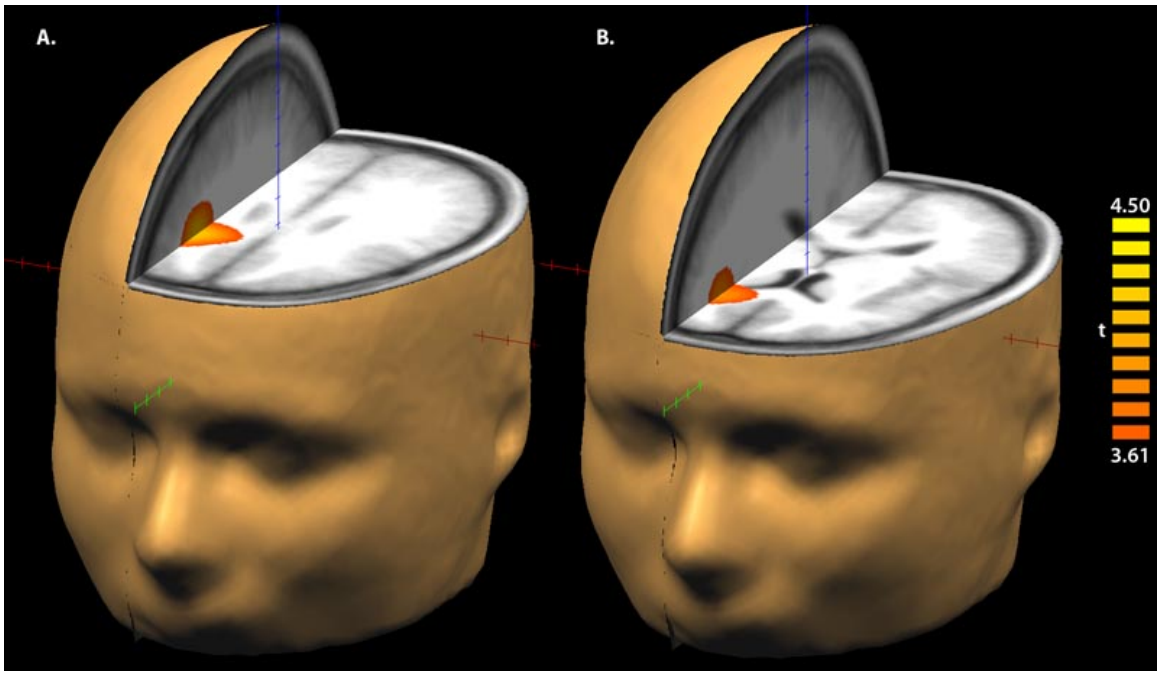


Figure 2-5: Cortical generators of theta activity as revealed by Beamforming and thresholded at; $p<.001$ (uncorrected for multiple comparisons), A) after High-Risk Wins and B) after High-Risk Losses. Regions in red and yellow denote significant increases in theta-band activity relative to baseline.

The Beamformer-constrained two-dipole forward solution, with dipoles fixed at the foci of increased theta-band activity (but allowed to rotate), yielded a solution with a mean Residual Variance of 31.8% during the FRN window. The three-dipole model, with an additional dipole obtained from the High-Risk Win condition, yielded a forward solution with 30.9% RV. Mirrored into the left hemisphere, the four-dipole and six-dipole models yielded solutions with

26.0% and 24.1% RV, respectively. An analysis of the P300 component using the High-Risk Wins waveform yielded increasingly accurate forward solutions with 18.1% RV (2-dipole), 13.9% RV (3-dipole), 9.5% RV (4-dipole), and 5.4% RV (6-dipole). An analysis using the High-Risk Losses waveform yielded nearly identical forward solutions with RVs of 18.2%, 13.9%, 11.1%, and 6.0%.

2.5 Discussion

A substantial body of literature suggests that reward processing – recognizing positive and negative feedback and registering the associated probabilities of each outcome – is mediated by a network of cortical and subcortical structures (see Holroyd & Coles, 2002 for review). This study has replicated the main findings of previous work: I observed significant FRN and P300 components following feedback in a gambling task. Recent investigations of induced oscillatory activity following reward feedback have revealed an induced increase in theta-band power (4 – 8 Hz) after feedback presentation (Cohen, 2007; Cohen, Elger, & Fell, 2008; Luu et al., 2003; Marco-Pallares et al., 2008). I have also replicated this finding: there was a significant increase in low-frequency power following reward feedback. I tentatively ascribe the observed increase in low-frequency activity to the theta band as this is parsimonious with other studies (Marco-Pallares et al., 2008) but I do not discount the possibility of additional signal generators in the low alpha band (8 – 10 Hz).

The mean amplitude of the P300 was modulated by the riskiness of the selected bet whereas the mean amplitude of the FRN was modulated by the valence of the outcome. Both the FRN and P300 responses are sensitive to stimulus probability (Cohen et al., 2007) and infrequent outcomes are known to increase the amplitude of these responses. In this study, the effects of

two related forms of stimulus probability must be considered: the *expected probability*, which is the implicit understanding formed by a test subject as to the likelihood of obtaining a win or a loss for a selected bet, and the *absolute probability* of a given stimulus, which is the frequency at which a stimulus was physically experienced. A recent theory suggests the FRN reflects activity of midbrain dopaminergic neurons coding for deviations from expected outcome (Holroyd & Coles, 2002) consistent with a Reinforcement Learning theory of the FRN (Krigolson et al., 2008; see also Sutton & Barto, 1998). Consequently, the size of the FRN should be larger subsequent to larger deviations from expected outcome. To rule out deviations from expectancy I compared two outcomes with identical expected probabilities: High-Risk Wins and Low-Risk Losses (both have an EP of 40%). If the FRN codes only for deviations from expected outcome one would expect to find no difference in the amplitudes of these two waveforms. Instead there was a considerable difference between the two ERPs. These results are especially noteworthy because of the choice of reward: test participants received a fixed, non-monetary reward of bonus course credit regardless of their performance in the gambling game. Although test participants had no salient motivation to care about the bets they placed or the feedback they received, the electrophysiological data from this study are similar to those observed in other studies on feedback processing. I interpret these data collectively to suggest that the FRN encodes relative risk in determining expected outcome, which is in turn broadly consistent with the theory that the FRN is affected by the motivational significance of events (Donkers et al., 2005; Yeung et al., 2005).

Theta-band activity was modulated by the riskiness of the selected wager but did not significantly differ with the valence of the outcome. The present study extends previous work by providing strong evidence that feedback-related theta power is generated by right hemisphere

medial frontal structures. This evidence comes from a novel electrical source imaging approach, the volumetric analysis of Beamformer data, which had not yet been applied to this phenomenon. These data also support theoretical arguments that implicate the anterior cingulate cortex in monitoring feedback in cognitive tasks (Holroyd & Coles, 2002).

Of interest is the extent to which the observed increase in induced theta-band output is related to the neural processes that give rise to the FRN. To address this I used a dipole-fitting approach with several candidate models using the foci obtained from the Beamformer analysis of the High-Risk Win and High-Risk Loss conditions. Two- and three-dipole solutions yielded only partially accurate forward solutions. This inability of theta foci to account for the generators of the FRN suggests the FRN and feedback-induced theta share only partially overlapping generators in right-hemisphere medial-frontal cortex. It may be the FRN also entails one or more frequency components outside of the theta band that could not be accounted for by dipoles constrained to be at generators of theta oscillations. I conclude that feedback-evoked FRN represents more than a transient phase-locking of feedback-induced theta. As a general rule in dipole modeling, increasing the number of dipoles improves the accuracy of the forward solution and diminishes the residual variance, however adding two and three left-hemisphere dipoles symmetric to those in the right hemisphere improved the model's fit to the FRN only slightly. Thus, the FRN and the feedback-induced theta in this study are similar in their tendency to be right-lateralized.

A Beamformer-constrained dipole analysis of the P300 yielded solutions with greater accuracy than those of the FRN. Additionally, the accuracy of the P300 solutions increased substantially when dipoles were mirrored into the left hemisphere, suggesting the presence of bilateral generators for the P300. This indicates that the P300 component is generated bilaterally and

may be more functionally and anatomically similar to the feedback-induced theta oscillation than the FRN. I believe this is most likely the result of the operational definition of the FRN in this study. In this analysis the FRN was identified as the difference between the evoked potentials to positive and negative feedback. The Beamformer-restrained dipole analysis thus localized electrical signals common to both positive and negative feedback. Applying this analytical technique to the feedback N200 may reveal an important difference in the relationship between induced oscillatory theta activity and the evoked electrical responses to positive and negative valence.

2.5.1 Theta-band Oscillations within a Reward Processing Network

Oscillations in the theta band have been suggested to provide functional coupling of disparate cortical and subcortical regions involved in both error and feedback processing (Luu et al., 2003). Such coupling is probably necessary to support the several sub-processes of reward processing such as discrimination of feedback stimuli and updating any ongoing registration of the probabilities of various outcomes. This notion is consistent with the suggestion that theta-band signals are critical for coordinating activity across large-scale networks (Buzsaki & Draguhn, 2004; Von Stein & Sarnthein, 2000). Furthermore, theta-band activity is believed to be critical during memory processes, for example during encoding stimuli into implicit memory (Klimesch, Doppelmayr, Russegger, & Pachinger, 1996) and during recognition tasks (Doppelmayr, Klimesch, Schwaiger, Stadler, & Rohm, 2000; Klimesch, Doppelmayr, Schwaiger, Winkler, & Gruber, 2000).

Luu et al. (2003) investigated the theta-band component of the evoked FRN (rather than induced theta) by bandpass-filtering ERP data between 4 – 12 Hz. Using a dipole-fitting

approach, their study observed that a pair of midline sources, one possibly in rostral ACC and another in dorsal medial frontal cortex, generated feedback-evoked theta components. Their study was unable to image sources of induced activity and was unable to resolve different contributions from the two hemispheres. The present results extend this finding in two ways: First, I was able to image the combined effects of induced and evoked theta. Second, by using bilateral multi-source Beamforming, my analysis was sensitive to theta-band signals generated in either hemisphere. Since significant voxels were observed in the right hemisphere only, I conclude that feedback-induced theta is substantially right lateralized, as has been suggested by previous work (Gehring & Willoughby, 2004; Marco-Pallares et al., 2008). It should be noted that the Beamformer images (Figure 2-5) are statistical parametric maps indicating regions of consistency across participants, rather than maps of grand-averaged theta activity per se. Individuals exhibited substantial variability in their Q maps, including some engagement of the left frontal lobe. This variability probably accounts for the tendency of dipole-fitting approaches to localize midline or bilaterally symmetric sources as the best fitting models when applied to grand-averaged data.

The approach to analyzing Beamformer volume maps in this study was conservative because it viewed each voxel independently (necessitating an arbitrarily high t-score threshold) rather than as members of larger clusters of functionally related voxels (as would a dipole-fitting approach). Consequently, regions of increased theta power may have been missed. I nevertheless conclude that the results are consistent either with a single theta signal generator on the medial wall of the right frontal lobe, or a group of generators within medial frontal cortex that are closely associated both functionally and anatomically. However, I do not rule out the possibility of less prominent contributing sources, especially in left frontal cortex. Because regions of increased

theta power following wins and losses only partially overlapped, I further speculate partially distinct networks, depending on its valence, process feedback.

2.5.2 The Role of Risk in Feedback-Related Brain Responses

The choice of a higher-risk/higher-reward bet led to significantly increased theta amplitude subsequent to feedback in the time-frequency analysis. The Beamforming analyses also found significantly increased Q values in medial frontal cortex following feedback on high-risk but not low-risk bets. This sensitivity to outcome probability is broadly consistent with previous work (Cohen et al., 2007) and might be due to two independent factors. First, the rewards and punishments on high-risk trials were necessarily of greater magnitude (as incentive to take the higher risk). This may contribute greater saliency to the feedback stimulus. Second, in this study participants were implicitly aware of the contingencies of higher and lower risk bets. Thus they may have entered an attentional set upon initiating high-risk bets that potentiated subsequent brain responses. Cohen et al. (2007) found that decreasing reward probability (as in the high- relative to low-risk conditions) led to greater theta-band power following wins but not following losses. By contrast, I found no such dissociation between risk and valence. It thus remains unclear whether attentional set might potentiate induced theta specifically for feedback stimuli or more generally for any subsequent stimulus.

