

Developing translational animal models for decision making: the Iowa Gambling Task case

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*Neuroscience
& Cognition*

Manuela D. Mitsogiannis
Student's number: 3302320

Supervisor: Leonie de Visser
Second reviewer: Ruud van den Bos

Contents

Introduction & thesis's aim	1
1 Modelling decision making in humans: the Iowa Gambling Task	3
1.1 Developing a simulation of real-life decision-making	3
1.1.1 What aspects of decision-making does the IGT investigate?	5
1.2 Neural substrates of decision making in the Iowa Gambling Task	7
1.2.1 Brain areas involved in IGT performance	7
1.2.1.1 Lesion studies	7
1.2.1.2 Neuroimaging studies	7
1.2.2 Neurotransmitters' modulation of IGT performance	8
1.2.2.1 Serotonin	8
1.2.2.2 Dopamine	10
1.3 Design factors affecting decision-making in the Iowa Gambling Task	12
2 Translating the Iowa Gambling Task protocol from humans to rodents	15
2.1 Existing animal models of the Iowa Gambling Task	15
2.1.1 IGT models developed for rats	15
2.1.1.1 The four-arm box maze model	15
2.1.1.2 The five-hole operant chamber model	16
2.1.1.3 The four-hole operant chamber model	19
2.1.2 IGT models developed for mice	22
2.1.2.1 The eight-arm radial maze model	22
3 Comparing the Iowa Gambling Task in humans and animals	24
3.1 Setup characteristics	24
3.1.1 Type of rewards and punishments	24
3.1.2 Frequency of gains & losses	25
3.2 Face validity of the rodent IGT	26
3.2.1 Behavioural patterns in the human vs. rodent IGT	26

3.3	Predictive/construct validity of the rodent IGT	27
3.3.1	Effects of individual traits	27
3.3.2	Modulation of serotonergic signaling	29
3.3.3	Modulation of dopaminergic signaling	30
	Conclusion: toward a rodent model of the Iowa Gambling Task	34
	Acknowledgements	36
	References	37

Introduction & thesis's aim

Decision-making under conditions of uncertainty and risk is an essential part of human life. Every day we are required to make complex choices between often conflicting options, of which we can only partially estimate the outcome. Frequently, we are faced with the possibility to choose either for the instant gratification of our needs, which may however result in negative long-term consequences, or for a course of action which may lead to high payoffs in the future: in such cases, refraining from responding to immediate reward cues is essential to engage in behaviours that are adaptive in the long-term. Therefore, it is not surprising that disruptions of decision-making-associated functions in humans have a severe negative impact on the quality of life of the affected individuals (Bechara et al., 1994), and that such abnormalities have been proposed to represent crucial factors for the development and/or the maintenance of a variety of psychiatric disorders, such as drug addiction, alcohol abuse, and pathological gambling (Bechara, 2001, 2003, 2005; Bechara and Damasio, 2002; Bechara et al., 2002; Bowden-Jones et al., 2005; Chambers and Potenza, 2003; Ernst and Paulus, 2005; Fein et al., 2004; Garavan and Stout, 2005; Lawrence et al., 2009a; Mazas et al., 2000; Petry, 2001; Potenza, 2008; Redish et al., 2008; Robinson and Berridge, 2003; Schoenbaum et al., 2006; Verdejo-Garcia et al., 2008; Yucel et al., 2007).

For the study of long-term efficiency of behaviour and decision-making under ambiguity in humans, the Iowa Gambling Task (IGT) (Bechara et al., 1994) represents one of the most precious experimental tools available to neuroscientists today. In fact, this monetary rewards-/punishments-based paradigm (described in detail in section 2.1) manages to incorporate in its design the unpredictability of options' outcomes, the need to weight risks and benefits associated to each available option, and the necessity to exert behavioural control to better perform in the long-term. Additionally, choices made in the IGT are suggested to be the product of both "cold" (explicit-rational) and "hot" (implicit-emotional) option evaluation processes, which compresence commonly characterizes real-life decisions (Bechara et al., 1997, 2000a; Bechara and Damasio, 2005; Damasio, 1994; Guillaume et al., 2009; Stocco and Fum, 2008).

From its first employment as a test assessing specific cognitive impairments of prefrontal cortex-damaged individuals (Bechara et al., 1994, 2000b,a), the task subsequently found application in the assessment of decision-making deficiencies in a variety of other clinical conditions, included damage to other brain areas (Bechara et al., 1999, 1998; Clark et al., 2003; Fellows and

Farah, 2005; Manes et al., 2002), substance abuse (Bechara et al., 2001; Bechara and Damasio, 2002; Bechara et al., 2002; Bechara and Martin, 2004; Dom et al., 2006; Ernst et al., 2003; Grant et al., 2000; Hanson et al., 2008; Tucker et al., 2004; Whitlow et al., 2004), problem gambling (Brand et al., 2005; Cavedini et al., 2002; Goudriaan et al., 2005, 2006), Parkinson's disease (Brand et al., 2004; Ibarretxe-Bilbao et al., 2009; Kobayakawa et al., 2008; Mimura et al., 2006; Pagonabarraga et al., 2007; Perretta et al., 2005), schizophrenia (Bark et al., 2005; Kester et al., 2006; Lee et al., 2007; Sevy et al., 2007; Shurman et al., 2005), obsessive-compulsive disorder (Cavedini et al., 2010; da Rocha et al., 2008; Lawrence et al., 2006; Starcke et al., 2010), eating disorders (Brogan et al., 2010; Cavedini et al., 2004a; Liao et al., 2009; Tchanturia et al., 2007), attention deficit hyperactivity disorder (Garon et al., 2006; Luman et al., 2008; Malloy-Diniz et al., 2007; Toplak et al., 2005), etc. The results of such studies, have not only helped to better characterize these pathologies, but, combined with findings on the effects of pharmacological treatments during the task and functional neuroimaging data, have contributed to expand significantly our knowledge of neural substrates underlying decision-making, and how their function is compromised in individuals with related deficits. Research on humans however presents a number of limitations, stemming from problems of practical and ethical nature. First of all, performance of invasive or unsafe interventions is morally unacceptable in human subjects, reducing possibilities for functional investigations. Secondly, laboratory gambling tasks such as the IGT have been criticized for a possible lack of ecological validity, as the risk of losses is never real, either because fake currency is used or because actual monetary penalties are not experienced (Madden et al., 2007). Finally, animal experiments allow better control of genetic and environmental factors which can potentially confound the interpretation of behavioural results.

For these reasons, the development of an animal model of the IGT has been recently considered, and first experimental paradigms have already been proposed for rodents (Rivalan et al., 2009; van den Bos et al., 2006b; Zeeb et al., 2009). However, in order to be able to employ such tasks as research tools, a fundamental question that needs to be answered beforehand is whether animal IGT paradigms can satisfy face, predictive and construct validity criteria. To date, for each of these translational IGT models the issue of validity has only partially been addressed. Therefore, the scope of this thesis will be the evaluation of current animal IGT tasks' efficacy in accurately reproducing every aspect of the original human protocol, and in assessing the same decision-making processes. For this reason a first section will be dedicated to the presentation of the human IGT and relevant results obtained with its application in various types of study. Subsequently, a second part of the thesis will concentrate on reviewing in detail animal models of the task that have been developed up until now. In the third chapter, animal IGT components will be compared to their original counterparts, and first experimental findings will be discussed in relation to the available human data. Finally, conclusions and future directions will be presented in the last section.

Chapter 1

Modelling decision making in humans: the Iowa Gambling Task

1.1 Developing a simulation of real-life decision-making

When it was designed by Bechara and colleagues in the early 90s (Bechara et al., 1994), the IGT was meant to be a tool to specifically test impairments of decision-making in a controlled laboratory setting. The need for an experimental task of this sort first emerged from the observation of patients who had suffered from ventromedial prefrontal cortical lesions. In these individuals, while laboratory-measured intellectual, memory and problem-solving capabilities are preserved, a striking tendency to make personal life choices detrimental to oneself, coupled with an inability to learn from previous mistakes, is developed after the injury (Bechara et al., 1994, 2000b,a). No specific test existed at the time to probe this particular functional deficit: in order to evaluate the extent of such impairments, Bechara and colleagues were thus confronted with the challenge of developing a neuropsychological task that could reproduce fundamental aspects of decision-making in real-life situations. The result of their work was an experimental decision-making model which implemented outcome uncertainty, and the possibility of obtaining rewards or incurring in punishments as a result of the choice made (Bechara et al., 1994).

In the original version of the IGT (Bechara et al., 1994), subjects are initially given a \$2000 loan of play money. They are then requested to repeatedly select a card from one of four decks of cards (A, B, C, D) positioned in front of them until they are told to stop. Each time a card is drawn from one of the decks, it is immediately turned and either a financial reward or a reward coupled with the payment of a penalty is announced to the subject. Participants are told, at the beginning of the task, that their goal is to maximize financial profit on the loan they received and that they are free to switch from any deck to another during the task. They are not given any indication of the total number of choices they will be requested to make, which is always set by the experimenter at 100

Original Task (ABCD)

Deck	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	
A(+100)			-150		-300		-200		-250	-350		-300		-250	-200		-300	-150			-300		-350		-200	-250		-150		-300	-250		-200			-150	-300				
B(+100)	0	0		0					-125		0	0		-125			0	0			-125		0	0		0		0		0		-125		0		0		0			
C(+50)			-50		-50		-50		-50	-75		-75					-75	-75			-50			-50	-50		-75	-50					-75	-50		-75	-50			-75	-50
D(+50)	0		0			0	0			-25	0	0			0				0		-25	0			0	0	0		-25		0		0		-25	0			0		

Figure 1.1: Example of a score-card, representing for the original version of the IGT. Negative numbers present inside each box indicate the monetary amount of the penalty incurred when the card corresponding to that box was turned. Empty boxes correspond to cards associated with a monetary gain only. The boxes containing '0' are like the empty boxes, i.e. correspond to cards with gains, without penalties. (Adapted from Bechara et al., 2000b)

Human IGT	
Number of options	4 (decks)
Type of reward	monetary gain
Type of punishment	monetary loss
Immediate outcome uncertainty	present
Prior experience with contingencies	none
Task duration	100 trials
Loss variation (same-type options)	included
Immediate payoff A/D difference	difference: 50\$; factor of 2
Long-term payoff A/D difference	difference: 5000\$ every 100 trials

Table 1.1: Parameters and settings in the human version of the IGT.

card selections. Both the amount of rewards and penalties and the position of penalties within a deck vary with each deck, according to a schedule fixed by the experimenter but unknown to participants (see Figure 1.1 for an example). For deck A and B, selection of a card always yields \$100, while for deck C and D rewards are set to \$50. Selecting a card from deck A or B however also leads to higher punishments: for both decks, ten trials result in the accumulation of a \$1250 penalty, while for decks C and D the same amount of trials generates a cumulative penalty of \$250. A difference in punishment frequency and magnitude between decks is furthermore obtained by associating five in ten trials on deck A and C with a penalty respectively ranging from \$150 to \$350 and from \$25 to \$75, while pairing only one in ten trials on deck B and D with a respective penalty of \$1250 and \$250. In order to perform well in the long run, participants should therefore orient their choice towards decks C and D (the “advantageous” decks), which yield a net gain of \$250 per ten trials, instead of deck A and B (the “disadvantageous” decks), associated with a net loss of \$250 per ten trials (for a summary of the Git’s main characteristics, see Table 1.1).

