KINDLING, DRUGS AND DECISION-MAKING: AN EXPLORATION OF THE EFFECT OF ANTICONVULSANT DRUGS AND PROVOKED SEIZURES ON A RAT GAMBLING TASK

by

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Abstract

Impulsivity is a major component of mania in bipolar disorder, and patients also show impairments in decision-making involving risk on the Iowa Gambling Task (IGT). Similar deficits are also observed in some patients with temporal lobe epilepsy (TLE), in which seizures originate in the amygdala and hippocampal formations, and incidence of pathological gambling is higher in both these populations. Anticonvulsant drugs are widely used in the treatment of epilepsy, but also as mood stabilizers and prophylaxis for the management of bipolar disorder. Unfortunately, little is still known about the precise mechanisms of action underlying their efficacy, and the specific behavioural aspect targeted by these drugs. Patients with damage to the basolateral amygdala (BLA) also show deficits in decision-making, and rats with BLA lesions have shown such deficits in a variety of behavioural tasks. Few studies have looked at the effect of BLA stimulation on risky decision-making. This project first aimed at exploring the effect of the three anticonvulsant drugs currently also used as mood stabilisers- carbamazepine, valproate and lamotrigine- on aspects of decision-making using a rat analogue of the IGT, the rat Gambling Task (rGT). We then investigated the effect of kindling of the BLA on this task, with the aim of antagonizing any behavioural effects with the anticonvulsant drugs. Thirty-two rats in total learned the rGT. Sixteen rats were used in the pharmacology study, and 16 were implanted unilaterally with a bipolar electrode into the BLA and stimulated twice daily until kindling had been established i.e. three class five seizures were observed. Carbamazepine appeared to slow processing speed, decreased premature responses and also blocked the pro-impulsive effect of amphetamine. Kindling increased choice of the small, but immediate reward option P1 and also increased premature responses. However, none of the changes observed were permanent and therefore, we could not assess the effect of carbamazepine on blocking the effect of kindling.

Further studies looking at chronic administration of anticonvulsants, and the effect of kindling on acquisition of the rGT, would help us understand the neurobiological mechanisms underlying vulnerability to impairments in decision-making under uncertainty associated with TLE and other psychiatric disorders.

Preface

This dissertation is an original intellectual product of the author, Melanie Tremblay and Dr. Catharine Winstanley. The electrode implantation surgeries in section 2.6 were performed by the author and Dr. Wendy Adams. All procedures were in accordance with the Canadian Council on Animal Care and the University of British Columbia Animal Care Committee (ACC) and were covered by the ACC protocol number A08-0519. All other procedures in both experiments included in this thesis were performed by the author. The studies and text included in this thesis were not published at the time of submission.

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List of Abbreviations

5CSRT	5 Choice Serial Reaction Time Task
5-HT	5-hydroxytryptamine
A	adenosine receptor
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
Amph	amphetamine
ANOVA	analysis of variance
AP	anterior-posterior
BD	bipolar disorder
BLA	basolateral amygdala
Ca^{2+}	calcium
CBZ	carbamazepine
CeA	central nucleus of the amygdala
CO_2	carbon dioxyde
D	dopamine receptor
DA	dopamine neurotransmitter
DOI	(+/-) -1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane
DV	dorsoventral
EPSP	excitatory post-synaptic potential
EEG	electroencephalogram
g	gram
GABA	gamma-aminobutyric acid
HDAC	histone deacetylase

Hz	hertz
IGT	Iowa Gambling Task
IP	intraperitoneal route
IQ	intelligence quotient
ITI	intertrial interval
LMG	lamotrigine
MES	maximal electroshock seizure
µm	micrometer
mg	milligram
mg/kg	milligram per kilogram
min	minute
ML	medial-lateral
mPFC	medial prefrontal cortex
ms	millisecond
N, T, P/Q, R –types	Neural, Transient, Purkinje, Residual –type calcium channel
Na^+	sodium
NAc	nucleus accumbens
NMDA	N-methyl-D-aspartate
K^+	potassium
OFC	orbitofrontal cortex
P(1-4)	pellet option 1 to 4
PFC	prefrontal cortex
PTZ	pentylenetetrazol

rGT	rat Gambling Task
Sal	saline solution
SAS	sustained amygdala stimulation
sec	second
SEM	standard error of the mean
Stim	stimulation
TLE	temporal lobe epilepsy
VPA	valproate

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Dedication

To my sister.

Sandra, I miss you every day. I love you more than you can imagine.

Life would not be the same if I did not have a twin sister.

1. Introduction

1.1 Impulsivity in neurological disorders

Impulsivity and impairments in decision-making have been observed in many psychiatric and neurological disorders. Cognitive deficits have been widely documented in both bipolar disorder (BD) and epileptic patients, especially in those with focal seizures originating in the temporal lobe. For example, some patients with temporal lobe epilepsy (TLE), mostly those with lower IQ, showed steeper cognitive decline over time compared to healthy individuals in areas such as memory, some executive functions, and psychomotor speed performance (Hermann et al., 2006). Another study demonstrated that the frequency of epileptic seizures in TLE patients may be predictive of semantic and episodic memory deficits, as well as psychomotor speed deficits (Wang et al., 2011). With respect to BD, a greater number of manic episodes was associated with lower scores on a test of verbal memory (Robinson & Ferrier, 2006). Impulsivity is also a major component of mania in BD. Hypomania-prone subjects showed increased choice of a small immediate reward compared to larger delayed ones, a measure of impulsivity, on a two choice impulsivity paradigm. They also showed stronger electroencephalogram (EEG) signals for rewarding outcomes (Mason, O'Sullivan, Blackburn, Bentall, & El-Deredy, 2012). Symptoms of impulse control disorders such as pathological gambling, which may resemble criterion for diagnosis of addiction and substance abuse, are also observed in BD and TLE patients (DSM-IV-TR, 2000). However, few studies focused on symptoms of pathological gambling in these populations. Nonetheless, one such study has observed symptoms of pathological gambling in patients with TLE as assessed by the Gambling Symptoms Assessment Scale (Cavanna et al., 2008).

1.2 The Iowa Gambling Task

In the past years, the Iowa Gambling Task (IGT) has been increasingly used as a neuropsychological test to assess gambling behaviours. This task uses rewards and punishments to assess risky and ambiguous decision-making in humans (Bechara, Damasio, Damasio, & Anderson, 1994). In this task, participants chose a card from one of four decks. Each card has a different monetary value. The goal of the task is to accrue as much money as possible, without previously knowing the contingencies associated with each decks of card. However, the cards in each deck are not equivalent. In decks A and B, the cards deliver larger amounts of monetary reward, but also higher penalties. Decks C and D have lower rewards, but also lower penalties such that the optimal strategy is to favour decks C and D. Ultimately, consistent choices from the tempting "high-risk high-reward" decks A and B lead to monetary losses over successive trials, whereas choosing form decks C and D leads to monetary gain.

1.2.1 The IGT in bipolar and temporal lobe epilepsy patients

Although healthy individuals learn the contingencies associated with each deck of cards and ultimately prefer the advantageous decks (C and D), subjects with neurological damage to the amygdala or ventromedial prefrontal cortex are impaired on this task (Bechara, Damasio, Damasio, & Lee, 1999). Of interest to this thesis, sub-optimal choices on the IGT have been observed in both TLE and BD patients. For example, non-planning impulsivity in BD patients was found to be associated with sub-optimal choices on the IGT (Christodoulou, Lewis, Ploubidis, & Frangou, 2006). Although another study found that BD patients ultimately learned the contingencies associated with the decks as well as healthy individuals, they made less consistent and more random choices compared to controls (Yechiam, Hayden, Bodkins, O'Donnell, & Hetrick, 2008). Deficits on the IGT (failure to increase choices of the

advantageous decks) across the task is also seen in TLE patients, although the location of brain involvement in TLE is less clear (Delazer et al., 2010; Delazer et al., 2011; Labudda et al., 2009; Yamano, Akamatsu, Tsuji, Kobayakawa, & Kawamura, 2011). There seem to be no difference whether the focus of epileptic seizures in TLE is in the left or right side in producing these effects (Delazer et al., 2011). Unfortunately, since patients suffering from either of these two disorders are often simultaneously on psychoactive medications for their conditions, it is difficult to detangle the contributions of the drugs and the disease in producing these cognitive effects.

