BRAIN MECHANISM UNDERLYING IOWA GAMBLING TASK: AN FMRI STUDY

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CERTIFICATE OF ORIGINALITY

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_____ (Signature)

Ma Shuangye (Name of Student)

September, 2013

DEDICATION

I dedicate this work to my parents and my husband, who have fully supported me throughout the Master study.

ABSTRACT

This study employed event-related functional Magnetic Resonance Imaging (fMRI) to measure the brain activation while performing the Iowa Gambling Task (IGT). The purpose was to explore the brain mechanism underlying decision-making process in ambiguous conditions, and has implications for impulsive behavior assessment and intervention.

The IGT simulates decision-making process under uncertain conditions. The neural process underlying the IGT was explained by the Somatic Marker Hypothesis (SMH), which described how the somatic signals generated from the body were represented and regulated in the brain, and how they then influenced the decision-making process. According to the hypothesis, a neural circuitry involving emotion, memory and behavioral system was engaged. This neural circuitry was generally supported by lesion studies and neuroimaging studies.

With event-related fMRI, it is possible to indentify distinct underlying neural substrates of the temporally separated task components involved in the IGT task. However, existing fMRI studies employing the IGT task are still relatively scarce and provide inconsistency results, partly due to the complexity of the task and the different control tasks employed by the studies. Furthermore, most fMRI studies only concerned the main contrast between risky and safe decks of cards but ignored the effect of another factor in the task design, the punishment frequency associated with the decks of cards, which may influenced subjects' preference on decks of cards.

This study explored the brain activation using fMRI during the performance

of the original design of the IGT with 2 by 2 factorial design, and aimed to uncover: 1) the brain activation related to the long-term outcome effect, i.e. the risky versus safe contrast; 2) whether this contrast would be influenced by the factor of punishment frequency; and 3) the brain activation related to the learning process in IGT.

The behavioral results showed that the subjects could gradually learn to choose more from the safe decks of cards and avoid the risky decks of cards during the task, and that they were more sensitive to the risky versus safe contrast under the condition with a higher punishment frequency. The neuroimaging results demonstrated that choices from the risky decks produced higher activation in anterior cingulate cortex (ACC), and this contrast was dominated by the one in decks of cards with a higher punishment frequency. The learning process was assessed by comparing brain activation during choices in the first half trials with those in the second half trials, which detected higher activation in insula, amygdala and hippocampus regions during the earlier phase of the task.

The results generally reflected the SMH framework: behavioral performance was related to the cortical region for the somatic states to influence the selection behaviors; and the time effect was reflected in the brain regions crucial to the generation and the cortical representation of the somatic state.

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LIST OF ABBREVIATIONS

ACC	Anterior Cingulate Cortex
ANOVA	Analysis of Variance
BAs	Brodmann Areas
BIS	Barratt Impulsivity Scale
BOLD	Blood Oxygenation Level Dependent
dlPFC	Dorsolateral Prefrontal Cortex
fMRI	Functional Magnetic Resonance Imaging
FOV	Field of View
GLM	General Linear Model
IGT	Iowa Gambling Task
IN	Insula Cortex
ITI	Inter-Trial Interval
mOFC	Mesial Orbitofrontal
MNI	Montreal Neurological Institute
PAG	Periaqueductal Gray

PBN	Parabrachial Nucleus
PET	Positron Emission Tomography
ROI	Region-of-Interest
RT	Reaction Time
SCRs	Skin Conductance Responses
SD	Standard Error
SE	Standard Error
SMH	Somatic Maker Hypothesis
TR	Repetition Time
vmPFC	Ventromedial Prefrontal Cortex

CHAPTER 1 INTRODUCTION

This chapter provides an overview of the present research study on the brain mechanisms underlying the Iowa Gambling Task (IGT). It begins by outlining the statement of purpose, followed by the background and justification of the study, and ends with the organization of the thesis.

Statement of Purpose

This study aims to investigate the mental processes related to decision-making involved in IGT in healthy adults. IGT is a sensitive test designed to detect and measure decision-making impairments in spite of intact general intellect and problem-solving abilities. This study employed event-related functional Magnetic Resonance Imaging (fMRI) to measure the physiological response of the brain whilst performing IGT. The purpose was to discover the brain mechanism underlying decision-making in ambiguous conditions, and have implications for impulsive behavior assessment and intervention. Normal young male adults were recruited as subjects for the study. All subjects played the clinical version of the IGT. Blood oxygen level dependent (BOLD) responses were used to capture the brain activation during the decision-making processes. The brain responses were compared between conditions when subjects intended to make different kinds of choices.

Background and Justification

IGT is an experimental neuropsychological task which simulates personal real-life decision-making. It factors uncertainty, reward and punishment and it was designed to detect and measure impairments in real-life decision-making in spite of intact general intellect and problem-solving abilities (Bechara et al. 1994).

In the task, subjects have to choose between risky decks of cards that yield high immediate gain but a larger further loss, and safe decks that yield lower immediate gain but a smaller future loss. Normal subjects could gradually learn to sacrifice immediate reward for future benefit to maximize the overall gain. However, neurological patients with lesions in prefrontal cortex and diverse psychiatric groups showed deficits in performing the task (Bechara et al. 1994, 1999, 2000).

The neural process involved in decision-making process under the situations of complexity and uncertainty, like the IGT task, was explained by the Somatic Maker Hypothesis (SMH) proposed by Damasio et al (1994), which described how the 'somatic marker' signals generated from the body were represented and regulated in the cortex to bias the decision-making process. According to SMH, the IGT task involved a cortical framework including the ventromedial prefrontal cortex (vmPFC), amygdala, insular cortex (IN), somatosensory cortex and brainstem nuclei, striatum, anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (dlPFC) (Bechara & Damasio, 2005). This hypothesized framework has been partly supported by lesion studies and neuroimaging studies.

With the event-related function magnetic resonance imaging technology, it is possible to study the cognitive processes involved in IGT and to clarify the contribution of different cortical regions. However, fMRI studies employed the IGT are still relatively scarce and revealed inconsistent results, partly due to the complex cognitive processes involved in the task (Li et al. 2010). In addition, current fMRI studies only focused on the main contrast between risky and safe decks but ignored the effect of another factor in the task design, the punishment frequency associated with the decks, which also influenced subjects' preferences for the decks (Horstmann, Villringer & Neumann 2013).

This study used the original design of the IGT with a 2 by 2 factorial design in event-related fMRI study to measure the physiological response during the task, to explore: 1) the brain activation related to the long-term outcome effect, i.e.: the risky versus safe contrast; 2) whether this contrast would be influence by the factor of punishment frequency and 3) the brain activation related to the learning process in IGT.

Organization of Chapters

The thesis consists of five chapters. Chapter 1 is the present introduction chapter. Chapter 2 is a literature review of the IGT task and the underlying neural mechanism. The research questions and the hypothesis of the current study will be proposed at the end of this chapter. Chapter 3 describes the design of the fMRI experiment task, data collection procedure and data analysis approaches. Chapter 4 presents the findings of the study, including behavioral and fMRI results. Chapter 5

discusses the findings and the implications of the current findings for the knowledge of the neural mechanism underlying the IGT.

CHAPTER 2 LITERATURE REVIEW

Introduction

This chapter provides an overview on the Iowa Gambling Task (IGT) and its underlying neural mechanism. Firstly the original design of IGT and the behavioural findings are introduced. Then studies on the neurobiological basis of the IGT are reviewed.

Task Design

Bechara et al (Bechara et al. 1994) firstly proposed the IGT paradigm to detect and measure the defects on decision-making in patients with damage to the ventromedial prefrontal cortex (vmPFC), in spite of intact general intellect and problem-solving abilities. This task simulates the uncertainty, reward and punishment in real-life decision-making. In the task, participants need to learn to sacrifice short-term profit in favor of long-term benefit.

The task requires subjects to choose a card from one of the four decks, which is labeled as deck A, B, C, and D, for 100 trials. Each card selection is associated with either a financial reward or a punishment. The schedules of these rewards and punishments have been pre-programmed and unknown to the subjects.

The payoff structure in each deck is shown in Table 2-1. Overall, the choices from deck A and B are risky, and the choices from deck C and D are safe when considering the long-term outcomes of the choices. Selections from deck A and B

bring high immediate rewards and even higher levels of delayed punishments, leading to a net loss of $250 per 10 trial*s;* whereas selections from deck C and D offer low immediate reward but lower levels of punishment, leading to a net gain of $250 per 10 trials.

The four decks also differ in the relative number of gains to losses (subsequently termed 'punishment frequency'), which is high for deck A and C and low for deck B and D. But there is no difference in profit when choosing decks with high or low punishment frequency. The 2 by 2 design in the payoff structure is summarized in Table 2-2.

Deck	Reward	Punishment	Net Profit per 10 trials
A	Win $100 (100% trials)	Lose $150 to $350 (50% trials)	-250
B	Win $100 (100% trials)	Lose $1250 (10% trials)	-250
C	Win $50 (100% trials)	Lose $25 to $75 (50% trials)	250
D	Win $50 (100% trials)	Lose $250 (10% trials)	250

Table 2-1: The payoff structure in the original version of IGT. The immediate reward is high in deck A and B ($100) and low in deck C and D ($50). The delayed punishment is higher in deck A and B and lower in deck C and D. And the punishment appears in 50% trials of deck A and C but only 10% trials of deck B and D. The overall profit is a loss of &250 in deck A and B, but a win of $250 in deck C and D

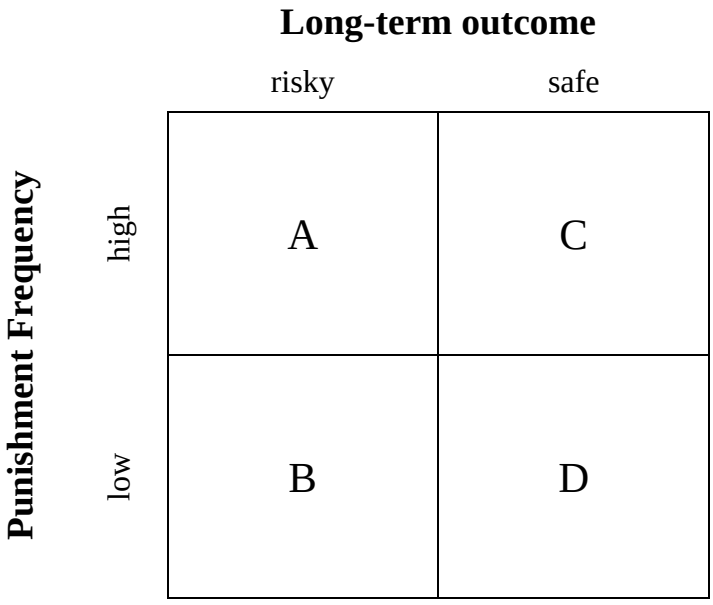

Table 2-2: The 2 by 2 design of the payoff structure in the four decks of cards. The payoff structures in each deck are determined by a combination of two factors: long-term outcome and punishment frequency.

The only successful strategy in the IGT is to select more cards from the safe decks (decks C and D) and avoid selecting cards from the risky decks (decks A and B). Thus, since the first study on the IGT (Bechara et al. 1994), the task performance in IGT is assessed by the number of cards picked from the safe decks minus the number of cards picked from the risky decks in a block of every 20 trials.

It has been widely demonstrated that normal subjects could learn over time to choose more cards from the safe decks and less from the risky decks so they showed a learning effect when performing the task (Bechara et al. 1994, Bechara et al. 1996). Meanwhile, patients with normal intellectual but decision-making deficits in real life showed poor performance during the whole course of the task (Bechara et al.

1994, Bechara et al. 1999, Bechara et al. 1997), which proved that patients' deficits in performance were due to insensitivity to future consequences other than insensitivity to reward or punishment, since their performance didn't improve in spite of increasing adverse future consequences.

At the beginning, the four decks of cards were presented manually. Later, Bechara et al (2000) developed a computerized version of the original task in which the decks were displayed on the computer screen and the inter-trial interval (ITI) between two consecutive card selections could be fixed by the experimenter, so that it allowed more convenient collections of behavioral and physiological data during the task. Compared with the manual version, there was a progressive change in the frequency or magnitude of punishment relative to reward. As a result, the negative consequences in the risky decks and positive consequences in the safe decks were both amplified, while the two factors payoff structure was kept.

The computerized version has been widely used in clinical studies and academic studies to test decision-making ability under initially uncertain conditions. Poor task performances have been demonstrated in various psychopathological groups, such as patients with anorexia nervosa (Cavedini et al. 2004) or obesity (Davis et al. 2004), psychopathic individuals (Mitchell et al. 2002; van Honk et al. 2002), substance-dependent individuals (Grant, Contoreggi & London 2000; Bechara & Damasio 2002), suicide attempters (Jollant et al. 2005), and patients with schizophrenia (Sevy et al. 2007), obsessive-compulsive disorder (Cavedini et al. 2002) or impulsive aggressive disorders (Best, Williams & Coccaro 2002).

In this study, the computerized original version of task was employed, following the schedule of rewards and punishments published in the IGT professional manual (Bechara 2007).

The neural substrates underlying the Iowa Gambling Task

The objective of this study is to find out the brain mechanism underlying the IGT, in order to improve our understanding in the decision-making process and the neurobiological sources of the decision-making impairments in neurological and psychiatric patients.

In this session, previous studies would be reviewed from both theoretical and empirical perceptivities. First, the Somatic Marker Hypothesis (SMH) proposed by Damasio (1994) is elaborated to provide a theoretical explanation of the IGT. Then the neural circuitry involved in the IGT proposed by the hypothesis is introduced (for an overview, see Bechara & Damasio 2005). Finally the proposed neural substrates are evaluated with evidences from neuroimaging studies.