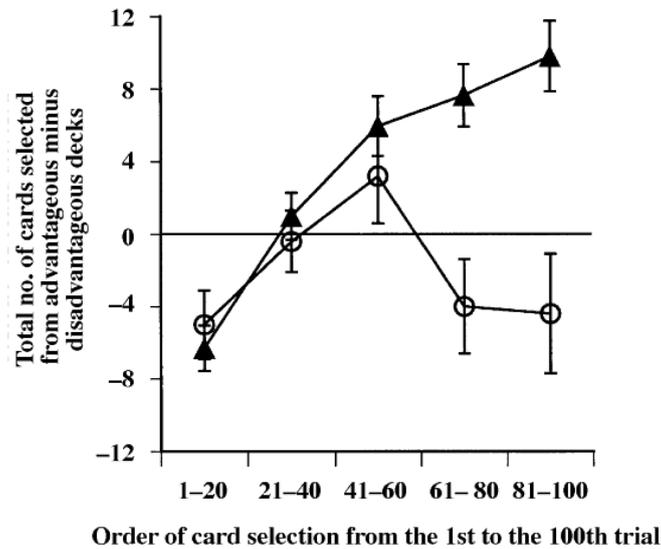


Figure 1.2: Pattern of card selection during the IGT, expressed as net scores of cards selected $((C + D) - (A + B))$; means \pm SEM) across blocks of 20 trials, in normal (filled triangles) and vmPFC-lesioned (open circles) subjects. After approximately two 20-trial blocks, a preference for advantageous decks starts to be exhibited by normal participants, while in vmPFC-lesioned selection of cards from disadvantageous decks persists even in late trials (adapted from Bechara, 2004).

In normal subjects, card selection throughout the whole test consistently demonstrates two phases, distinguishable by the pattern of choices between decks. In a first stage, individuals sample cards from all decks, repeatedly turning cards from the “disadvantageous” decks A and B, possibly because of the higher immediate monetary gains. As the task proceeds, however, participants gradually shift their choice towards the “advantageous” decks, and at the end of the task decks A and B are only occasionally selected again (Bechara et al., 1994, 1997, 1996, 1998, 2000b). In contrast, in patients with damage to ventromedial prefrontal cortex (vmPFC) / medial orbitofrontal cortex (mOFC) regions, there is no development of such preference, as subjects continue to choose cards from decks A and B frequently even during late trials. Furthermore, in these individuals disadvantageous card selections are performed regardless of explicit knowledge of the task contingencies (Bechara et al., 1994, 1999, 2000b, 2003; Bechara, 2004) (Figure 1.2). Thus, the IGT appears to capture elements of real, “hot” decision-making that are absent in common tests of executive functions.

1.1.1 What aspects of decision-making does the IGT investigate?

In contrast with other neuropsychological tasks assessing risky decision-making such as the Cambridge Gamble Task (CGT) (Rogers et al., 1999), the Game of Dice Task (GDT) (Brand et al., 2005) and the Cups task (Weller et al., 2007), in which participants have to select between options as-

sociated with explicit gain/loss probabilities, the IGT requires subjects to learn about the contingencies associated with each possible option as the task progresses. Therefore, researchers have proposed a distinction between decision-making processes during the first 20-40 trials of the IGT, in which choice outcomes are still highly unpredictable for participants, and the subsequent trial blocks, in which loss/gain probabilities have been figured out (either implicitly or explicitly) and riskier options can be identified in most normal individuals (Bowman et al., 2005; Maia and McClelland, 2004; Stoltenberg and Vandever, 2010). In particular, the first and last halves of the task have been related respectively to “decision under ambiguity” and “decision under risk” mechanisms (Bechara, 2004; Brand et al., 2006, 2007b). This theoretical subdivision has been given support by studies demonstrating an association between healthy subjects’ performance during late IGT trial blocks and that of the Cups task (Weller et al., 2010), of the GDT, and furthermore of tasks assessing executive functions, which are proposed to play an important role in decision-making on the basis of explicit task rules (Brand et al., 2007b).

The distinction between these two types of decision-making is an important one, as these processes have been related to different neural substrates and mechanisms (Brand et al., 2006, 2007b; Hsu et al., 2005). Decision under ambiguity has been proposed to rely on the function of the “limbic loop”, the fronto-striatal connection linking the limbic cortex (i.e. the mOFC and the anterior cingulate cortex (ACC)) to the ventral striatum and receiving inputs from the amygdala and the hippocampus (Alexander and Crutcher, 1990; Alexander et al., 1991; Groenewegen et al., 1997), while decision under risk has been associated to activity of both the limbic loop and the “cognitive loop”, which connects dorsolateral prefrontal cortical regions with the dorsal striatum (Alexander and Crutcher, 1990; Alexander et al., 1991; Groenewegen et al., 1997). The association of these distinct brain networks with their respective decision-making category also resonates with the shift in from an exploratory to an exploitative behavioural strategy observed in normal participants after the development of “hunches” (de Visser et al., 2010; van den Bos et al., 2006a). In order to gain more knowledge on each of the options included in the tasks and discover which is most advantageous, it is fundamental for participants to adopt a strategy that favours exploration of each deck in the first trials of the IGT. In these uncertain contexts, decision-making promoting exploratory actions has been hypothesized to involve the OFC (Doya, 2008), which, in concert with the amygdala and ventral striatum, appears to be crucial for learning, representing and monitoring the long-term value of multiple choice options which guide goal-directed behaviour (Bechara et al., 1999; Cardinal et al., 2002; de Visser et al., 2010; Kringelbach and Rolls, 2004). However, once subjects have gained sufficient experience in the task and are able to discriminate between decks with a lower or higher long-term payoff, it is best for them to stop exploring and start exploiting the options that have been identified as advantageous, regardless of the immediate penalties they might incur in. Under conditions of environmental predictability, decision-making oriented towards discarding immediate rewards for future high magnitude ones is thought to rely predominantly on the activity of the “cognitive loop”, which enables cognitive control over choice behaviour so that a long-term rewarding strategy can be maintained (Doya, 2008; Ernst

et al., 2002; McClure et al., 2004a; Ridderinkhof et al., 2004; Tanaka et al., 2004).

1.2 Neural substrates of decision making in the Iowa Gambling Task

1.2.1 Brain areas involved in IGT performance

1.2.1.1 Lesion studies

Following initial validation studies on vmPFC lesion patients, the IGT has been applied to the study of decision-making processes in presence of several other focal brain damages. These investigations have allowed researchers to identify brain structures essential for such processes in uncertain situations.

In addition to the vmPFC, an area that has been proved necessary for choosing advantageously in the course of the IGT is the amygdala. Focal damage to this region has been found to relate to worse performance in the IGT, and furthermore to a general insensitivity to emotionally-valenced stimuli, a finding consistent with the conceptualization of the IGT as a tool in assessing “hot” decision-making (Bechara et al., 1999, 2003; Brand et al., 2007b,a).

In contrast with lesions to the amygdala, damage to the dorsolateral prefrontal cortex (DLPFC), a brain region associated with working memory functions, in general has not been correlated with a disrupted IGT performance (Bechara, 2003; Bechara et al., 1998, 2000b, 2002; Fellows, 2004). Some studies however have reported decision-making impairments in the IGT also in subjects exhibiting lesions in this area (Clark et al., 2003; Fellows and Farah, 2005; Manes et al., 2002), possibly due to differences in patients’ selection (for example, studies performed by Bechara and colleagues mainly included lesioned subjects with evident decision-making problems in real-life situations, while Manes and colleagues excluded individuals with past or present psychiatric diagnoses) and extension of prefrontal damages (Buelow and Suhr, 2009). However, this data might also be explainable considering the potential role of the DLPFC during the “decision under risk” phase of the IGT (Brand et al., 2006, 2007b).

1.2.1.2 Neuroimaging studies

Findings from neuroimaging studies have in general confirmed results obtained from lesion patients. Both in healthy subjects and various patient populations, performance of the IGT has been consistently associated with frontal lobe activation, in particular at the level of the vmPFC/medial orbitofrontal cortex (mOFC) (Adinoff et al., 2003; Bolla et al., 2003; Ernst et al., 2002; Lawrence et al., 2009b; Li et al., 2010; Tucker et al., 2004; Windmann et al., 2006). In addition, several other brain areas, included those implicated in executive and working memory functions, have been found to be involved in decision-making during the IGT, suggesting a relative role of “cold”

decision-making processes in the task, which might be relevant during the “decision under risk” phase. For instance, investigation of brain activity by positron emission tomography (PET) during the task in healthy subjects (using a forced-selection IGT variant for control) has revealed mostly right-sided activation of, besides mOFC/vmPFC regions, the DLPFC, the anterior cingulate cortex (ACC), the anterior insula (IC), the parietal cortex (PC), the thalamus, and the cerebellum (Ernst et al., 2002). The same regions, and furthermore the posterior cingulate cortex (PCC) and the ventral striatum, have been found to be active during the IGT by a functional magnetic resonance imaging (fMRI) study, employing a control task with explicit card-associated win/losses and no differences in long-term payoff between decks (Li et al., 2010).

Moreover, performance in the IGT has been shown to be correlated to neural activation levels in various brain areas suggested to be essential for successful task completion by lesion studies. In abstinent cocaine users, better IGT performance has been associated with increased activity of the OFC (Bolla et al., 2003), and negatively correlated with perfusion in the anterior cingulate gyrus and the middle, medial, and superior frontal gyri, which are part of the DLPFC (Tucker et al., 2004). In healthy subjects, total net scores (number of advantageous minus disadvantageous cards selected) have been found to positively correlate with the magnitude of medial prefrontal, lateral orbitofrontal and insular regions’ activity, and additionally with activation of the pre-supplementary motor area and secondary somatosensory cortex, during the decision-making phase preceding the selection of a “risky” (disadvantageous) deck (Fukui et al., 2005; Lawrence et al., 2009b). Additionally, within normal participants lower than average IGT net score were shown to be paired with lower DLPFC’s oxygenation levels (Suhr and Hammers, 2010), again supporting the involvement of the “cognitive loop” in the IGT and the subdivision of the task according to how much is known, either implicitly or explicitly, of its contingencies.