The results differ from previous reports in other respects: Whereas this study found feedback-induced modulations only in the theta band, Marco-Pallares et al. (2008) and Cohen et al. (2007) also found an increase in power over frontal scalp within the 20 to 30 Hz band at an approximate latency of 250-400 ms following wins relative to losses – a reward-induced response. I found no such increase in this band. These differences may reflect fundamental

differences in how reward type modulates feedback processing. In both previous studies the amount of monetary compensation depended on the participant's performance, whereas subjects in this study received fixed, non-monetary reward. It may be that this higher-frequency activity is the result of exogenous motivation that enhanced the saliency of wins relative to losses among their participants. Further investigation of these discrepant results may elucidate how motivational states are represented during feedback processing.

2.6 Acknowledgements

I thank Richard Worsey and Andrew Butcher for assistance with experimental design and Dr. Robert Williams and Dr. Robert Sutherland for helpful discussion. G.J.C. was supported by an NSERC USRA scholarship. This work was supported by the Alberta Gaming Research Institute and an NSERC Discovery Grants to M.S.T.

Chapter 3: Experiment Two. The FRN and P300 encode information about future decisions.

3.1 Abstract

Humans possess sophisticated mechanisms to monitor the outcome of a chosen action and to update the expected outcome of that action – a cognitive operation called *feedback processing*. Electroencephalography can be used to observe the electrical responses in the cortex to these processes. Two evoked components have been heavily implicated in mediating feedback processing: the mediofrontal Feedback-Related Negativity (FRN) and the posterior P300. Changes in FRN amplitude have been linked to response switching and adaptive learning and may represent a mechanism controlling learning. In the present study, a gambling game was used to study FRN and P300 responses to positive (winning) and negative (losing) outcomes. FRN and P300 amplitudes were significantly higher during feedback on winning trials when participants subsequently selected a different bet type. These results suggest that electrical indices of action selection are observable during feedback processing, possibly preceding conscious perception.

3.2 Introduction

It is necessary for sentient organisms to monitor the outcomes of their actions in order to optimize future behaviors. An essential component of action monitoring is *feedback processing*, the cognitive process of discerning rewarding (positive) outcomes from punishing (negative) outcomes. This process can be studied in the laboratory using human subjects participating in gambling-type paradigms with variable risk and reward while brain electrical responses are

gathered using electroencephalography (EEG; Gehring & Willoughby, 2002; Holroyd & Coles, 2002).

I previously implemented a modified version of the Iowa Gambling Task (Bechara et al., 1994) to investigate feedback processing mechanisms in the human brain. This paradigm is noteworthy because it is a probabilistic learning task with negative- and positively-weighted wagers. Participants are instructed to maximize their earnings over the experiment and thus tend to gravitate towards the positively-valued wager over time.

At least two Event-Related Potentials (ERPs) have been identified and characterized in mediating feedback processing: the Feedback-Related Negativity and the P300. The FRN is a negative deflection in the electroencephalogram at frontocentral scalp approximately 250 ms after receiving feedback. The P300 is a characteristic positive deflection in the EEG at posterior scalp approximately 300-350 ms that has been observed in numerous cognitive tasks (Polich & Kok, 1995). In the context of feedback processing the P300 is known to be sensitive to the perceived riskiness but insensitive to the valence of a selected action (Yeung et al., 2005; Yeung & Sanfey, 2004). Early evidence indicated a relationship between abnormal evoked feedback components and damage to frontal cortex (Gehring & Knight, 2000), and feedback-related EEG spectra were hypothesized to represent the activity of a mediofrontal computational system used to evaluate the magnitude to which an encountered outcome deviated from the expected outcome learned through experience (Holroyd & Coles, 2002). In the ensuing years, empirical evidence from numerous studies lent support to this theory and extended it to implicate FRN activity in mediating behavioral control and adaptive learning. For example, in a gambling game not unlike the one used in this paradigm, Yasuda et al. (2004) observed behavioral switching after large unexpected losses and corresponding increases in FRN amplitude during the

processing of these losses. Bellebaum et al. (2008) noted that FRN amplitude correlated with error avoidance in a different gambling task, and multiple investigations by Krigolson and Holroyd (Holroyd & Krigolson, 2007; Krigolson & Holroyd, 2007b; Krigolson et al., 2008) tie FRN amplitude to learning and behavioral adaptation in various tests of skill.

Because feedback processes like the FRN are associated with behavioral adaptation and improvement over time, it is seems reasonable to posit that the magnitude of evoked feedback spectra correlate with subsequent decisions made on a trial-by-trial basis. Such a direct relationship has not yet been established. Worse, the operational definition of the FRN has to date been the difference in EEG activity based on whether the experienced feedback was rewarding (positive feedback) or punishing (negative feedback), irrespective of the subsequent action chosen by a participant. Information about the subsequent bet type is lost as the computed ERP collapses across this factor. Because of the nature of betting strategies in certain gambling tasks that are used to study it, the FRN may be disproportionately influenced by one or the other level of the factor switch/stay. For example, if one outcome (e.g. wins) tends to trigger participants to repeat the same behaviour (stay), whereas the other outcome (loss) tends to trigger participants to change behaviors (switch), then the operational definition of the FRN as the effect of valence is insufficient. Instead, what may be needed is an analysis in which valence and risk are held constant and the ERP during the FRN window is contrasted between the subsequent action (switch or stay). The paradigm used in Experiment 1 is well suited to test this theory both because it is known to generate robust feedback-related EEG spectra and because it is a probabilistic learning task and participants must appropriately implement feedback to adapt their behavior.

The present study thus tested the hypothesis that FRN and P300 amplitudes differ not only based on valence and bet size as is frequently reported, but also based on the action subsequently taken by participants in the paradigm. Because the FRN is theorized to represent deviation from expectancy, and because large FRN amplitudes are correlated with response switching (Yasuda et al., 2004), I further hypothesized that the largest FRN amplitudes would be observed during High-Risk Win and Low-Risk Loss conditions when participants subsequently switched to the other bet type on the next round.

3.3 Materials and Methods

3.3.1 Participants

Thirty-three undergraduate students at the University of Lethbridge participated for course credit but not monetary reward. Because the analysis would subdivide the four main experimental outcomes into eight conditions based on the bet placed in the subsequent round (Switch or Stay), I selected the subset of participants with at least 35 trials in each of the four main conditions to maximize statistical power. Thus, data from 17 participants (6 female, mean age 22.5, 2 left-handed) were entered into this analysis. Participants were screened with the Canadian Problem Gambling Index (Ferris & Wynne, 2001) to exclude individuals who gamble excessively and none reached exclusion criteria (the mean CPGI score was 0.4). Procedures were in accordance with the Declaration of Helsinki and were approved by the University of Lethbridge Human Subject Research Committee; all participants gave written informed consent.

3.3.2 Behavioral Tests

Participants completed the Sensation Seeking Scale (SSS; Zuckerman, Eysenck, & Eysenck, 1978) prior to the commencement of the gambling task. The SSS is a composite test that assesses four aspects of an individual's personality: thrill-seeking, experience-seeking, disinhibition, and susceptibility to boredom. Participants completed a questionnaire on general physical and mental health to exclude participants with visual deficits or psychiatric/neurological disorders and none reached exclusion criteria. Finally, because participants in gambling games are known to form implicit assumptions of the relative riskiness of available bets (Bechara et al., 1994; Cavedini et al., 2002; Goudriaan et al., 2005), participants completed a computerized version of the Iowa Gambling Task (IGT) prior to EEG acquisition so that they had the implicit knowledge that large bets were disadvantageous over long-term play. The odds of wining in the gambling task during the subsequent EEG recording session were identical to the IGT. Employing the IGT as a pre-screening task also allowed us to ensure that our participants were responsive to the specific parameters of the feedback in our task.

3.3.3 EEG Gambling Task

Subjects participated in the same paradigm used in Experiment 1, which framed the task in the context of a gambling game and was suitable for the ERP technique (similar also to previous tasks used to elicit the FRN; see Gehring & Willoughby, 2002; Hewig et al., 2006; Nieuwenhuis, Holroyd et al., 2004; Oya et al., 2005; Yacubian et al., 2006; Yeung et al., 2005). The paradigm consisted of a main screen with a horizontal bar at the top, which displayed the subject's current winnings or losses. Buttons at the center of the screen allowed the participant to specify either a small ($50) or large ($100) bet and to play the selected bet by clicking with a computer mouse.

Upon pressing the play button, a central fixation cross appeared. A colored square then appeared after a random (uniformly distributed) duration of 500 to 1500 ms. A green square indicated a win and a red square indicate loss on the current trial. This feedback stimulus remained visible for 1000 ms and then the betting screen reappeared. Participants either won or lost the value of their wager. The win/loss schedule was pseudorandom (randomized within runs of 10 trials) with a 0.6/0.4 win/lose probability for the $50 bet and a 0.4/0.6 win/lose probability with the $100 bet. Thus there were four possible outcomes: High-Risk Win (40% chance after betting "high"), High-Risk Loss (60% chance after betting "high"), Low-Risk Win (60% chance after betting "low"), and Low-Risk Loss (40% chance after betting "low"). Participants played the game until 400 trials had been completed.

3.3.4 EEG Recording and Analysis

The electroencephalogram was recorded from 128 sites at a 500 Hz sampling rate using Ag/AgCl electrodes in a geodesic net (Electrical Geodesics Inc., Eugene, OR, USA). Electrode placement was recorded with a Polhemus Fast-Trak (Polhemus, Colchester, VT, USA) for later registration with the EEG dataset. Impedances were maintained below 100 kiloohms. The montage was initially referenced to the vertex and then digitally re-referenced to an average reference. Data were imported into the BESA software package (Megis Software, Grafelfing, Germany) for further analysis. The record was visually inspected for bad channels and the signal from a small number of electrodes was replaced with interpolated signal (approximately five per participant; ocular, reference, and channels of interest were not interpolated). Ocular artifacts were corrected using the adaptive artifact correction algorithm (Ille, Berg, & Scherg, 2002a). HEOG and VEOG threshold voltages were 150 μV and 250 μV respectively. Data were notch

filtered at 60 Hz to eliminate line noise. The electroencephalogram was then segmented into epochs with a duration of 1200 ms, including a 200 ms pre-stimulus baseline and a 1000 ms post-stimulus window.

The analysis of the EEG data was divided into two stages. I first sought to replicate the common findings that the frontocentral FRN was modulated by the Valence (Win/Loss) and the Riskiness (High/Low) of the wager and that the posterior P300 was modulated only by the Riskiness of the wager. Trials were thus created for the four main experimental outcomes: High-Risk Win, High-Risk Loss, Low-Risk Win, and Low-Risk Loss. Next, to quantify the differences in these evoked components with respect to the choice the participant would make in the subsequent trial, trials were redefined based on whether the participant chose the same bet type on the subsequent trial (Stay condition) or changed to the other bet type (Switch condition). There were thus eight possible conditions, depicted in Table 3-1.

Table 3-1. Possible experimental outcomes. Conditions wherein a participant placed the same bet on the subsequent round (Stay conditions) are denoted in green and conditions wherein a participant changed bets on the subsequent round (Switch condition) are denoted in red.

First Bet	*Outcome*	*Second Bet*	*Condition Name*
High-Risk	*Win*	High-Risk	High-Risk Win Stay
	Win	Low-Risk	High-Risk Win Switch
	Loss	High-Risk	High-Risk Loss Stay
	Loss	Low-Risk	High-Risk Loss Switch
Low-Risk	*Win*	High-Risk	Low-Risk Win Switch
	Win	Low-Risk	Low-Risk Win Stay
	Loss	High-Risk	Low-Risk Loss Switch
	Loss	Low-Risk	Low-Risk Loss Stay

In both analyses the FRN was identified as the mean amplitude of the negative-going deflection in the averaged ERP at electrode FCz during the 200-300 ms post-feedback and the P300 was measured as the mean amplitude of the positive deflection in the averaged ERP at electrode CPz during the 300-350 ms post-feedback window. These timings are consistent both with my previous study (Christie & Tata, 2009) and broadly consistent with other investigations into feedback processing. Data were quantified using mixed-model ANOVAs with two levels of the factor Risk (High/Low), two levels of the factor Valence (Win/Loss) and, where necessary, two levels of the factor Subsequent Bet (Switch/Stay). Post-hoc pairwise T-tests were used as needed to validate the direction of the differences from the ANOVA.