An overview of the Somatic Marker Hypothesis (SMH)

The SMH grew from the study on famous case of Phineas Gage (for an overview, see Harlow 1869) and Elliot (EVR, Damasio, Tranel & Damasio 1991), both of them suffered from severe everyday decision-making deficits caused by the damages to the frontal lobes. The case of Gage linked the frontal lobe with the function of decision-making, judgment and personality. The fact that EVR became

unable to make decisions after a bilateral ablation of the vmPFC caused by a brain tumor highlighted the function of this area in decision-making.

Later, several patients with bilateral lesions of the vmPFC, similar to EVR, were studied in the Iowa laboratory to clarify the cause of the disability related to this region. All of them suffered from real-life decision-making impairments. They often made decisions against their best interests and were unable to learn from previous mistakes, and they also have difficulties in planning for the future. Contrast to their decision-making impairments, they showed normal intellect and intact problem-solving abilities in several neuropsychological tests in laboratory settings (Bechara et al. 1998). However, other studies found that they had difficulties in expressing emotion and feelings in appropriate situations (Saver & Damasio 1991; Bechara et al. 1998). These observations highlighted the linkage between the disability in decision-making following vmPFC damage and abnormalities in emotions and feelings, leading to Damasio's Somatic Marker Hypothesis (Damasio 1994, 1996).

The hypothesis suggested that the decision-making process was influenced by the emotional biasing signals generated from the body (named as 'somatic marker signals') when facing different options. Failure to use such emotion-based signals to bias the decision-making process would cause decision making deficits, especially in complex and uncertain situations.

This hypothesis was strongly supported by the study from the Iowa laboratory, in which behavioral performances of normal subjects and vmPFC patients were examined with synchronized skin conductance responses (SCRs) recordings and assessments to their awareness level of the successful strategy (Bechara et al. 1996).

The SCRs reflected the arousal level of the autonomic nervous system thus they were used as the measurement of emotional and sympathetic responses (Carlson 2010).

Bechara et al (1997b) found that there were several stages in the learning process according to participants' awareness level of the task strategy (see Figure 2-1, Bechara et al. 1997b, p. 1294). In these four stages, participants demonstrated that SCRs other than conceptual knowledges contributed to advantageous behavioral performances.

As shown in Figure 2-1a, after sampling all four decks and before engaging any losses, normal subjects seemed to prefer the risky decks associated with higher immediate gains (decks A and B) (The light yellow column, Stage I, 'Pre-punishment'). After engaging losses in each deck, they began to generate higher skin conductance responses (SCRs) when intending to select from the risky decks (decks A and B) compared with when intending to select from the safe decks (deck C and D) (The dark yellow column, Stage II, 'Pre-hunch'), but they didn't report preferences on any of the decks in this stage. Gradually they would formulated a 'hunch' that in the long run the risky decks (decks A and B) with a high immediate gain were 'bad' choices and the safe decks (decks C and D) with a low immediate gain were 'good' choices, and they would begin to select more from the safe decks and avoid the risky decks without conceptually realizing the reason (The pink column, Stage III, 'Hunch'). In the last stage, some of the subjects might conceptually realize that the risky decks were associated with a high immediate gain but a long-term overall loss and the safe decks were associated with a low

immediate gain but a long-term overall gain (The red column, Stage IV, ’Conceptual’).

Unlike the control group, patients failed to avoid the risky decks even after conceptually realizing that these decks were ‘bad’ in the long run (see Figure 2-1b). And patients never showed different SCRs before intending to choose from risky decks or safe decks.

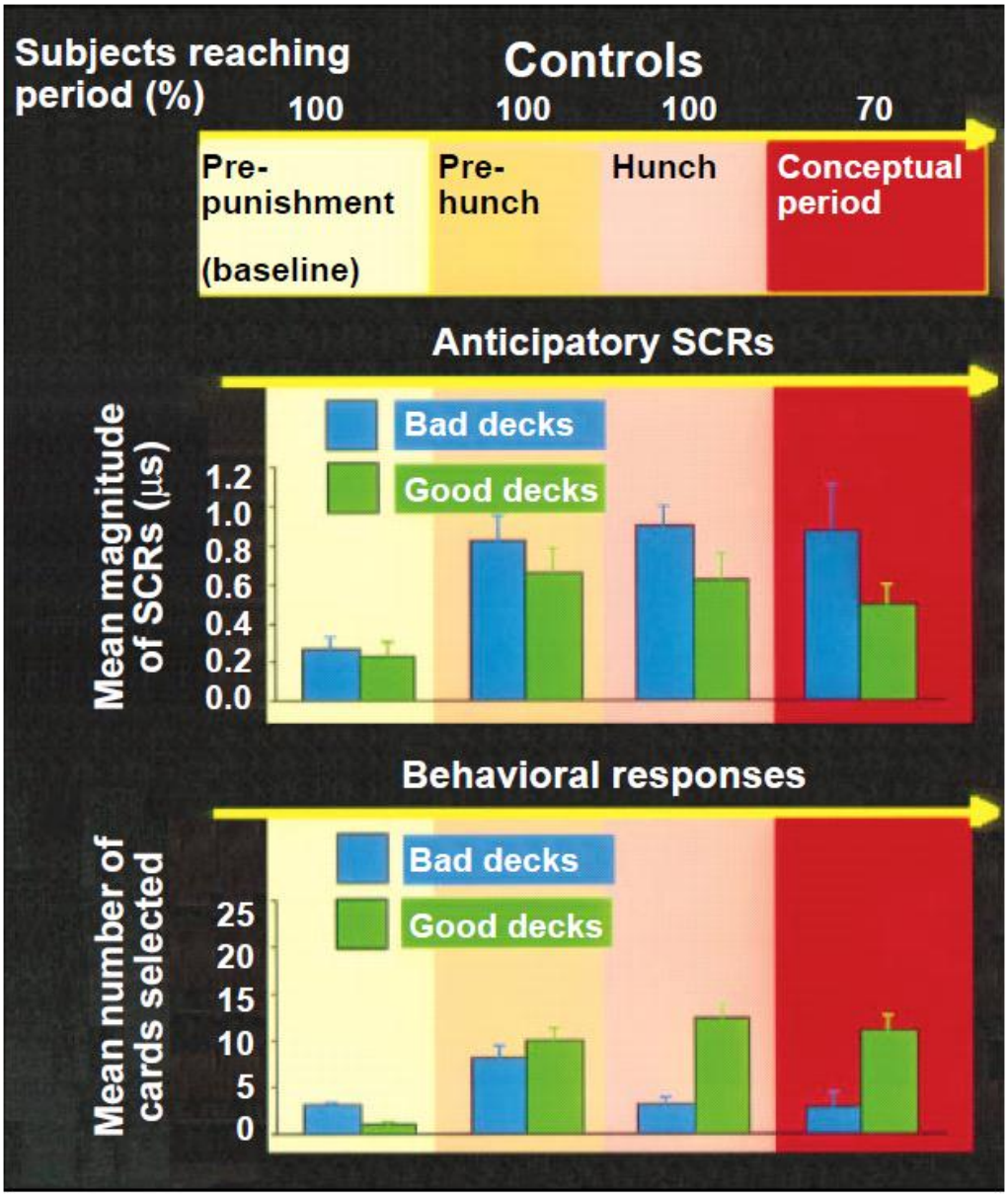

Figure 2-1a: Presentation of the four stages in IGT performance in normal controls according to performance and the SCRs associated with the same cards (Source: Bechara et al. 1997b). Note: copyright permission has been granted.

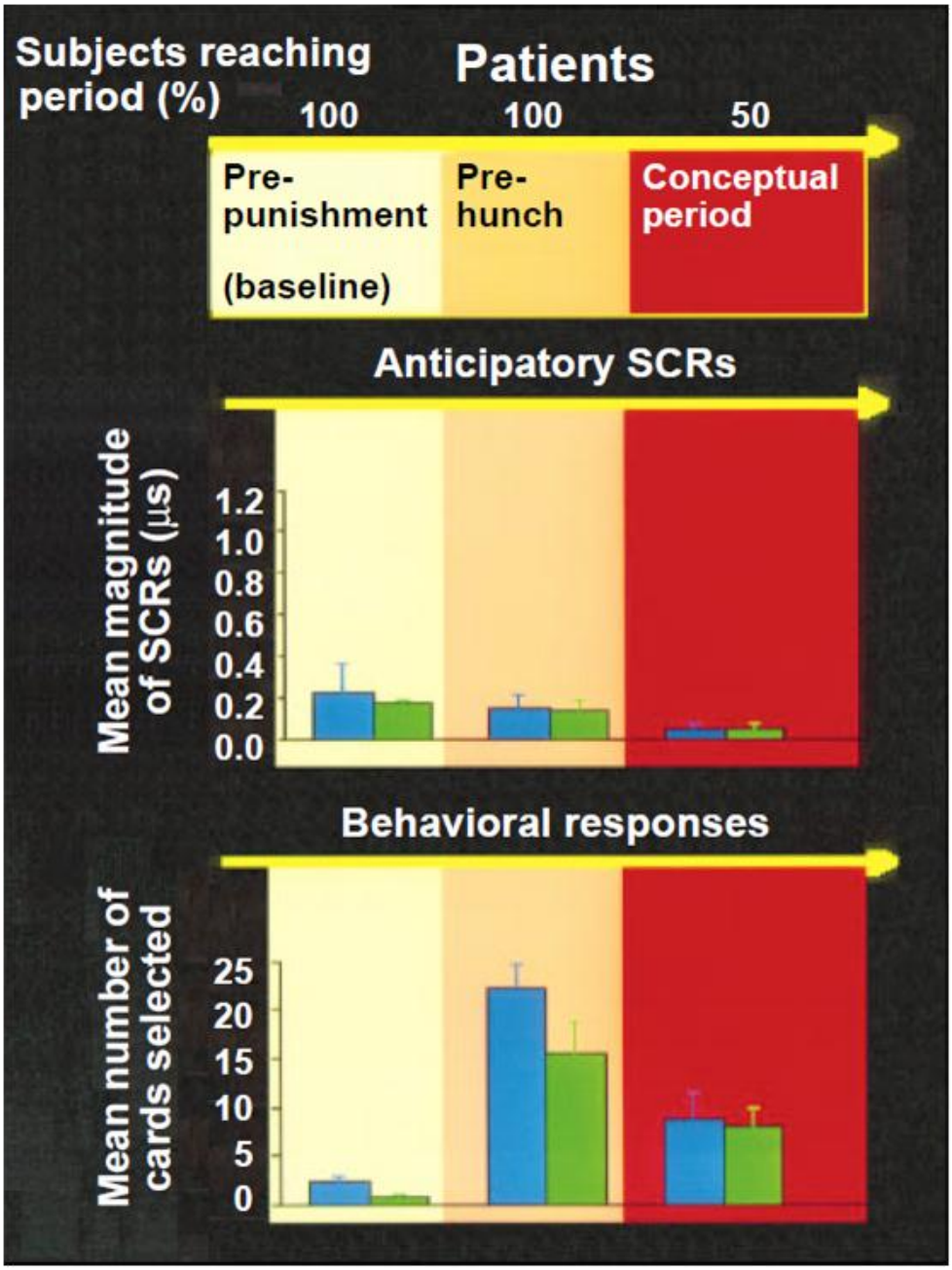

Figure 2-1b: Presentation of the three stages in IGT performance in vmPFC patients according to performance and the SCRs associated with the same cards. (Source: Bechara et al. 1997b). Note: copyright permission has been granted.

These observations on the relationship between the generation of SCRs when facing response options, advantageous behavioral performance and conceptual knowledge of the task strategy questioned the sufficiency of conceptual knowledge alone on beneficial decision-making and demonstrated the importance of emotional response in complex and initially ambiguity decision-making process, like the IGT.

As summarized by Bechara and Damasio (Bechara & Damasio 2005), an emotion was

> …a collection of changes in body and brain states triggered by a dedicated brain system that responds to specific contents of one's perceptions, actual or recalled, relative to a particular object to event (page 339).

The changes in the body involved both internal changes in milieu and viscera and external changes in musculoskeletal system. These body related changes which hallmark an emotion were named as 'somatic states'.

The somatic states could be triggered by primary inducers and secondary inducers. Primary inducers were innate or learned stimuli that would automatically and obligatorily elicit somatic states when presented in the environment; and secondary inducers were the 'thought' or 'memory' of primary inducers which would induce the somatic states belonging to the specific primacy inducer when presented in working memory. Thus the developments of secondary inducers highly depended on the developments of the primary inducers until the secondary ones had been acquired normally.

The somatic state induced by every response option served as an indicator of the 'emotional' values of that response and influenced the decision-making process

either explicitly or implicitly. In complex and uncertain situations when reasoned cost-benefit analysis is impossible, these somatic states which signal the prospective consequences of options assisted in selecting more advantageous responses.

Neural substrate underlying the IGT proposed by SMH

The SMH theory also provides a theoretical framework on which neural regions will be engaged during the performance of the IGT. According to the SMH, several neural substrates serve as key components in the process of biasing the decision-making by the somatic signals (Figure 2-, Garcia et al 2009, p. 51). Although the SMH has been criticized by other researchers (Dunn, Dalgleish & Lawrence 2006) on the role of peripheral processes in decision-making, the involvement of the brain regions proposed by SMH were confirmed.

As mentioned above, the somatic state could be elicited by either primary inducers or secondary inducers. Amygdala is a critical area for triggering somatic state by primary inducer and it couples the features of the primary inducers with the somatic states associated (Figure 2-2a), while vmPFC is the triggering structure for secondary inducers and it couples the knowledge of the secondary inducers with its somatic states pattern in a given situation (Figure 2-2 b). But it is hard to separate the processing of primary or secondary inducers in a normal brain since they could be elicited by the same stimuli at the same time.