1.2.2 Neurotransmitters’ modulation of IGT performance

1.2.2.1 Serotonin

Serotonergic neurotransmission is considered to be involved in the cognitive control of behaviour by prefrontal cortical areas (e.g the DLPFC) and the inhibition of impulsive behavioural responses (Daw et al., 2002; Doya, 2008; Soubrié, 1986; Winstanley et al., 2004). Thus, serotonin appears to be a candidate neurotransmitter in the regulation of choice behaviour during the IGT, especially in regards to late phases of the task, when behavioural control needs to be enforced in order to stop responding to high immediate rewards and pursue a long-run advantageous choice strategy. Indeed, several lines of evidence implicate functioning of the serotonergic system as a relevant modulatory factor of IGT decision-making. For instance, genetic studies have revealed that particular serotonin transporter polymorphisms are associated with IGT performance. In particular, increased choice of the disadvantageous options in the IGT (especially during the second half of the task) has been observed in healthy female subjects, major depression patients and obsessive-

compulsive disorder patients carrying the short allele of the serotonin transporter-linked polymorphic region (5-HTTLPR(s)) (da Rocha et al., 2008; He et al., 2010; Homberg et al., 2008; Must et al., 2007; Stoltenberg and Vandever, 2010; van den Bos et al., 2009), which has been associated with a lower gene expression and reuptake function of the serotonin transporter (SERT) (Greenberg et al., 1999; Heils et al., 1996; Lesch et al., 1996) and, importantly, with changes in activity of brain areas involved in decision-making during the IGT. For example, the short allele has been related to lower functional coupling of the amygdala and cingulate cortical areas (Pezawas et al., 2005; Roiser et al., 2009), higher functional coupling between the amygdala and vmPFC and insular cortex areas (Friedel et al., 2009; Heinz et al., 2005; Pezawas et al., 2005), higher amygdala activation in response to negative emotional stimuli (Bertolino et al., 2005; Canli et al., 2005; Furmark et al., 2004; Hariri et al., 2002a,b, 2005; Hariri and Holmes, 2006; Heinz et al., 2007; Smolka et al., 2007) and in resting conditions (Canli et al., 2006; Rao et al., 2007), and lower resting activity of the vmPFC (Rao et al., 2007).

Further studies on male volunteers have yielded conflicting results: while He et al. (2010) have reported worse IGT performances in the first half of the task (trials 1–40) for participants exhibiting an *s/s* genotype as compared to other allelic combinations, Stoltenberg and Vandever (2010) have found, in contrast, subjects presenting at least one *s* allele to perform better than participants homozygous for the long (*l*) allele, but only in the first 20 trials of the task. Overall, this data indicates that serotonergic signaling might be involved in IGT decision-making as supposed on the basis of its general central functions, although with possible gender-dependent effects particularly in the “decision under ambiguity” phase of the task. In addition to serotonin transporter polymorphisms, other gene variants related to serotonin function have been associated with deficits in decision-making during the IGT. The ACGCCG haplotype of the tryptophan hydroxylase (TPH)-1 gene, involved in serotonin synthesis, has been in fact recently reported to associate with lower IGT performance in female borderline personality disorder subjects (Maurex et al., 2009). Interestingly, 5HTTLPR-*s/s* genotypes and single nucleotide polymorphisms in the TPH-1 gene, along with polymorphisms in the serotonin-related TPH-2 and monoamine oxidase A (MAOA) genes, have also been associated with an inability to improve performance, based on contingency learning, in the course of the task (Jollant et al., 2007) (a finding consistent with a possible function of serotonin in impulse control).

Data in support of the modulation by serotonergic signaling of decision-making during the IGT comes additionally from studies investigating the effect of substances acting on the serotonin system. For example, acute oral administration of 5-hydroxytryptophan (5-HTP), a metabolic intermediate in the biosynthesis of serotonin from tryptophan, has been shown to produce impairments in IGT performance in the “decision under ambiguity” phase of the task (trial 1–20) in normal subjects (Gendle and Golding, 2010). In-depth analysis of choice behaviour in this trial block revealed that subjects exhibited a reduction in deck exploration coupled with a preference for the initially highly and frequently rewarding deck B, in accordance with the hypothesized role of serotonin in behavioural control and maintenance of exploitative responses during the IGT.

Furthermore, in OCD patients under therapy with serotonin reuptake inhibitors, chronic treatment with risperidone, an antipsychotic agent with type-2 serotonin (5-HT₂) receptors antagonist properties shown to dose-dependently increase extracellular concentrations of 5-HT in rat frontal cortex (Hertel et al., 1997), was found to improve overall IGT performance in a subgroup of individuals initially exhibiting worse performances (Cavedini et al., 2004b). On the other hand, chronic use of MDMA, which effects on the serotonergic system results in serotonin depletion at central level, has been found to correlate with lower final scores in a modified version of the IGT (in which cards represented exclusively a gain or a loss) compared to cannabis or no drug consumption conditions (Quednow et al., 2007). Thus, pharmacological data confirms the involvement of serotonin in promoting choice behaviours which might be immediately penalizing, but are rewarding in the long-run.

1.2.2.2 Dopamine

Midbrain dopamine neurons' activation and dopaminergic signaling at the level of the frontal cortex, amygdala and striatum are thought to play a role in processing of reward-related (and to some extent punishment-related) information, positive and negative reinforcement learning, signaling reward risk, encoding the incentive salience of stimuli, reward-dependent action selection, and high-order cognitive processes (although dopamine's causal involvement in many of these functions is still debated) (Berridge, 2007; Doya, 2008; Floresco and Magyar, 2006; Montague et al., 2004; Schultz, 2002, 2010; Salamone et al., 2007). In a decision-making framework, enhancing dopaminergic activity is considered to facilitate environmental exploration in conditions of uncertainty, by reinforcing risk-taking behaviours and enabling an individual to sustain response costs in anticipation of a possible high magnitude reward (Fiorillo et al., 2003; Floresco et al., 2008; Montague et al., 2004; van den Bos et al., 2006a). Dopaminergic signaling therefore is implicated in IGT decision-making processes, with a likely prominent role in the first phases of the task. Changes in functioning of the dopaminergic system have been in fact shown to modulate behaviour during the IGT by a variety of studies.

Genetic investigations have identified two factors involved in dopaminergic signaling mechanisms which variation can affect IGT performance, namely the catechol-O-methyltransferase (COMT) enzyme and the D4 dopamine receptor (DRD4). COMT has a fundamental role in the degradation of dopamine in the PFC following release (Karoum et al., 1994; Mazei et al., 2002; Tunbridge et al., 2004, 2006; Yavich et al., 2007). The rs4818 C/G polymorphism of the COMT gene, which results in an 18-fold divergence of enzymatic activity between the high activity variant (G allele) or low activity variant (C allele) (Nackley et al., 2006), has been shown to significantly affect performance in the IGT. In particular, male subjects homozygous for the G allele were found to select more cards from advantageous options compared to C allele carriers, although they showed less pre-planning in "cold" problem-solving tasks, suggesting that low prefrontal dopaminergic activity positively affects IGT performance (Roussos et al., 2008). Another COMT

gene polymorphism, Val158Met, has been furthermore associated with differences in decision-making during the IGT. In Met/Met genotype healthy female subjects, in which the corresponding COMT protein variant shows a decreased activity compared to its Val/Val counterpart, leading to constitutively higher dopamine prefrontal cortical levels (Chen et al., 2004; Lotta et al., 1995; Mannisto and Kaakkola, 1999), choice behaviour during the task was demonstrated to be more disadvantageous compared to that of Val/Val individuals. Furthermore, co-presence of Met/Met and 5-HTTLPR-s/s genotypes was related to a worse performance, compared to other possible combinations (van den Bos et al., 2009). Interestingly, it has been recently suggested that, compared to the COMT Val allele, the Met allele is associated to higher levels of exploratory decisions based upon the degree of uncertainty about whether choosing different options might yield better outcomes (Frank et al., 2009), indicating that prefrontal dopamine levels might be especially important in exploration under ambiguous conditions, and that a high PFC dopaminergic activity might produce impairments in the IGT through the enhancement of “directed explorative selection” of decks A and B, which present high magnitude rewards.

Polymorphisms in the variable number of tandem repeats (VNTR) region of the DRD4 gene, which encodes a D₂-like dopamine receptor highly expressed in human prefrontal and limbic brain regions (Meador-Woodruff et al., 1996; Mulcrone and Kerwin, 1997), have also been related to different patterns of choice behaviour in the IGT. Healthy male carriers of the seven repeats (7R) allele of this gene, associated with lower transcriptional/translational levels and diminished in vivo receptor responsivity compared to the four repeats (4R) allele (Brody et al., 2006; Ebstein, 2006; Hutchison et al., 2003, 2005; Hamarman et al., 2004; McGough et al., 2006), have been recently reported to choose significantly more cards from disadvantageous decks in the IGT, but to perform equally well in “cold” decision-making tasks, compared to participants presenting the 4R allele (Roussos et al., 2009). Additionally, the two repeats (2R) allele of the DRD4 gene, which responsiveness to dopamine (measured as the ability to inhibit intracellular cAMP formation upon receptor activation) is intermediate between the 7R and 4R variants (Asghari et al., 1995), has been shown to affect IGT performance in relation to 5-HTTLPR genotype. In homozygous carriers of this allele, an increase in disadvantageous choices compared to mainly homozygous 4R carriers was found in absence of the 5-HTTLPR-s/s genotype, but this effect was reversed in presence of the 5-HTTLPR-s/s genotype (Ha et al., 2009). In general, the effects of the 7R allele on IGT performance might be related to an increase in novelty-seeking (Ebstein, 2006; Ebstein et al., 1996), likely promoting exploration of decks in the task.

A more direct evidence regarding dopamine’s role in decision-making during the IGT has been provided by a study in which dopaminergic signaling was manipulated via acute administration of a branched-chain amino acids (BCAA) mixture, which has been demonstrated to lower the plasma ratio of dopamine’s precursor amino acids, and to increase prolactin levels in response to a decrease in dopaminergic activity (Harmer et al., 2001; Gijssman et al., 2002). Compared to placebo, healthy male participants to the IGT treated with the BCAA mixture were found to choose similarly to controls during the first part of the task, but to select more from disadvan-

tageous decks in late trials, which resulted in a worse overall performance in terms of amount of money accumulated. As prolactin levels were increased in those subjects, the authors suggested that this inability to change choice behaviour was related to a reduction in dopamine levels, thus indicating a fundamental function of dopaminergic signaling in advantageously guiding decision-making during the IGT in normal individuals (Sevy et al., 2006). In support of this hypothesis, dopamine release in the ventral striatum has been recently found to be associated with better IGT performance in healthy male participants (Linnet et al., 2010). These findings appear to be in contrast with those of Roussos et al. (2008) and van den Bos et al. (2009); however, it must be noted that COMT activity influences dopamine activity especially at the level of the PFC, while Sevy et al. (2006) manipulated overall central dopamine levels and Linnet et al. (2010) studied dopamine release specifically in subcortical structures. Moreover, analysis of the disadvantageous decision-making of COMT Met/Met revealed that subjects mainly paid a lower attention to losses than wins, a result consistent with reports of a lower efficiency in aversive stimuli processing in Met/Met individuals (Drabant et al., 2006; Jabbi et al., 2007; Smolka et al., 2005), while worse IGT performance upon BCAA treatment was related to a lowered attention to past outcomes distant in time compared to recent ones. Therefore, the dopamine-dependent effects on IGT decision-making analyzed in these studies likely refer to different neural substrates and mechanisms of action. The positive correlation found between IGT performance and dopamine release by Linnet et al. (2010) can be interpreted considering that phasic increases in midbrain neurons' dopamine release in the ventral striatum are believed to encode reward prediction error signals critical for stimulus-outcome association learning (Doya, 2008; Grace et al., 2007; McClure et al., 2004b; O'Doherty et al., 2004; Schultz and Dickinson, 2000; Schultz, 2010). On the other hand, results by Sevy et al. (2006) could be explained taking into account that tonic dopamine levels have been proposed to signal the net expected rate of rewards (net benefit expected per time unit) associated with a response option (Niv, 2007): since changes in peripheral amino acid availability have been shown to produce general reductions in central dopamine release (Le Masurier et al., 2005; Montgomery et al., 2003), BCAA administration could interfere with the representation of long-term expected reward values, forcing individuals to rely on more recent information for decision-making. Alternatively, since changes in behaviour were detected in the last phase of the task, disruption of such representations might have been produced by deficits in working memory (important in decision-making under risk) (Sevy et al., 2006).