3.4 Results

3.4.1 Behavioral Results

The mean score on the SSS was 21.4 (S.D.=7.01; the maximum possible score is 40). The breakdown of the individual sub-tests is as follows (S.D. in parentheses; the maximum possible score on each sub-test is 10): Disinhibition 4.2 (3.01); Boredom 2.8 (2.38); Thrill-seeking 7.4 (2.72); Experience-seeking 6.2 (1.75).

The mean score on the IGT, as defined by the number of advantageous deck selections (decks C and D) minus the number of disadvantageous deck selections (decks A and B), was 6.9 (S.D.=26.30; the maximum score is 100 and the minimum is -100). Participants improved significantly between the first and last 20 card selections; $t_{14}=3.556$; $p=.003$[1].

[1] Data from two participants were lost and were not entered into this analysis.

Participants placed significantly more advantageous Low bets in the fourth block of the gambling game than in the first block, $t(16)=2.798$; $p=.013$ (see Figure 3-1).

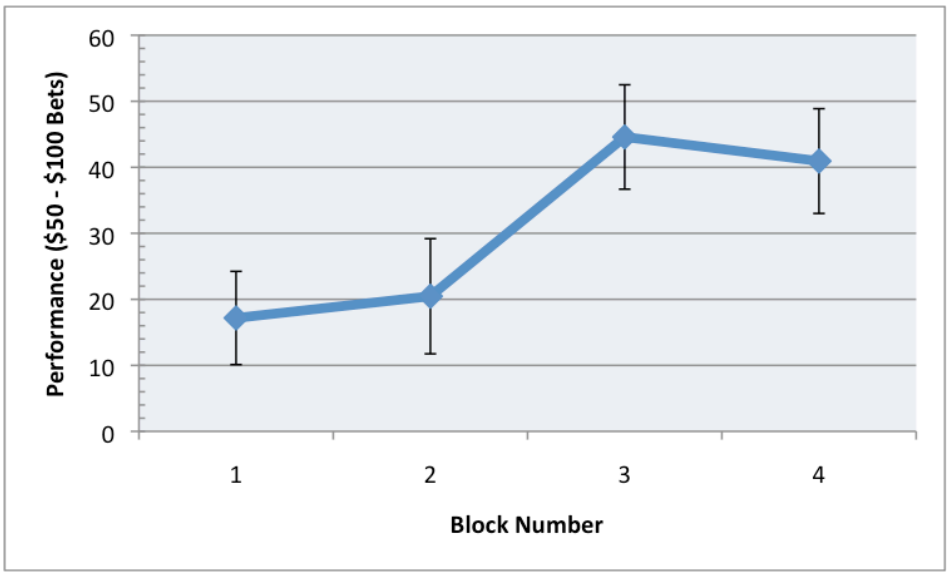


Figure 3-1: Behavioral performance as defined by the number of advantageous $50 bets placed minus the number of disadvantageous $100 bets placed during each block of 100 bets. Participants improved significantly between the first and final blocks of the experiment.

The distribution of selected trials and the subset of valid trials entered into the EEG analyses is presented in Table 3-2. The most common experimental conditions were Low-Risk Loss Stay and Low-Risk Loss Switch, consistent with participants placing the Low-Risk wager most often.

Table 3-2. Play behavior across all four blocks. 'Total' denotes the number of bets placed for a particular bet type irrespective of the subsequent bet type. 'Switch' indicates the participants selected the opposite bet type on the subsequent trial and 'Stay' indicates the participant chose the same bet type on the subsequent trial. 'Accepted' denotes the number of trials that were defined as artifact-free and were used in the subsequent EEG analyses. Standard Error of the Mean is denoted in parentheses.

		Total	*Switch*	*Stay*
High-Risk Win	*Total*	59.3 (4.2)	23.3 (3.3)	35.9 (4.0)
	Accepted	51.5 (3.9)	20.4 (3.1)	31.2 (3.6)
High-Risk Loss	*Total*	79.6 (5.6)	42.7 (5.9)	36.6 (5.3)
	Accepted	66.0 (3.7)	35.6 (5.5)	30.2 (5.0)
Low-Risk Win	*Total*	154.4 (5.7)	40.4 (5.2)	113.9 (8.5)
	Accepted	134.7 (6.2)	34 (4.3)	100.6 (8.5)
Low-Risk Loss	*Total*	106.7 (3.7)	25.6 (3.5)	80.5 (6.8)
	Accepted	93.6 (4.4)	23.0 (3.0)	70.1 (6.7)

3.4.2 EEG Results

In the replication analysis there was both an FRN at electrode FCz and a P300 at electrode CPz (see Figure 3-2). The mean amplitude of the FRN was modulated by Risk, $F_{1,16}$=24.481; p<.001, and by Valence, $F_{1,16}$=9.149; p=.008, but the Risk by Valence interaction was not significant, $F_{1,16}$=1.876; p=.190. Pairwise comparisons revealed the FRN to be significantly larger for the two High-Risk conditions relative to the two Low-Risk conditions, t_{16}>4.451; p<.001, and significantly larger for the two Win conditions relative to the two Loss conditions, t_{16}>2.586; p<.02 (Figure 3-2). The mean amplitude of the P300 (Figure 3-3) was modulated by Risk, $F_{1,16}$=26.771; p<.001, but not by Valence, $F_{1,16}$=0.019; p=.893, and the Risk by Valence

interaction was not significant, $F_{1,16}$=0.741; p=.402. Pairwise comparisons revealed the P300 to be significantly larger for the two High-Risk conditions relative to the two Low-Risk conditions, t_{16}>4.394; p<.001.

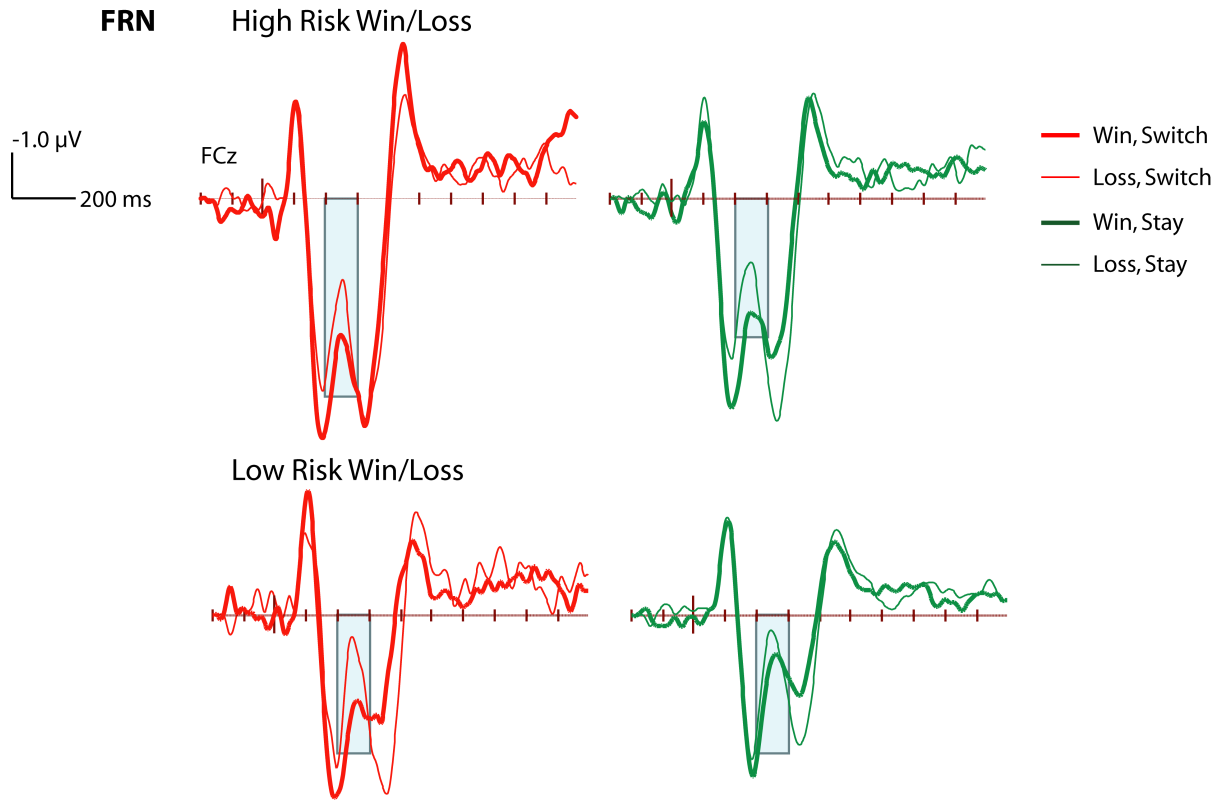


Figure 3-2: Grand-averaged ERP waveforms for the FRN holding Subsequent Bet (switch/stay) constant for High-Risk (top) and Low-Risk (bottom) conditions. The FRN was measured at electrode FCz from 200-300 ms post-feedback. The waveform is colored red when participants subsequently switched to the other bet type on the next trial and is colored green when participants subsequently stayed on the same bet type on the next trial. Thick lines denote wins and thin lines denote losses. FRN amplitude was significantly larger to wins than losses at each of the four conditions.

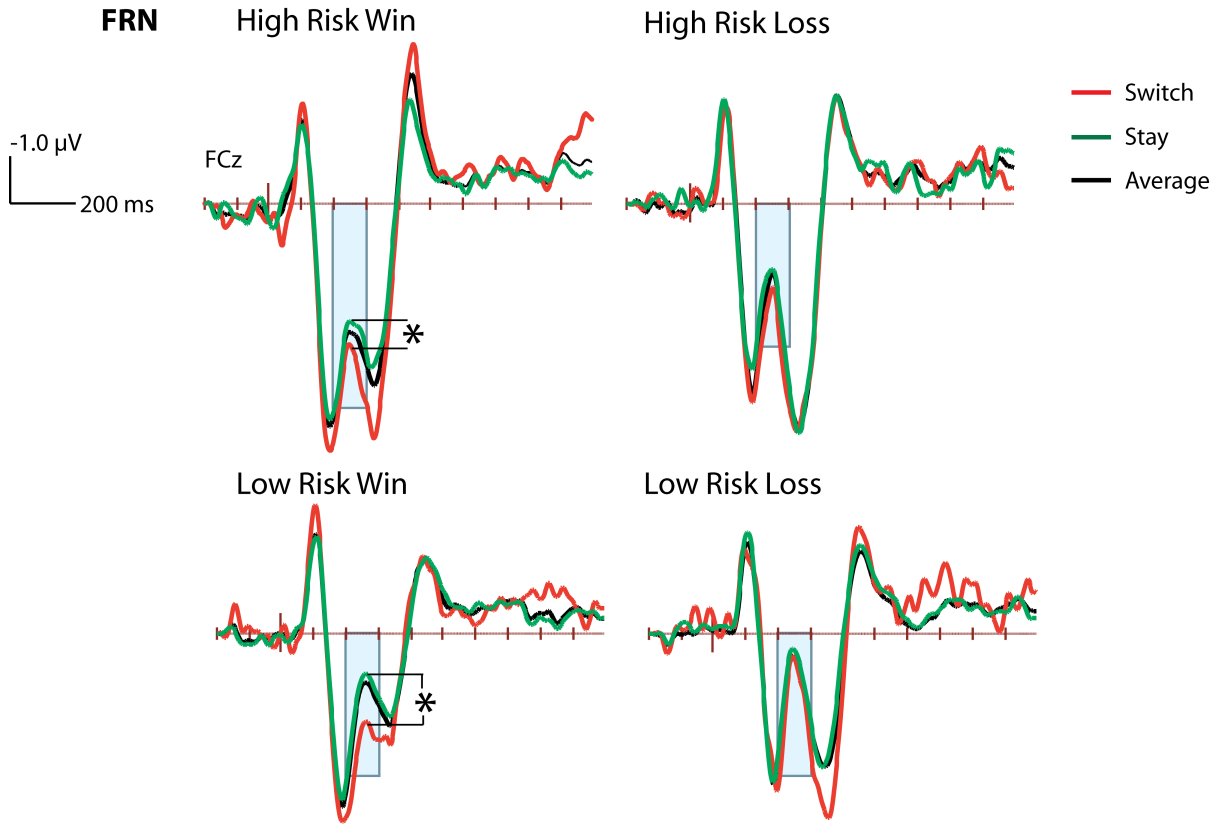


Figure 3-3: Grand-averaged ERP waveforms for the FRN. The FRN was measured at electrode FCz from 200-300 ms post-feedback. The waveform is colored red when participants subsequently switched to the other bet type on the next trial and is colored green when participants subsequently stayed on the same bet type on the next trial. Significant differences are marked with asterisks (*).