1.3 Bipolar disorder

Bipolar disorder is an affective disorder which affects about 1% of the population and is equally distributed in men and women. There are three major types of BD (bipolar I, bipolar II, and cyclothymia), each characterized by the severity and duration of the mood episodes. For example, at least one manic episode is required for a diagnosis of bipolar I disorder, whereas bipolar II disorder involves at least one less severe hypomanic episode. Both types of BD are also accompanied by episodes of major depression, as well as periods of remission where normal mood may be observed between episodes. Cyclothymia is associated with periods of hypomania and mild depression. A manic episode is characterized by an elevated mood and marked impulsivity, which may or may not be accompanied by psychotic symptoms. Suicide risk is also much higher in bipolar-depression than in the general population (Balázs et al., 2006; Jamison, 2000). Researchers have tried to understand the biological basis for BD, and numerous theories have been proposed, from frontostriatal dysfunction to neuroinflammation and degeneration to vasculature impairments (Kim, Rapoport, & Rao, 2010, 2011; Kubota et al., 2009; Passarotti & Pavuluri, 2011). However, there is little that has been definitively established about the precise neurological mechanisms underlying the disorder.

1.4 Dopamine dysregulation syndrome and animal model of bipolar disorder

A dopamine dysregulation syndrome hypothesis has been suggested as being involved in the etiology of BD. This hypothesis proposes that a cyclical variation in dopamine levels, with elevated dopamine during mania and low levels of the neurotransmitter during depressive episodes, would be involved in the disorder (Berk et al., 2007). Based on this observation, administration of the non-selective dopamine agonist amphetamine has been used as an animal model for BD to mimic symptoms of manic episodes such as hyperactivity and impulsivity. Amphetamine acts pre-synaptically on the dopamine transporter by impairing reuptake of the catecholamine. It also overwhelms tyrosine hydroxylase, the enzyme that metabolizes dopamine leading to increased dopamine in the synapse. In humans, drugs which non-selectively increase dopamine release in the prefrontal cortex such as cocaine have been shown to alter task learning and decision-making on the IGT (Verdejo-Garcia et al., 2007). However, the effects of amphetamine on impulsivity vary depending on the task used. For example, a study found increased inhibition in some cognitive tasks such as the stop task and the Go/No Go task and also decreased discounting on a delay-discounting task following acute administration of the drug (de Wit, Enggasser, & Richards, 2002). In rats, acute administration of amphetamine has been found to increase choice of a large delayed reward compared to a small immediate one (Floresco, Tse, & Ghods-Sharifi, 2008; Winstanley, Theobald, Dalley, & Robbins, 2005). The opposite effect has been observed with administration of dopamine D_1 and D_2 antagonists (Wade, de Wit, & Richards, 2000).

Of particular relevance to this thesis, acute administration of both a moderate and high dose of amphetamine increased premature responding, a measure of motor impulsivity, and impaired performance on a rat analogue of the IGT, the rat Gambling Task (Zeeb, Robbins, &

Winstanley, 2009). In this task, acute administration of $D_{2/3}$ agonist or D_1 agonist or antagonist did not affect performance, whereas D_2 antagonist improved performance. Increases in premature responding- the inability to withhold from making a motor response prior to the presentation of a target stimulus- have been reliably observed following administration of amphetamine using the five-choice serial reaction time task (5CSRT)- an animal analogue of the continuous performance test which measures motor impulsivity and attention in humans (e.g. Cole & Robbins, 1987; Harrison, Everitt & Robbins, 1997; Pattij, Janssen, Vanderschuren, Schoffelmeer, & van Gaalen, 2007; van Gaalen, Brueggeman, Bronius, Schoffelmeer & Vanderschuren, 2006; van Gaalen, Unger, Jongen-Relo, Schoemaker, & Gross, 2009). Therefore, in this thesis, we used acute amphetamine administration to model aspects of BD and assessed the effect of antiepileptic drugs in moderating the effect of amphetamine administration.

1.5 Epilepsy

Epilepsy is a neurological disorder that affects approximately 1% of the world's population and is also equally distributed between the sexes (Shin & McNamara, 1994). It is characterized by recurrent spontaneous seizures, where a group of neurons fire simultaneously. The seizure state is known as the ictal phase, and is followed by the post-ictal period. The term interictal period is used to describe events between seizures. A higher incidence of anxiety, depression and psychosis has been observed in epileptic patients as compared to the general population (Harden & Goldstein, 2002; Schmitz, 2005; Torta & Keller, 1999). Even though some researchers claim that depression may be a risk factor for developing epilepsy, others suggest that depression is comorbid with epilepsy and may occur as a result of intractable epilepsy (Kanner, 2003; Lambert & Robertson, 1999; Schmitz, 2005). Depressive interictal symptoms increase in severity during the post-ictal phase (Kanner, Soto, & Gross-Kanner, 2004).

Risk for suicide, which may itself be seen as a highly impulsive behaviour, is also ten times higher in individuals with intractable epilepsy compared to the general population (Kanner, 2003).

Seizures are believed to be due to an imbalance between the glutamate excitatory and gamma-aminobutyric acid (GABA) inhibitory systems (Holmes & Ben-Ari, 2001). In fact, the interictal state is mostly controlled by the GABA system whereas the pre-ictal and ictal events result from a dysregulated glutamate excitatory system. There are many types of epilepsy, each having a different degree of severity, neurological involvement, and behavioural correlate. For example, epileptic seizures are divided into two broad categories. Generalized seizures involve the entire brain and lead to loss of consciousness. In contrast, partial seizures, also called focal seizures, originate in a specific area of the brain, such as the temporal lobe. In simple-partial seizures, patients remain conscious whereas in complex-partial seizures they do not. Partial seizures may evolve into generalized seizures, in which case they are called secondary generalized seizures (Shin & McNamara, 1994). Another severe type of epilepsy in which the entire brain is in constant state of seizure is called status epilepticus. This type of seizure requires immediate medical assistance and may lead to death.

Unfortunately, even though many antiepileptic agents have been developed and are used as prophylaxis for epilepsy, none have been found to cure the disorder and epileptic seizures remain refractory for many individuals, especially those suffering from complex-partial epilepsy (Schmidt & Loscher, 2005). Most anticonvulsant drugs act by suppressing the abnormal hyperexcitability of neurons in the brain of epileptic patients. At the resting state, during the inactive period in a normal neuron, a difference in electrical charge between the inside and outside of the cell membrane can be observed. At this state, the inside of the neuron is more

negative compared to the outside. The intracellular space mostly has negatively charged protein molecules which stay in the cell and positively charged potassium ions which flow across the cell membrane. The extracellular space mostly has positively charged sodium and calcium ions and negatively charged chloride ions. An action potential occurs when equilibrium of the resting potential is disturbed by a rapid influx of positive ions in the cell through ion channels. One factor in pathological neuronal hyperexcitability which has been involved in the etiology of epileptogenesis, may be a slow inactivation of sodium channels. In the same way, pathological slowing of fast-inactivating voltage gated sodium channels and persistent sodium currents in non-inactivating sodium channels may also be involved in the disorder (Köhling, 2002). Because of the possible involvement of sodium currents in the disorder, many anticonvulsant drugs act on voltage-gated sodium ion channels. Epileptic seizures have also been associated with brain damage which may be related to the range of cognitive deficits observed in patients. Excessive glutamate release and the entry of calcium ions into the neurons are believed to be in part responsible for the neurological damage observed (Olney, 1985).