1.3 Design factors affecting decision-making in the Iowa Gambling Task

Performance on the IGT is resistant to several variations in its design: for example, no differences in these terms have been found between a computerized version and the original paper-based task (Bechara et al., 2000b; Bowman et al., 2005), between the use of real and play money (Bow-

man and Turnbull, 2003) (but only if participants are informed of the presence of better and worse decks (Ferne and Tunney, 2006)), and between protocols that either include or exclude fixed time delays between trials (Bowman et al., 2005). However, interventions on rewards and punishments' frequencies, magnitudes or pattern of occurrence can all determine significant changes on choice behaviour during the IGT.

Modifying immediate reward magnitude differences between advantageous and disadvantageous decks can markedly influence IGT long-term performance. In a study in which immediate gains and losses were varied in decks A and B, but differences in long-term payoffs and punishments between options were kept as in the original IGT, it was found that raising the disadvantageous : advantageous ratio of rewards per selection from 2:1 to 4:1 or 6:1 resulted in a worse overall performance (based on the cumulative amount of money collected) and an increase in the number of disadvantageous decks' cards selected during the task, while decreasing this ratio to 1:1 produced an improvement in performance and a decrease in the number of disadvantageous decks' choices (van den Bos et al., 2006a). Thus, reward magnitude is a factor that can guide decision-making in the IGT towards riskier choices.

Not only magnitude, but also frequency of rewards against punishments can determine striking differences in terms of task outcome. For instance, several studies reported that, while normal subjects in the IGT gradually abandon the high-loss-frequency disadvantageous deck A as the task progresses, avoidance does not appear to develop as strongly for the low-loss-frequency deck B, which keeps being selected at rates comparable to those of the high-loss-frequency advantageous deck C (and sometimes of deck D) even in late trials, a phenomenon termed "prominent deck B" (Bark et al., 2005; Ferne and Tunney, 2006; MacPherson et al., 2002; O'Carroll and Papps, 2003; Toplak et al., 2005; Wilder et al., 1998). Interestingly, recent research employing a modified version of the IGT in which advantageous decks are associated with a high frequency of losses, while disadvantageous decks present losses with a lower frequency, revealed that, regardless of their worse overall payoff, disadvantageous decks were chosen more than their counterpart throughout the task (Chiu et al., 2008; Lin et al., 2009). In this version of the IGT, probability of encountering losses versus gains was quite high for the advantageous options (80% of the trials), indicating that an excessive risk of being punished and not being rewarded to advantageous options, in presence of frequently rewarding, rarely punishing options might impact behaviour in the task more than long-term outcomes.

Selection of options presenting a low frequency of losses in the original IGT might also be partly a product of the fixed reinforcement schedule employed by this task. The "prominent deck B" phenomenon, for example, could be partially dependent on the presentation of high magnitude punishments only after eight selections from this deck. In fact, such a delayed presentation of penalties in association to this option makes its choice rationally advantageous, at least at the beginning of the task (Dunn et al., 2006; Ferne and Tunney, 2008; Maia and McClelland, 2004). Since gains are always delivered with each card selection during testing, placement of losses within the reinforcement schedule might be crucial in determining participants' learning about

the task contingencies, and thus choice behaviour. This would explain why, for instance, altering presentation of penalties to provide earlier punishments in all decks results not only in the restoration to normal levels of vmPFC lesions patients' performance, but also in an earlier development of preference for advantageous decks in healthy controls (Fellows and Farah, 2005; Fernie and Tunney, 2008).

Chapter 2

Translating the Iowa Gambling Task protocol from humans to rodents

2.1 Existing animal models of the Iowa Gambling Task

Modelling decision-making under uncertainty in animals had been, and still is, a difficult-task for researchers: in humans, these processes comprise many variables, which complicates the development of both a human and animal experimental model (Madden et al., 2007), and some of the features present in current laboratory gambling paradigms for humans, such as the risk to incur in a final overall loss, seem almost impossible to reproduce in animals without compromising the model's validity (Zeeb et al., 2009). Nevertheless, there is a particular animal behaviour which demonstrates significant analogies to human behaviour in risky or ambiguous situations, and which has been the focus of scientific studies aimed at translating decision-making tasks from humans to common laboratory species (e.g. rodents): foraging. Decision-making in the context of natural foraging behaviour contains elements of risk and uncertainty, due to environmental variability; requires animals to evaluate immediate, but also long-term costs and benefits for each foraging option that might be available; consists of moments in which exploration is needed in order to familiarize with the resources offered by the environment, and identify which option to later exploit. Important parallels therefore might be made between the IGT in humans and tasks involving a choice between alternative food-reinforcement schedules.

2.1.1 IGT models developed for rats

2.1.1.1 The four-arm box maze model

The first experimental protocols aimed at reproducing the characteristics of the human IGT in rodents were proposed in a paper by van den Bos and colleagues in 2006 (van den Bos et al., 2006b).

The apparatus chosen for testing in this model is a box divided in three different areas: a starting zone, a choice zone, and an arena divided in 4 parallel arms (Figure 2.1). The goal arms, labeled A, B, C and D, are provided with internal visual cues (symbols of different shapes and colours) to help animals in differentiating them during the task, and contain “monetary rewards” or “monetary punishments” in the form of normal or quinine-treated (bitter) sugar pellets, respectively.

Before testing, animals are habituated to the taste of the sugar pellets and briefly allowed to explore the maze (10 minutes). During testing (10 trials a day for 12 days), the prearranged schedule of wins and losses associated to the decks in the IGT are represented by a fixed plan of distribution of sugar and quinine-pellets for each arm of the box. Like for the decks in the human IGT, two “disadvantageous” and two “advantageous” arms are present. In the former case, the chance of obtaining high immediate rewards combined with the incurrance of a net loss in the long term is reproduced by presenting three sugar pellets instead of quinine-treated pellets once every ten choices. In the latter case, the possibility of receiving low immediate rewards but having a net gain over multiple choices is replicated by administering one sugar pellet instead of quinine-treated pellets for eight in ten selections. The uncertainty of rewards and punishments per choice provided by the human task is maintained by varying, in the prefixed gain-penalty schedule, the sequence of sugar or quinine pellets presentation between blocks of ten trials in all the arms.

By setting the reinforcement schedule between arms in such manner, selection of only “advantageous” options during the test results therefore in a net long-term gain over the exclusive choice of “disadvantageous” arms of five pellets every ten trials, corresponding to a long-term payoff ratio between “advantageous” and “disadvantageous” arms of 2.67.

In the protocol assembled by van den Bos and colleagues, an additional variation of the experiment to control for aspecific effects of exploratory strategies differences between rat strains was also included: in this test, two goal arms were replaced by two empty arms, leaving only one “advantageous” and one “disadvantageous” long-term option.

Translations for the parameters and settings of the human IGT in this rodent IGT version are summarized in Table 2.1.

2.1.1.2 The five-hole operant chamber model

A novel gambling paradigm focused on reproducing in particular the ‘risk of loss’ feature of the human IGT was recently developed by Zeeb and colleagues (Zeeb et al., 2009). In this model, animals are introduced to a five-hole operant chamber, containing a curved wall with five available holes. Four out of five response hole, equipped with an infrared sensor each, can be illuminated by a stimulus-light located in the back of the wall and are connected to a single tray-light- and infrared-sensor-equipped food magazine, located opposite to the holes (Figure 2.2). During the task, gains are represented by the delivery of sucrose pellets, while losses correspond to a ‘time-out’ period, in which no reward can be obtained.

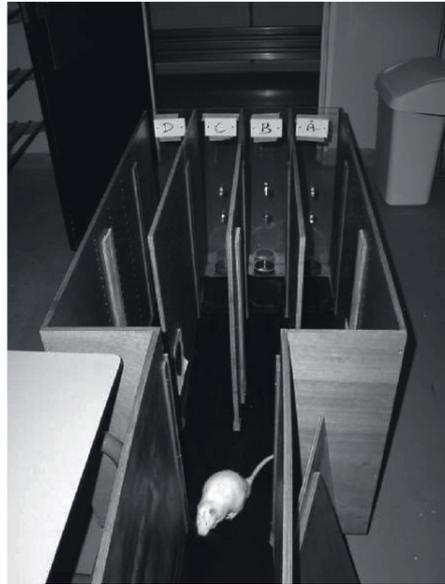


Figure 2.1: Apparatus used in the four-arm box maze IGT model for rats. (Adapted from van den Bos et al., 2006b.)

	Human IGT	Four-arm box maze rIGT
Number of options	4 (decks)	2-4 (arms)
Type of reward	monetary gain	sugar pellets
Type of punishment	monetary loss	quinine-treated sugar pellets
Immediate outcome uncertainty	present	present
Prior experience with contingencies	none	none
Task duration	100 trials	120 trials
Loss variation (same-type options)	included	not included
Immediate payoff A/D difference	difference: 50\$; factor of 2	difference: 2 pellets; factor of 3
Long-term payoff A/D difference	difference: 5000\$/100 trials	difference: 50 pellets/100 trials; ratio 2.67
Additional sessions required: experimental apparatus habituation (10 minutes).		

Table 2.1: Parameters and settings characterizing the four-arm box maze rodent version of the IGT (rIGT), in comparison with the human task. A: "advantageous" options; D: "disadvantageous" options.

As in other rodent models of the IGT, the experimental session is preceded by a habituation (two 30 minutes blocks, with sugar pellets placed in both the response holes and the food magazine) and a training session. Training is divided in two phases: first, animals are trained to perform nose-pokes in an illuminated response hole (varying between trials across holes 1, 2, 4, 5) within 10 seconds from light onset to obtain a sugar pellet. After five sessions (100 trials per session), animals are then trained on a forced-choice version of the gambling task for another seven sessions. During this second training phase, aimed at ensuring learning of nose-poke-reward contingencies for each response hole in all animals (a feature not present in the human IGT, in which participants are naive in this sense) and preventing the formation of biases towards a particular hole, once a trial is initiated by a nose-poke in the illuminated food magazine (an event that triggers the deactivation of the tray-light) one of the four response hole is illuminated following a 5-seconds inter-trial interval (ITI). A response to the indicated hole within 10 seconds corresponds to either the delivery of a reward, signaled by the activation of the tray-light, or the start of a timeout punishment period, signaled by flashing of the stimulus-light for its entire duration. A response to the food magazine after reward or punishment signaling initiates a new trial (tray-light activated). Failure to respond result in an omission, whereas premature responses are punished by a 5-seconds timeout (signaled by the illumination of the whole chamber). Following the completion of training, rats are subjected to the real gambling task, in which all the response holes (1, 2, 4, 5) are illuminated at the beginning of a trial, thus allowing the animals to choose where to direct their response (Figure 2.2). Testing sessions, lasting each 30 minutes, are performed daily until stable choice patterns are observed over three sessions.