In the Subsequent Bet analysis the mean amplitude of the FRN was modulated by Risk, $F_{1,15}$[2]=27.903; p<.001, by Valence, $F_{1,1}$5=14.149; p=.002, and by Subsequent Bet, $F_{1,15}$=30.166; p<.001. None of the of the two-way interactions were significant. Pairwise comparisons revealed that the FRN was significantly larger in the Switch relative to the Stay condition for the High-Risk Win condition, t_{16}=2.606; p=.019, and the Low-Risk Win condition, t_{16}=3.510;

[2] One participant did not have any trials in the High-Risk Loss Switch condition and was excluded from the appropriate analyses.

p=.003, but not for the High-Risk Loss, t_{15}=1.546=.143, or Low-Risk Loss, t_{16}=1.622; p=.124, conditions (Figure 3-3).

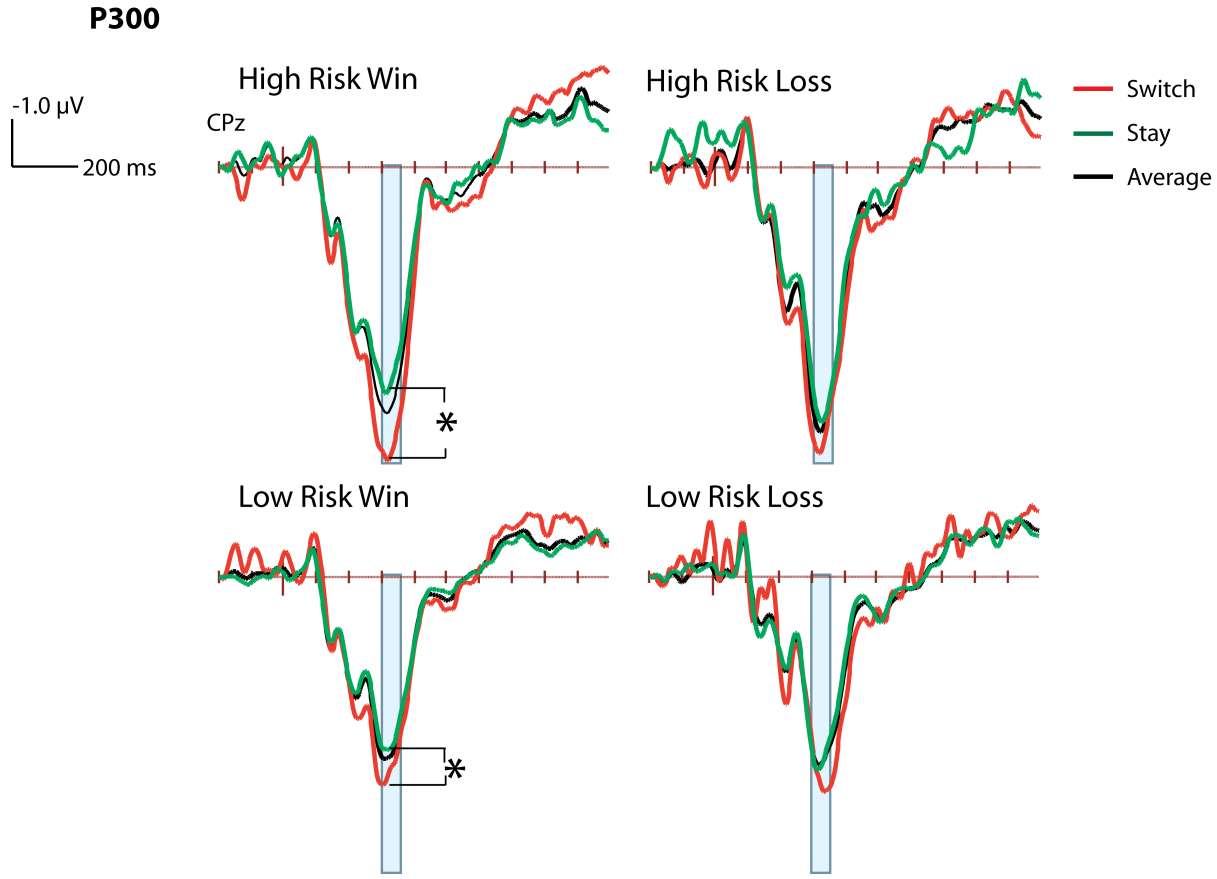


Figure 3-4: Grand-averaged ERP waveforms for the P300. The P300 was measured at electrode CPz from 300-30 ms post-feedback. The waveform is colored red when participants subsequently switched to the other bet type on the next trial and is colored green when participants subsequently stayed on the same bet type on the next trial. Significant differences are marked with asterisks (*).

The mean amplitude of the P300 was modulated by Risk, $F_{1,15}$=18.813; p=.001, and by Subsequent Bet, $F_{1,15}$=9.052; p=.009, but not by Valence, $F_{1,15}$=0.142; p=.711. The Valence by

Subsequent Bet interaction was significant, $F_{1,15}$=5.024; p=.041. Pairwise comparisons revealed that the P300 was significantly larger in the Switch relative to the Stay condition for the High-Risk Win condition, t_{16}=2.356; p=.032, and the Low-Risk Win condition, t_{16}=2.368; p=.031, but not for the High-Risk Loss, t_{15}=1.160=.264, or Low-Risk Loss, t_{16}=0.657; p=.521, conditions (Figure 3-4). The three-way Risk by Valence by Subsequent Bet interaction was not significant, $F_{1,15}$=0.009; p=.925.

3.5 Discussion

Previous studies have implicated the evoked FRN and P300 with registering and processing deviations from an expected outcome, with the FRN sensitive both to the valence (positive/negative) of the outcome and the perceived riskiness of the chosen bet, and the P300 sensitive only to the perceived riskiness of the chosen bet. The present study replicates the most common observations of these studies. An FRN was observed over fronto-central electrode sites that was significantly affected by the riskiness of the chosen bet. Although there was a significant main effect of valence on FRN amplitude, the interaction between risk and valence was not significant and I conclude that the FRN was not modulated by valence in this paradigm. A P300 was observed over centro-parietal electrodes that was significantly affected by the riskiness of the chosen bet but not by the valence of the outcome. These findings replicate those observed in Christie and Tata (2009) and extend the body of scientific knowledge by linking both FRN and P300 amplitudes with the subsequent action made in this gambling paradigm. When participants were informed they had won the selected bet, and when they would subsequently go on to choose the other bet type on the next trial, both the FRN and P300 were significantly larger than when they placed the same bet type on the next round. FRN

amplitude is known to reflect valence and perceived risk, but in this case I found significant differences in the ERP during the FRN latency window, and at the same electrode as the FRN, even when valence and risk were held constant. This finding is novel and merits further consideration.

FRN amplitude is sensitive to stimulus probability (Krigolson & Holroyd, 2007b) and P300 amplitude is sensitive to the rate at which a stimulus is encountered (Polich, 2007). In this experiment both the High-Risk Win Switch and Low-Risk Win Switch conditions were encountered less frequently than their Stay counterparts, and so one possible interpretation is that the differences in FRN and P300 amplitudes in this study arose solely due to outcome probability. I would argue against this explanation as it "puts the cart before the horse"; it is contingent on participants having already formulated a strategy for the next round before feedback was processed on the present round. It is unclear when participants formulate their strategy and the data offer no support for this hypothesis. I instead propose that participants have *not* yet formulated a strategy, and that the observed differences in FRN and P300 amplitudes in the two Win-Switch conditions (relative to the two Win-Stay conditions) reflect fundamental differences in the processing of rewarding feedback that subsequently influence the bet selected at a later time. Although there is, again, no evidence in this paradigm to support this hypothesis, it is supported by literature linking FRN amplitude with adaptive decision-making. FRN amplitude is positively correlated with response switching (Yasuda et al., 2004), with improved adaptive learning (Krigolson & Holroyd, 2007a, 2007b), and with error avoidance (Bellebaum & Daum, 2008). There is thus substantial precedent that evoked feedback responses represent more than the mere registration of win or loss. To my knowledge though, this study is the first to demonstrate a direct relationship between FRN amplitude and subsequent choices.

The only observed increases in FRN and P300 amplitude occurred when participants won a bet and subsequently switched to the other bet. As participants were instructed to win as many points as possible, it stands to reason the subsequent decision to switch bets was made because the participant believe he or she was unlikely to win again with the same bet. Because risk and reward are confounded in this paradigm there are a few possible interpretations of this decision. Since participants improved significantly over the duration of the experiment it is fair to assume they developed, if not explicitly then implicitly, the understanding that the High-Risk wager was disadvantageous to long-term play. It is therefore possible that the increased ERP amplitudes during the High-Risk Win Switch condition represent the registration that the experienced outcome was better than expected, and the increased FRN and P300 activity served to devalue that action on the subsequent trial. This theory fails to explain the increased ERP amplitude observed in the Low-Risk Win Switch condition. Instead, it may be that the activity observed in the two Win Switch conditions represent some type of neural signal to disengage from a rewarding outcome to pursue another, more rewarding outcome – in other words, to stop *exploiting* a given action and to start *exploring* for another, more rewarding action, consistent with the theory that the evoked FRN and P300 represent a reinforcement-learning mechanism in mediofrontal cortex to mediate adaptive decision making (Holroyd & Coles, 2002; Sutton & Barto, 1998). More research is necessary to elucidate how these ERP components are implicated in future decision-making.

It would be informative to correlate a participant's evoked FRN and P300 amplitudes during the Win Switch conditions with the rate of response switching during the experiment. Unfortunately, such a correlation is highly confounded because the amplitude of an individual subject's ERP is frequently related to the number of trials used in computing that average (Luck,

2005). Time-frequency analysis on a trial-by-trial basis may yield sufficiently stable data to assess individual differences in EEG activity preceding changes in bets, which in turn would offer compelling insight into brain electrical responses preceding changes in action selection.

3.6 Acknowledgements

I thank Wendy Maynes-Anderson for assistance with data collection and Andrew Butcher for programming assistance. This work was supported by an NSERC Discovery Grants to M.S.T.

Chapter 4: Discussion

The experiments in this thesis investigated electrical responses in the human brain during feedback processing in a gambling game. These responses include the evoked FRN and P300, and induced changes in theta-band power. Experiment 1 used Beamformer source localization to determine that the generators of feedback-induced theta power comprised partially overlapping regions in right medial frontal cortex for win and loss conditions, possibly including the Anterior Cingulate Cortex (ACC). To my knowledge this represents the first study to source-localize this activity. Experiment 1 also investigated the relationship between induced and evoked theta activity by identifying the extent to which the generators of induced theta activity also accounted for the scalp topography of the FRN and P300. I placed dipoles at the same locations as the foci of the identified generators of induced theta better and allowed these dipoles to freely rotate to best explain the P300 than the FRN. Neither evoked component was well described (the best solution had 5.4% RV), which suggests that evoked and induced generators share only partially overlapping cortical generators with frontal cortex. As the paradigm used in both experiments is a free-choice task, Experiment 2 investigated differences in feedback-related ERPs based on subsequent gambling decisions. Significant increases in FRN and P300 amplitudes were observed during feedback processing when participants subsequently switched from one bet type to the other on the subsequent trial. This novel finding is broadly supported by empirical observations in other studies and within the theoretical framework of a dopaminergic reinforcement learning system in frontal cortex.

4.1 The Functional Significance of Theta Oscillations

Theta rhythms are among the most robust oscillations observable in the human brain and have been linked to a number of cognitive processes beyond feedback processing, including executive function (Sauseng, Hoppe, Klimesch, Gerloff, & Hummel, 2007), memory (Klimesch, 1999; Sammer et al., 2007), visuospatial processing (Buzsaki, 2005), attention (Gross et al., 2004), and conscious perception (Doesburg, Green, McDonald, & Ward, 2009). It is believed that distant cortical regions interact by phase-locking within the theta band to form re-entrant cortico-cortical "loops" to exchange and process information (Varela, Lachaux, Rodriguez, & Martinerie, 2001). Recent findings using EEG support this theory; theta-band synchronization has been demonstrated between ACC and dorsolateral PFC during the Stroop task (Hanslmayr et al., 2008; Stroop, 1935). It may be that feedback processing entails synchronous activity between ACC and other frontal cortex structures to mediate the numerous subprocesses of feedback processing, perhaps including orbitofrontal cortex to update outcome expectancy (Wallis, 2007) and dorsolateral PFC to update working memory and in the control of overt attention (MacDonald, Cohen, Stenger, & Carter, 2000). To date no such analysis has been performed.