1.6 Anticonvulsant drugs

1.6.1 Mechanism of action of anticonvulsant drugs

Many classes of drugs are used in the treatment of epilepsy with general sedatives such as the barbiturates and benzodiazepines being among the earliest treatments used. Anticonvulsant drugs have since then been developed specifically for the treatment of epilepsy. The main goal of these drugs is to prevent abnormal discharges without affecting normal neurotransmission. Three of these compounds- valproate, carbamazepine and lamotrigine- are also widely used as mood stabilizers and prophylaxis for the management of BD. The current first line treatment for BD is lithium. While this drug is very effective at controlling the manic symptoms of BD, poor

patient tolerance and concerns over the narrow therapeutic window between effective and toxic doses has lead physicians to seek alternative treatment options, such as the anticonvulsant drugs. Different anticonvulsant drugs vary in their mechanisms of actions, their side effect profiles, their addictive and tolerance potential, as well as their efficacy for specific types of epilepsy. For example, drugs such as valproate and phenytoin appear to be more suited for the management of generalized epilepsy whereas carbamazepine, oxcarbazepine and lamotrigine seem more efficient in the management of partial epilepsy (Tudur Smith, Marson, Chadwick, & Williamson, 2007). However, the mechanisms of action underlying anticonvulsants efficacy and the specific behavioural aspects targeted by some of these drugs are not fully understood. Some known mechanisms of action of anticonvulsants used in this thesis: valproate, carbamazepine and lamotrigine, will be summarized here.

Valproate (2-propylpentanoate) started to be used in 1967 for the treatment of epilepsy and is now used for a variety of disorders such as BD and migraines (Peterson & Naunton, 2005). In the nervous system, valproate acts by a combination of effects. On the inhibitory system, valproate potentiates and prolongs GABA activity inhibiting GABA reuptake, and also increasing GABAergic synaptic growth (Eckstein-Ludwig, Fei, & Schwarz, 1999; Laeng et al., 2004). It also acts by interacting with enzymes involved in the synthesis and degradation of GABA (Johannessen, 2000). Valproate may also increase dopamine release in the prefrontal cortex via action on the serotonin (5-HT) system (Ichikawa & Meltzer, 1999). In addition, valproate blocks voltage-gated sodium channels and the T-type calcium channels, thereby decreasing inward currents of both of these ions and inhibiting depolarization of the membrane and the creation of action potentials (Johannessen, 2000; Köhling, 2002). Valproate's prevention of neurotoxic levels of calcium entry into the cell may be the mechanism involved in its

neuroprotective effects. This compound also modifies AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors which decrease post-synaptic responsiveness, and has a direct action on the NMDA (N-methyl-D-aspartate) receptors by increasing the magnesium blockade at post-synaptic receptors (Gobbi & Janiri, 2006). In addition, valproate acts on second messenger intracellular signaling cascades, as well as on gene regulation and transcription by inhibiting histone deacetylase (Nalivaeva, Belyaev, & Turner, 2009).

Carbamazepine (5*H*-dibenzo[*b,f*]azepine-5-carboxamide) was first used as an anticonvulsant drug in 1965. It inhibits action potentials by shifting the steady-state inactivation of the voltage-gated sodium channels to a hyperpolarized state, which makes it harder for the cell to fire. It also inhibits calcium entry, decreasing at the same time the release of glutamate and aspartate excitatory neurotransmitters (Gould, Quiroz, Singh, Zarate, & Manji, 2004; Köhling, 2002). Carbamazepine potentiates GABA induced chloride currents on $GABA_A$ receptors, more specifically the α1, β2, and γ2 subunits (Granger et al., 1995). Carbamazepine is structurally similar to the tricyclic anti-depressant drug imipramine. Therefore, it may also work by inhibiting catecholamine reuptake, and has been found to also increase release of dopamine through $5\text{-}HT_{1A}$ receptors (Ichikawa & Meltzer, 1999). This drug has also been found to work as an adenosine receptor antagonist (Faingold & Browning, 1987).

Finally, lamotrigine (6-[2,3-dichlorophenyl]-1,2,4-triazine-3,5-diamine) was first used to treat epilepsy in 1994 and has been since adopted for the management of bipolar depression. It is distinct from the other anticonvulsant drugs as it does not modulate the GABA system (Czuczwar & Patsalos, 2001). It acts rather by blocking voltage-dependent sodium channels, reducing glutamate release, and modulates the N, P/Q, and R-types voltage-activated calcium channels (Köhling, 2002). Lamotrigine may also affect potassium channels, but studies are

inconsistent concerning its mechanism (Cunningham & Jones, 2000). It is also believed that lamotrigine may act on the 5-HT system since it has a strong antidepressant effect as observed in the forced-swim test in mice (Bourin, Masse, & Hascoet, 2005). However, again, the data concerning the action of lamotrigine on the 5-HT receptors is not clear. For example, one study found that lamotrigine decreased the density of 5-HT_{1A} receptors in the frontal cortex, but had no effect in the hippocampus (Vinod & Subhash, 2002), while another found no effect of lamotrigine on the 5-HT_{1A} receptors in any region (Shiah, Yatham, Lam, & Zis, 1998).

1.6.2 Anticonvulsant drugs and cognition

Second generation anticonvulsant drugs such as carbamazepine and valproate are considered first line treatments for complex partial and secondary generalized epilepsy, and are also widely used for the control of BD. However, they both have consistently been found to lead to cognitive impairment in humans. As an example, valproate has been found to lead to visuomotor and attentional deficits (Gallassi et al., 1990). Carbamazepine has also been associated with deficits in speed of processing and verbal memory, amongst other (Hermann, Meador, Gaillard, & Cramer, 2010). On the contrary, newer generation antiepileptic drugs such as lamotrigine have been reported to have fewer side-effects and a better tolerability profile in both children and adults. Some studies have found an improvement in cognitive functions in BD patients with a depressive episode treated with lamotrigine (Dias et al., 2012). However, improvement in cognition may be due to the capacity of lamotrigine to partially alleviate some symptoms of depression, which may themselves contribute to the cognitive deficits observed.

Nonetheless, the better cognitive profile of lamotrigine has been demonstrated in multiple studies. When compared to carbamazepine, epileptic patients taking lamotrigine showed better performance on the stroop color-word interference task and in the phonetic fluency task (Lee et

al., 2011). Also, patients taking carbamazepine did worse on tasks of processing and reading speed, as well as on memory tasks compared to those treated with lamotrigine (Meador et al., 2001). In BD, although valproate and carbamazepine may be efficient in controlling manic episodes, lamotrigine seems to be more helpful to protect against or reduce the impact of a depressive episode compared to a manic episode (Herman, 2004). Some antiepileptic drugs including lamotrigine also appear to have neuroprotective effects (Pitkanen & Kubova, 2004). Nonetheless, it is difficult to differentiate the contribution of drug treatments, disorders, and brain mechanisms in producing or alleviating cognitive effects observed in patients with BD and TLE.

1.7 Animal models of epilepsy

Along with human studies, animal models of epilepsy have been developed in order to try to understand the mechanisms involved in epilepsy and as a way to evaluate the efficacy of new anticonvulsant drugs. A variety of animal models exist which may or may not feature epileptogenesis, the development of spontaneous seizures that is seen in individuals with the disorder. Some of these models include the acute or reactive models such as the GABA antagonist pentylenetetrazol (PTZ) model or the maximal electrochock seizure (MES) model. These do not model epileptogenesis as the seizure occurs as a single acute reaction to the manipulation. Post-status epilepticus models include those in which epileptogenesis may evolve following an extended (often more than two hours) provoked status seizure using glutamate agonists such as the pilocarpine or kainate models, or following an extensive electrical stimulation such as the sustained amygdala stimulation (SAS). The risk of death in the animals is elevated in such models. Genetic models of epilepsy have also been developed, which mostly model generalized epilepsy. Finally, the kindling model of epilepsy is performed by repeated

low intensity unilateral or bilateral electrical stimulations into a specific brain region. This model is the most similar to the clinical phenomenology observed in TLE (Loscher, 2002).