In both forced-option training and the actual IGT task, two of the response holes are associated with small rewards and short, infrequent timeouts (P1: one pellet 90% of the trials + 5-seconds timeout 10% of the trials; P2: two pellets 80% of the trials + 10-seconds timeout 20% of the trials) the remaining two holes correspond to big rewards and long, frequent timeouts (P3: three pellets 50% of the trials + 30-seconds timeout 50% of the trials; P4: four pellets 40% of the trials + 40-seconds timeout 60% of the trials). Optimal performance within this paradigm is therefore achieved by choosing options with a small immediate amount of sugar pellets delivered (the “advantageous” P1 and P2 response holes), which however allow to accumulate an overall session reward amount superior to that obtainable by selecting high immediate reward options (the “disadvantageous” P3 and P4 response holes). Occurrence of gains and losses is determined pseudo-randomly, to ensure uncertainty of outcome for every selection.

According to the reinforcement schedule provided by this rodent IGT version, choosing “advantageous” options constantly during the test sessions would thus result in a maximal theoretical cumulative gain of 706 pellets, while selecting only “disadvantageous” holes would lead to a maximal theoretical cumulative gain of 234 pellets (maximum cumulative benefit ratio between “advantageous”/“disadvantageous” options = 3.02; calculations performed using minimal trial length (5 seconds)). However, it should be noted that, in this time-based design, the element of trial duration per individual rat plays a fundamental role in determining the actual magnitude of

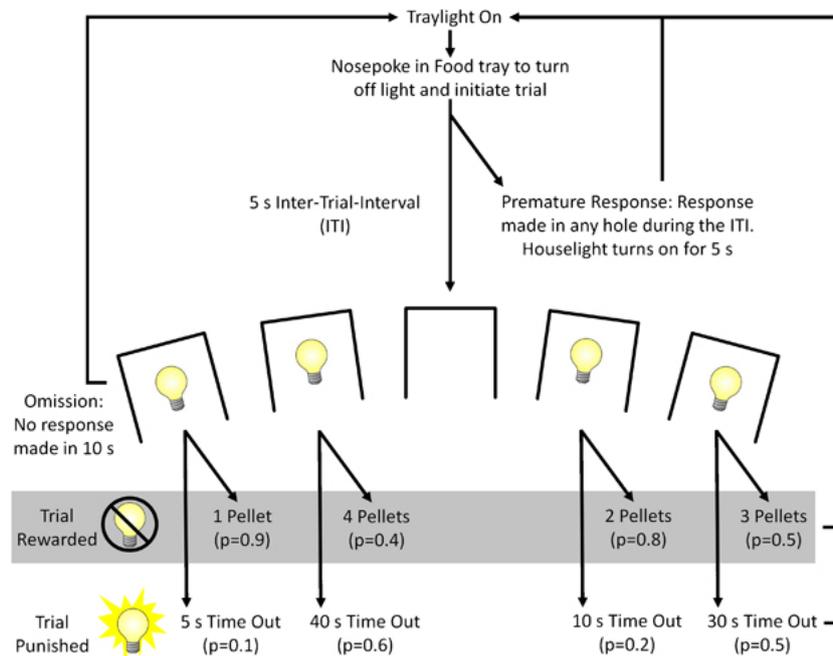


Figure 2.2: Schematic diagram of the five-hole operant chamber IGT task apparatus and design. Stimulus-lights are represented by light bulbs. Reinforcement/punishment schedules for each option are indicated in brackets by the probability of reward delivery or ‘timeout’ period onset. If the animal is rewarded, stimulus-lights are turned off, and the animal receives a choice-specific number of pellets in the re-illuminated food tray. If the animal is punished, all lights are turned off except for the stimulus-light in the chosen hole, which flashes for the duration of the timeout. A nose-poke at the level of the food tray (not shown in the picture) after a selection initiates a new trial. (Adapted from Zeeb et al., 2009.)

long-term payoffs associated with each option.

Translations for the parameters and settings of the human IGT in this rodent IGT task design are summarized in Table 2.2.

2.1.1.3 The four-hole operant chamber model

Recently, Rivalan and colleagues (Rivalan et al., 2009) proposed an alternative operant chamber-based rodent IGT design, which goal is to test complex decision-making processes involved in the human paradigm within a single session, as provided in the original IGT. As in the model of Zeeb and colleagues (Zeeb et al., 2009), the testing apparatus consists in an operant chamber adapted from the five-choice serial reaction time task (Robbins, 2002; Winstanley et al., 2003). In this version, however, a transparent vertical partition containing a central opening, from which each response hole is equally distanced, divides the chamber in half (Figure 2.3). Rewards are represented by the delivery of standard food pellets, while punishments are associated with ‘time-out’ periods, during which response holes are inactive. As in the original IGT, each selection is

	Human IGT	Five-hole operant chamber rIGT
Number of options	4 (decks)	4 (holes)
Type of reward	monetary gain	sugar pellets
Type of punishment	monetary loss	'timeout' periods
Immediate outcome uncertainty	present	present
Prior experience with contingencies	none	acquired during training and sessions required to achieve stable choice patterns (29 total 30 minutes sessions)
Task duration	100 trials	30 minutes
Loss variation (same-type options)	included	included
Immediate payoff A/D difference	difference: 50\$; factor of 2	difference: 2 pellets (average); factor of 2.33
Long-term payoff A/D difference	difference: 5000\$/100 trials	difference: 261 pellets/session (average); ratio 3.23
Additional sessions required: experimental apparatus habituation (2*30 minutes), operant conditioning training (5*100 trials).		

Table 2.2: Parameters and settings characterizing the five-hole operant chamber version of the IGT (rIGT), in comparison with the human task. A: "advantageous" options; D: "disadvantageous" options.

rewarded, and some are additionally punished.

Similarly to the other rodent models of the IGT, training for the acquisition of the basic operant responses is performed before the actual experimental phase. During these sessions (30 minutes each, repeated until 100 pellets are obtained within a session) animals are trained to associate two consecutive nose-pokes (ensuring voluntary choice performance) in one of the four illuminated holes with the delivery of one food pellet. A nose-poke-indicated selection results in food delivery combined with the deactivation of all stimulus-lights, except for that corresponding to the chosen hole, until the reward is collected. Once the learning criterion is reached, animals are also habituated to receive variable reward amounts (one/two pellets) per selection (two 15-minutes block per reward amount).

During the subsequent test session (1 hour of duration), animals are again requested to respond to one of the available options, but "advantageous" and "disadvantageous" selection schedules are now introduced. "Advantageous" options are represented by response holes associated with the immediate delivery of only one pellet, but also short timeout durations ("deck C": one pellet per selection + 12-seconds timeout 25% of the trials; "deck D": one pellet per selection + 6-seconds timeout 50% of the trials; same theoretical overall maximum gain). On the other hand, disadvantageous options correspond to response hole that provide always two pellets as a reward upon selection, but also long timeout durations ("deck A": two pellets per selection + 222-seconds timeout 50% of the trials; "deck B": two pellets per selection + 444-seconds timeout 25% of the trials; same theoretical overall maximum gain). Punishments are assigned to each selection in a pseudo-random manner, so to maintain immediate outcome unpredictability.

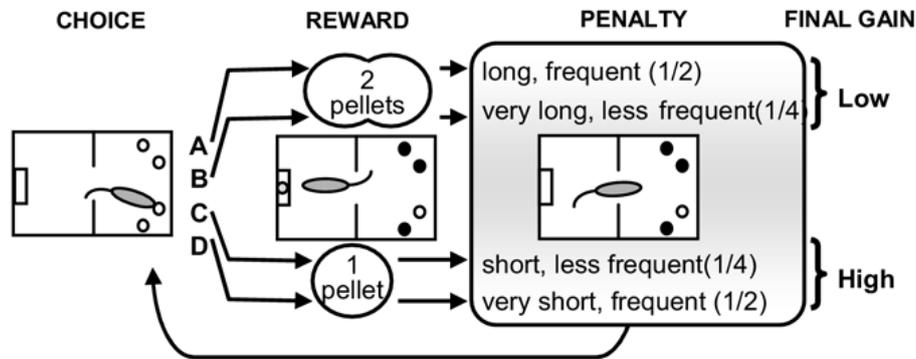


Figure 2.3: Schematic representation of the four-hole operant chamber IGT task apparatus and design. At the beginning of each trial, the animal can perform a choice over four active response holes (A, B, C, D, left scheme). Once a selection has been made, according to the hole selected a reward of variable magnitude is delivered (middle scheme), but a punishing timeout period could additionally occur (right scheme). Open circles in the right part of the chamber represent active, illuminated response holes; filled circles indicate inactive, non-illuminated holes (post-selection) (Adapted from Rivalan et al., 2009.)

	Human IGT	Four-hole operant chamber rIGT
Number of options	4 (decks)	4 (holes)
Type of reward	monetary gain	food pellets
Type of punishment	monetary loss	'timeout' periods
Immediate outcome uncertainty	present	present
Prior experience with contingencies	none	none
Task duration	100 trials	60 minutes
Loss variation (same-type options)	included	included
Immediate payoff A/D difference	difference: 50\$; factor of 2	difference: 1 pellet; factor of 2
Long-term payoff A/D difference	difference: 5000\$/100 trials	difference: 240 pellets/test; ratio 5.00
Additional sessions required: operant conditioning training (30 minutes/session, undefined session number), reward amount training (2*15 minutes).		

Table 2.3: Parameters and settings characterizing the four-hole operant chamber version of the IGT (rIGT), in comparison with the human task. A: "advantageous" options; D: "disadvantageous" options.

Based on the reinforcement schedule employed during testing, choosing either “advantageous” or “disadvantageous” options during this session would result to a theoretical overall payoff of 300 or 60 pellets per response hole, respectively (maximum benefit ratio “advantageous”/“disadvantageous” options = 5.00; theoretical payoffs calculated considering a standard trial duration of 9 seconds). As in the four-hole operant chamber design, individual trial duration represents however a variable influencing actual long-term outcomes associated with each response hole.

Translations for the parameters and settings of the human IGT in this rodent IGT variant are summarized in Table 2.3.

2.1.2 IGT models developed for mice

2.1.2.1 The eight-arm radial maze model

Van den Bos and colleagues (van den Bos et al., 2006b) adapted their rodent model of the IGT also for use in mice. The apparatus used in this case consists in an eight-arm radial maze; two of the arms are used as starting areas, while four are employed as goal arms (Figure 2.1). Again, to facilitate discrimination between different goal arms, discrete picture cues are provided at their entrance. Sweetened puffed wheat cereal pieces are used as rewards, while losses are represented by the same type of food items treated with quinine.

Like in the rat four-arm maze version of the IGT, testing is preceded by habituation to the taste of both penalties and rewards, and a 5 minutes session in which animals can explore the maze’s arms. During testing (15 trials a day for 9 days), mice can choose between two “advantageous” and two “disadvantageous” arms. “Advantageous” options correspond to goal arms in which, instead of quinine treated food, a small reward amount of 5-10 mg is encountered in eight out of ten visits. “Disadvantageous” arms, on the other hand, allow mice to obtain higher immediate rewards in the form of 20-30 mg of sugar cereal pieces, but only once every ten trials. Outcome uncertainty is provided by varying pseudo-randomly the position of rewards and punishments per choice every ten-trials-block.