It is well established that the hippocampus (HPC) is a substantial generator of theta-band neural activity (see for e.g. Maurer & McNaughton, 2007). However, the source localizations performed in this thesis do not lend evidence that the HPC is a generator of feedback-related theta activity. This is unsurprising; the HPC is a deep structure that has largely resisted functional imaging using EEG. The hippocampus may be involved in mediating feedback processing in ways not detectable using EEG. For example, it is well known that HPC damage is associated with marked deficits in declarative memory (Scoville & Milner, 1957), and the

ability to consciously integrate the encountered feedback during the experiment (approximately 45 minutes) is almost certainly essential for good performance. That said, it is not generally believed that the HPC is involved in generating procedural and implicit memories. An interesting observation is that participants in this paradigm are generally not consciously aware of its win/loss ratio. Informal debriefings suggest that participants often implemented nonspecific strategies such as, "I change to the other bet whenever I lost" or, "I'd place the $50 bet twice and then the $100 once, then repeat". Broadly construed, this is in turn consistent with one of the interesting observations of participants in the original IGT: subjects improve their performance over time without being consciously aware of the task's probabilities. Given this, it is unclear what role, if any, HPC activity plays is mediating feedback processing. It may be that frontal theta rhythms are "inherited" from HPC theta activity, and that frontal cortex and the HPC form a network that exchanges information via theta phase locking (Hyman, Zilli, Paley, & Hasselmo, 2005) . Such a network has been theorized for nearly 75 years (Papez, 1937), and it is exciting that modern neuroimaging techniques are finally able to shed empirical to the specific mechanics of this system.

4.2 Risk and Decision Making

In both experiments I described the $100 wager as the "High Risk" bet and the $50 wager as the "Low Risk" bet. This definition follows from the expected value (EV) of the two bets, with the larger bet having a net negative EV and the smaller bet having a net positive EV. As participants are instructed to score as many points as possible, and because of the $100 bet's negative EV, one may argue that a participant's decision to place the large bet (especially late in the task when he or she has likely formed an implicit understand that the large bet is

disadvantageous) may originate from a decision to "take a chance" at receiving an unlikely large reward. However, this behavior does not conform to the pattern of decision-making other researchers define as 'risky'. For example, in a study wherein participants had to obtain a minimum number of points in a particular round to receive a reward, participants would routinely choose actions with greater variance, even if the expected value was the same, to score sufficient points to obtain their reward (Mishra & Lalumière, 2010). Such patterns of "risky" decision-making are also consistent with real-life risky behaviors such as crime, drug use, and unsafe sex (Mishra & Lalumière, 2009). 'Risk', as used to define the wagers in this paradigm, is clearly different from the concept of risk as it pertains to decision making.

At least three factors make it difficult to interpret the results in these experiments with the psychosocial definition of risky decision making. First, participants were not informed as to each bet's EV, and although most participants at least implicitly formed an accurate expectation of the EV for the two bets, this knowledge was not available to them throughout the entirety of the task. Second, although participants did have a visual record of their performance during the task (the horizontal bar at the top of the main betting screen depicted the participant's performance), participants did not know precisely how many bets remained in the task. Finally, as shall be discussed in section 4.4, participants were not rewarded based on their performance in the task. Additionally, although there is substantial evidence as to the neural processes mediating feedback processing, there is comparatively less research unifying these mechanisms with those governing risky or safe decision making. It is known, though, that risk-averse behavior is correlated with baseline EEG activity in right-hemisphere prefrontal cortex (Gianotti et al., 2008) and with activity in bilateral dorsolateral prefrontal cortex (Fecteau et al., 2007), and it is also known that FRN amplitude inversely correlates with the frequency with which

participants experience large aversive outcomes (Bellebaum & Daum, 2008). Risky decision making may thus arise via a combination of neocortical activities, including responses in mediofrontal cortical to signal deviations from expectancy and responses in frontal cortex to either inhibit or disinhibit an appropriate response.

4.3 Dopamine, Reinforcement Learning and Attention

A substantial literature implicates dopamine (DA) as a chemical signal between mesencephalic and frontal cortex structures to process deviations from expected outcomes (Berridge & Robinson, 1998; Miller & Cohen, 2001; Schultz, Dayan, & Montague, 1997). It is important to note that the activity of dopaminergic circuits does not uniquely code for hedonism or reward as is described in popular literature. Using a classical conditioning paradigm (Pavlov, 1927) Schultz et al. (1997) observed that mesencephalic dopaminergic cells would fire robustly to the onset of a juice reward, ostensibly signaling the onset of reward delivery. Over time however, the same cells would fire in response not to the onset of the reward, but to a predictive cue that signaled the delivery of the reward. The animal had learned to pair a cue with an expected reward, and changes in the activity of mesencephalic DA cells tracked this paired conditioning. Finally, after establishing this relationship, subsequently withholding the juice reward resulted in DA cells *not* firing at the approximate time the juice reward was expected – coding for a negative deviation from expectancy.

Though not a classical conditioning paradigm, participants in these experiments nevertheless learned, at least implicitly, to associate the small wager with a more frequent positive outcome and the large wager with a more frequent negative outcome. It is not possible to directly image neural activity in the mesencephalon using EEG (although such imaging has recently been made

possible using fMRI; see D'Ardenne, McClure, Nystrom, & Cohen, 2008), but it is generally believed that the change in electrical activity observed in the ACC during feedback processing represents the cortical synaptic target of DA activity in the midbrain (Holroyd & Coles, 2002). The two experiments in this thesis further extend this theory. The evoked components measured in Experiment 1 differed significantly between the High-Risk Win and Low-Risk Loss conditions, despite having the same expected probability of 40%, and the evoked components in Experiment 2 differed for the High-Risk Win and Low-Risk Win conditions depending on the bet selected in the subsequent round. Collectively, these results extend the functional importance of evoked mediofrontal electrical activity. It is unlikely that mediofrontal EEG activity codes solely for deviation from expectancy, but instead represents the activity of some network that uses feedback to affect learning.

A potentially worthwhile avenue for future research involves studying feedback processing mechanisms in pathological gamblers. Preliminary data from a pilot study indicate that participants who score high on the CPGI (7 or higher, and indicative of problem gambling) may not learn as quickly as control participants that the $100 bet is negatively valued (data not published). It is probable that this behavioral deficit arises from deficiencies in feedback processing mechanisms in gamblers. Although feedback processing has been studied in pathological gamblers using fMRI (Reuter et al., 2005), I know of no study to date that used the EEG technique to investigate feedback mechanisms in gamblers (see though Regard, Knoch, Gutling, & Landis, 2003).

One reason for reward processing is to maintain engagement with a valuable behaviour and to disengage from behaviours that are detrimental. Problem gamblers exhibit an inability to disengage attention while playing VLT games (Diskin & Hodgins, 1999), possibly related to

hyperactivation of a reward signal during gambling. At the other extreme, individuals with Attention Deficit/Hyperactivity Disorder (ADHD) tend to have difficulty maintaining behavioral engagement on a task. ADHD affects approximately 5% of children (Schonwald & Lechner, 2006) and tends to persist into adulthood. A prominent theory of ADHD proposes that it also arises from a reward-processing deficit (Haenlein & Caul, 1987; Holroyd, Baker, Kerns, & Muller, 2008; Sagvolden, Johansen, Aase, & Russell, 2005; Sonuga-Barke, Taylor, Sembi, & Smith, 1992). Despite the contrast in behavioural manifestations, ADHD and PG are substantially comorbid (Goudriaan, Oosterlaan, de Beurs, & Van den Brink, 2004), suggesting that these conditions might share a common dysfunction in reward-processing mechanisms. The interaction between DA activity during feedback processing and attentional mechanisms has received little study, although there are at least two lines of evidence linking these phenomena: (1) The treatment for ADHD typically involves the prescription of DA-stimulant drugs such as methylphenidate or dextroamphetamine, and (2), in laboratory studies, participants are faster and more accurate at the deployment of attention to spatial locations that have been associated with reward (Maunsell, 2004). It may be that feedback processing mechanisms interact with attention to prioritize information and to control the process of engagement and disengagement of attention to relevant stimuli. Future research in Dr. Matthew Tata's laboratory aims to elucidate this interaction between reward processing and attention.

Finally, because future bet switching has an observable index in the EEG during feedback processing it may be possible to perform real-time analysis to determine the probability of bet switching *before* participants perform the action. Such "pre-conscious" neural activity is supported by other studies that observed characteristic brain responses prior to or in the absence of conscious perception (Binsted, Brownell, Vorontsova, Heath, & Saucier, 2007; Libet,

Gleason, Wright, & Pearl, 1983), and is consistent with the Somatic Markers hypothesis posited by Bechara et al. (1994) to explain emotional decision making during the IGT.

4.4 Limitations of the Present Studies

There are at least three factors that limit the interpretability of the results presented in this thesis.

First, participants in these studies were not financially compensated and received 2% bonus course credit irrespective of their task performance. This is unlike most studies of feedback processing that use variable cash reward based on a participant's performance. This limitation has been discussed in detail in the discussion of Experiment 1 but the major points bear repeating: participants significantly improved over the course of both experiments and demonstrated feedback-related EEG spectra consistent with other studies.

Second, I have not observed the beta-band (20-30 Hz) power increases observed by Cohen et al. (2007) and Marco-Pallares et al. (2008). In these studies beta activity was observed subsequent to positive feedback and was maximal during unlikely wins. This activity was not observed in Experiment 1. It is unlikely that this failure stems from the choice of experimental paradigm. The paradigm used in this thesis was a probabilistic learning task wherein participants learned to optimize performance by selecting a positively-valued wager (the $50 bet) more frequently than a negatively-valued wager (the $100 bet). Although this is inconsistent with Marco-Pallares et al. who used a fixed-probability task adapted from Gehring and Willoughby (2002), it *is* broadly consistent with Cohen et al., who implemented a blocked gambling paradigm wherein participants had to continuously learn new reward probabilities and associations throughout the experiment. It is also unlikely that this failure to replicate arises due to

insufficient statistical power. Electrical power decreases as the frequency of the EEG increases and as a general rule the number of trials that must be sampled scales linearly with the frequency of interest; if changes in the theta band (4-7 Hz) require approximately 15-20 trials to reach significance, changes in the beta band (20-30 Hz) require approximately 60-80 trials to reach significance (personal communication, Anthony Herdman, Department of Psychology, Simon Fraser University). In Experiment 1 there were insufficient trials in the High-Risk Win and High-Risk Loss conditions (approx. 20) to observe beta rhythms, but there were sufficient trials in the Low-Risk Win and Low-Risk Loss (approx. 60-75). Finally, it is also unlikely that this failure to replicate arose due to the use of the dense-array, high-impedance EEG system (EGI 128-channel HydroCel Geodesic Sensor Net) available at the University of Lethbridge, as similar systems have been used to study high-frequency oscillations in other studies (Gruber, Muller, & Keil, 2002; Muller, Gruber, & Keil, 2000; Sokhadze et al., 2009). The best explanation is thus the one posited in the discussion to Experiment 1: beta-band activity may reflect the processing of variable reward. Although no study has yet investigated the interaction between reward type and beta activity, preliminary data from an ongoing study with paid participants do *not* suggest this is the case. It may be that the factors previously listed interact in an unknown manner to attenuate beta-band activity. At present the role of beta-band oscillations during feedback processing remains poorly understood.