The generation of the somatic signals is a complex process and relies on several sets of system: 1) the features of the inducers are processed subliminally via the thalamus or explicitly via the sensory cortex; 2) the somatic states are evoked via

effector structures like the hypothalamus and the autonomic brainstem nuclei which produce internal changes and other effectors structures like the ventral striatum, the periacqueductal gray (PAG), and other brainstem nuclei which produce external changes; 3) the afferent inputs from the active somatic states are sent to the cortical structures to represent the feelings of the somatic states non-consciously in the parabrachial nucleus (PBN) or consciously in the insula, the somatosensory cortex and the posterior cingulate gyrus); 4) particular representations of the somatic states are strengthened or weakened in the working memory system (the dlPFC) during the deliberation of a decision. This process is achieved by reinforcing or deleting the 'thought' brought into working memory depending on the strength of the somatic state triggered by it. Some options are endorsed and others are rejected before any of them are translated into actions.

Then the somatic signals act on the striatum (non-consciously) and the anterior cingulate cortex (ACC) or the supplementary motor area (SMA) (consciously) to bias behavioral responses (Figure 2-2 c).

In summary, according to the SMH, the cortical areas involved in the IGT task include the following neural regions:

1) The vmPFC and the amygdala for the triggering of somatic states;
2) The somatosensory cortices, the insula and the posterior cingulate gyrus for cortical representations of somatic states;
3) The dlPFC for working memory representations of somatic states;

4) The striatum, the anterior cingulate cortex (ACC) and the supplementary motor area (SMA) for implementing motor responses and behavioral actions.

The involvement of these brain structures was generally supported by lesion studies. Poor IGT performance and failure to generate SCR during risky selections were observed in a number of studies recruiting patients with damage to the ventromedial prefrontal / mesial orbitofrontal cortex (vmPFC/mOFC) (for example, see Bechara 1994, 1997, 1999, 2004); and also in patient group with the amygdale lesions (Bechara et al. 1999, 2004). Compared with patients with vmPFC lesion, the amygdala groups were unable to generate SCRs during the feedback of win and loss. Tranel et al (Tranel, Bechara & Denburg 2002) suggested a more specific role of the right OFC/vmPFC in IGT performance, but this study was limited by the small sample size. Some other studies suggested that other prefrontal areas were also crucial for IGT performance, like the dlPFC (Bechara 2004, Tranel, Bechara & Denburg 2002, Fellows & Farah 2005, Clark, Cools & Robbins 2004, Manes et al. 2002), and the dorsomedial prefrontal (Manes et al. 2002). A preliminary study with patients with right-sided or left-sided lesions to the somatosensory/insula cortex (Bechara et al. 1997a) found that only the right-sided lesion group showed deficit performance compared with the control group. Bechara et al (2004) proved that the ACC, especially the right-sided part, was also important for IGT performance.

The lesion studies provided important evidences on the neural substrate proposed by SMH. But the lesion studies were limited in the fact that lesions in the patients were not limited; they were rarely confined to clearly defined brain areas. Lesions in most patients with the vmPFC damages often extended into other part of the frontal loves and basal forebrain (Clark & Manes 2004).

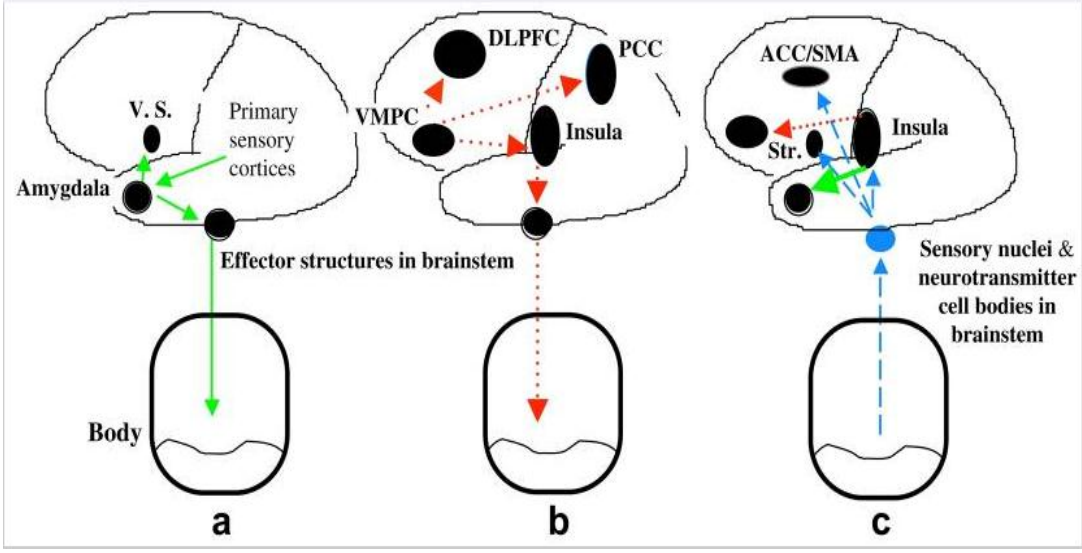

Figure 2-2: The illustration of all the brain regions involved in IGT performance according to the SMH (Source: Garcia et al 2009). a) The amygdala is the triggering structure for primary inducers. It couples the feature of the inducers with its somatic states. The features of the inducers were processed via sensory cortex. The somatic states were evoked via effectors structures in brainstem and ventral striatum (V.S.). (b) The vmPFC is the triggering structure for secondary inducers. It couples the memories or thoughts of the primary inducers with previous feelings represented in the cortical regions including insula, posterior cingulate gyrus (PCC). (c) The overall somatic states act on the striatum and the anterior cingulate cortex (ACC) / supplementary motor area (SMA) to influence the behavioral responses. Note: copyright permission has been granted

Neuroimaging studies on the neural substrates of IGT

Functional neuroimaging also provides evidence to evaluate the neural substrates proposed in SMH. Several studies investigated the neural activations when participants performed the IGT, using the technique of Positron Emission Tomography (PET) or functional Magnetic Resonance Imaging (fMRI).

PET studies

Ernst et al. (2002) explored the neural network when healthy participants performed a modified version of the IGT using PET. They used a control task in which participants were asked to pick cards from the four decks in a specified order other than to make a choice, in order to isolate the decision-making process involved in IGT. The contrast between the control task and the IGT task revealed a predominantly right sided network of prefrontal and posterior cortical regions, including the OFC/vmPFC, the anterior cingulate cortex (ACC), the dorsolateral prefrontal cortex (dlPFC) and the inferior parietal lolube (IPL). Ernst et al. (2002) 's findings confirmed the activation of the vmPFC in the IGT, and also revealed the involvement of the working memory and visual attention related networks. The significant correlations between task performance and regional cerebral blood flow were found in the right ventrolateral PFC and the right anterior insula. Activations in the subcortical areas were also found in the contrast, including the basal ganglia, the thalamus and the left cerebellum.

Ernest et al (2003) investigated the brain activation while performing the IGT in

adults with attention deficit hyperactivity disorder (ADHD) and healthy controls. Task related activations were detected in the insula, the ventral and dorsal PFC in both groups. The activation was less extensive in the ADHD group compared with the control, without the ACC and the hippocampus, although there was no group difference in performance.

In a subsequent study using a similar protocol, increased activations in the right OFC and decreased activation in the right dorsolateral OFC were indentified in the cocaine users who were impaired in the IGT performance, compared with the controls (Bolla et al. 2003). The task performance was correlated with the activation of right OFC in both groups.

Adinoff et al (2003) studied the relationship between resting state regional blood flow measured by PET and the task performance in the IGT in healthy control and abstinent cocaine users. Unlike the above findings, no relationship was detected between task performance and resting state activity in the OFC in either group. The relationship was detected only in the ACC and the left dlPFC.

Another repeated study with cocaine users in a more acute phase of abstinence (Tucker et al. 2004) found negative correlation between the IGT performance and the activity in the ACC, the medial frontal gyrus and the superior frontal gyrus. The ACC could be labeled as part of the mOFC/vmPFC regions, and all of other regions are parts of the dlPFC region.

A similar study by Bolla et al (2005) compared the brain activation in the abstinent marijuana users and the control group with no drug use history when they performed the IGT. The marijuana users showed lower activation in the right lateral

OFC and the right dlPFC, and higher activation in the left cerebellum.

There is one PFT study which tried to further reveal sex differences in activation when performing the task (Bolla et al. 2004). Regional task related activations were found in different brain regions in men and women. Men showed greater activation in the right lateral OFC than women, and women activated the left dlPFC, the left medial frontal gyrus and the temporal lobe more than men.

Brain regions related to the IGT task according to the PET studies were summarized in Table 2-3. These studies revealed a generally consistent network including the OFC/vmPFC, the ACC and the dlPFC, which partly supported the neural substrates proposed by the SMH. The prominent right side activation of this network was detected in most studies, while the prominent left side activation of cerebellum was revealed in two studies.

The limitation of the PET studies lied in its limited temporal resolution, which made it impossible to indentify distinct underlying neural substrates of the temporally separated task components , which are basically the activation resulted from the decision phase and the activation from the feedback phase.

Table 2-3: Summary of the brain activations involved in the IGT according to the PET studies. Including 1) brain areas showing higher activation when subjects performed the IGT compared with that in the control task in healthy controls (Ernse et al.,2002); 2) brain areas showing significant correlation with the IGT task performance (Adinoff et al., 2003) and 3) brain areas showing abnormal activation in patients compared with healthy controls (others

Brain Areas	*Cortical Areas*	vmPFC/ OFC	dlPFC	ACC	Somatosensory	Insula	SMA	IPL	*Subcortical Areas*	Basal Ganglia	Amydala	Brainstem Nuclei	Hippocampus	Thalamus	Cerebellum
Contrast between IGT task and control task:															
Neural loop of SMH		√	√	√	√	√	√			√	√	√			
Ernst et al. 2002		√	√	√		√				√				√	√
Ernst et al. 2003		√	√			√							√		
Bolla et al. 2003		√	√												
Adinoff et al. 2003			√	√											
Tucker et al. 2004		√	√	√											
Bolla et al. 2005			√	√											√

FMRI studies

Existing fMRI studies with the IGT were still relatively scarce and increasing recently. Although a range of fMRI studies used similar but simpler gambling tasks to detect the neural mechanism of decision-making under risky conditions (for a review, see Krain et al. 2006). However, information for decision making was provided explicitly in these tasks and thus these studies failed to involve the strategic learning process in task design which was important in the IGT (Li et al. 2010).

Compared to PET, fMRI technique has a better temporal and spatial resolution, permitting the investigation on distinct neural substrates for different task components in the IGT. The flaw of fMRI data is that it was known to have a signal dropout in several brain areas due to distortion artifacts (Cusack et al. 2005), including one of the crucial brain regions in the IGT, the OFC/vmPFC region.

Here, considering the purpose of this study, only fMRI studies employed the original or slightly modified IGT task were reviewed and only activation maps in healthy controls related to the decision-making phase were concerned. Exiting fMRI results could be separated into two categories according to the contrast used in the studies: one is the contrast between the IGT task and self-designed control task, another is the contrast between the factors involved in the ITG task design, i.e.: the contrast between risky and safe decision-making.

Tanabe et al (2007) used a modified IGT task to compare brain activations in 18 healthy participants, 14 substance-dependent individuals (SD), and 16 SD with

gambling problems (SDPG). In the modified IGT task, the subjects only chose to 'play or pass' trials after the computer selected the cards in the decision condition, and they were explicitly told to 'play or pass' in the no decision condition. The contrast between active and passive decision-making across all groups revealed activation in the right orbitofrontal (BA 10), the right ventral lateral frontal/insula (BA 47), the bilateral anterior cigulate (BA 32/24) and the nucleus accumbens. Comparisons in controls and the two clinical groups showed reduced activations in both patients groups in the ventral medial frontal (BA 25/11), the superior frontal cortex regions (BA 9/10) and the right frontopolar (BA 10).

Frangou et al (2008) studied brain activations of patients with bipolar disorder and healthy controls when they performed the original IGT. They used the control task in which subjects were required to select cards as in the IGT task but were informed that no reward or punishment were associated with the decks in this condition. In normal group, subtraction between the IGT task and the control task revealed the bilateral ventral prefrontal cortex (BA11, 47), the dorsolateral prefrontal cortex (BA6, 8, 9, 46, 10), predominantly on the right side, the right parietal cortex (BA7), the thalamus and the cerebellum bilaterally. In patient group, activation in these regions was attenuated but increased in the superior and middle temporal gyrus.

Li et al (2010) combined the original version of the IGT and three variant version of the IGT in their study to increase the number of trials during the fMRI session .To control the recording duration, there was a 4-s interval limitation for each trial. In the control task, subjects were instructed to select a certain deck. Contrast between

the IGT and the control task revealed an activation patter which was generally consistent with the neural circuitry hypothesized in the SMH, but it didn't reveal significant activation in the amygdala and the hippocampus region.

Recently, the same protocol was used to investigate the neural correlates of the IGT in adolescent binge drinkers and age-matched adolescents who had never consumed alcohol (Lin et al., 2013). The brain regions activated during the IGT averaged across the two groups were similar to Li's study (2010). Binge drinkers, compared to non-drinkers, showed worse performances on the task and higher activity in the left amygdala and the bilateral insula.

The above studies adopted block design so that they were limited to the investigation to whether the detected contrast was mainly resulted from the decision-making phase or the feedback phase. In order to examine the brain regions related to different cognitive components involved in the task, event-related fMRI were used in some other studies.

Fukui et al (2005) firstly studied the brain activation in fifteen healthy subjects using event-related fMRI. They compared the neural activity during selections from the risky decks versus the one during selections from the safe decks. The contrast revealed activations in the superior part of the anterior cingulate cortex (ACC) and the adjacent medial frontal gyrus. The detected activation was relatively superior to the vmPFC/mOPF while still being involved in the SMH neural framework, and it was significantly correlated with the task performance. The absence of the orbitfrontal region in the contrast was attributed to the signal dropout by the author.