1.7.1 The kindling model of TLE

Kindling may be described as a permanent increase in seizure susceptibility and lower seizure threshold over time as the number of stimulations increase. Once established, this increase sensitivity to seizure is irreversible (Goddard, McIntyre, & Leech, 1969). In the kindling model, seizures evolve through stages of severity that begin in an area of the brain and spreads to finally involve the whole brain to reach secondary generalized epilepsy (Pinel & Rovner, 1978). Many areas of the brain have been shown to be potential targets for kindling. Stimulation of the amygdala or hippocampus is often used to model TLE. A criterion for an animal model of epilepsy is that a drug that is effective in treating epilepsy should also be effective in blocking seizures in animals and *vice versa*. For example, the PTZ model was found to predict efficacy of drugs against absence seizure whereas the MES model pre-selects drugs against generalized epilepsy. All anticonvulsant drugs used in the experiments for this thesis have shown to possess anticonvulsant effects on the amygdala kindling model, but also in the clinical population suffering from partial seizures. Valproate and lamotrigine were also found to block development of kindling leading to epileptogenesis whereas carbamazepine failed to block kindling development. Nonetheless, all three drugs were effective against elicited seizure in fully kindled animals (Loscher, 2002). For this reason, as well as that kindling resembles the phenomenon observed in TLE patients, this thesis used unilateral kindling of the amygdala as a model for TLE.

1.8 The amygdala and decision-making

By its interaction with brain regions associated with reward-processing information, the amygdala appears to play an important role in decision-making (Baxter & Murray, 2002). For example, the amygdala possesses reciprocal connections with the prefrontal cortex such as the orbitofrontal cortex, as well as with structures heavily influenced by the dopamine system such as the nucleus accumbens (NAc). Most neurons in the amygdala are glutamatergic and GABAergic. The amygdala is involved in emotion processing, classical conditioning and association with affective stimuli, to name but a few of the functions ascribed to this region (Baxter & Murray, 2002; Cardinal, Parkinson, Hall, & Everitt, 2003). More specifically, the basolateral amygdala (BLA) appears to be strongly involved in learning of associations between stimuli and their reward value.

Researchers have found that damage to the amygdala increases risk taking behaviours in humans (Shiv, Loewenstein, Bechara, Damasio, & Damasio, 2005). Individuals with bilateral amygdala damage were found to choose significantly more often from the risky, disadvantageous options on the IGT (Bechara, Damasio, & Damasio, 2003; Bechara et al., 1999). This could explain why patients with TLE in which seizure begin in the amygdala formation may be more likely to display impaired decision-making under risk. However, the extent of the damage in human patients is difficult to control. Animal models may therefore be useful to investigate the implication of the amygdala, as well as of epileptic seizures, in contributing to cognitive impairments. In rats, previous studies showed that BLA inactivation alter decision-making by decreasing choice of a risky lever on a risk discounting task, even when such choices resulted in less reward (Ghods-Sharifi, St Onge, & Floresco, 2009). Lesions to the BLA also decreased choice of a larger delayed reward in favour of a small immediate one on a delay discounting task,

suggesting increased impulsivity (Winstanley, Theobald, Cardinal, & Robbins, 2004). On the rat gambling task (rGT), BLA lesions have also been found to increase choices of the disadvantageous options (Zeeb & Winstanley, 2011).

Although cognitive deficits have been observed in patients with TLE, few studies have assessed cognition in the amygdala kindling model of TLE in animals. In one study comparing rats who have been bred to be predisposed to fast versus slow amygdala-kindling, impairments in learning, choice accuracy, and memory were observed on a delayed alternation task in the kindled and not kindled fast-kindling rats, indicating that susceptibility to seizures could be associated with cognitive deficits (D. C. McIntyre, McLeod, & Anisman, 2004). Fast kindling rats also showed lower levels of anxiety on the open arm elevated plus maze, and were slower on acquisition of the Morris water maze, a task which assesses spatial learning (D. McIntyre & Anisman, 2000). However, to my knowledge, no study has looked at the relationship between seizures originating from the amygdala and decision-making involving risk or ambiguity in an animal model of TLE. Understanding the neurobiology underlying decision-making in an animal model of TLE could therefore advance understanding of both normal and impaired decision-making in TLE patients. In addition, observing the implication of anticonvulsant drugs in impairing cognition may help detangle the implication of drug treatment and disorders such as TLE and BD in inducing the cognitive deficits observed.

This thesis investigated the effect of three anticonvulsant drugs, and kindling on different aspects of decision making using the rat Gambling task. In order to detangle the individual contribution of medications and disease on the deficits observed in humans, we first investigated the effects of the anticonvulsants valproate, lamotrigine and carbamazepine alone, and later in a model of BD using acute amphetamine administration. We hypothesized that valproate and

carbamazepine would lead to more cognitive effects in the rats than would lamotrigine, paralleling the effects observed in human patients. We also believed that rats would make more premature responses following amphetamine administration as seen in a previous study (Zeeb et al., 2009) and that the various drugs may block this effect. In another cohort of rats, we explored the effects of unilateral kindling of the amygdala on this same task. We expected to observed deficits in choices on the rGT in the kindled rats since symptoms of pathological gambling and deficits in decision-making have been observed in some patients with TLE. Since we found an effect of carbamazepine on behaviour, we tested this drug at a dose that did not cause cognitive effects prior to a single stimulation on kindled rats. Although we were not clear on the effect of such experimentation, we wanted to explore whether the drug would improve or worsen cognition that could have been impaired by kindling.

2. Material and Methods

2.1 Subjects

Subjects were 32 Long Evans rats (16 in the antiepileptic drug experiment and 16 in the kindling experiment) from Charles River Laboratories, Saint Constant, Canada, weighing between 250 - 275 g at the start of the experiment. Rats were housed in a climate-controlled colony room on a reversed 12 hours light-dark cycle (lights off 08.00; temperature 21°C). Water was always available *ad libitum.* Subjects were pair-housed from the time of their arrival and free fed for a week, during which the experimenter handled them daily. Rats were then food restricted to 85% of their initial free feeding weight on a daily diet consisting of 14 g of standard laboratory rat chow, plus the sugar pellets earned in the task (~5 g per day). Behaviour testing began one week following the start of food restriction. Rats were trained between 12:00 pm and 5:00 pm five days a week. All housing conditions and testing were in accordance with the Canadian Council on Animal Care, and the University of British Columbia Animal Care Committee approved all experimental procedures prior to the beginning of the study.

2.2 Behavioural apparatus

Behavioral testing took place in 16 standard five-hole operant chambers from Med Associates Inc, Vermont, USA. These were individually housed in a ventilated and sound-attenuating cabinet. Each chamber featured five response holes on one side, and a food magazine, which was positioned midline on the wall opposite to these response holes. Each response hole, as well as the food magazine was equipped with a stimulus light at the back and a horizontal infra-red beam passing across to detect a nose-poke. The response holes and the food magazine were positioned two cm above a bar floor. The food magazine delivered sucrose pellets rewards (45 mg; Bioserv, New Jersey) from a connected pellet dispenser fitted outside of

the chamber. Each chamber was also furnished with a house light to allow for illumination and was controlled by a software written in Med PC by CAW running on an IBM-compatible computer.

2.3 Behavioural testing

On training days, rats were transported to the testing room in their home cage prior to being placed in the operant chamber. Rats were consistently placed in the same operant chamber for the duration of behavioural testing.