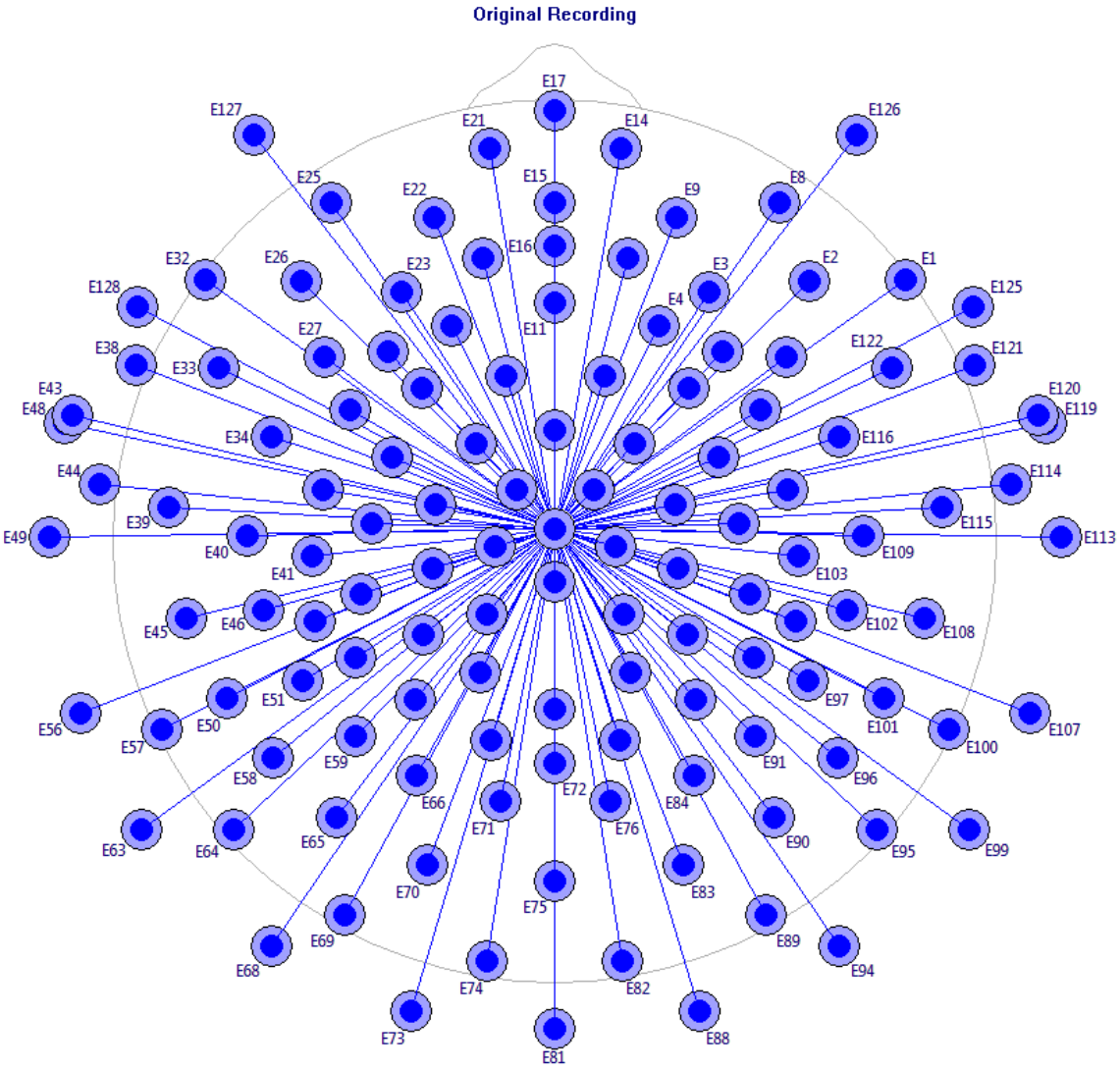
Third, any EEG analysis requires sufficient signal-to-noise to identify electrical spectra of interest from the background electrical activity of the brain. This necessitates a minimum number of trials in a given condition – approximately 15-20 for studies examining low-frequency (e.g. theta) power changes and perhaps more for ERP analyses. Participants were encouraged in both experiments to perform as well as possible. This led to a situation wherein some

participants performed the task *so well* that there were insufficient trials to analyze and they were excluded from analysis. Although these participants were in the minority in Experiment 1, approximately half the participants in Experiment 2 were excluded for not having sufficient trials. The exclusion of these high-performing participants restricted the possibility of analyzing feedback processing mechanisms in participants where, arguably, these mechanisms were most effective. An investigation comparing theta (and possibly beta) power changes between high- and low-performing individuals might offer compelling insight into individual differences in feedback processing mechanisms.

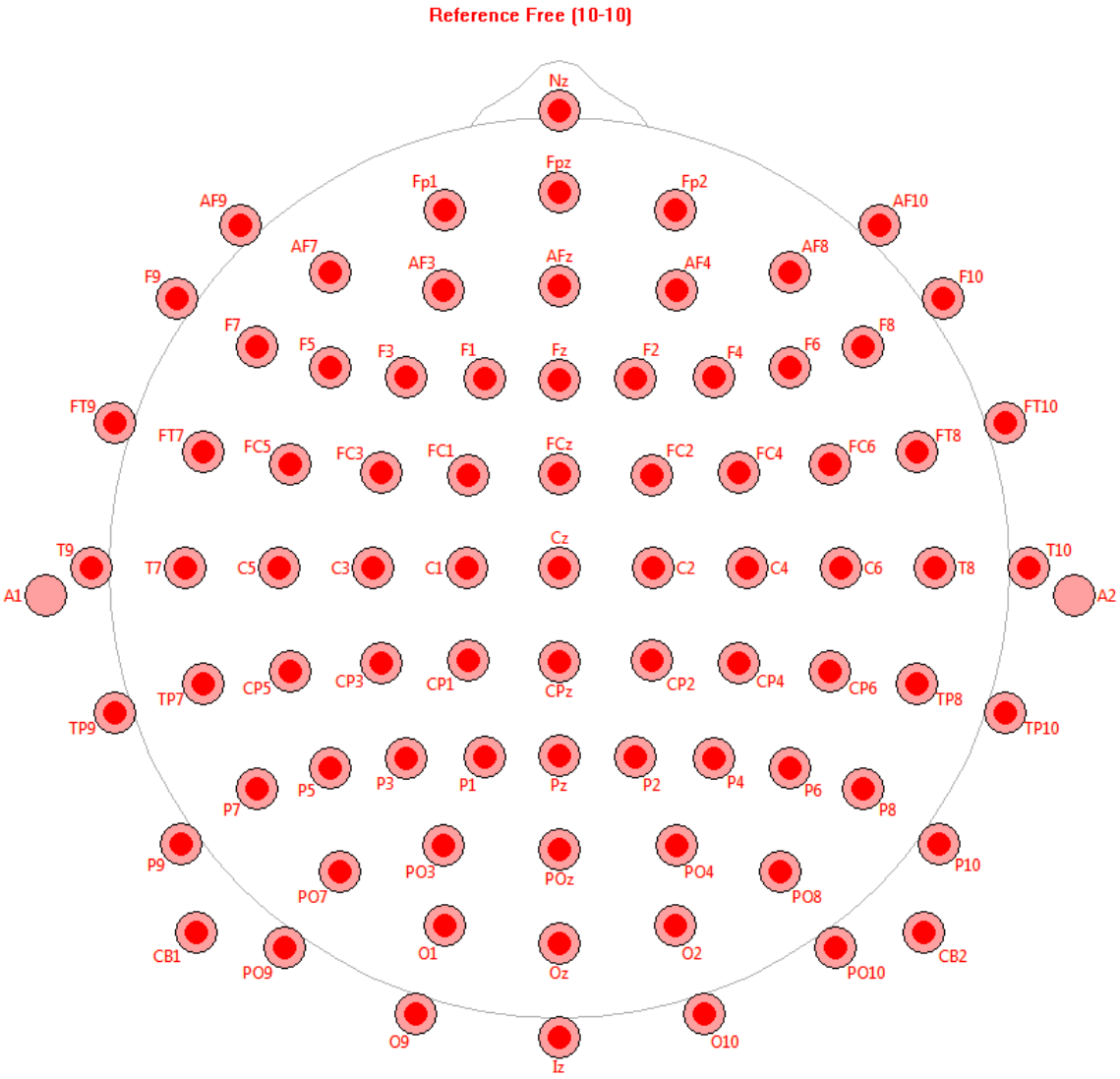
4.5 Summary

A number of characteristic brain responses were observed in response to processing rewarding and punishing feedback in a gambling game, including the evoked FRN and P300 and increases in induced theta-band EEG activity. Changes in induced EEG activity have received substantially less scrutiny than changes in evoked EEG activity. Experiment 1 indicates that induced changes are generated in mediofrontal cortex but that they share only partial cortical overlap with the generators of evoked feedback responses. Experiment 2 suggests that FRN and P300 amplitudes can be modulated by the subsequent response placed in a gambling game. This finding is especially noteworthy because it demonstrates a further factor that affects the amplitude of evoked feedback-related activity, and because it links evoked EEG responses to future decision making. In turn, this extends the functional significance of evoked responses beyond the detection of violations to expectancy to an active cognitive processes implicated in learning mechanisms.

Appendix A: EGI HydroCel Geodesic Sensor Net Electrode Locations



Appendix B: International 10-10 Electrode Placement Locations



Appendix C: Canadian Pathological Gambling Index

Subject Code _____

Date _____

*Some of the next questions may not apply to you, but please try to be as accurate as possible. Thinking about the past **12 months**:*	never	sometimes	Most of the time	Almost always	Don't Know
Have you bet more than you could really afford to lose?					
Have you needed to gamble with larger amounts of money to get the same feeling of excitement?					
When you gambled, did you go back another day to try to win back the money you lost?					
Have you borrowed money or sold anything to get money to gamble?					
Have you felt that you might have a problem with gambling?					
Has gambling caused you any health problems, including stress or anxiety?					
Have people criticized your betting or told you that you had a gambling problem, regardless of whether or not you thought it was true?					
Has your gambling caused any financial problems for you or your household?					
Have you felt guilty about the way you gamble or what happens when you gamble?					

Appendix D: Zuckerman Sensation Seeking Scale

Directions: Each of the items below contains two choices, A and B. Please circle the letter of the choice which most describes your likes or the way you feel. In some cases you may find items in which both choices describe your likes or feelings. Please choose the one which better describes your likes or feelings. In some cases you may find items in which you do not like either choice. In these cases mark the choice you dislike least. Do not leave any items blank.

It is important you respond to all items with only one choice, A or B. We are interested only in your likes or feelings, not in how others feel about these things or how one is supposed to feel. There are not right or wrong answers as in other kinds of tests. Be frank and give your honest appraisal of yourself.

1.	A	I like "wild" uninhibited parties.
	B	I prefer quiet parties with good conversation.
2.	A	There are some movies I enjoy seeing a second or even a third time.
	B	I can't stand watching a movie I've seen before.
3.	A	I often wish I could be a mountain climber.
	B	I can't understand people who risk their necks climbing mountains.
4.	A	I dislike all body odors.
	B	I like some of the earthy body smells.
5.	A	I get bored seeing the same old faces.
	B	I like the comfortable familiarity of everyday friends.
6.	A	I like to explore a strange city or section of town by myself, even if it means getting lost.
	B	I prefer a guide when I am in a place I don't know well.
7.	A	I dislike people who do or say things just to shock or upset other people.
	B	When you can predict almost everything a person will do and say he or she must be a bore.

8.	A	I usually don't enjoy a movie or a play where I can predict what will happen in advance.
	B	I don't mind watching a movie or play where I can predict what will happen in advance.
9.	A	I have tried marijuana or would like to.
	B	I would never smoke marijuana.
10.	A	I would not like to try any drug which might produce strange and dangerous effects on me.
	B	I would like to try some of the new drugs that produce hallucinations.
11.	A	A sensible person avoids activities that are dangerous.
	B	I sometimes like to do things that are a little frightening.
12.	A	I dislike "swingers" (people who are uninhibited and free about sex).
	B	I enjoy the company of real "swingers."
13.	A	I find that stimulants make me uncomfortable.
	B	I often like to get high (drinking liquor or smoking marijuana).
14.	A	I like to try new foods that I have never tasted before.
	B	I order the dishes with which I am familiar, so as to avoid disappointment and unpleasantness.
15.	A	I enjoy looking at home movies, travel slides, or home videos.
	B	Looking at someone's home movies, travel slides, or home videos bores me tremendously.
16.	A	I would like to take up the sport of water-skiing.
	B	I would not like to take up water-skiing.
17.	A	I would like to try surf-board riding.
	B	I would not like to try surf-board riding.