In a later study, Lawrence et al (2009) developed a modified version of IGT

adapted for event-related fMRI recording to study the distinct role of prefrontal regions in IGT. First, the variable ITIs were imposed and adjusted for the subjects' reaction time to fix the duration of the task, and the ITIs also served as the baseline in fMRI analysis; Second, the time windows for subject to make the choices and receive the feedback were separated; Last, the original payoff structure of the decks was altered by adjusting the punishment frequency in all the four decks to be 50%. Thus, the number of trials in each condition (i.e. choices from the risky and the safe decks, choices resulting in wins and losses) were increased so as to optimize the statistical power in fMRI analysis. In the control task, subjects were instructed to select a specific deck. By comparing brain activation during this modified version of the IGT task and the control task, Lawrence et al found that decision-making produced higher activation in the anterior cingulate cortex / medial OFC (BA 24,32,11), and the precentral gyrus (BA 6/4). By comparing brain activation between choices from the risky versus safe decks, they found higher activations in the middle/superior occipital cortex (BA 19), the anterior cingulate gyrus (BA 32), the superior medial frontal cortex (BA 10/9), the inferior OFC/insula (BA 47) and the inferior frontal operculum (BA 47). More specifically, correlations between brain activations and task scores were detected in the superior medial frontal gyrus (BA 10), the pre-SMA (BA 6/8) and the inferior OFC/insula (BA 47).

The same protocol was used in a subsequent study (Jollant et al. 2010) to explore the neural basis of poor decision-making in suicide attempters. Compared to controls, suicide attempters showed poor task performances and decreased activations during risky choices relative to safe choices in the left lateral

orbitofrontal (BA 47) and the occipital cortices (BA 19) accordingly in a regions-of-interest (ROIs) analysis. The ROIs used were independently defined in 15 male healthy controls referred to Lawrence's study (2009).

Lawrence's version of IGT enabled examination of the neural basis associated with different aspects of the task by separating the decision-making phase and feedback phase. However, the alteration in the punishment frequency of decks changed the 2 by 2 factorial design in the original task. Thus, the effect of punishment frequency was ignored in this version of IGT in fMRI study. Also, the validity of this version has not been studied in clinical population, which made it difficult to compare with the amount of clinical studies using the IGT as a measurement of decision-making ability in patients.

As summarized in Table 2-4, studies that investigated the contrast between IGT task and control task revealed consistent results in the orbitofrontal region (BA10, 11 and 12), supporting the framework of SMH. The SMH proposed that decision-making process in the IGT required the orbitofrontal region to integrate the knowledge and information in the memory system with the emotional processing of the stimuli to evaluate the affective value of the stimuli. Meanwhile, these studies generally supported the role of some other brain regions proposed by the SMH, like the dlPFC, ACC and SMA, although the whole activation maps varied across studies. The inconsistency might be due to the different design of the control tasks in these studies.

On the other hand, the two studies (Fukui et al. 2005; Lawrence et al. 2009) that looked into the contrast involved in the design of the task, i.e.: the contrast between

the risky and safe decisions, repeatedly detected higher ACC activation when subjects were pondering to select from the risky decks. Lawrence et al (2009) also detected significant activation in other frontal regions like the dlPFC (BA 9, 10) and the inferior OFC (BA47).

Table 2-4: Summary of the brain activations when performing IGT in fMRI studies. Including 1) Contrast between IGT task and control task; 2) Contrast between selections from risky versus safe decks. The activated brain area is labeled according to the reported Broadmann Area (BA).

Brain Areas	*Cortical Areas*	vmPFC/OFC (BA 10,11/12)	dlPFC (BA 9, 46)	ACC (BA 24, 32)	Somatosensory	Insula (BA 13, 14)	SMA (BA 6, 7)	inferior OFC (BA 47)	middele/superior occipital	*Subcortical Areas*	Basal Ganglia	Amydala	Brainstem Nuclei	Hippocampus	Thalamus	Cerebellum
Contrast between IGT task and control task																
Neural loop of SMH		√	√	√	√	√	√				√	√	√			
Tanabe et al., 2007		√		√				√			√					
Frangou et al., 2008		√	√				√	√							√	√
Lawrence et al., 2009		√		√			√									
Li et al., 2010		√	√	√	√	√	√						√			
Contrast between risky versus safe decks																
Fukui et al., 2005				√												
Lawrence et al., 2009			√	√				√	√							

Research Question and Hypothesis

Except for the factor of the risky versus safe desk, the design of the IGT task also includes another factor, punishment frequency. The factor of punishment frequency is unrelated to the profit; therefore it is neglected by most IGT studies, in which they typically accessed the task performance by subtracting the number of cards selected from the safe decks with that from the risky decks and making the number of selected cards from each deck invisible. As a matter of fact, these studies assumed that the punishment frequency is irrelevant to the basic assumption of the IGT on how normal subjects generated somatic signals and shifted their preference to particular decks. However, over the past years, in contrast to the basis assumption of the IGT, an increasing number of studies have pointed out that the punishment frequency also influenced the choice behavior of the normal subjects (Lin et al. 2007, Chiu, Lin 2007, Caroselli et al. 2006, Caroselli et al. 2006, Martino et al. 2007, Fernie & Tunney 2006). The "prominent deck B phenomenon" was repeated detected, which refers to the finding that normal subjects prefer the risky deck B, which yields low punishment frequency but has a negative long-term outcome. Some of these studies even suggested that the primary variable affecting subjects' choices was punishment frequency rather than the long-term outcome in both normal (Horstmann, Villringer & Neumann 2013) and clinical groups, thus they questioned the basic assumption of the IGT task and also the validity of this task.

In a recent study by Lin et al (2013), they recruited subjects to play a three runs of the IGT task and analyzed subjects' preference to each of the four decks in each run.

They found that the two factors dominated choice behavior of the subjects in different stages: in the first run of the task, the punishment frequency dominated the choice behavior, in the second run, both of the two factors influenced the choice behavior, and in the third run, subjects seemed to be able to avoid the deck B and only favor the two decks with positive long term outcome. The finding of Lin's study implies that during the IGT task the influence of punishment frequency is 'immediate' and that of the long term outcome is 'learnt' and relatively 'later'. There seems an interaction between these two factors over time. Lin's study showed the interaction trend but he didn't explore into it. Also, currently there is no fMRI studies discussed how the interaction effect of these factors influence brain activation during performing the IGT.

In this study, the original design of the IGT with 2 by 2 factorial design was employed in an event-related fMRI study, to clarify the effect of the three factors, which were time, the long outcome and punishment frequency, on both subjects' behavioral performance and brain activation maps. The following two questions would be answered: 1) How these three factors would influence subjects' behavioral choices? Especially what is the interaction effect? And 2) how the interaction effect in these three factors would affect subjects' brain activations?

It is hypothesized that: behaviorally, 1) subjects would learn to select more from the safe decks and avoid the risky decks across the task, i.e.: the effect of the long-term outcome will increase over time; 2) it is easier for subjects to learn to avoid the risky deck A than the risky deck B , i.e.: the effect of the long-term outcome to subjects' behavioral choices is weaker in the condition with low punishment

frequency; 3) subjects preference to the decks with different punishment frequency would not change over time, i.e.,; the effect of punishment frequency is consistent over time. Accordingly, we expected to find in the related brain activation maps: 1) there would be higher activation in the medial prefrontal cortex areas when subjects pondering to select from the risky decks than the safe decks, and activation in these areas may be correlated with performance and additional involved in task learning; 2) besides, this activation difference would be prominent in the condition with high punishment frequency.

In additional analysis, we also wish to access the brain regions related to the learning process, we predict there would be higher activation in the brain area related to the generation of the somatic states (i.e.: Amygdala) in the earlier stage of the task, and higher activation in the brain area related to the voluntary behavioral choice (i.e.: ACC) in the later stage of the task.

CHAPTER 3 METHOD

Introduction

This chapter describes the method and set-up of the experiment conducted to investigate the neural processes associated with the IGT. It covers the sampling methods, task design, instruments and measurements used in the experiment. The procedures for fMRI data collection and analysis will also be elaborated.

Subjects

In view of the reported sex and age differences in task performance and brain activity during performing IGT, only male, young adults were recruited for the current study. The inclusion criteria are male right-handedness subjects with the age range of 18 to 30, and subjects with any neurological or psychiatric disorder history were excluded. A total of 24 subjects were recruited from Hangzhou Normal University. They were recruited by posting recruitment notices in the campus and screened based on the selection criteria mentioned above.

Table 3-1 shows their demographic information. This study was approved by the Human Subjects Ethics Sub-committee of both Hong Kong Polytechnic University and Hangzhou Normal University (see Appendix I).

Before the experiment, the purpose of the experiment and the right as a subject in the study was explained. After reading the Inform Sheet for the experiment

(Appendix II), all participants gave written informed consent in accordance with the principles expressed in the Declaration of Helsinki (see Appendix III). All participants received a small sum of cash as compensator for the cost of transportation for attending the experiment and an extra cash reward based on their performance in the experimental task.

Experimental Task Design

The clinical version of the IGT was used in the study with several technical changes to suit the fMRI scanning.

Table 3-1 illustrates the payoff structure in the design of the decks. The IGT program used in this study was written in Erpime 2.0 software (Psychology Software Tools, Pittsburgh, PA).

		Long-term Outcome	
		risky' decks (result in a net loss)	**safe' decks (result in a net win)**
Punishment Frequency	**high (loss in 50% trials)**	**A** Win $100 in 100% trials but **Lose** $150 to $ 350 **in 50% trials**, resulting in **a net loss** of 250 per 10 trials	**C** Win $50 in 100% trials but **Lose** $25 to $75 **in 50% trials**, resulting in **a net win** of 250 per 10 trials
	low (lose in 10% trials)	**B** Win $100 in 100% trials but **Lose** $1250 **in 10% trials**, resulting in **a net loss** of 250 per 10 trials	**D** Win $50 in 100% trials but **Lose** $250 **in 10% trials**, resulting in **a net win** of 250 per 10 trials

Table 3-1: The payoff structure of the decks follows a 2 by 2 factorial design. The schedule of rewards and punishments in each deck is determined by a combination of two factors: long-term outcome and punishment frequency

Subjects were presented with four decks of cards and required to choose a card from any of them in each trial. Every time subjects made their selections, there would be the following message displayed: ‘‘You Win $ X!’’ or ‘‘You Win $ X! But lose $ Y.’ (X, Y denote a specific amount of money). The instructions used in the study were translated from a previously published study (Bechara, Tranel & Damasio 2000), and the details can be found in Appendix IV.

> …It is important to know that the computer does not make you lose money at random. However, there is no way for you to figure out when or why you lose money. You may find yourself losing money on all of the decks, but some decks will make you lose more than others. Even if you lost a lot of money, you can still win if you stay away from the worst decks (p2194).

The subjects were also instructed that they must try to win as much money as possible, since they would play the game using real money (Renminbin, RMB) and be paid with their final gain (divided by 100).

Several changes were implanted in the experiment in order to suit the fMRI data collection. First, the duration for each selection was limited to 3.5s. If subjects failed to make their choice after 3.5s, they would miss this trial and wouldn’t win or lose any money. This duration has been proved to be long enough for subjects to make a selection (Cella et al. 2007; Li et al. 2010). Second, there was a 2s feedback phase after the selection, and an inter-trial interval of 0.5-6s with only a fixation cross in the center of the black screen. Each trial lasted 6-8 seconds. Third, subjects used two MRI-compatible response boxes with both hands to select a deck. Reversed card-display arrangement (ABCD and DCBA) were used for half of the

subjects to counterbalance the card position effect. For each subject, they would perform 100 trials of the IGT task. A typical trial in IGT is demonstrated in Figure 3-1.

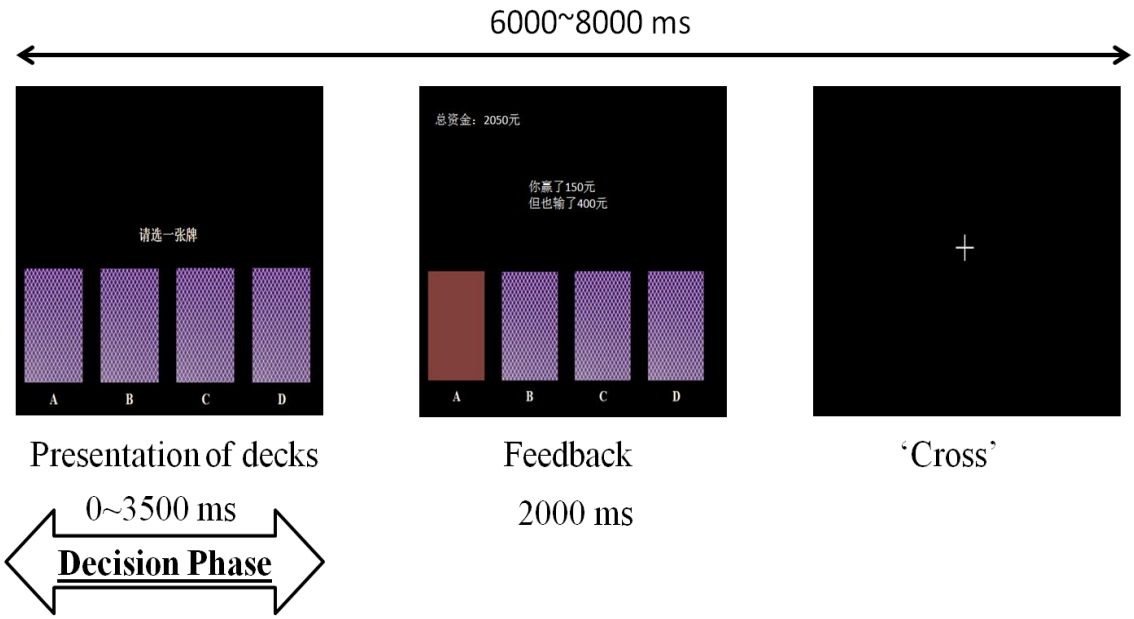

Figure 3-1: A typical trial in Iowa Gambling Task. Each trial lasted 6-8s. In each trial, the duration for selection was limited to 3.5s, followed by a 2s feedback phase and 0.5-6s inter-trial interval. Brain activation during the decision–phase, i.e., onset from the presentation of decks was analyzed in this study.