2.3.1 Habituation and training.

All subjects were initially habituated to the testing chambers by freely accessing sucrose pellets placed in each response hole. Following two such 30 min sessions, animals were trained to nose poke in the response holes when they were illuminated using a revised version of the Five-Choice Serial Reaction Time Task (5-CSRTT) adapted for the rat Gambling task (rGT). The rGT task uses the four most peripheral holes omitting the middle hole. In the rGT Four-Choice training, a light in one of the four peripheral holes become illuminated. Animals were rewarded when they performed a nose poke in the appropriate aperture within 10 sec. The illuminated hole varied in location across trials. Each session lasted for 30 min. Rats started training of a forced-choice version of the rGT once accuracy in responding to the illuminated hole attained more than 80 percent, with less than 20 percent trials omitted. Omitted trials were ones in which rats failed to respond within 10 sec.

2.3.2 The rat Gambling Task—Forced-Choice.

In the rGT, each hole is associated with a different probability of reward and punishment. The order of these associations was counterbalanced from left to right across the array between

two versions of the task in order to avoid biases in hole position preferences. Sixteen of the 32 subjects (eight in each of the anticonvulsant and kindling project) performed version A of the rGT, and the other 16 rats performed version B. In version A, the first hole on the left of the array (hole 1) corresponded to option 1, hole 2 corresponded to option 4, hole 4 corresponded to option 2, and hole 5 corresponded to option 3. In version B, hole 1 corresponded to option 4, hole 2 corresponded to option 1, hole 4 corresponded to option 3, and hole 5 corresponded to option 2. Option 1 was rewarded with 1 sucrose pellet on 90% of trials, and was punished on 10% of trials with a 5 sec time-out penalty (P1). Option 2 was rewarded with 2 sucrose pellets on 80% of trials, and was punished on 20% of trials with a 10 sec time-out penalty (P2). Option 3 was rewarded with 3 sucrose pellets on 50% of trials, and was punished on 50% of trials with a 30 sec time-out penalty (P3). Finally, option 4 was rewarded with 4 sucrose pellets on 40% of trials, and was punished on 60% of trials with a 40 sec time-out penalty (P4). The position of these holes and associated probability of reward and punishment, once allocated, remained unchanged for the duration of the behavioural testing. These reinforcement contingencies were allocated such that the best option was P2, and consistent choice of this option led to the maximal amount of sucrose pellets over time. The larger sucrose pellet options lead to larger gains on rewarded trials, but consistent choices of these options also led to larger punishments over time and less possibility to complete as many trials and earn as much reward within the 30 min allocated for a session. Rats began the rGT training on a forced-choice version of the task where rats were presented with only one illuminated hole. This ensured that all rats sampled each of the different options and learned the contingencies associated with these options. Rats were trained on the forced-choice version of the rGT for seven to ten trials.

2.3.3 The rat Gambling Task—Full Program.

A trial started with a nose-poke in the illuminated food magazine. This nose-poke extinguished the light. Following a 5 sec inter-trial interval (ITI), stimulus lights in the four peripheral response holes (holes 1, 2, 4, and 5) illuminated for 10 sec. A nose-poke in any of the response holes before the end of the ITI was considered a premature response. A premature response led to illumination of the house light for a 5 sec time-out duration after which the tray light illuminated and a new trial could be initiated by a nose-poke in the food magazine. If the animal failed to respond in an illuminated response hole within 10 sec, all stimulus lights extinguished and the tray light became illuminated, at which point a new trial could be initiated. This failure to respond was considered a choice omission. However, a nose-poke response in one of the holes within 10 sec extinguished all stimulus lights and led to either delivery of a reward or a time-out punishment depending on the contingencies associated with the different options. A punished trial led to flashing of the stimulus light in the chosen hole at 0.5 Hz for the duration of the associated punishment time-out while the other stimulus lights were extinguished. No rewards were delivered on such trials. Following the time-out period, the tray light illuminated and a new trial could be initiated by a nose-poke therein. There was no consequence in making multiple responses in the food magazine. Each session lasted for 30 minutes after which the rat was transported back to its home cage and food was distributed by the experimenter. Figure 1 shows a schematic of the rGT.

2.4 Electrical kindling of the amygdala

On surgery day, rats were implanted with a bipolar stimulating electrode (Plastic Products Company) unilaterally into the left amygdala and allowed to recover for a week (see surgery section 2.6 below). Rats were singled housed following implantation of the stimulating

electrode. Rats were then trained again to stable baseline behaviour on the rGT prior to start of amygdala stimulation. Reaching stability required 15 sessions. Rats were separated into two equal groups (n = 8) matched for baseline performance. One group received sham stimulations and the other received electrical amygdala stimulation. These groups were later switched so that the rats which previously received sham stimulation in the first period of the experiment then received electrical stimulation and vice versa, therefore all rats were kindled in this experiment.

Stimulation occurred twice daily, five days a week, with a minimum of four hours between stimulations. On stimulation days, the experimenter turned the stimulation generator on, plugged the stimulation lead into the Master-8-Pulse generator (A.M.P.I.) and set up the stimulation chamber prior to bringing the rats into the room. Proper functioning of the stimulator vas verified by insuring that the stimulation light briefly illuminated when the stimulation button was pressed. Rats were transported from their housing room to the stimulation room adjacent to the behavioural testing room in their home cage. Rats were stimulated one at a time by the experimenter. The animal was taken from its home cage and the dust cap attached to the electrode was removed. The insulated stimulation lead was attached to the implanted electrode and the rat placed into a transparent plexiglas chamber in which the bottom was covered with brown paper. The experimenter allowed the animal to acclimatize to the chamber for 30 sec before stimulation occurred. This delay diminished the likelihood that the chamber would elicit a seizure by conditioning. Stimulation was triggered by the experimenter by quickly pressing and releasing the stimulation button on the generator. The current intensity for stimulating the amygdala was of 400 μA peak to peak; monophasic square wave of 1 ms pulse, 60 Hz, and of 1 sec in duration. The experimenter promptly detached the stimulation lead from the electrode after stimulation offset and monitored the animal's seizure using a monitoring sheet. The animal

was allowed to recover from the seizure prior to being picked up by the experimenter, after which the dust cap was reinstalled and the rat returned to its home cage. The brown paper in the stimulation chamber was refreshed between rats. If the stimulation was the first one of that day, the rat was returned to its colony. If this was instead the second stimulation of that day, which was performed just before usual testing time, the rat returned to their home cage for 30 min prior to being placed into the operant chamber to start the rGT program, which at this stage of the experiment occurred every second day. The procedure for behavioural testing was the same as for regular testing explained above.

Stimulations were performed until 3 bilateral clonic class 5 convulsions were elicited. Although they often were, these 3 convulsions were not required to be consecutive. The scale from Pinel & Rovners's (1978) extension of Racine's (1972) 5-class scale of limbic convulsion severity was used to determine convulsion class. Table 1 shows the convulsion class monitoring sheet used in order to assess seizure. In this scale, class 1 and 2 seizures are limbic seizures whereas classes 3 to 8 are motor seizures and considered generalized clonic seizures. Class 5 and 6 seizures were considered as fulfilling the criterion for full kindling. Class 7 and 8 seizures required termination of stimulations for the animal, exclusion of the subject from the experiment, and immediate euthanasia by CO_2. The convulsion classes were described as follow: class 1: immobility, twitching of the whiskers and mild facial movements such as chewing movements of the jaw and eye closure; class 2: a class 1 seizure with more severe facial movements and nodding of the head; class 3: a class 2 seizure with unilateral forelimb clonus; class 4: a class 2 seizure with bilateral forelimb clonus accompanied by rearing; class 5: a class 4 seizure with loss of balance and only one fall; class 6: a class 5 seizure with multiple rearing and falling episodes; class 7: a class 6 seizure accompanied by running fits; class 8: running fit with periods of tonus.

Poor reaction to stimulation necessitated exclusion of two animals. These animals were euthanized with CO_2.