18.	A	I would like to take off on a trip with no pre-planned or definite routes, or timetable.
	B	When I go on a trip I like to plan my route and timetable fairly carefully.
19.	A	I prefer the “down-to-earth” kinds of people as friends.
	B	I would like to make friends in some of the “far-out” groups like artists or “punks.”
20.	A	I would not like to learn to fly an airplane.
	B	I would like to learn to fly an airplane.
21.	A	I prefer the surface of the water to the depths.
	B	I would like to go scuba diving.
22.	A	I would like to meet some persons who are homosexual (men or women).
	B	I stay away from anyone I suspect of being “gay” or “lesbian.”
23.	A	I would like to try parachute jumping.
	B	I would never want to try jumping out of a plane with or without a parachute.
24.	A	I prefer friends who are excitingly unpredictable.
	B	I prefer friends who are reliable and predictable.
25.	A	I am not interested in experience for its own sake.
	B	I like to have new and exciting experiences and sensations even if they are a little frightening, unconventional, or illegal.
26.	A	The essence of good art is in its clarity, symmetry of form and harmony of colors.
	B	I often find beauty in the “clashing” colors and irregular forms of modern paintings.

27.	A	I enjoy spending time in the familiar surroundings of home.
	B	I get very restless if I have to stay around home for any length of time.
28.	A	I like to dive off the high board.
	B	I don't like the feeling I get standing on the high board (or I don't go near it at all).
29.	A	I like to date members of the opposite sex who are physically exciting.
	B	I like to date members of the opposite sex who share my values.
30.	A	Heavy drinking usually ruins a party because some people get loud and boisterous.
	B	Keeping the drinks full is the key to a good party.
31.	A	The worst social sin is to be rude.
	B	The worst social sin is to be a bore.
32.	A	A person should have considerable sexual experience before marriage.
	B	It's better if two married persons begin their sexual experience with each other.
33.	A	Even if I had the money I would not care to associate with flighty rich persons in the 'jet set.'
	B	I could conceive of myself seeking pleasures around the world with the "jet set."
34.	A	I like people whoa are sharp and witty even if they do sometimes insult others.
	B	I dislike people who have their fun at the expense of hurting the feelings of others.
35.	A	There is altogether too much portrayal of sex in movies.
	B	I enjoy watching many of the "sexy" scenes in the movies.
36.	A	I feel best after taking a couple of drinks.
	B	Something is wrong with people who need liquor to feel good.

37.	A	People should dress according to some standards of taste, neatness, and style.
	B	People should dress in individual ways even if the effects are sometimes strange.
38.	A	Sailing long distances in small sailing crafts is foolhardy.
	B	I would like to sail a long distance in a small but seaworthy sailing craft.
39.	A	I have no patience with dull or boring persons.
	B	I find something interesting in almost every person I talk with.
40.	A	Skiing fast down a high mountain slope is a good way to end up on crutches.
	B	I think I would enjoy the sensations of skiing very fast down a high mountain slope.

References

Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition, 50*(1-3), 7-15.

Bellebaum, C., & Daum, I. (2008). Learning-related changes in reward expectancy are reflected in the feedback-related negativity. *European The Journal of Neuroscience, 27*(7), 1823-1835.

Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Research Reviews, 28*(3), 309-369.

Binsted, G., Brownell, K., Vorontsova, Z., Heath, M., & Saucier, D. (2007). Visuomotor system uses target features unavailable to conscious awareness. *Proceedings of the National Academy of Science, 104*(31), 12669-12672.

Buzsaki, G. (2005). Theta rhythm of navigation: link between path integration and landmark navigation, episodic and semantic memory. *Hippocampus, 15*(7), 827-840.

Buzsaki, G., & Draguhn, A. (2004). Neuronal Oscillations in Cortical Networks. *Science, 304*, 1926 - 1929.

Cavedini, P., Riboldi, G., Keller, R., D'Annucci, A., & Bellodi, L. (2002). Frontal lobe dysfunction in pathological gambling patients. *Biological Psychiatry, 51*(4), 334-341.

Christie, G. J., & Tata, M. S. (2009). Right frontal cortex generates reward-related theta-band oscillatory activity. *Neuroimage, 48*(2), 415-422.

Cohen, M. X. (2007). Individual differences and the neural representations of reward expectation and reward prediction error. *Social Cognitive and Affective Neuroscience, 2*(1), 20-30.

Cohen, M. X., Elger, C. E., & Fell, J. (2008). Oscillatory Activity and Phase-Amplitude Coupling in the Human Medial Frontal Cortex during Decision Making. *Journal of Cognitive Neuroscience, 21(2)*, 390-402.

Cohen, M. X., Elger, C. E., & Ranganath, C. (2007). Reward expectation modulates feedback-related negativity and EEG spectra. *Neuroimage, 35*(2), 968-978.

D'Ardenne, K., McClure, S. M., Nystrom, L. E., & Cohen, J. D. (2008). BOLD responses reflecting dopaminergic signals in the human ventral tegmental area. *Science, 319*(5867), 1264-1267.

Delgado, M. R., Nystrom, L. E., Fissell, C., Noll, D. C., & Fiez, J. A. (2000). Tracking the hemodynamic responses to reward and punishment in the striatum. *Journal of Neurophysiology, 84*(6), 3072-3077.

Diskin, K. M., & Hodgins, D. C. (1999). Narrowing of Attention and Dissociation in Pathological Video Lottery Gamblers. *Journal of Gambling Studies, 15*(1), 17-28.

Doesburg, S. M., Green, J. J., McDonald, J. J., & Ward, L. M. (2009). Rhythms of consciousness: binocular rivalry reveals large-scale oscillatory network dynamics mediating visual perception. *PLoS One, 4*(7), e6142.

Donkers, F. C., Nieuwenhuis, S., & van Boxtel, G. J. (2005). Mediofrontal negativities in the absence of responding. *Cognive Brain Research, 25*(3), 777-787.

Doppelmayr, M., Klimesch, W., Schwaiger, J., Stadler, W., & Rohm, D. (2000). The time locked theta response reflects interindividual differences in human memory performance. *Neuroscience Letters, 278*(3), 141-144.

Everitt, B. J., Dickinson, A., & Robbins, T. W. (2001). The neuropsychological basis of addictive behaviour. *Brain Research Review, 36*(2-3), 129-138.

Fecteau, S., Pascual-Leone, A., Zald, D.H., Liguori, P., Theoret, H., Boggio, P.S., & Fregni, F. (2007). Activation of Prefrontal Cortex by Transcranial Direct Current Stimulation Reduces Appetite for Risk during Ambiguous Decision Making. *The Journal of Neuroscience, 27(23)*, 6212-6218.

Ferris, J., & Wynne, H. (2001). *The Canadian Problem Gambling Index: Final Report*. Ottawa, ON: Canadian Centre on Substance Abuse.

Fisher, R. (1918). The Correlation Between Relatives on the Supposition of Mendelian Inheritance. *Transactions of the Royal Society of Edinburgh, 52*, 399-433.

Gehring, W. J., & Knight, R. T. (2000). Prefrontal-cingulate interactions in action monitoring. *Nature Neuroscience, 3*(5), 516-520.

Gehring, W. J., & Willoughby, A. R. (2002). The medial frontal cortex and the rapid processing of monetary gains and losses. *Science, 295*(5563), 2279-2282.

Gehring, W. J., & Willoughby, A. R. (2004). Are all medial frontal negativities created equal? Toward a richer empirical basis for theories of action monitoring. In M. Ullsperger & M. Falkenstein (Eds.), *Errors, conflicts and the brain. Current opinions on performance monitoring* (pp. 14-20). Leipzig: Max Planck Institute of Cognitive Neuroscience.

Gianotti, L.R.R., Knoch, D., Faber, P.L., Lehmann, D., Pascual-Marqui, R.D., Diezi, C., Schoch, C., Eisenegger, C., & Fehr, E. (2008). *Psychological Science, 20(1)*, 33-38.

Gossett, W. (1908). The probable error of a mean. *Biometrika*.

Goudriaan, A. E., Oosterlaan, J., de Beurs, E., & Van den Brink, W. (2004). Pathological gambling: a comprehensive review of biobehavioral findings. *Neuroscience & Biobehavioral Reviews, 28*(2), 123-141.

Goudriaan, A. E., Oosterlaan, J., de Beurs, E., & van den Brink, W. (2005). Decision making in pathological gambling: a comparison between pathological gamblers, alcohol dependents, persons with Tourette syndrome, and normal controls. *Cognitive Brain Research, 23*(1), 137-151.

Green, J. J., Conder, J. A., & McDonald, J. J. (2008). Lateralized frontal activity elicited by attention-directing visual and auditory cues. *Psychophysiology, 45*(4), 579-587.

Green, J. J., & McDonald, J. J. (2008). Electrical Neuroimaging Reveals Timing of Attentional Control Activity in Human Brain. *PLoS Biology, 6*(4), e81.

Green, J. J., & McDonald, J. J. (2010). *A practical guide to beamformer source reconstruction for EEG.* In T. C. Handy (Ed.), *Brain Signal Analysis* (pp. 79-98). Cambridge, MA: MIT Press.

Gross, J., Kujala, J., Hamalainen, M., Timmermann, L., Schnitzler, A., & Salmelin, R. (2001). Dynamic imaging of coherent sources: Studying neural interactions in the human brain. *Proceedings of the National Academy of Sciences, 98*(2), 694-699.

Gross, J., Schmitz, F., Schnitzler, I., Kessler, K., Shapiro, K., Hommel, B. et al. (2004). Modulation of long-range neural synchrony reflects temporal limitations of visual attention in humans. *Proceedings of the National Academy of Sciences, 101*(35), 13050-13055.

Gruber, T., Muller, M. M., & Keil, A. (2002). Modulation of induced gamma band responses in a perceptual learning task in the human EEG. *Journal of Cognitive Neuroscience, 14*(5), 732-744.

Haenlein, M., & Caul, W. F. (1987). Attention deficit disorder with hyperactivity: a specific hypothesis of reward dysfunction. *Journal of the American Academy of Child and Adolescent Psychiatry, 26*(3), 356-362.

Hagoort, P., Hald, L., Bastiaansen, M., & Petersson, K. M. (2004). Integration of word meaning and world knowledge in language comprehension. *Science, 304*(5669), 438-441.

Hanslmayr, S., Pastotter, B., Bauml, K. H., Gruber, S., Wimber, M., & Klimesch, W. (2008). The electrophysiological dynamics of interference during the Stroop task. *Journal of Cognitive Neuroscience, 20*(2), 215-225.

Hewig, J., Trippe, R., Hecht, H., Coles, M. G., Holroyd, C. B., & Miltner, W. H. (2006). Decision-Making in Blackjack: An Electrophysiological Analysis. *Cerebral Cortex, 17(4)*, 865-877.

Hoechstetter, K., Bornfleth, H., Weckesser, D., Ille, N., Berg, P., & Scherg, M. (2004). BESA source coherence: a new method to study cortical oscillatory coupling. *Brain Topography, 16*(4), 233-238.

Holroyd, C. B., Baker, T. E., Kerns, K. A., & Muller, U. (2008). Electrophysiological evidence of atypical motivation and reward processing in children with attention-deficit hyperactivity disorder. *Neuropsychologia, 46*(8), 2234-2242.

Holroyd, C. B., & Coles, M. G. (2002). The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. *Psychological Review, 109*(4), 679-709.

Holroyd, C. B., Hajcak, G., & Larsen, J. T. (2006). The good, the bad and the neutral: electrophysiological responses to feedback stimuli. *Brain Research, 1105*(1), 93-101.

Holroyd, C. B., & Krigolson, O. E. (2007). Reward prediction error signals associated with a modified time estimation task. *Psychophysiology, 44*(6), 913-917.

Holroyd, C. B., Larsen, J. T., & Cohen, J. D. (2004). Context dependence of the event-related brain potential associated with reward and punishment. *Psychophysiology, 41*(2), 245-253.

Holroyd, C. B., Pakzad-Vaezi, K. L., & Krigolson, O. E. (2008). The feedback correct-related positivity: sensitivity of the event-related brain potential to unexpected positive feedback. *Psychophysiology, 45*(5), 688-697.

Hyman, J. M., Zilli, E. A., Paley, A. M., & Hasselmo, M. E. (2005). Medial prefrontal cortex cells show dynamic modulation with the hippocampal theta rhythm dependent on behavior. *Hippocampus, 15*(6), 739-749.