Considering the aforementioned reinforcement schedule, the average long-term payoff associated with “advantageous” arms is of 60 mg of sweetened cereal pieces every ten trials, while for “disadvantageous” arms is of 25 mg of rewarding food pieces only, resulting in a payoff difference of 35 mg for each ten-trial-block (long-term payoff ratio between “advantageous” and “disadvantageous” arms = 2.4).

Translations for the parameters and settings of the human IGT in the mouse IGT version are summarized in Table 2.4.

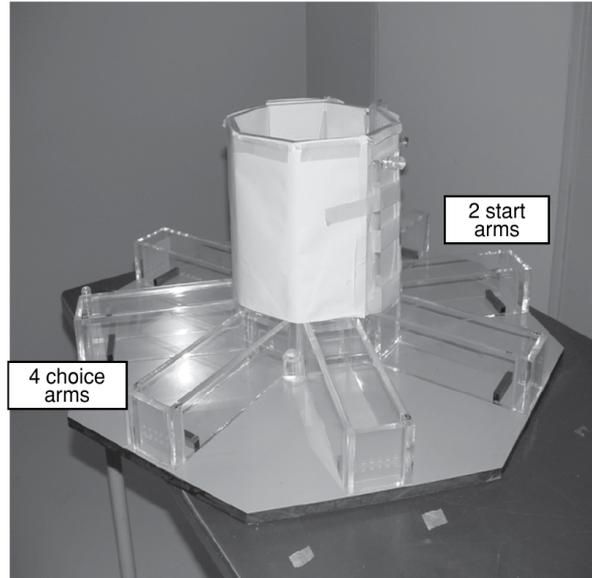


Figure 2.4: Apparatus employed in the eight-arm radial maze mouse version of the IGT. Two of the arms in the radial maze are utilized as starting chambers (order randomized across trials), while four arms opposite to those representing the start area correspond to goal arms. (Adapted from van den Bos et al., 2006b.)

	Human IGT	Eight-arm radial maze mIGT
Number of options	4 (decks)	4 (arms)
Type of reward	monetary gain	sweetened puffed wheat cereal pieces
Type of punishment	monetary loss	quinine-treated sweetened cereal pieces
Immediate outcome uncertainty	present	present
Prior experience with contingencies	none	none
Task duration	100 trials	135 trials
Loss variation (same-type options)	included	not included
Immediate payoff A/D difference	difference: 50\$; factor of 2	difference: 16.25 mg food (average); factor of 3.33
Long-term payoff A/D difference	difference: 5000\$/100 trials	difference: 350 mg food/100 trials; ratio 2.40
Additional sessions required: experimental apparatus habituation (5 minutes).		

Table 2.4: Parameters and settings characterizing the eight-arm radial maze mouse variant of the IGT (mIGT), in comparison with the human task. A: “advantageous” options; D: “disadvantageous” options.

Chapter 3

Comparing the Iowa Gambling Task in humans and animals

3.1 Setup characteristics

3.1.1 Type of rewards and punishments

In all the IGT translational protocols previously described, rewards are represented by food pellets. As discussed in earlier sections, food represents a valuable type of positive reinforcer for the development of animal models of risky decision-making, since foraging behaviour in uncertain environments and human behaviour in gambling tasks share several features. Moreover, utilizing food as a reinforcer presents some practical advantages in comparison to other types of rewards, such as the possibility of precise magnitude quantification, easiness in administration and low impact on general psychological / physical functions (in contrast with psychoactive drugs, such as amphetamine, which mimic the effects of primary reinforcers at central level but also produce major side effects, e.g. the emergence of hyperactivity). On the other hand, the incentive value of food reward depends on an animal's motivational state (hunger/satiety) (Cardinal et al., 2002): therefore, interpretation of choice behaviour in animal IGT models might be confounded by this highly uncontrollable factor. Although manipulation of the animals' drive for food through the employment of different pre-test food deprivation levels have been found to have no impact on decision-making for the four-hole operant chamber model (Rivalan et al., 2009), it cannot be completely excluded that this hypothesis could hold true for other rodent IGT versions.

In addition, it is important to note that in the human IGT a secondary positive reinforcer, money, is employed. The use of money during the task allows to materially experience both "wins" and "losses" of this specific reward every time a selection is made. The probability associated with each trial of incurring in financial penalties appears to be central for performance in the

IGT (Fernie and Tunney, 2008): for instance, a high frequency of losses can lead human subjects to discard decks that are advantageous in the long-term (Chiu et al., 2008; Lin et al., 2009). In contrast, the use of primary reinforcers such as food determines a fundamental difficulty in reproducing “losses”: rewards are instantly consumed, instead of accumulated, eliminating the possibility of an intervention aimed at decreasing the amount of reinforcer obtained during the course of the task. In order to deal with this issue, immediate punishment in the four-arm box maze / eight-arm radial maze models is accomplished through the administration of quinine-treated instead of normal food items while in the five-hole operant chamber and four-hole operant chamber models, punishments are represented by delays. In both cases, an actual decrease of a positive reinforcer is achieved, since choosing disadvantageous options has a negative impact on the total amount of food pellets actually consumable during the test. Nevertheless, employing unpalatable food or delays cannot reproduce an absolute resource deficit as a final outcome. Moreover, the use of time delays as immediate punishments might introduce several confounding factors in the task.

In the human IGT, a conflict between the possibility of obtaining high reward amounts in the long-term and that of gaining immediate gratifications is present between advantageous and disadvantageous decks, and in that sense participants demonstrating high levels of cognitive impulsivity, i.e. an inability to delay gratification, are expected to perform worse than low cognitive impulsivity individuals in the task (Bechara et al., 2000a). Indeed, an association between steeper discounting in a delay-discounting paradigm and a higher number of disadvantageous selections in the IGT has been reported in cocaine-dependent subjects (Monterosso et al., 2001). Employing long and short reward delays respectively as high and low magnitude punishments, in contrast, would aid individuals exhibiting high cognitive impulsivity in better performing during the IGT, since big losses (i.e. longer timeouts) in the task are associated with disadvantageous options. This possibility unfortunately has not been explored for either the four-hole or five-hole operant chamber models, and therefore remains an issue to be examined in further studies. In addition, combining the use of punishing delays with the imposition of a time-limit for task completion establishes an effective dependency of the long-term rewarding properties of each option on the response speed of the individual animal, therefore making motor performance and, in case of the five-hole operant chamber model (in which premature responses trigger a timeout period), motor impulsivity other likely confounding variables in these tasks. Furthermore, this setup complicates the interpretation of results for bad performers: since these animals would have actually completed less trials than good performers by the end of the task, their performance might just reflect a scarce experience with the task contingencies compared to other subjects.

3.1.2 Frequency of gains & losses

As discussed in section 1.3, gain/loss frequencies associated with each response option can be an important determinant of choice behaviour during the IGT (Chiu et al., 2008; Lin et al., 2009). Regarding this task variable in the rodent IGT models here examined, a number of discrepancies

with the original human task can be identified.

First of all, in the four-arms box maze / eight-arm radial maze and the five-hole operant chamber models, all available disadvantageous options are related to infrequent, high immediate rewards and frequent punishments (which in case of the five-hole operant chamber task are also of high magnitude), while all advantageous options are associated with frequent, although small, gains and infrequent losses. This establishes an important conceptual difference between the human IGT and these tasks: while in the original paradigm subjects are especially required to exert control over the tendency to respond to the frequently rewarding, initially advantageous deck B, in the two rodent models high losses frequencies might instantly drive choice behaviour away from disadvantageous options. Considering this divergence, as an ulterior consequence of the employment of such reinforcement schedules the investigation of the “prominent deck B” phenomenon, or of the potential role of reversal learning in the IGT (Dunn et al., 2006; Fellows and Farah, 2005; Maia and McClelland, 2004) might be limited.

Secondly, in the four-arms box maze / eight-arm radial maze model there is no difference in gain/loss frequency terms neither between the two advantageous or two disadvantageous options, while in the five-hole operant chamber this difference is present, but each option varies both in long-term payoff value, and in gain/loss schedule structure. Therefore, these two IGT model could be thought of respectively as simpler and more complex than the human task, a fact that potentially impairs the comparison of choice behaviour between humans and animals.

3.2 Face validity of the rodent IGT

3.2.1 Behavioural patterns in the human vs. rodent IGT

In the four-arms box maze and five-hole operant chamber rodent IGT models, animals appear to be able to learn which options are advantageous in the long term, and to adapt their choice behaviour consequently: results of the two tasks with Wistar and Long Evans rats in the first case, and Long Evans rats in the second case, demonstrated the development of a significant preference in choice, with advantageous options being selected in the last trials more than 70% of the times (van den Bos et al., 2006b; Zeeb et al., 2009) (Figure 3.1, 3.2). Similar data were obtained in C57BL/6 mice employing the eight-arm radial maze model, confirming the face validity of this mouse IGT version (van den Bos et al., 2006b). The results obtained with Wistar Han rats on the basis of the four-hole operant chamber model also suggested effective learning of contingencies and a gradual development of choice preference for advantageous options, but this behavioural change was not found to be significant (Rivalan et al., 2009) (Figure 3.3). This was due to the fact that about 40% of the animals failed the task, either because they did not develop any option preference, or because they developed a significant preference for disadvantageous options. Although failure of the IGT by a portion of participants has also been observed in healthy humans, usually this subset of individuals corresponds only to a 20-30% of subjects (Bechara et al.,

2000a; Bechara and Damasio, 2002; Crone et al., 2004). In this particular experimental protocol, which tests behaviour in a single session of 60 minutes, animals might not be able to familiarize sufficiently with all the response-associated contingencies, especially considering that choosing disadvantageous options (which characterizes the beginning of the task, when exploration of options occurs) is related to the potential onset of timeouts spanning several minutes: in short, under this experimental design, a 60 minutes test might represent only the “decision under ambiguity”, exploratory phase of the human IGT task. Since a consistent subgroup of animals in this paradigm developed a clear preference for disadvantageous options by the end of the task, arguing against the impossibility to learn an association between disadvantageous option’s responses and outcomes due to long timeouts as a factor modulating choice behaviour, better face validity of this model could be achieved simply by implementing longer task durations. However, failure to develop a clear advantageous behavioural pattern might also be due to the fact that punishments are not enough effective within the task framework. In the four-hole operant chamber, each trial is rewarded, and can probabilistically involve a timeout penalty: there is no danger to perform a choice and subsequently obtain no food pellets. The perception of reward delays as punishments therefore depends majorly on the animals’ knowledge that the task will be limited in time to a specific duration. Since rats never perform the actual gambling task before testing, and that test sessions have a different duration in respect to operant response acquisition sessions, reward delays might not be correctly evaluated during decision-making in this IGT version.

It is important to note that rodent behavioural patterns observed in the five-hole operant chamber IGT version are also not completely comparable with human learning curves in the IGT: preference for advantageous option is already present in the initial task sessions, and remains quite constant as testing proceeds. In this experimental design, in fact, learning of options’ contingencies in this rodent IGT model is likely obtained before the actual decision-making test, by systematically exposing animals to the task contingencies during forced-choice training sessions (Zeeb et al., 2009). Thus, only the “decision under risk” phase of the human IGT is represented by this model. In this case, validity criteria could be met by including the contingency-training sessions in the actual IGT task.