2.5 Drugs

Sodium valproate, carbamazepine and lamotrigine (Sigma-Aldrich, Oakville, Canada) were administered through the intraperitoneal (IP) route. Valproate was dissolved in distilled water and administered at a volume of 1 ml/kg and doses of 50 mg/kg, 100 mg/kg, and 200 mg/kg. Carbamazepine was dissolved in 3 parts polyethylene glycol 400 and 2 parts 0.9% sterile saline solution at a volume of 2 ml/kg and doses of 7.5 mg/kg, 15 mg/kg, and 30 mg/kg. Lamotrigine was dissolved in 1 part polyethylene glycol 400 and 1 part 0.9% sterile saline solution at a volume of 1 ml/kg and doses of 1 mg/kg, 3 mg/kg, and 10 mg/kg. Both lamotrigine and carbamazepine requested extensive sonication in order for the drug to completely dissolve. Amphetamine was dissolved in 0.9% sterile saline solution in a dose of 1 mg/kg. The drugs were administered in the order of: valproate, lamotrigine, carbamazepine, and amphetamine preceded by each of the three anticonvulsant drugs. Administration of each drug challenge followed a Latin Square schedule. The Latin Square was designed in order for each dose or drug to be followed and preceded by each other across the group. We used a diagram-balanced design with three doses and a vehicle as follows: A = vehicle, B = smallest dose, C = middle dose, D = highest dose; ABCD, BDAC, CADB, DCBA.

Valproate was administered 15 min before testing, lamotrigine and carbamazepine were administered 30 min before testing. A wash out period of a minimum of one week during which rats were tested drug-free followed each drug challenge. During the amphetamine challenge, the anticonvulsant drug was administered at a time-point sufficiently ahead of the amphetamine administration to allow the drug's activity to peak (i.e. 15 min for valproate and 30 min for the

other 2 drugs), and amphetamine was injected 10 min before testing. In this challenge, doses of the anticonvulsants were 200 mg/kg of valproate, 10 mg/kg of lamotrigine, and 15 mg/kg of carbamazepine. These were the highest behaviourally-silent doses tested in the initial Latin Square design. For the amphetamine challenge, the design was as follows: A = saline-saline, B = saline amphetamine, C = valproate-amphetamine, D = lamotrigine-amphetamine, E = carbamazepine-amphetamine; ABCDE, BECAD, CDEBA, DBAEC, EADCB. Rats were tested to a stable behavioural baseline prior to beginning of pharmacological challenges. Each drug was administered on a three-day schedule which started with a baseline testing day. A dose of the drug or the vehicle was administered the following day. The third day constituted of a day off testing allowing for washing off the drug.

In the kindling experiment, the effect of 4 mg/kg of carbamazepine prior to a single stimulation was also assessed once kindling of the two groups was completed and stability in behaviour was achieved. This dose was chosen as it did not lead to any behavioural effect on its own. All 16 rats were divided into two behaviourally matched groups, each including half of the first kindling and half of the second kindling groups. The 3 days drug administration schedule was similarly observed in this phase of the experiment. The carbamazepine challenge began about two weeks after the end of kindling for the second stimulation group and four weeks following end of kindling for the first group, during which rats were trained on the rGT. During this challenge, one of the newly made groups received carbamazepine and the other group received the vehicle solution on one day, and these groups were switched on the following injection day according to a counterbalanced design. Carbamazepine was administered IP 30 min prior to stimulation, and 30 min elapsed following stimulation prior to behavioural testing.

2.6 Surgery

All 16 rats in the kindling experiment underwent left unilateral bipolar electrode implantation into the amygdala. Rats were anesthetized by isoflurane inhalation and placed into a stereotaxic frame with incisor bar set at -3.3 for a flat skull position. The coordinates for the location of the implantation site was based on a rat brain atlas (Paxinos and Watson, 1998), on previous studies (Barnes, Pinel, Wig, Stuettgen, & Holzel, 2003; Howland, Hannesson, Barnes, & Phillips, 2007; Winstanley et al., 2004) and modified based on observations from pilot data. The location for implantation was as follows: anterior-posterior (AP): -2.8; medial-lateral (ML): $\pm$4.8; dorsoventral (DV): -9.0. The AP coordinate was taken from bregma, the ML coordinate from the midline, and the DV coordinate from the skull. Anafen was given as analgesic. Following surgery, rats were single housed in their home cages and the experimenter monitored recovery twice daily for at least 7 days prior to the start of behavioural testing. During this recovery period, rats were fed 20 g of standard lab rat chow daily and water was available *ad libitum*. Complications from surgery necessitated the exclusion of two animals.

2.7 Data analysis

All data were analyzed using SPSS for Windows (version number 20.0, IBM corp). The data for choice behaviour in all pharmacological challenges and in the kindling experiment was subjected to a two-way repeated-measures analysis of variance (ANOVA). The drug challenges were analyzed with drug dose (vehicle plus doses of the compound), and choice (four levels: P1-4) as within subject factors.

For the analysis of the kindling experiment, data were organised with respect to the time at which all rats were at the same stage five seizure for three sessions, regardless of the groups (first or second to undergo stimulation), or how many stimulations were required to attain class

five seizures. Rats' behaviour once kindled was then compared to their pre-stimulation baseline, as well as to post-kindling behaviour. Data from post-kindling sessions were also sorted so that all rats post-kindling corresponded to the 3 sessions that were 7 sessions after the end of stimulation. Choice was configured with condition (three levels: before, kindling, and after kindling ended), session (three sessions), and choice (four levels: P1-4), as the within-subjects factors. In the carbamazepine-kindling experiment, behaviour after drug administration was compared to an average of the 3 post-kindling sessions. Choice of the four different options (P1-4) and condition (3 levels: post-kindling, vehicle, carbamazepine) were included as within-subjects factors. Risky versus conservative preference was the between subject factor for all analysis.

Research using the human IGT often operationalizes subjects' performance as good or bad on the task by analyzing the degree to which subjects preferred the advantageous options over the disadvantageous options, typically subtracting the number of choices from the disadvantageous decks from those made from the advantageous packs (Zeeb et al., 2009). Applying this approach to the current dataset, the degree of preference for the better options shown by each individual rat was calculated using the formula [(P1 + P2) – (P3 + P4)]. If this formula generated a negative value for any animal, it would indicate a preference for the disadvantageous high-risk high-reward option. Such animals were classified as "risky" whereas all others were categorized as "conservative". This distinction was added as a between-subjects factor (risk group) in all analyses.

For the other parameters that were not separated by choice such as premature responses, trials, omissions, collection latency and choice latency, session or dose was the only within-subjects factor. Further ANOVA analysis was performed comparing the different conditions or

doses of the drugs if a significant main effect of condition or an interaction was achieved at a p-value of less than 0.05. Violation of the sphericity assumption revealed with Mauchly's test was corrected using the Greenhouse-Geisser procedure. Pairwise comparisons were used as post-hoc comparisons for simple main effects if multiple groups were analyzed, and t-tests if only two groups were compared.

Choices and premature responses were counted as percentages to take into account the number of trials or choices made. The number of trials in which subjects chose an option in a given session was calculated as: the number of choices of a particular option / number of total choices made x 100. The percentage of premature responses was calculated as: the number of premature responses made / total number of trials initiated in a session x 100. This was done in order to account for the variations within each subject or due to the different conditions, which could be influenced by other parameters such as choice and collection latency or the number of trials made and therefore may otherwise have been mistaken for changes due to the experimental manipulation. In order to reduce the effect of an artificial ceiling (i.e. 100%), all data expressed as a percentage was subjected to an arcsine transformation prior to further analysis.

2.8 Histology

After completion of each of the anticonvulsant and the kindling experiments, rats were sacrificed by exposure to carbon dioxide. The brains of the subjects in the anticonvulsant experiment were not harvested. Brains of subjects in the kindling experiment were removed and postfixed for 24 hours in a solution of 4% phosphate-buffered paraformaldehyde for 24 hours before being stored in a 30% sucrose solution. The brains were later frozen and the area of the amygdala was sliced into 50 μm sections. Sections were mounted on glass slides coated with 2% cryo-gel before staining with Cresyl Violet. Placement of the unilateral bipolar electrode into the

amygdala during surgery and possible damage to the area were determined and mapped with reference to a neuroanatomical rats' brain atlas (Paxinos and Watson, 1998).