Ille, N., Berg, P., & Scherg, M. (2002a). Artifact correction of the ongoing EEG using spatial filters based on artifact and brain signal topographies. *Journal of Clinical Neurophysiology, 19*(2), 113-124.

Ille, N., Berg, P., & Scherg, M. (2002b). Artifact correction of the ongoing EEG using spatial filters based on artifact and brain signal topographies. *Journal of Clinical Neurophysiology, 19*(2), 113-124.

Jensen, O., & Tesche, C. D. (2002). Frontal theta activity in humans increases with memory load in a working memory task. *European The Journal of Neuroscience, 15*(8), 1395-1399.

Klimesch, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. *Brain Research Reviews, 29*(2-3), 169-195.

Klimesch, W., Doppelmayr, M., Russegger, H., & Pachinger, T. (1996). Theta band power in the human scalp EEG and the encoding of new information. *Neuroreport, 7*(7), 1235-1240.

Klimesch, W., Doppelmayr, M., Schwaiger, J., Winkler, T., & Gruber, W. (2000). Theta oscillations and the ERP old/new effect: independent phenomena? *Clinical Neurophysiology, 111*(5), 781-793.

Krigolson, O. E., & Holroyd, C. B. (2007a). Hierarchical error processing: different errors, different systems. *Brain Research, 1155*, 70-80.

Krigolson, O. E., & Holroyd, C. B. (2007b). Predictive information and error processing: the role of medial-frontal cortex during motor control. *Psychophysiology, 44*(4), 586-595.

Krigolson, O. E., Pierce, L. J., Holroyd, C. B., & Tanaka, J. W. (2008). Learning to Become an Expert: Reinforcement Learning and the Acquisition of Perceptual Expertise. *Journal of Cognitive Neuroscience, 21(9),* 1834-1841

Lee, J. H., Durand, R., Gradinaru, V., Zhang, F., Goshen, I., Kim, D. S. et al. (2010). Global and local fMRI signals driven by neurons defined optogenetically by type and wiring. *Nature, 465*(7299), 788-792.

Libet, B., Gleason, C. A., Wright, E. W., & Pearl, D. K. (1983). Time of conscious intention to act in relation to onset of cerebral activity (readiness-potential). The unconscious initiation of a freely voluntary act. *Brain, 106(3)*, 623-642.

Liu, X., Powell, D. K., Wang, H., Gold, B. T., Corbly, C. R., & Joseph, J. E. (2007). Functional dissociation in frontal and striatal areas for processing of positive and negative reward information. *The Journal of Neuroscience, 27*(17), 4587-4597.

Luck, S. J. (2005). *An Introducion to the Event-Related Potential technique*. Cambridge, MA: MIT Press.

Luu, P., Tucker, D. M., Derryberry, D., Reed, M., & Poulsen, C. (2003). Electrophysiological responses to errors and feedback in the process of action regulation. *Psychological Science, 14*(1), 47-53.

MacDonald, A. W., Cohen, J. D., Stenger, V. A., & Carter, C. S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science, 288*(5472), 1835-1838.

Marco-Pallares, J., Cucurell, D., Cunillera, T., Garcia, R., Andres-Pueyo, A., Munte, T. F. et al. (2008). Human oscillatory activity associated to reward processing in a gambling task. *Neuropsychologia, 46*(1), 241-248.

Maunsell, J. H. (2004). Neuronal representations of cognitive state: reward or attention? *Trends in Cognitive Sciences, 8*(6), 261-265.

Maurer, A. P., & McNaughton, B. L. (2007). Network and intrinsic cellular mechanisms underlying theta phase precession of hippocampal neurons. *Trends in Neurosciences, 30*(7), 325-333.

McClure, S. M., Berns, G. S., & Montague, P. R. (2003). Temporal prediction errors in a passive learning task activate human striatum. *Neuron, 38*(2), 339-346.

McClure, S. M., York, M. K., & Montague, P. R. (2004). The neural substrates of reward processing in humans: the modern role of FMRI. *Neuroscientist, 10*(3), 260-268.

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience, 24*, 167-202.

Miltner, W. H. R., Braun, C. H., & Coles, M. G. H. (1997). Event-related brain potentials following incorrect feedback in a time-estimation task: Evidence for a "generic" neural system for error detection. *Journal of Cognitive Neuroscience, 9*(6), 788 - 798.

Mishra, S., & Lalumière, M.L. (2009). Is the crime drop in the 1990s in Canada and the USA associated with a general decline in risky and health-related behavior? *Social Science & Medicine, 68(1)*, 39-48.

Mishra, S., & Lalumière, M.L. (2010). You can't always get what you want: The motivational effect of need on risk-sensitive decision-making. *Journal of Experimental Social Psychology, 46*, 605-611.

Muller, M. M., Gruber, T., & Keil, A. (2000). Modulation of induced gamma band activity in the human EEG by attention and visual information processing. *International Journal of Psychophysiology, 38*(3), 283-299.

Nieuwenhuis, S., Holroyd, C. B., Mol, N., & Coles, M. G. (2004). Reinforcement-related brain potentials from medial frontal cortex: origins and functional significance. *Neuroscience & Biobehavioral Reviews, 28*(4), 441-448.

Nieuwenhuis, S., Slagter, H. A., von Geusau, N. J., Heslenfeld, D. J., & Holroyd, C. B. (2005). Knowing good from bad: differential activation of human cortical areas by positive and negative outcomes. *European The Journal of Neuroscience, 21*(11), 3161-3168.

Nieuwenhuis, S., Yeung, N., Holroyd, C. B., Schurger, A., & Cohen, J. D. (2004). Sensitivity of electrophysiological activity from medial frontal cortex to utilitarian and performance feedback. *Cerebral Cortex, 14*(7), 741-747.

O'Doherty, J., Dayan, P., Schultz, J., Deichmann, R., Friston, K., & Dolan, R. J. (2004). Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science, 304*(5669), 452-454.

O'Doherty, J. P., Deichmann, R., Critchley, H. D., & Dolan, R. J. (2002). Neural responses during anticipation of a primary taste reward. *Neuron, 33*(5), 815-826.

Oliveira, F. T., McDonald, J. J., & Goodman, D. (2007). Performance monitoring in the anterior cingulate is not all error related: expectancy deviation and the representation of action-outcome associations. *Journal of Cognitive Neuroscience, 19*(12), 1994-2004.

Oya, H., Adolphs, R., Kawasaki, H., Bechara, A., Damasio, A., & Howard, M. A., 3rd (2005). Electrophysiological correlates of reward prediction error recorded in the human

prefrontal cortex. Proceedings of the National Academy of Sciences*, 102*(23), 8351-8356.

Pagnoni, G., Zink, C. F., Montague, P. R., & Berns, G. S. (2002). Activity in human ventral striatum locked to errors of reward prediction. *Nature Neuroscience, 5*(2), 97-98.

Papez, J. W. (1937). A proposed mechanism of emotion. *Journal of Neuropsychiatry and Clinical Neurosciences, 7*(1), 103-112.

Pavlov, I. (1927). Conditioned Reflexes. Oxford: Oxford University Press.

Polich, J. (2007). Updating P300: an integrative theory of P3a and P3b. *Clinical Neurophysiology, 118*(10), 2128-2148.

Polich, J., & Kok, A. (1995). Cognitive and biological determinants of P300: an integrative review. *Biololgical Psychology, 41*(2), 103-146.

Regard, M., Knoch, D., Gutling, E., & Landis, T. (2003). Brain damage and addictive behavior: a neuropsychological and electroencephalogram investigation with pathologic gamblers. *Cognitive and Behavioral Neurology, 16*(1), 47-53.

Reuter, J., Raedler, T., Rose, M., Hand, I., Glascher, J., & Buchel, C. (2005). Pathological gambling is linked to reduced activation of the mesolimbic reward system. *Nature Neuroscience, 8*(2), 147-148.

Sagvolden, T., Johansen, E. B., Aase, H., & Russell, V. A. (2005). A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. *Behavioral Brain Sciences, 28*(3), 397-419; discussion 419-368.

Sammer, G., Blecker, C., Gebhardt, H., Bischoff, M., Stark, R., Morgen, K. et al. (2007). Relationship between regional hemodynamic activity and simultaneously recorded EEG-theta associated with mental arithmetic-induced workload. *Human Brain Mapping, 28*(8), 793-803.

Sanfey, A. G., Loewenstein, G., McClure, S. M., & Cohen, J. D. (2006). Neuroeconomics: cross-currents in research on decision-making. *Trends in Cognitives Sciences, 10*(3), 108-116.

Sauseng, P., Hoppe, J., Klimesch, W., Gerloff, C., & Hummel, F. C. (2007). Dissociation of sustained attention from central executive functions: local activity and interregional connectivity in the theta range. *European The Journal of Neuroscience, 25*(2), 587-593.

Schonberg, T., Daw, N. D., Joel, D., & O'Doherty, J. P. (2007). Reinforcement learning signals in the human striatum distinguish learners from nonlearners during reward-based decision making. *The Journal of Neuroscience, 27*(47), 12860-12867.

Schonwald, A., & Lechner, E. (2006). Attention deficit/hyperactivity disorder: complexities and controversies. *Current Opinions in Pediatrics, 18*(2), 189-195.

Schultz, W. (2007). Behavioral dopamine signals. *Trends in Neurosciences, 30*(5), 203-210.

Schultz, W., Dayan, P., & Montague, P. R. (1997). A neural substrate of prediction and reward. *Science, 275*(5306), 1593-1599.

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal Neurology, Neurosurgery & Psychiatry, 20*(1), 11-21.

Sokhadze, E. M., El-Baz, A., Baruth, J., Mathai, G., Sears, L., & Casanova, M. F. (2009). Effects of low frequency repetitive transcranial magnetic stimulation (rTMS) on gamma frequency oscillations and event-related potentials during processing of illusory figures in autism. *Journal of Autism and Developmental Disorders, 39*(4), 619-634.

Sonuga-Barke, E. J., Taylor, E., Sembi, S., & Smith, J. (1992). Hyperactivity and delay aversion--I. The effect of delay on choice. *Journal of Child Psychology and Psychiatry, 33*(2), 387-398.

Stroop, J. R. (1935). Studies of Interference in Serial Verbal Reactions. *Journal of Experimental Psychology, 18*, 643 - 662.

Sutton, R. S., & Barto, A. G. (1998). Reinforcement learning: an introduction. *IEEE Transactions on Neural Networks, 9*(5), 1054.

Van Veen, B. D., van Drongelen, W., Yuchtman, M., & Suzuki, A. (1997). Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. *IEEE Transactions on Biomedical Engineering, 44*(9), 867-880.

Varela, F., Lachaux, J. P., Rodriguez, E., & Martinerie, J. (2001). The brainweb: phase synchronization and large-scale integration. *Nature Reviews Neuroscience, 2*(4), 229-239.

Von Stein, A., & Sarnthein, J. (2000). Different frequencies for different scales of cortical integration: from local gamma to long range alpha/theta synchronization. *International Journal of Psychophysiology, 38*(3), 301 - 313.

Wallis, J. D. (2007). Orbitofrontal cortex and its contribution to decision-making. *Annual Reviews of Neuroscience, 30*, 31-56.

Yacubian, J., Glascher, J., Schroeder, K., Sommer, T., Braus, D. F., & Buchel, C. (2006). Dissociable systems for gain- and loss-related value predictions and errors of prediction in the human brain. *The Journal of Neuroscience, 26*(37), 9530-9537.

Yasuda, A., Sato, A., Miyawaki, K., Kumano, H., & Kuboki, T. (2004). Error-related negativity reflects detection of negative reward prediction error. *Neuroreport, 15*(16), 2561-2565.

Yeung, N., Holroyd, C. B., & Cohen, J. D. (2005). ERP correlates of feedback and reward processing in the presence and absence of response choice. *Cerebral Cortex, 15*(5), 535-544.

Yeung, N., & Sanfey, A. G. (2004). Independent coding of reward magnitude and valence in the human brain. *The Journal of Neuroscience, 24*(28), 6258-6264.

Zuckerman, M., Eysenck, S., & Eysenck, H. J. (1978). Sensation seeking in England and America: cross-cultural, age, and sex comparisons. *Journal of Consulting and Clinical Psychology, 46*(1), 139-149.