Experimental Procedures

All the data collection procedures were conducted in the MRI lab in the Center for Cognition and Brain Disorders (CCBD) of Hangzhou Normal University.

Before the IGT task, subjects were asked to complete the demographic questionnaire (Appendix V), the handedness questionnaire for Chinese (Appendix VI) (Li, 1983) and the Barratt Impulsiveness Scale (BIS-11) for Chinese population (Li et al., 2011). The BIS-11 questionnaire (Patton & Stanford, 1995) assesses the personality and behavioral construct of impulsiveness. The BIS-11 has been widely used to assess impulsiveness and its relationship to other clinical phenomena (Stanford et al. 2009). The BIS-11 for Chinese population was translated from the original English version and adapted for use in the Chinese context, and the reliability and validity were tested among Chinese citizens and university students. The original English version of the BIS-11 is shown is Appendix VII, the Chinese version of the BIS-11 is shown in Appendix VIII, and the permission letter for use of the BIS-11 is shown in Appendix IX. The BIS questionnaire was used to exclude subjects with abnormal level of impulsiveness.

Then subjects completed the fMRI scanning safety checklist and entered the scanning room following the instruction of the professional MRI scanning technician in CCBD.

Prior to the IGT task, 8 minutes resting fMRI data were collected. These resting data were collected for another study which was not related to this study. After the resting scanning, subjects were given the instruction of the IGT task. And they were given a chance to practice four trials on a dummy version to become familiar with

the task procedure, the screen display and the response box. The dummy version is similar to the actual experimental task, except that subjects were instructed to select each of the four decks, one by one from left to right, instead of making their decisions. Then another 11.7 minutes of fMRI data were collected while subjects were performing the IGT task, followed by 5 minutes structural MRI data collection. Only the fMRI data collected during the IGT task and the MRI data were used in this study.

After the scanning, subjects were asked to complete the awareness test from a former similar study (Lawrence et al. 2009, Appendix X), to test whether they had developed explicit awareness of the rules for winning the task. They were asked to describe the strategy they had used, and answer two additional questions: (1) whether they had picked more cards from any particular deck(s) or avoided any particular deck(s), and (2) why they had done so. They would be marked as learners if they discovered that cards from risky decks resulted in a long-term loss, whereas cards from safe decks produced a long-term gain. Otherwise, they would be marked as non-learners.

Statistical Analysis on Behavioral Data

All statistical analyses on the behavioral data were computed by SPSS 16.0. The significant level was set as $p \leq 0.05$. For all within-subject effects in the repeated measure Analysis of Variance (ANOVA), Greenhouse-Geisser was reported to correct the significance to compensate for the violation of sphericity. Bonferroni

adjustments with $p \leq 0.01$ were applied to the significance levels of all post-hoc comparison.

Data Acquisition

The fMRI data were acquired on a GE (General Electric) Signa 3T system. During the scanning, subjects lay on the scanner beds and viewed visual stimuli back-projected onto a screen through a mirror, with one two-button response box in each hand. Foam pads were used to help to minimized head motion.

For each subject, 351 T2*-weighted whole-brain volumes depicting BOLD contrast (Ogawa et al. 1990) were acquired over 11.7 min with 3 mm thickness (repetition time (TR) = 2 s, flip angle (FA) = 90°, field of view (FOV) = 24cm, in-plane resolution = 64*64 pixels).

High resolution T1 anatomical images were also acquired to assist the normalization of functional images. 180 sagittal slices were acquired with an isotropic 1 mm thickness (FOV = 250*250mm, repetition time (TR) = 8100, echo time (TE) =3.1ms, flip angle (FA) = 8 deg, voxel size = 1*1*1, TI (prepare time) = 450, bandwidth = 31.25 kHz).

Data Procession

Data were analyzed by SPM8 (http://www.fil.ion.ucl.ac.uk/spm/; Wellcome Trust Center for Neuroimaging, London, UK) implemented in Matlab 7 (Mathworks, Inc, Natick, MA) using an event-related model (Josephs et al. 1997).

First, quality assurance was conducted by viewing the data in MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/) and applying the artifact detection software ART developed by the Gabrieli Lab in MIT (http://web.mit.edu/swg/software.htm). The ART software can effectively detect and mark scans with artifacts, and then these scans were excluded by using them as covariates in subsequent analysis.

The raw data were then converted into NIFTI format, and the data pre-procession contained four steps:

1) Slice timing correction was applied to correct the time differences between slices in each 3D volume.

2) Head motion correction was performed by realigning the EPI images to the first one of each run. In this step, head motion curve in 6 directions would be generated for each subject, and those with severe head motion (more than 3 mm in any direction) would be excluded.

3) In the normalization step, the EPI Images were firstly co-registered to the anatomical MRI images of the same subjects, then transformation parameters were estimated by mapping the MRI images to the Montreal Neurological Institute (MNI) template, and finally the normalization parameters obtained from the transformation were applied to the EPI images, to generate the normalized EPI images.

4) Finally, these EPI images were smoothed with a 6 mm FWHM kernel.

To obtain the effect of interest in individual-level analysis, the preprocessed EPI images were analyzed by General Linear Model (GLM). The GLM were built with the trials where subjects selected cards from deck A, B, C and D as the regressors,

and the head movement curve in 6 directions and the outlier images as covariates. Specifically, the regressors were generated by convolving the onset times of each kind of event with a canonical hemodynamic response functions (HRF). When no selection was made, these trials were excluded from the analysis. The data were high-pass filtered with a cut-off period of 128 s to remove slow drift.

Finally, contrast images were generated for each subject to examine the main hypotheses, including:

1) Choices from risky (A+B) versus safe (C+D) decks, choice from risky versus safe decks with a high punishment condition, i.e.: choices from deck A versus deck C, and choice from risky versus safe decks with a low punishment condition, i.e.: choices from deck B versus deck D. The three contrasts accesses the effect of the key factor in IGT design, i.e.: the long-term outcome, and whether its effect would be influenced by another factor, punishment frequency, which was also involved in the task design.

2) Choices in the first half versus second half trials: this contrast assesses the learning effect.

The contrast images were then entered into one-sample t tests to generate the group statistical results. The t-test maps were threshold at a voxel-wise p value of 0.001(uncorrected) and a cluster level p value of 0.05 (FWE corrected; FWE: family wise error). Activations were reported corresponding to the standardized MNI coordinate space. The activation coordinates were also converted into Talairach and Tournoux atlas (Talairach, Tournoux 1988) using Brett's mni2tal toolbox

(http://imaging.mrc-cbu.cam.ac.uk/imaging/mniTalairach) to label the number of Brodmann Areas (BAs).

CHAPTER 4 RESULTS

Introduction

This chapter is divided into two parts. The first part presents the demographic characteristics of the subjects and behavioral results on the experimental task. The second part presents the brain activation maps during the decision phase, including the following three contrasts: the brain activation maps during choice in the first half versus the second half trials; the brain activation maps during choice from risky versus safe decks; and brain activation during choice from high versus low punishment frequency decks.

Demographic Characteristics of Subjects

Twenty-four male college students were recruited from the Hangzhou Normal University in mainland China. As shown in Table 4-1, their age range is from 19.3 to 25.8 (Mean age = 21.7, SD (standard error) = 1.8) and they have received between 13 to 18 years of education (Mean year = 14.9, SD = 1.6). All of them were right handed with no history of neurological or psychiatric disorders. All subjects completed the Barratt Impulsivity Scale (BIS), and their scores are shown in Figure 4-1 in the possible range of 0 to 100.

Subject	Age (year)	Year of Education (year)	Handedness
1	20.2	13.0	R
2	22.4	15.0	R
3	20.4	14.0	R
4	20.3	14.0	R
5	19.3	13.0	R
6	21.4	14.0	R
7	25.0	18.0	R
8	25.8	18.0	R
9	22.3	16.0	R
10	22.3	16.0	R
11	23.4	16.0	R
12	22.2	16.0	R
13	23.8	17.0	R
14	19.8	14.0	R
15	20.9	14.0	R
16	23.2	17.0	R
17	24.3	16.0	R
18	20.5	14.0	R
19	20.0	13.0	R
20	19.8	13.0	R
21	20.8	14.0	R
22	19.7	13.0	R
23	21.0	14.0	R
24	22.7	15.0	R
Mean	21.7	14.9	
Std	1.8	1.6	
Max	25.8	18.0	
Min	19.3	13.0	

Table 4-1: Demographic information of the participants.

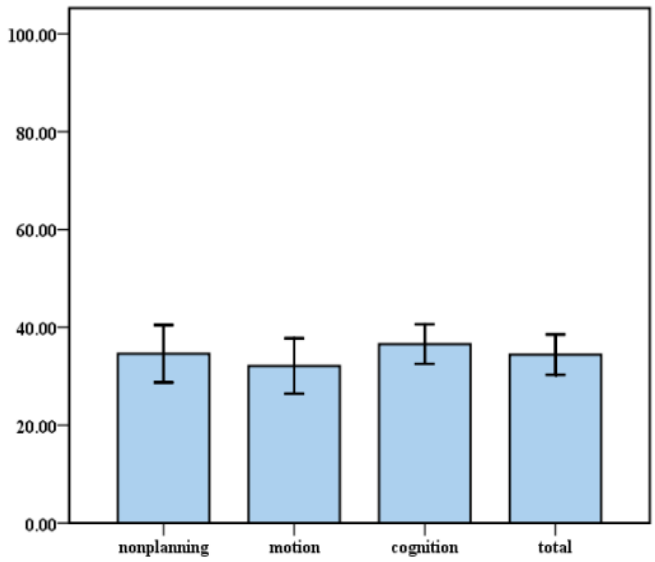

Figure 4-1: The BIS profile of the subjects. The possible range in from 0 to 100

Behavioral Performance on Iowa Gambling Task

IGT Score

In the total of 2400 trials, subjects made 1225 (47%) risky choices (deck A and deck B), 1169 (45%) safe choices (deck C or D), and missed 6 of them (0.23%). Their individual performance on the IGT task varied with total net scores ranging from -54 to 74 (mean -2.33 ±[SD] 31.27) out of a total possible range of –100 to +100.

Reaction Time (RT)

The average reaction time (RT) for all the trials was 675.17 ±[SD] 309.62 ms. There was no relationship between-subjects' IGT scores and their mean RTs (r =

0.215, p = 0.314). The average RT for the 1225 choices from risky decks was 653.65 ±[SD] 426.96 ms, while the one for the 1169 choices from safe choice was 683.22 ±[SD] 444.04 ms. There was no difference between the RTs for choices from risky decks versus safe decks (t = -1.661, p = 0.097), hence RT will not be discussed in the following analysis.

Learning Effect

Figure 4-2 shows subjects' IGT score across the course of the experiment in every 20 trials (one block equals 20 trials). Subjects selected more cards from the risky decks in the first half of the trials and learned to select more cards from safe decks in the second half of the trials. With their performance in the 5 blocks of per 20 trials as the repeated factor, repeated-measure ANOVA was used to assess the learning effect. Mauchly's test shows that the assumption of sphericity had been violated, $\chi^2(9) = 26.036$, p=0.002, therefore the degree of freedom was corrected using Greenhouse-Geisser estimates of sphericity. The results indicated that there was a significant learning effect on IGT score, F (2.426) = 3.746, P =0.023, suggesting that overall subjects' performance improved over time, as expected.

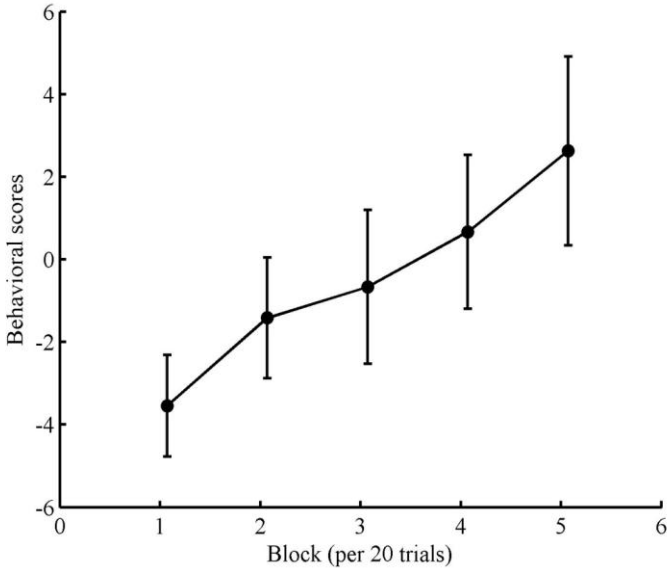

Figure 4-2: IGT scores (mean and standard error (SE)) across the course of the experiment in every 20 trials as a block.

Deck Effect

Although scores increased over the course of the experiment, showing that subjects were shifting their preference for decks with a higher long-term outcome, there were only on average 2.62 more cards selected from the safe than from risky decks in the last block of the experiment. A separate analysis of subjects' choices from each of the four decks was conducted to reveal their preference for cards in the 4 decks over 5 blocks. Table 4-2 and Figure 4-3 show the number of cards selected from each deck in each block. The number of cards selected from deck A decreased from the beginning of the experiment; preference for deck B lasted over the whole course of the experiment; and the number of cards selected from deck C and D increased over the experiment and became comparable to deck B in the last block.