3 Results

3.1 Anticonvulsant drugs

3.1.1 rGT baseline behaviour

All 16 rats completed the anticonvulsants challenge, receiving each dose of each drug and were all included in the analysis. Early on, rats performing the rGT showed individual preferences for the different options, which were clearly defined prior to start of the drug challenges. We also observed that a sub-group of rats had a strong preference for the risky options (choice option: $F(1.863, 26.085) = 20.428$, $p < 0.001$; choice option x risk group: $F(1.863, 26.085) = 27.526$, $p < 0.001$). Using the classification methodology outlined in data analysis section 2.8, most rats (n= 12) were categorized as conservative but a subgroup (n = 4) were labeled as risky due to their preference for the disadvantageous options. Therefore, the analysis in this thesis took into account these individual differences. Pairwise comparisons showed that, the conservative rats chose the different options in this manner: P2 > P3 > P1 > P4. These rats chose the best option P2 significantly more frequently than all other options, and the option P1 significantly more often than P4. A different pattern was observed in the risky rats who chose in this manner: P3 > P2 > P1 > P4. Risky rats significantly preferred the disadvantageous option P3 above all other options, which did not differ between them. Figure 2 shows the baseline choice behaviour for the conservative and risky rats prior to start of the anticonvulsant challenge. Even though the optimal pattern of choice based on the probability of reward associated with the different option should be P2 > P1 > P3 > P4, rats were clearly sampling all of the different options, and some rats more than others were tempted by those with a possibility of higher reward.

As described in the methods, rats were trained until behaviour was stable on all parameters over at least 3 sessions. Rats in this experiment performed 33 sessions before

reaching stability. At this point, a difference between the risky and conservative rats was observed in that risky rats completed less trials per session, probably due to the delivery of longer and more frequent time-out penalties associated with the high reward options (trial- risk group: $F(1, 14) = 9.400$, $p = 0.008$; risky: $M = 71.500$, $SEM = 4.784$; conservative: $M = 117.64$, $SEM = 9.117$). However, risky rats also took longer to choose an option compared to the conservative rats, which could also reduce the number of trials completed (choice latency- risk group: $F(1, 14) = 7.359$, $p = 0.017$; risky: $M = 1.619$, $SEM = 0.274$, conservative: $M = 0.995$, $SEM = 0.108$). No other parameters significantly differ between the two groups (premature responses, omission, collection latency: all Fs <1.354).

3.1.2 Valproate

Figure 3 shows the effect of valproate on choice behaviour for all rats, and for each of the conservative and risky group. Despite the lack of any main effects on choice (dose: $F(3, 42) = 1.084$, NS; dose x option: $F(3.777, 52.871) = 1.319$, NS), statistical analysis indicated that valproate was differentially affecting decision-making depending on rats' preference for the risky options (dose x risk group: $F(3, 42) = 3.558$, $p = 0.022$). However, when the effect of the drug was analysed in the risky and conservative rats separately, we detected no significant effects in either group (conservative rats: dose: F(3, 33) = 2.432, NS; dose x option: F(9, 99) = 0.779, NS; risky rats: dose: F(3, 9) = 2.356, NS; dose x option: F(9, 27) = 1.494, NS). The significant interaction term from the main ANOVA likely indicates that the drug was having differential effects in the two groups on certain choices e.g. increasing choice of P2 in conservative but not risky animals, but that none of these effects were significantly different from the baseline performance of each group. As such, these effects cannot be considered robust or to reflect a genuine change in choice behavior. The drug did not affect any other parameters,

regardless of the baseline behaviour of the rats (dose, dose x risk group, dose x choice: all Fs < 1.924, NS). Table 2 shows the data for the different components of decision-making assessed in the valproate administration challenge in the conservative and risky rats.

3.1.3 Lamotrigine

Lamotrigine did not affect choices of the different options, regardless of rats' preference for the risky and conservative option (dose: $F(3, 42) = 2.577$, NS; dose x option: $F(4.666, 65.326) = 1.143$, NS; dose x risk group: $F(3, 42) = 1.735$, NS; risk group: $F(1, 14) = 1.960$, NS). Figure 3 shows the effect of lamotrigine on choice behaviour for all rats, and for each of the conservative and risky group. Similarly, no other variable was significantly affected by the drug (dose, dose x risk, dose x choice: all Fs < 2.100, NS). Table 4 shows the data for the various parameters in the lamotrigine administration challenge in the conservative and risky rats.

3.1.4 Carbamazepine

There was no effect of carbamazepine on choices of the different options at any dose, regardless of the baseline behaviour of the animals (dose: $F(3, 42) = 1.722$, NS; dose x option: $F(4.910, 68.747) = 1.866$, NS; dose x risk group: $F(3, 42) = 2.300$, NS; risk group: $F(1, 14) = 2.413$, NS). Figure 5 demonstrates the effect of carbamazepine on choice behaviour for all rats, and for each of the conservative and risky group. However, an ANOVA and pairwise comparisons showed that, although the lower dose of carbamazepine did not have an effect, both a moderate and higher dose of the drug equally reduced premature responding in all rats (dose: $F(3, 42) = 7.916$, $p < 0.001$; dose x risk group: $F(3, 42) = 2.406$, NS; risk group: $F(1, 14) = 0.208$, NS; vehicle vs CBZ 15 mg/kg: $p = 0.003$; vehicle vs CBZ 30 mg/kg: $p = 0.003$). Figure 6 shows the effect of carbamazepine on premature responses.

Furthermore, each concentration of carbamazepine increased the latency to choose an option in all rats, although there was no differerence between the lower and moderate dose of the drug in creating this effect (dose: $F(1.714, 23.999) = 9.072$, $p = 0.002$; risk group: $F(1, 14) = 17.688$, $p = 0.001$; vehicle vs CBZ 7.5 mg/kg: $p = 0.002$; vehicle vs CBZ 15 mg/kg: $p = 0.016$; vehicle vs CBZ 30 mg/kg: $p = 0.001$). Figure 7 shows the effect of carbamazepine on choice latency. The highest dose of carbamazepine also increased the latency to collect reward in the conservative, but not risky, animals, although there was no overall difference between the risky and conservative rats (dose x risk group: $F(1.344, 18.820) = 4.378$, $p = 0.040$; risk group: $F(1, 14) = 0.323$, NS; conservative- dose: $F(3, 33) = 18.048$, $p < 0.001$; conservative- vehicle vs CBZ 30 mg/kg: $p = 0.012$). Figure 8 shows the effect of carbamazepine on collection latency. Carbamazepine did not alter omissions (dose: $F(3, 42) = 2.100$, NS; dose x risk group: $F(3, 42) = 0.412$, NS) or trials completed (dose: $F(2.086, 29.201) = 1.051$, NS; dose x risk group: $F(2.086, 29.201) = 0.119$, NS). Table 4 shows the data on the various parameters assessed in the carbamazepine administration challenge for both groups of rats.