3.3 Predictive/construct validity of the rodent IGT

3.3.1 Effects of individual traits

The relationship between individual differences and IGT performance has been investigated in the case the four-hole operant chamber rodent task model (Rivalan et al., 2009). In particular, an association between risk taking, reward sensitivity and IGT performance was demonstrated in male Wistar Han rats. When compared to a subgroup of good decision makers in the IGT, i.e. rats that developed a strong preference for long-term advantageous choices as the task progressed, a subset of animals performing poorly during the IGT was also found to be more sensitive to

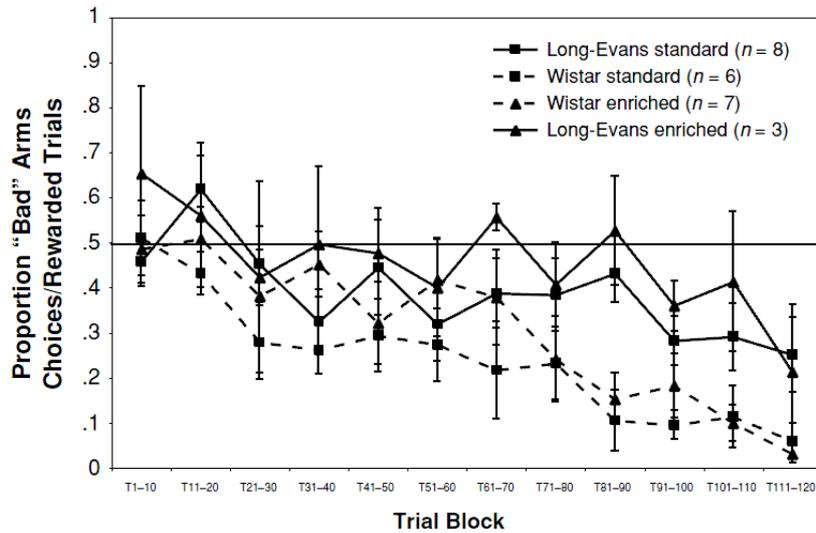


Figure 3.1: Proportions of choices for the disadvantageous arms per block of 10 goal arm choices (mean ± SEM) of Wistar and Long-Evans male rats, housed under either standard or enriched (i.e., with a shelter and gnawing sticks in the homepage) conditions, in the four-arm box maze IGT model. In all groups, selection of disadvantageous options gradually decreases with trials, with a more marked reduction for Wistar rats' groups. (Adapted from van den Bos et al., 2006b.)

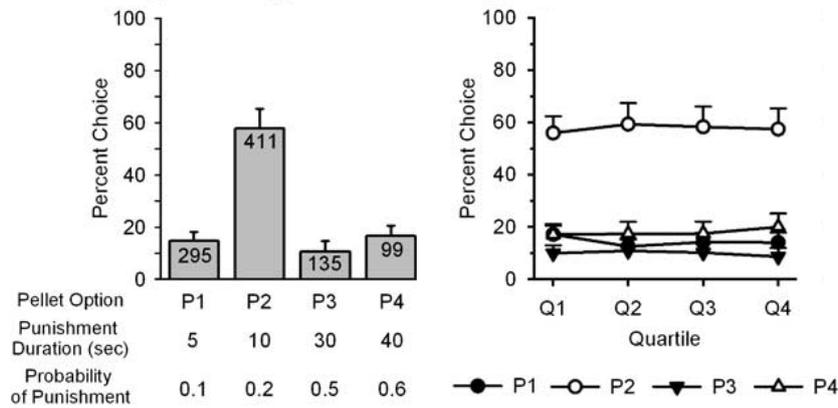


Figure 3.2: Percent choices for the four options (mean + SEM) of Long-Evans rats in the five-hole operant chamber rodent IGT model. Left panel: animals show a significant preference for the two-pellet option, associated with a modest gain but also smaller and less frequent punishments. The punishment duration (in seconds) and punishment probability associated with each option are indicated below the x-axis. Numbers located inside each bar represent the total number of pellets theoretically obtainable if the corresponding option is exclusively chosen in a 30-minutes test; this variable is calculated using the absolute minimum trial length (5 seconds). Right panel: choice behaviour analyzed during the task across different session quartiles (each 25% of trials) reveals the constant presence of a preference for the two-pellet option throughout testing. (Adapted from Zeeb et al., 2009.)

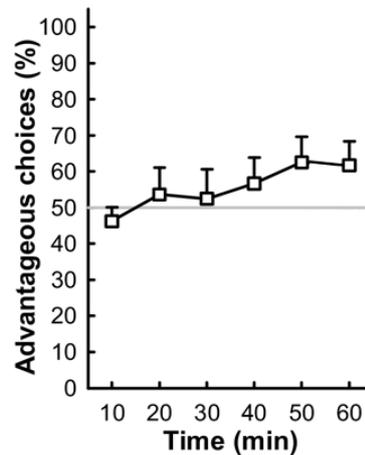


Figure 3.3: Percentage of advantageous choices over total number of selections (mean + SEM) of Wistar Han rats in the four-hole operant chamber IGT rodent model. Overall, no significant preference can be observed per option, although a trend towards an increase in advantageous options' selection is noticeable. (Adapted from Rivalan et al., 2009.)

rewards, as they ran faster to obtain a food reward in a runaway paradigm (Crespi, 1942) and sustained higher amounts of effort to earn food in the context of a progressive ratio schedule of food reinforcement (Hodos, 1961). Moreover, these individuals were found to be more risk-prone, exposing themselves more frequently to potentially dangerous environments in the light/dark emergence test (Dellu et al., 1993) and in the elevated plus-maze test (Cruz et al., 1994). This data is consistent with both findings from human studies employing healthy participants, which have shown that poor IGT performers also exhibit riskier choice patterns in two tasks assessing decision-making under risk, the GDT (Brand et al., 2007b) and the Cups task (Weller et al., 2010) (see section 1.1.1), and the observation that in clinical populations exhibiting poor decision-making reward hypersensitivity appears to underlie deficits in IGT performance (Kobayakawa et al., 2010; Must et al., 2006). Thus, this model seems to satisfy predictive and construct validity criteria.

3.3.2 Modulation of serotonergic signaling

Data regarding the effects of serotonergic signaling modulation on performance of rodent IGT models is available for the four-arm box maze and five-hole operant chamber versions of the task. In both cases, interventions have supported the validity of the experimental paradigms designed.

In the case of the four-arm box maze model, performance of the rodent IGT was analyzed in either homozygous or heterozygous SERT knockout female rats, and in parallel with IGT performance of human carriers of the 5-HTTLPR s or l allele (Homberg et al., 2008). SERT^{-/-} and SERT^{+/-} rats demonstrated more advantageous decision-making compared to SERT^{+/+} animals

particularly in the second half of the trials (Figure 3.4), a result seemingly in contrast with human data, which showed that *s/s* genotype individuals, in which SERT gene expression and protein function is reduced, performed worse during the task (da Rocha et al., 2008; He et al., 2010; Homberg et al., 2008; Must et al., 2007; van den Bos et al., 2009). However, findings from SPECT imaging research have indicated the presence of a significantly greater SERT availability in individuals homozygous for the *s* versus the *l* allele (van Dyck et al., 2004). Moreover, a recent PET study, controlling for potential confounding effects of combining two variants of the *l* allele (one of which is associated with phenotypical characteristics comparable to those of the *s* allele) into a single *l/l* genotype group, showed that 5-HT_{1A} autoreceptor binding potential in prefrontal and limbic cortical areas is specifically increased in female subjects carrying the *s* allele, which could reflect a compensatory greater 5-HT_{1A} receptor density or a lower extracellular concentration of 5-HT in response to a slight decrease in reuptake (Lothe et al., 2009). Therefore, 5-HTTLPR-*s/s* female individuals are likely more like comparable to SERT+/+ female animals in terms of serotonergic functioning.

Considering the five-hole operant chamber model, rodent IGT performance in male Long-Evans rats was analyzed after intraperitoneal administration of either a 5-HT_{1A} autoreceptor agonist (8-OH-DPAT) alone or in combination with a 5-HT_{1A} antagonist (WAY100635) (Zeeb et al., 2009). 8-OH-DPAT was found to impair performance, resulting in animals decreasing choice of the best option available (P2) in favour of less advantageous ones (P1, P3) (Figure 3.5), and these effects were effectively blocked by co-treatment with WAY100635. Taking into account the previously mentioned evidence suggesting a decreased 5-HT efflux in prefrontal cortical and limbic areas of subjects presenting a 5-HTTLPR-*s/s* genotype, this finding is in line with most of the human data, which indicates a relation between lower central extracellular 5-HT, either hypothesized on genetic basis (da Rocha et al., 2008; He et al., 2010; Homberg et al., 2008; Must et al., 2007; van den Bos et al., 2009) or achieved through pharmacological intervention (Cavedini et al., 2004b; Quednow et al., 2007), and lower performance in the IGT.

In synthesis, in both the models described, findings related to the modulation of serotonergic signaling by genetic or pharmacological intervention reproduced successfully results obtained in humans, supporting the predictive validity of these tasks. Moreover, considering the hypothesized roles of serotonin in the control of behaviour and in decision-making processes involved in IGT performance (see section 1.2.2), these data indicate satisfactory construct validity for both experimental protocols hereby analyzed.

3.3.3 Modulation of dopaminergic signaling

Data on the effects of dopaminergic signaling manipulations on choice behaviour in rodent IGT models has been obtained for the five-hole operant chamber protocol (Zeeb et al., 2009). Employing this experimental design with male Long-Evans rats as subjects, acute administration of d-amphetamine (leading to an increase in extracellular dopamine concentrations in the PFC

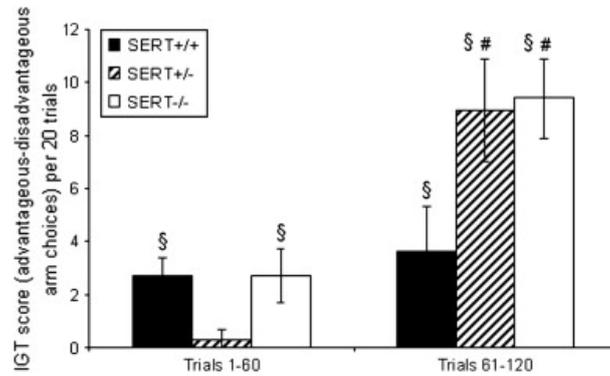


Figure 3.4: Comparison of SERT^{-/-}, and SERT^{+/-}, SERT^{+/+} female rats' IGT net scores (advantageous - disadvantageous selections; mean ± SEM) over the first phase (trials 1–60) and the second phase (trials 61–120) of the four-arm box maze IGT model. § Significant difference (p<0.05) from a zero IGT score; # significant score improvement (p<0.05) from trials 1–60 to trials 61–120. (Adapted from Homberg et al., 2008.)