A two-factor repeated measures analysis of variance revealed that there was a significant main effect of deck ($F = 3.428$, $p=0.04$) and interaction effect of deck * block ($F= 2.870$, $p = 0.012$) on the preference of cards, but no significant main effect of block ($F= 2.043$, $p=0.095$) on the preference. Pairwise comparisons on decks with the Bonferroni Adjustment suggested a significant difference in a preference for deck A and deck B ($p=0.008$).

Deck	**Block**				
	1	**2**	**3**	**4**	**5**
A	5.46	4.83	4.08	3.08	2.17
B	6.21	5.88	6.25	6.58	6.50
C	4.08	4.54	4.63	5.54	5.75
D	4.04	4.75	5.04	4.79	5.54

Table 4-2: Mean number of cards selected from each deck over the five blocks (20 trials in each block).

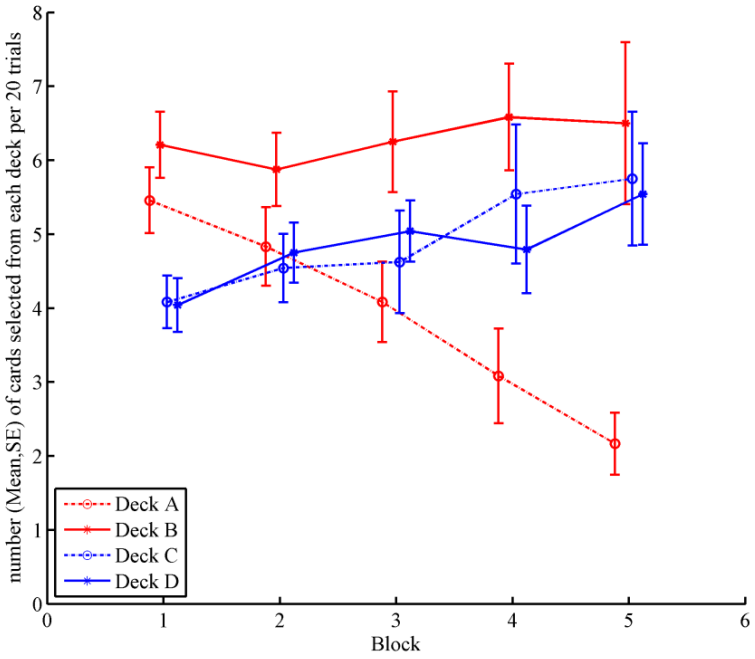

Figure 4-3: Mean number of cards selected from each deck in the Iowa Gambling Task over the five blocks (20 trials in each block). (Red lines indicate decks indentified as risky in the original publication of the task. Dotted lines indicate decks with higher punishment frequency. Bars represent SE.)

A two factor model: effect of long-term outcome and punishment frequency

A three-factor repeated measures ANOVA was carried out to test the effect of long-term outcome, punishment frequency and block on the preference of cards. The main effect of outcome ($F = 0.314$, $p = 0.718$) and block ($F= 2.043$, $p = 0.095$) are not significant, but the main effect of frequency ($F = 5.745$, $p=0.025$) is significant. There is also a significant interaction effect of between outcome* frequency ($F = 7.643$, $p = 0.011$), outcome*block ($F = 3.746$, $p = 0.023$) and

outcome*frequency*block (F = 3.755, p = 0.016), but no significant interaction effect of frequency* block (F = 1.353, p = 0.265).

fMRI maps related to Iowa Gambling Task

Brain Activation during Choices from Risky versus Safe Decks

A comparison of brain activity during choices from risky versus safe decks was conducted to reflect the brain maps related to the factor of long-term outcome, which revealed the Anterior Cingulate Cortex (ACC) (BA 32/24), especially the right-side, showed significant greater activation when making risky choices (Table 4-3, Figure 4-4).

Regional activations	Side	BA	Volume (voxels)	Coordinate (x, y, z)	Voxel (Z-value)
Anterior Cingulate Cortex	R	24/32	117	12 39 24	4.211
				0 45 12	4.036
				6 36 18	3.866

Table 4-3: Brain regions showing significantly higher activation during choices from risky (deck A and B) versus safe (deck C and D) decks (peak level p < 0.001 uncorrected, cluster level p < 0.05 FWE corrected). Note: L = left, R = right. Coordinates refer to the cluster peak voxel in mm (MNI) and coordinates in italics refer to 2 local maxima more than 8 mm apart. BA estimated from mni2tal conversion with positive = right (x), anterior (y), and superior (z).

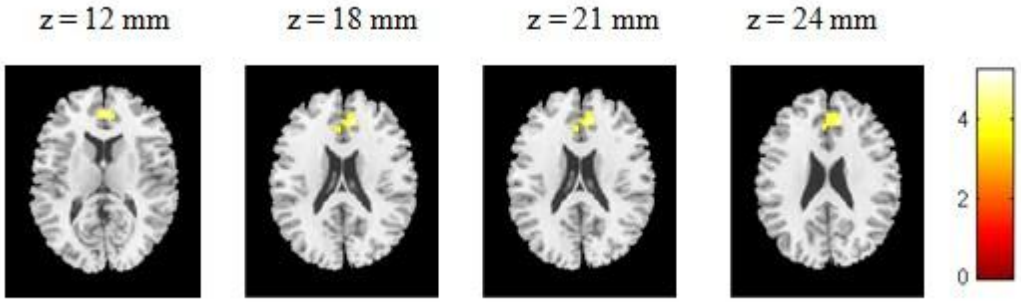

Figure 4-4: Significant brain activity during choices from risky (deck A and B) minus safe decks (deck C and D) (peak level $p < 0.001$ uncorrected, cluster level $p < 0.05$ FWE corrected). Activations are displayed on axial sections starting at z = 18 in neurological orientation (left is left).

To explore the interaction effect between long-term outcome and punishment frequency, brain activity during choices from risky versus safe decks were compared in the condition of high punishment frequency (i.e., deck A versus deck C) or low punishment frequency (i.e., deck B versus deck D). The deck A versus deck C contrast revealed similar but more focal activation map to the original contrast (Table 4-4), while the deck B versus deck D contrast detected no significant results under the threshold of uncorrected $p < 0.001$ in the peak level and corrected $p < 0.0$ 5 in the cluster level.

To examine whether the significant neural activity in the above contrasts was related to task performance, the area showed significant activation in the main contract was defined as region-of-interest (ROI) and the activity of this ROI in the above contrasts were extracted and correlated with the total IGT score. Only the

ROI activity in the (deck A > deck C) contrast is significantly correlated with the IGT score (r= 0.4245, p=0.0387), but not the one in the (deck B > deck D) contrast or in the main contrast.

The interaction effect between long-term outcome and block (time) was also accessed by comparing the brain activity before the risky versus safe selections in the first half trials and the second half trials separately, but no interaction effect was found in the related brain maps.

Regional activations	Side	BA	Volume (voxels)	Coordinate (x, y, z)			Voxel (Z-value)
Anterior Cingulate Cortex	R	32	36	9	42	9	4.495
				0	*45*	*9*	3.904

Table 4-4: Brain regions showing significantly higher activation during choices from risky (deck A) versus safe (deck C) decks under the condition of a high punishment frequency (peak level $p < 0.001$ uncorrected, cluster level $p < 0.05$ FWE corrected). Note: L = left, R = right. Coordinates refer to the cluster peak voxel in mm (MNI) and coordinates in italics refer to two local maxima more than 8 mm apart. BA estimated from mni2tal conversion with positive = right (x), anterior (y), and superior (z).

Brain Activation during Choices in the First Half versus the Second Half Trials

Contrast of choices in the first half minus the second half trials revealed that there was greater brain activity in the hippocampus, parahippocampus, amygdala and insula during choices in the first half trials (Figure 4-5, Table 4-5). In this contrast, a stringent threshold was used to obtain result maps with clearly defined

clusters, which was uncorrected $p < 0.0001$ in the peak level and corrected $p< 0.05$ in the cluster level. The reversed contrast failed to detect significant activation under the threshold of uncorrected $p < 0.001$ in the peak level and corrected $p < 0.05$ in the cluster level.

Regional activations	Side	BA	Volume (voxels)	Coordinate (x, y, z)			Voxel (Z-value)
Parahippocampal Gyrus/Hippocampus	R	28/35	164	21	-27	-15	5.021
Amygdala				*21*	*-6*	*-15*	4.831
				9	*-42*	*-6*	4.685
Parahippocampal Gyrus	L	28/35	76	-24	-30	-12	4.783
Hippocampus				*-27*	*-15*	*-21*	4.698
				-18	*0*	*-15*	3.949
Insula	L	13	15	-39	-15	3	4.758
Insula	L	13	27	-42	-6	-6	4.080
				-39	*6*	*-3*	4.257
				-36	*0*	*-9*	4.068

Table 4-5: Brain regions showing significantly higher activation during choices in the first half trials versus the second half trials (peak level p < 0.0001 uncorrected, cluster level p < 0.05 FWE corrected). Note: L = left, R = right. Coordinates refer to the cluster peak voxel in mm (MNI) and coordinates in italics refer to 2 local maxima more than 8 mm apart. BA estimated from mni2tal conversion with positive = right (x), anterior (y), and superior (z).

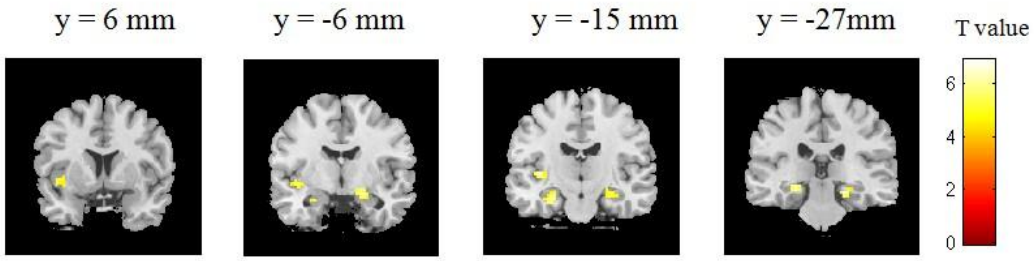

Figure 4-5: Significant brain activity during choices in the first half trials minus the second half trials (peak level p < 0.0001 uncorrected, cluster level p < 0.05 FWE corrected). Activations are displayed on the coronal sections in neurological orientation (left is left).

CHAPTER 5 DISCUSSION

This study investigated the brain mechanism involved in the Iowa Gambling Task in normal young adults, using event-related functional magnetic resonance imaging. It explored how participants' behavioral performances were influenced by the factors that existed in the IGT task design, and how these factors were processed.

Behaviorally, this study showed that normal subjects' performances gradually improved across the course of the task, which meant that, consistent with the general assumption on the IGT performance (Bechara et al. 1994, 1996), subjects learnt over time to choose more cards from decks with an advantageous long-term outcome. This study also replicated the results of recent behavioral studies (Horstmann, Villringer & Neumann 2013, Lin et al. 2007) which found that subjects' preferences in the IGT were influenced by not only the long-term outcome, but also the punishment frequency associated with the decks. There was also a significant interaction effect between the two factors. Subjects were more sensitive to the effect of the long-term outcome under the condition with a high punishment frequency. Further analysis found that the preference for decks specifically induced by the factor of the long-term outcome would change across the course of the task, but the preference specifically induced by the punishment frequency would be consistent. In the task, subjects consistently preferred decks with low punishment frequency and tried to avoid decks with a high punishment frequency from the beginning of the task, while they needed to gradually learn to prefer the safe decks and avoid the risky decks. This finding suggests that the learning process in the IGT was only induced by the effect of the long-term outcome, and thus provided a response to the

critiques on the general assumption of the IGT made by some recent behavioral studies, which questioned the way the original task was designed to assess the performance of IGT by calculating the difference between safe and risky decks which only took into account the long-term outcome.

The comparison of the brain activation during the risky versus the safe choices revealed higher activations in a cluster of the medial frontal gyrus, the right-sided anterior cingulate cortex (BA 32/24). This finding generally matched the results in previous fMRI studies (Lawrence et al. 2009, Fukui et al. 2005), although Lawrence et al.'s (2009) study detected more widely distributed activation in the middle/superior occipital cortex and other frontal regions such as the dlPFC (BA9, 46) and the inferior OFC (BA 47). One possible explanation was the age differences in the subjects in these studies. Subjects aged from 22 to 57 years old with a mean age of 32.7 were recruited in Lawrence et al.'s (2009) study, when younger populations aged around 20 years-old were studied in both Fukui et al (2005) and this study. Most importantly, the IGT task in Lawrence et al.'s study was slightly different from the original design. Lawrence et al. adjust the punishment frequency in all the four decks to be the same, thus they optimized statistical comparison between the risky and the safe decks and allowed more sensitive detection on this contrast. On the other hand, their results were limited without considering the effect of the punishment frequency.

According to the SMH, the ACC played a role in the biasing function at a conscious level, which was guided by knowledge and awareness (Bechara &

Damasio 2005). Evidence from other studies also supported this view of the ACC's function in voluntary or willful decision making. Several studies have implicated the function of ACC as an interface between motivation, cognition and action (Hadland et al. 2003, Paus 2001, Matsumoto, Suzuki & Tanaka 2003). By conducting the ACC lesion study in rhesus monkeys, Kennerley et al. (2006) further proved that in such a process, the ACC's role was guiding voluntary choices from the learnt value of selection actions, instead of neither detecting nor correcting errors. The comparison between the risky and safe decks did not reveal any specific finding in the vmPFC, suggesting that these contrast conditions were matched in terms of the demands on the function of the vmPFC, which is emotion-memory integration in the SMH framework.

In the current study, one of the most important questions is how the two factors of long-term outcome and punishment frequency interacted to influence subjects' performance on the decks. Consistent with the behavioral finding that subject are more likely to learn to prefer decks with positive long-term outcome under the condition with a higher punishment frequency, it was found the higher activation in ACC before risky choices was dominated in the condition with a high punishment frequency. In the context of high punishment frequency (deck A and deck C), subjects shift their preference to the safe deck as predicted by the SMH. However, in the context of very low punishment frequency (decks B and deck D), both decks seems safe with only occasionally punishment that people fail to distinguish their difference on long-term outcome. The recent study by Lin et al. (2013) with three runs of the IGT task revealed that subjects could only learn to avoid risky decks

with a high punishment frequency in the first two runs of the task and they could learn to avoid risky decks with a low punishment frequency in the third run of the task. Crone et al. (2005) explained this phenomenon in the way that the infrequent punishment was discount as its consequences were forgotten too quickly. Subjects need to avoid the risky decks over longer time than the assumption made by the original design in the condition with a low punishment frequency. In the SMH framework, those negative somatic markers were assumed to be represented in the insula and then be translated into response shifting.

The interaction effect between the long-term outcome and time was examined by comparing the main contrast in first half trials and in second half trials separately. No significant activity was detected partly due to the inter-subjects variance on the learning process.

This study explored the brain areas related to the learning process in IGT by comparing brain activation during the first and the second half of the experiment. Learning in a crucial aspect in IGT but it has rarely been examined in former studies partly due to the averaged block design of most previous fMRI studies. Memory and emotion systems including the hippocampus, the parahippocampus, the amygdala and the insula cortex were activated higher in the early stage of the task, showing that there was a learning process guided by somatic states mainly at the early stage of the task.

The amygdala was the crucial structure for the triggering of the somatic state by the primary inducer, which coupled the feature of the primary inducers with the

associated somatic states. This function of the amygdala was supported by several animal and human studies (Bechara, Damasio & Damasio 2003). As described earlier, once the somatic states were induced, signals from its activation would be relayed back to the subcortical and cortical structures and then influence activity in several regions. One region was the memory system, so that particular representation of response options was reinforced or eliminated in the memory, to help bias the options and plans. This process of affectively influenced memory happening in the amygdale-parahippocampus-hippocampus circuitry was supported by other studies (McGaugh, Cahill & Roozendaal 1996; Richter-Levin 2004).

The enacted somatic states also acted on cortical regions such as the insula, which help to generate conscious feelings of the somatic states. Unlike the amygdale-parahippocampus-hippocampus circuitry, the function of insula in SMH framework is more like a cortical representation of the generated somatic state. Existing findings and theories supported the role of the insula in playing a crucial role in emotional awareness (Bechara & Damasio 2005). Neuroimaging studies discovered that the activation of the insula were consistently associated with pain (Wager et al. 2004), touch (Lindgren et al. 2012), disgust (Calder et al. 2007), empathy (Lamm, Decety & Singer 2011, Ebisch et al. 2011), risk and uncertainty (Bossaerts 2010) . The activation of insula was also associated with subsequent behavior shifting (Paulus et al. 2003; Wrase et al. 2007). Particular in a recent study by Wrener et al. (2013), they found that the activation within insula was associated with IGT task performance only in individuals who had a high level of interceptive

awareness, which indicated that the insula represented the somatic markers more strongly with increased interceptive awareness.

There is no higher brain activation in the second half trials when comparing to the first half trial. This rough definition of the task stage by separating it into half by half only allowed the exploration on the activity in the earlier stage of the task, but not the later stage of the task, as there is notably inter subject variance in terms of learning stage. In order to obtain the learning stage of the subjects, there need to be physiological measurements during the IGT performance, which can directly reflecting the activity level of the somatic marker, and it need to be synchronized with the fMRI recording.

As stated in the literature review, there were 3 stages of processes in the framework of SMH including generation of the somatic states, cortical representation of the somatic stated and biasing behavioral choices by the somatic signals. In the SMH framework, conflicting somatic states might sometimes be triggered by primary or secondary inducers simultaneously, and signals from their activations would then be relayed back to cortical structures such as the insula to cause conscious feelings. This would also occur in the memory system, in which the stronger or fittest somatic states, would be reinforced while others would be eliminated. As a result, an overall positive or negative somatic state would be generated and signals to bias the selection responses would be provided. Current results mostly reflected the SMH framework: The regions found to reflect

behavioral performance (i.e. ACC) is the cortical region for the somatic states to influence the selection behaviors; the detected regions reflecting the time effect were crucial to the generation and the cortical representation of the somatic state.

APPENDICES

Appendix I Ethics Approval Letter

THE HONG KONG POLYTECHNIC UNIVERSITY
香港理工大學

To	CHEUNG Vinci (Department of Rehabilitation Sciences)		
From	TSANG Wing Hong Hector, Chair, Departmental Research Committee		
Email	rshtsang@	Date	04-May-2012

Application for Ethical Review for Teaching/Research Involving Human Subjects

I write to inform you that approval has been given to your application for human subjects ethics review of the following project for a period from 26-Apr-2012 to 30-Jun-2015:

Project Title:	Brain basis of Iowa Gambling Task
Department:	Department of Rehabilitation Sciences
Principal Investigator:	CHEUNG Vinci

Please note that you will be held responsible for the ethical approval granted for the project and the ethical conduct of the personnel involved in the project. In the case of the Co-PI, if any, has also obtained ethical approval for the project, the Co-PI will also assume the responsibility in respect of the ethical approval (in relation to the areas of expertise of respective Co-PI in accordance with the stipulations given by the approving authority).

You are responsible for informing the Departmental Research Committee in advance of any changes in the proposal or procedures which may affect the validity of this ethical approval.

You will receive separate email notification should you be required to obtain fresh approval.

TSANG Wing Hong Hector

Chair

Departmental Research Committee

Appendix II Inform Sheet

Host: Department of Rehabilitation Sciences, The Hong Kong Polytechnic University

Collaborator: The Centre for Cognition and Brain Disorders, Hangzhou Normal University

Information Sheet for Participants

Brain basis of Iowa Gambling Task

You have been asked if you may take part in the above-named research project which involves completing a paper-and-pen assessments and undergoing a magnetic resonance imaging (MRI) scanning in one or two experimental session(s). This information sheet tells you about the research project and MRI so that you can decide if you or your child would like to participate.

What is the objective of the project?

The study aims to investigate the physiological response of the brain to drug-related cues in Iowa Gambling Task. The purpose is to find out neural mechanism underlying affective desion-making.

What are the procedures?

The participant will be invited to attend 1 - 2 experimental session(s) of a total of 1.5 hours approximately. During the session(s), the participant will complete a set of questionnaire on his/her demographic information, and daily life habits, mental health and personality. Then the participant will be interviewed on his/her general health and informed about the safety measure for the brain imaging that follows. The participant will then undergo magnetic resonance imaging in a scanner for about 60 minutes, during which you will lay down to rest and to play in a gambling task.

Traveling expense will be reimbursed upon completion of the experiment.

What is an MRI Scan, and what does it involve?

MRI scans do not have any X-rays or any kind of harmful radiation and there is no pain. MRI scan is a safe and non-invasive procedure that measures brain structure, connectivity, and activity. It is a type of medical imaging technique based on the principles of magnetic resonance, and with advanced technology, high quality of images of brain structures would be produced and used for analysis. Participants will contribute to scientific research which may benefit others. Before the scan, we will ask the participants for some general health information to ensure safety. After this, participant will lay still inside the scanner for about 60 minutes, wearing headphones. The participant may ask to stop at any time.

During the scan there is a low banging noise and please be reminded to stay calm and relaxed to avoid bodily movements. The doctors/nurses can be seen through a window. A hand held Patient Communication System (PCS), a rubber ball, can be pressed at any time to talk to us or stop the scan. No injections, blood tests or drugs are required, and participant can leave straight after the scan.

Pen and Paper tests.

These are simply short tests with words, numbers and pictures. They are fun to do and can be done on the same day with MRI scan.

Interested to take part in this project?

Host: Department of Rehabilitation Sciences, The Hong Kong Polytechnic University

Collaborator: The Centre for Cognition and Brain Disorders, Hangzhou Normal University

You are free to decide whether or not to take part in the project. Participant can stil withdraw from the project at any time in the future. If you decide to take part in the project, al the information (including personal information and MRI scan information) will be kept strictly confidential, and protected by the declaration of confidentiality.

Participants will receive compensation for time and travel expenses of a maximum of RMB100.

What is the cost for participation?

There will be no cost for participating in this study.

The study has been approved by the Research Committee, The Hong Kong Polytechnic University.

Should you have any questions about this project, please contact:

DR Vinci CHEUNG, Department of Rehabilitation Sciences,
The Hong Kong Polytechnic University
or
Prof Zang Yufeng, The Centre for Cognition and Brain Disorders,
Hangzhou Normal University

Tel: (852) 2766 7578 (Office)

主辦單位：香港理工大學康復治療系
協辦單位：杭州師範大學認知與腦疾病研究中心

爱荷华赌博实验的大腦機理

研究計劃資料

我們誠意邀請你參加上述研究計劃。是次研究中你會完成一至兩節用紙筆進行的評估及磁力共振掃描。本單張會告訴你有關這項計劃和磁力共振掃描的資料，讓你決定你是否參與。

這項研究的目的是什麼？

研究目的為探討爱荷华赌博实验的脑机制，以了解个体间情感决策能力差异的原因。

這項研究的步驟是什麼？

參加者會參與一或兩節約共一个半小时的實驗。其間，參加者會完成一份有關其一般資料、生活習慣、精神狀態及性格的問卷。然後參加者會進行一個訪問，是關於參加者的一般健康，以及得悉有關接著的磁力共振掃描的安全措施。參加者會接受約六十分鐘的磁力共振掃描，只需要躺下进行一次虚拟的扑克牌游戏。

完成後，參加者將會獲發進行實驗的有關支出的補貼。

什麼是磁力共振掃描？它是如何進行？

磁力共振掃描絕無有害幅射及X光，及不會引起痛楚。磁力共振掃描是一種安全及不具入侵性的掃描科技，它是一種利用磁場原理，再加上電腦科技，將腦部組織、組織間的聯絡，及細胞活動顯示成為圖像的醫學影像技術。參加者將為醫學界研究作出貢獻並幫助他人。掃描前，我們會訪問參加者的一般健康資料以肯定其適合進行此項掃描及測試。之後，參加者會載上耳筒，靜止地躺在掃描器內６０分鐘。參加者可以隨時要求停止。

掃描過程中，參加者會聽到儀器發出的少量噪音，請參加者盡量保持鬆弛和平靜，避免移動身體。參加者將可以從窗裏看到醫生或護士，如欲與控制室內的醫護人員談話或終止掃瞄，可輕按手持的橡皮球，即病人溝通系統。掃描前將不須注射或服食任何藥物，亦不須進行血液測試。參加者於磁力共振掃描後即可離去。

紙筆測試

這些是一些很簡單的測試，用字，數字，和圖片。這些都是很有趣味的和可以在做掃描的同一天進行的。

有興趣參加這研究嗎？

你可以自由決定你是否參加本項研究。參加者可以在任何時間終止參與而無須說明理由。所有資料(包括個人資料)只會用作研究用途，將絕對保密，並受保密聲明的約束。

參與研究的費用：

參加者無需為參與研究付出任何費用。

此項目已得到香港理工大學研究倫理委員會的批准

如有興趣或任何疑問，請聯絡

香港理工大學康復科學系 張穎思博士 或

杭州師範大學認知與腦疾病研究中心 臧玉峰教授

電話：(852) 2766 7578 (辦公室)

Appendix III Consent Form

Host: Department of Rehabilitation Sciences, The Hong Kong Polytechnic University
Collaborator: Center for Cognition and Brain Disorder, Hangzhou Normal University

CONSENT FORM

Project title: Brain basis of Iowa Gambling Task
Investigators: Dr. Vinci Cheung (Assistant Professor, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University)
Ms. Ma Shuangye (Mphil candidate, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University)
Prof Zang Yufeng (Center for Cognition and Brain Disorder, Hangzhou Normal University)
Prof. Chetwyn Chan (Chair Professor, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University)

Project Details: The study aims to investigate the physiological response of the brain to Iowa Gambling task in normal youths. The purpose is to find out neural mechanism underlying affective decision-making.

Potential risks: minimal

Consent

I, _____ (Name of Participant), have been explained the details of this study. I, _____ (Name of Participant) voluntarily consent to participate in this study. I understand that I can withdraw from this study at any time without giving reasons, and my withdrawal will not lead to any punishment or prejudice against me. I am aware of any potential risk in joining this study. I also understand that my personal information will not be disclosed to people who are not related to this study and any direct personal identifiers will not appear on any publications resulted from this study. I understand that the result of the paper-and-pen and MRI assessments are solely for the purpose of research, and NOT for clinical diagnostic purposes. I know that I will receive a traveling reimbursement of a maximum of RMB 100 for completing the experiment.

Since we are planning to accumulate a large local dataset, we sincerely ask for your consent to allow us to put data collected from you in archive for future research. Your contribution is invaluable to the database.

I wish / do not wish* the data collected to be kept in archives for future research purposes.

I can contact the chief investigators Dr. Vinci CHEUNG or Prof, Zang Yufeng at telephone (852) 27667578 or email vinci.cheung@ for any questions about this study. If I have complaints related to the investigator(s), I can contact Mr KY Leung, secretary of Departmental Research Committee, at (852) 27665398 or via rskleung@

I know I will be given a signed copy of this consent form.

_____ _____
Signature (Participant) Date

_____ _____
Signature (Witness) Date

*Please delete as inappropriate.