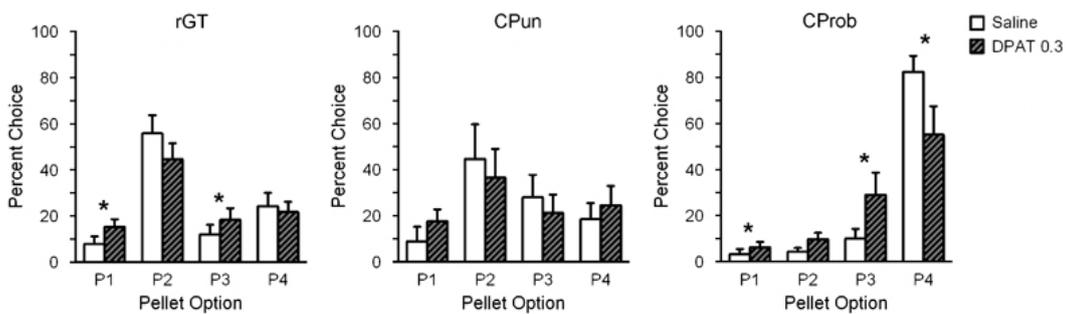


Figure 3.5: Effect of serotonergic signaling modulation by 8-OH-DPAT administration (0.3 mg/kg) on percent choices for the four options (mean + SEM) in the five-hole operant chamber IGT model (rGT), in a first task variant employing fixed punishing timeouts (10 seconds) across options (CPun) and in a second task variant employing fixed punishment probabilities (20% of selections) across options (CProb). * Significant difference (p<0.05) in a drug vs. vehicle paired samples t-test. (Adapted from Zeeb et al., 2009.)

and striatal regions, such as the nucleus accumbens (Butcher et al., 1988; Carboni et al., 1989; Hamilton et al., 2000; Kankaanpaa et al., 1998; Kuczenski and Segal, 1997; Maisonneuve et al., 1990; Parker and Cubeddu, 1986; Pontieri et al., 1995; Sharp et al., 1987; Shoblock et al., 2003; Zetterstrom et al., 1983)), was found to result in a worse task performance as, compared to saline-treated animals, d-amphetamine-treated animals shifted their choice from the most advantageous P2 option to the more frequently but less rewarded P1 option, an effect that was related to an increase in probability- and delay- discounting (as measured by task variants employing respectively constant delay durations and constant punishment probabilities between options) (Figure 3.6a). However, D₁ and D₂/D₃ receptor agonists (SKF 81297 and quinpirole, bromocriptine) failed to modify choice behaviour in the rodent IGT. On the other hand, the D₂ receptor antagonist eticlopride was found to significantly improve animals' performance in the IGT by decreasing selections of P3 and P4 options in favour of P2 without affecting probability- or delay-discounting rates (Figure 3.6b), but only at a low dose (0.01 mg/kg), while the D₁ receptor antagonist SCH23390 did not affect behaviour during the task.

Overall, these results present some similarities, but also some discrepancies, with human findings. As previously discussed, in human decision-making under ambiguity a higher prefrontal dopamine level correlates with a worse IGT performance: thus, D-amphetamine data appears to fit well with human results. However, it should be noted that high PFC dopamine levels are proposed to enhance exploration in the direction of alternative options that might yield higher gains; still, the five-hole operant chamber task animals probably represents mostly the "decision under risk" phase of the IGT, in which enhancement of dopamine transmission might play a different role. Additionally, based on choice behaviour in the probability- and delay-discounting tasks, the response shift observed in the rodent IGT was explained by the study authors to likely relate to an amphetamine-dependent increase in the ability of aversive stimuli to control behavior, which contrasts with the finding that COMT Met/Met individuals appear to have an attentional imbalance in favour of rewards (van den Bos et al., 2009). In any case, divergences between human and animal data in this case might be explained by differences in terms of length of exposure (lifelong vs. acute) to and neural substrates affected (PFC vs. cortical and limbic areas) by the considered modifications in dopamine transmission.

In contrast with amphetamine administration, dopamine receptor antagonists treatment does not seem to produce changes in rodents' choice behaviour comparable with those reported in human subjects. While cerebral dopamine depletion by BCAA administration has been shown to produce deficits in human IGT performance especially in the "decision under risk" phase of the task, blockage of dopamine transmission in the five-hole operant chamber was found to either have no effects on decision-making or even determine a performance improvement. In the latter case, however, predictive validity of the model could be supported since D₂ receptor antagonists, through the block of inhibitory autoreceptors, can actually stimulate dopaminergic neurons' firing (and thus enable the production of strong prediction error signals) (Zeeb et al., 2009).

In conclusion, the five-hole operant chamber model seems to partially meet both predictive

and construct validity criteria; nevertheless, it must be emphasized that current knowledge on the role of dopamine in the IGT, but also in general in decision making, does not allow yet to formulate clear evaluations in regard to these types of validity. More research will be therefore needed in humans to fully understand the feasibility of this animal IGT version.

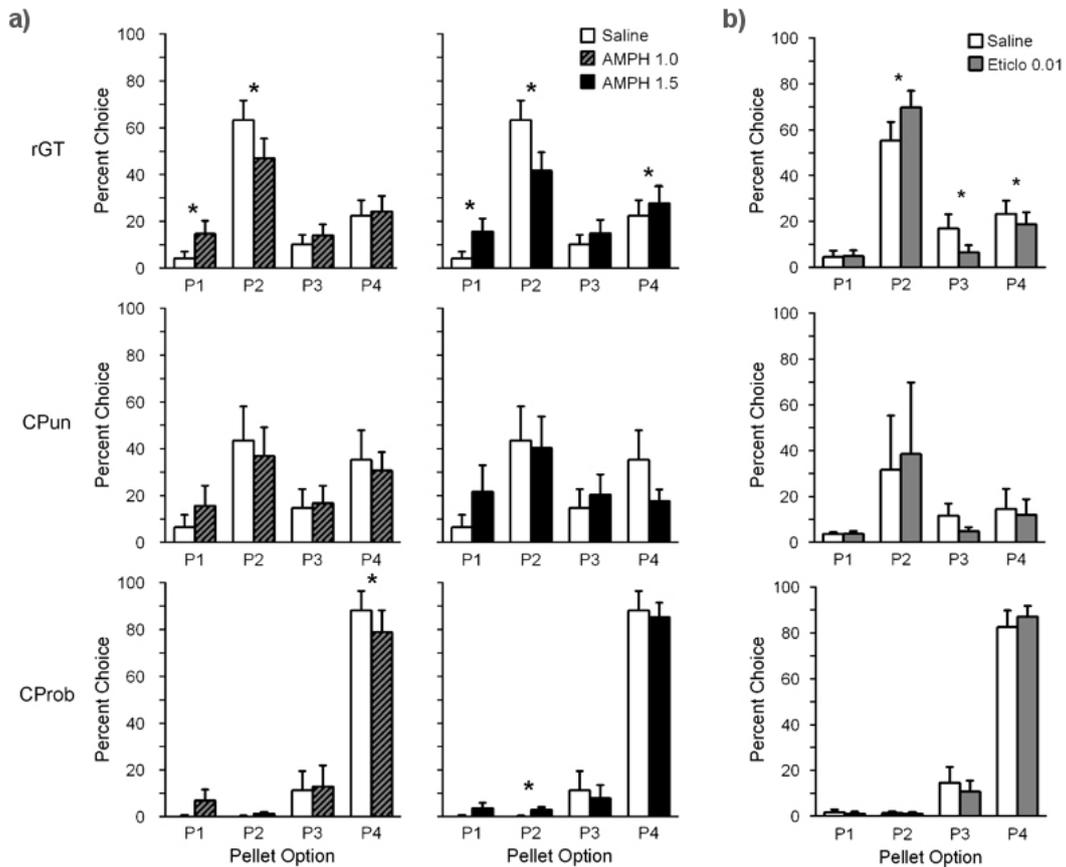


Figure 3.6: Effect of dopaminergic signaling modulation on percent choices for the four options (mean + SEM) in the five-hole operant chamber IGT model (rGT), in a first task variant employing fixed punishing timeouts (10 seconds) across options (CPun) and in a second task variant employing fixed punishment probabilities (20% of selections) across options (CProb). (a) Effects of d-amphetamine administration (1.0 and 1.5 mg/kg) on choice behaviour in the three task setups; (b) Effects of eticlopride administration (0.01 mg/kg) on choice behaviour in the three task setups. * Significant difference ($p < 0.05$) in a drug vs. vehicle paired samples t-test. (Adapted from Zeeb et al., 2009.)

Conclusion: toward a rodent model of the Iowa Gambling Task

Based on the small amount of data currently available, the existing animal IGT models appear for the most part to satisfy face, predictive and construct validity criteria, which are classically proposed to be essential in the evaluation of an animal model's feasibility in psychiatric research (Belzung and Griebel, 2001; McKinney and Bunney, 1969; Willner et al., 1992). However, it must be noted that construct and predictive validity haven't been tested to a full extent in none of the models here presented: for instance, no pharmacological data is available in case of the four-arm maze box and the four-hole operant chamber IGT models. Crucially, no rodent IGT version has been so far tested in presence of brain lesions which have been found to compromise human task performance, yet this type of data would be the most reliable in order to assess construct validity. The dependency of IGT performance on the function of brain structures such as the OFC in the task has been substantiated by several lesion and neuroimaging studies (see section 1.2.1). In contrast, the roles of dopamine and serotonin in IGT performance, on which this validity has been evaluated for the four-arm maze box and the five-hole operant chamber, are still poorly understood: not many human studies have focused on directly manipulating these neurotransmitters (for example through pharmacological intervention), thus most of what is currently hypothesized concerning their function in the task is based on correlational data (a consideration applicable also to individual traits analyzed by Rivalan et al. (2009)); in addition, as seen in case of dopamine, findings from different studies often appear to be discordant. More research will be therefore needed in both humans and animals to effectively estimate the general validity of current animal IGT models.

Considerations on the use of rodents in decision-making models

In the early study by van den Bos and colleagues (van den Bos et al., 2006b), relevant differences were observed between strains in terms of behavioural strategies and level of performance in the four-arms box maze IGT model. This suggests that decision-making processes differ between strain, in accordance to the particular cognitive and behavioural traits associated with each of

them. Therefore, the discussion of rodent IGT versions' results should always take into account the analysis of characteristics such as baseline anxiety levels (de Visser et al., 2010), baseline exploratory behavioural strategies, learning capabilities, sensitivity to risk and rewards/punishments of each strain employed which might significantly influence task performance. In that sense, the control tests proposed in studies by Zeeb et al. (2009) and Rivalan et al. (2009), and the introduction of empty arms provided by the four-arms box maze model are both useful tools that might all be included in a comprehensive rodent IGT model.

Future directions

The most prominent issue presented by current IGT animal models is probably the use of rewards and punishments which fail to accurately reproduce the monetary gains and losses provided in the original human task. In order to overcome this obstacle in terms of validity, one possibility that might be considered in future studies is the use, during testing, of token reinforcers which animals have been in precedence trained to exchange for food (or other primary reinforcers). Token reinforcement procedures have been previously experimented in rats with positive results (Boakes et al., 1978; Hackenberg, 2009; Madden et al., 2007; Malagodi et al., 1975), but whether these animals would be motivated to work for these "currencies" in the ambiguous conditions of the IGT, and could discriminate between advantageous/disadvantageous options based on the amount of tokens gained or lost with each task trial remains to be investigated.

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