主辦單位：香港理工大學康復治療系
協辦單位：杭州師範大學認知與腦疾病研究中心

參加者同意書

科研題目：影响爱荷华赌博实验表现的大脑機理
科研人員：張穎思博士（香港理工大學康復治療科學系助理教授）
马霜叶 （香港理工大學康復治療科學系硕士研究生）
臧玉峰教授（杭州師範大學認知與腦疾病研究中心教授）
陳智軒教授（香港理工大學康復治療科學系讲座教授）

科研內容：研究目的為探討爱荷华赌博实验中的脑机制以增进对于情感决策的神经机制的理解

潛在危險性：最少

本人_____（參加者姓名）已瞭解此次研究的具體情況。本人_____（參加者姓名）願意參加此次研究，並明白參加者有權在任何時候、無任何原因放棄參與此次研究，而此舉不會導致參加者受到任何懲罰或不公平對待。本人明白參加此研究課題的潛在危險性以及參加者的資料將不會洩露給與此研究無關的人員，參加者的名字或相片不會出現在任何出版物上。

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由於單位有計劃為本地累積一個大的資料庫，我們誠邀你同意讓我們將從你所收集的資料放入存儲庫內以供將來研究之用。你對資料庫的供獻是無價的。

就以上的描述，本人同意 / 不同意*將在本計劃中從本人所收集的資料存儲以供將來研究之用。

本人可以用電話 (852) 27667578 或電郵 vinci.cheung@ 來聯繫此次研究課題負責人，張穎思博士或臧玉峰教授。若本人對此研究人員有任何投訴，可以聯繫梁先生（部門科研委員會秘書），電話：(852) 27665398，或電郵 rskleung@ 。

本人亦明白，參與此研究課題需要本人簽署一份同意書。

簽名（參加者）：_____ 日期：_____

簽名（證人）：_____ 日期：_____

Appendix IV Instructions

实验指导语

- 实验开始后，你面前的屏幕上将会出现四叠扑克牌，分别标记为 A，B，C，D。
- 请你每次通过按 1，2，3，4 四个按键中的任意一个，选择一叠牌拿一张牌：
- ‘1’代表选择 A，‘2’代表选择 B，‘3’代表选择 C，‘4’代表选择 D。
- 每次你拿牌后，电脑会告诉你，你赢了一些钱。我无法告诉你能赢多少钱，你可以随着实验的进行去发现。每次你赢钱后，你的总资金会增加。
- 然而，几乎每隔一段时间，你拿牌后，电脑会告诉你，你赢了一些钱，但同时你也输掉了一些钱。我无法告诉你何时会输钱以及你会输掉多少钱。你可以随着实验的进行自己去发现。每次你输钱后，总资金会减少。
- 你有绝对自由的在任何时候选择从其他的任意牌堆拿牌。
- 这个游戏的目标是赢尽可能多的钱，如果你发现自己无法赢，请尽可能避免输。
- 我无法告诉你这个游戏会持续多久。你必须持续进行，直到电脑出现停止画面。
- 你会得到 2000 元的借款（起始总资金）来开始游戏。实验过程中你可以一直看到你借了多少钱来进行这个游戏，最后计算你的输赢时，将首先扣除掉这一部分。
- 需要特别注意的是，如同任何一个真正的扑克牌游戏一样，一旦游戏开始电脑不会再改变牌的顺序。虽然没有办法可以精确计算出何时你会输钱，但是这个游戏是公平的。电脑不是随机让你输的，也不会基于你上一次的选择来让你输。另外，每一叠牌中每种颜色的牌的数目是相同的，也就是说牌的颜色并不会告诉你哪一叠牌是更好的选择。因此你完全不必尝试去搞清楚出电脑的安排。我可以告诉你的就是有几叠牌可能比其他的要差。你可能会发现选它们都很差，但有几叠会比其他的更差。不管你发现自己输了多少钱，只要你能避开最差的几叠牌，你仍然能赢。
- 请向对待真正的金钱一样对待游戏中的金钱，做出的任何决定都应该和你在使用你自己的金钱时一致。
- 你最后获得的奖金数目等于你在游戏中赢得的钱的数目除以 100。

Instructions

- In front of you on the screen, there are four decks of cards A, B, C, and D.
- I want you to select one card at a time, by clicking on the card, from any deck you choose.
- Each time you select a card, the computer will tell you that you won some money. I won't tell you how much money you will win. You will find out along the way. Every time you win, the green bar gets longer.
- Every so often, however, when you click on a card, the computer tells you that you won some money, but then it says that you lost some money too. I don't tell you when you will lose, or how much you will lose. You will find out as we go along. Every time you lose, the green bar gets smaller.
- You are absolutely free to switch from one deck to the other at any time, and as often as you wish.
- The goal of the game is to win as much money as possible, and if you can't win, avoid losing money as much as possible.
- You won't know when the game will end. You must keep on playing until the computer stops.
- I am going to give this $2000 credit, the green bar, to start the game. The red bar here is a reminder of how much money you borrowed to play the game, and how much money you have to pay back before we see how much you won or lost.
- It is important to know that just like in a real card game, the computer does not change the order of the cards after the game starts. You may not be able to figure out exactly when will you lose money, but the game is faire. The computer does not make you lose money at random, or make you lose money based on the last card you picked. Also, each deck contains an equal number of cards of each color, so the color of the cards does not tell you which decks are better in this game. So you must not try to figure out what the computer is doing. All I can say is that some decks are worse than the others. You may find all of them bad, but some are worse than the others. No matter how much you find yourself losing, you can still win if you stay away from the worst decks. Please treat the play money in this game as real money, and any decision on what to do with it should be made as if you were using your own money.

Appendix V Demographic Questionnaire

Subject No. (DP/NC/AU/OC)_____ Data: _____

你的答案只会供学术研究之用

出生日期: _____ (日/月/年)　　性别: 男/女　　现就读年级/最高学历: _____

出生周数: 足月(40周或以上) /或/ 比预产期早____周_____日

父亲/家里的领袖在你出生时的职业:_____

吸烟: 平均每日____枝, 持续了____年

饮酒:平均每日_____份酒，持续了____年

最后一次饮用咖啡/茶等兴奋性饮料是在实验前_____（小时）

今天是否有身体不适的感觉: 是/否。若“是”，可否具体描述_____

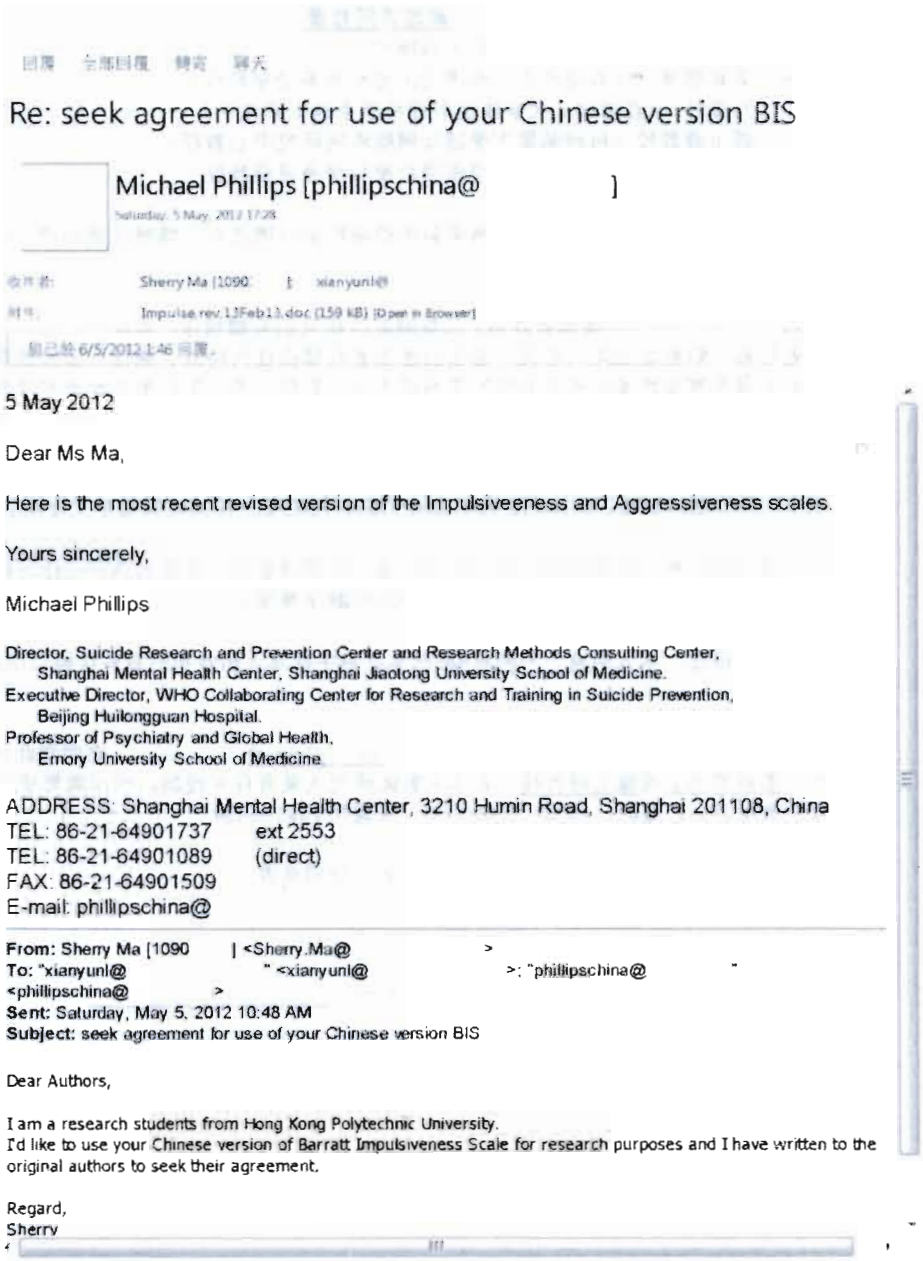
过去七天所服的常规药物名称: _____ 每天服量: _____

今天所服过之药物名称: _____ 每天服量: _____

目前或以往是否患有: (请圈上适当的答案)

过度活跃症Hyperactivity	有/没有
头部损伤Head injury	有/没有
神经疾病Neurological disease	有/没有
听觉障碍Hearing impairment	有/没有
精神发展迟缓Mental retardation	有/没有
基因疾病Genetic disorder	
(如: 结节性脑硬化tuberose Sclerosis, 脆性x基因Fragile X)	有/没有
曾否因病住院Hospital admission (原因:_____)	有/没有
曾否停学超过半年(原因:_____)	有/没有
直属亲人曾否患过任何精神病	有/没有

Appendix VI Permission Letter for use of the BIS-11



回覆　全部回覆　轉寄　刪去

Re: seek agreement for use of your Chinese version BIS

Michael Phillips [phillipschina@]

Saturday, 5 May, 2012 17:28

收件者: Sherry Ma [1090]; xianyunl@

附件: Impulse rev 13Feb13.doc (159 kB) [Open in Browser]

5 May 2012

Dear Ms Ma,

Here is the most recent revised version of the Impulsiveeness and Aggressiveness scales.

Yours sincerely,

Michael Phillips

Director, Suicide Research and Prevention Center and Research Methods Consulting Center,
Shanghai Mental Health Center, Shanghai Jiaotong University School of Medicine.
Executive Director, WHO Collaborating Center for Research and Training in Suicide Prevention,
Beijing Huilongguan Hospital.
Professor of Psychiatry and Global Health,
Emory University School of Medicine

ADDRESS: Shanghai Mental Health Center, 3210 Humin Road, Shanghai 201108, China
TEL: 86-21-64901737 ext 2553
TEL: 86-21-64901089 (direct)
FAX: 86-21-64901509
E-mail: phillipschina@

From: Sherry Ma [1090 | <Sherry.Ma@ >
To: "xianyunl@ " <xianyunl@ >; "phillipschina@ "
<phillipschina@ >
Sent: Saturday, May 5, 2012 10:48 AM
Subject: seek agreement for use of your Chinese version BIS

Dear Authors,

I am a research students from Hong Kong Polytechnic University.
I'd like to use your Chinese version of Barratt Impulsiveness Scale for research purposes and I have written to the original authors to seek their agreement.

Regard,
Sherry

回覆　全部回覆　轉寄　聊天

RE: seek agreement for research use of BIS

Stanford, Matthew S. [Matthew_Stanford@b...

Sunday, 6 May, 2012 22:21

收件者: Sherry Ma [1090]

Sherry,

You certainly have my permission to use the BIS-11. Good luck with your research.

Best Regards,

Matthew S. Stanford, Ph.D.
Professor
Department of Psychology and Neuroscience
Baylor University
One Bear Place # 97334
Waco, TX 76798-7334
tel: 254-710-2236
fax: 254-710-3033
www.mentalhealthgracealliance.org<http://www.mentalhealthgracealli

Physical Address:
Baylor Sciences Facility
Attn: Psychology & Neuroscience
101 Bagby Avenue
Waco TX 76706

From: Sherry Ma [1090] [Sherry.Ma@]
Sent: Saturday, May 05, 2012 1:04 PM
To: Stanford, Matthew S.
Subject: seek agreement for research use of BIS

Dear Prof. Standford,

I am a research students from Hong Kong Polytechnic University. I am going to use the Chinese version of Barratt Impulsiveness Scale for research purposes and I have written to the authors of the Chinese version to seek their agreement.

The reference of the Chinese version is:
Reliability and validity of an adapted Chinese version of Barratt Impulsiveness Scale

Appendix VII Awareness Test

Questions

1. Please describe any strategy you used

2. Did you pick more cards from any particular deck(s)?

3. Did you avoid any particular deck(s)?

4. Why?

问题

5. 在这个游戏中你是否使用了某种特别的策略

6. 是否会更多选择某一（几）叠牌？如果是，请具体写出是哪一（几）叠牌

7. 或者是否会避免选择某一（几）叠牌？如果是，请具体写出是哪一（几）叠牌

8. 你为什么会采用这样的选择方式

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