3.1.5 Anticonvulsant drugs and amphetamine

From the 16 rats who underwent pharmacological administration, three were removed from the analysis of the amphetamine challenge due to excessive sedation or extremely low number of trials performed following drug administration. Choice of the different options was not affected by amphetamine alone, nor when amphetamine was preceded by the various anticonvulsant drugs (dose: $F(4, 44) = 1.872$, NS; drug x option: $F(12, 132) = 0.812$, NS; drug x risk group: $F(4, 44) = 0.968$, NS; risk group: $F(1, 11) = 0.048$, NS). Figure 9 shows the effect of the various anticonvulsants and amphetamine on choice behaviour for all rats, and for each of the conservative and risky group. Premature responses were differentially affected by co-

administration of the different drugs in conservative and risky rats (drug: $F(4, 44) = 5.095$, $p = 0.002$; drug x risk group: $F(4, 44) = 3.152$, $p = 0.023$; risk group: $F(1, 11) = 0.082$, NS; conservative- drug: $F(4, 36) = 2.737$, $p = 0.044$; risky- drug: $F(4, 8) = 11.813$, $p = 0.002$). Pairwise comparisons revealed that in the conservative rats, amphetamine administration increased the number of premature responses made (saline-saline vs saline-amph: $p = 0.018$). In these rats, carbamazepine was the most effective in significantly blocking this increase in premature responses (saline-amph vs CBZ-amph: $p = 0.030$) whereas lamotrigine failed to block this effect of amphetamine administration (saline-saline vs LMG-amph: $p = 0.046$). Valproate followed by amphetamine did not significantly increase nor block the effect of amphetamine and therefore, the number of premature responses made in this condition did not differ from saline (saline-saline vs VPA-amph: NS) or amphetamine administration (saline-amph vs VPA-amph: NS).

In the risky rats, amphetamine did not significantly increase the number of premature responses made (saline-saline vs saline-amph: NS). However, when amphetamine was preceded by valproate or lamotrigine, rats made more premature responses compared to saline administration (saline-saline vs VPA-amph: $p = 0.017$; saline-saline vs LMG-amph: $p = 0.005$). However, carbamazepine had no effect on increasing premature responses when administered prior to amphetamine in this group (saline-saline vs CBZ-amph: NS). Figure 10 demonstrates the anticonvulsants efficacy in blocking the effect of amphetamine administration on premature responding. None of the anticonvulsant drugs followed by amphetamine altered any of the other variables measured (latency to choose an option, omissions made, trials performed, or time to collect a reward; drug, drug x risk group: all $Fs < 1.802$, NS). Table 5 shows the data for the

various parameters assessed in the anticonvulsant and amphetamine challenge for both groups of rats.

3.2 Kindling

3.2.1 rGT baseline behaviour

From the 16 rats in the kindling experiment, four rats were excluded from the analysis due to death following surgery (n = 2), failure to reach level five seizures (n = 1), or poor response to stimulation (n = 1). Similar to the behaviour observed in the antiepileptic drug challenge, rats demonstrated individual preferences for the different options while performing the rGT. This was observed prior to surgery and remained unchanged before start of stimulation (choice option: $F(1.555, 15.554) = 9.758$, $p = 0.003$). Once again, a sub-group of rats (n = 4) were categorized as risky, and the remainder as conservative (choice option x risk group: $F(1.555, 15.554) = 6.055$, $p = 0.016$). Pairwise comparisons showed that most rats like those in the anticonvulsant challenge, the conservative rats, chose the best option P2 most frequently in this order: P2 > P4 > P3 > P1. These rats chose the option P2 significantly more than all other options, which did not differ between each other. In contrast, the risky rats chose in this order: P4 > P2 > P3 > P1. Although their choice of options P4, P2 and P3 did not differ, they chose the option P1 significantly less. It can be noted that the order of the other choice preference differed somewhat from the rats in the anticonvulsant experiment. Figure 11 shows the baseline choice behaviour for the conservative and risky rats prior to start of kindling.

Again, rats were trained until behaviour was stable on all parameters over at least 3 sessions prior to and following surgery. Rats performed 53 sessions prior to surgery and 9 sessions post-surgery prior to start of stimulation. We observed that the risky rats were slower to choose an option compared to the conservative rats prior to start of stimulation, as was observed

in the anticonvulsant drug experiment (choice latency- risk group: $F(1, 10) = 21.068$, $p < 0.001$; risky: $M = 1.943$, $SEM = 0.318$; conservative: $M = 0.789$, $SEM = 0.111$). However, all rats performed a similar number of trials (trial- risk group: $F(1, 10) = 4.855$, NS). No other variables were significantly different between risky and conservative rats (premature responses, omission, collection latency: all Fs < 1.594).

3.2.2 Histology

Histological analysis revealed that electrodes were located either in the basolateral amygdala (BLA; n = 7), and in the central nucleus of the amygdala (CeA; n = 5). Pictures in Figure 5 show both locations although typical slices did not show tracks in such an evident way. We found no signs of neuronal damage. The impact of electrode location on performance was therefore conducted on five consecutive sessions prior to end of stimulation in order to include sessions prior to, and in which criteria for full kindling was reached. There was no significant difference in the effect of stimulation whether the electrode was located in the BLA or in the CeA on any of the behavioural measures (all Fs < 0.215, NS). Therefore, the two groups were pooled together for the remaining analysis. Table 6 shows the data for the various parameters assessed. There was no difference in the average number of stimulations necessary to reach class five seizures ($t(4) = 1.795$, NS). Together, 17.7 stimulations on average were required to reach basic requirement for full kindling. Although seizure duration time was not systematically assessed, the duration of the behavioural seizure lasted for about 40 sec once rats reached a level 5 seizure, which is consistent with previous studies using amygdala kindling (e.g. Howland et al., 2007). Figure 12 shows the placement of the bipolar stimulating electrodes.

3.2.3 Effect of kindling on rGT

Analysis revealed that kindling significantly altered choice behaviour (all conditions: $F(2, 20) = 9.821$, $p = 0.001$; condition x option: $F(6, 60) = 2.327$, $p = 0.044$). We also found a significant main effect when comparing kindling data to pre kindling (condition: $F(1, 10) = 9.926$, $p = 0.010$), as well as between kindling and after stimulation (condition: $F(1, 10) = 17.432$, $p = 0.002$). More specifically, kindling selectively increased choice of P1, which did not depend on rats' baseline preference (P1: all conditions: $F(2, 20) = 9.579$, $p < 0.001$; condition x risk group: $F(2, 20) = 3.015$, NS; pre vs during kindling conditions: $F(1, 10) = 10.198$, $p = 0.010$; post vs during kindling conditions: $F(1, 10) = 18.348$, $p = 0.002$; options P2, P3 and P4 all Fs < 2.186, NS).

There was no difference when comparing choice behaviour prior to and after stopping stimulation (condition: $F(1, 10) = 2.644$, NS; risk group $F(1, 10) = 0.237$, NS) showing that any effect of kindling disappeared once stimulation ceased. A difference emerged between the risky and conservative rats if the post-kindling sessions were analysed by themselves or in comparison to the kindling sessions (condition x risk group: $F(1, 10) = 6.211$, $p = 0.032$; post kindling, risk group: $F(1, 10) = 5.665$, $p = 0.039$). However, although choice between the groups appeared different, there was no significant change when comparing pre vs post kindling within each subject group i.e. the choice behavior of each groups of rats after kindling did not differ statistically from their baseline choice behaviour (condition x risk group $F(1, 10) = 2.551$). The statistical difference reported is therefore not indicative of a genuine change in choice caused by kindling in this subgroup, but rather a reduction in variation around the mean. Figure 13 shows the effect of kindling on the different choice option.

Kindling increased the number of premature responses made (all conditions: $F(2, 20) = 13.363$, $p < 0.001$; condition x risk group: $F(2, 20) = 6.264$, $p = 0.008$; risk group: $F(1, 10) = 1.348$, NS). When comparing premature responding made prior to kindling and during kindling, risky rats made significantly more of these impulsive responses (condition- pre-kindling vs kindling: $F(1, 10) = 25.706$, $p < 0.001$; condition x risk group: $F(1, 10) = 10.568$, $p = 0.009$; risky- pre-kindling vs kindling: $p < 0.001$; conservative- pre-kindling vs kindling: NS). There were no differences in premature responding between the pre- and post-kindling sessions, indicating that the increase in impulsivity observed in the risky rats was not long-lasting (condition pre vs post-kindling: $F(1, 10) = 0.117$, NS; condition x risk group: $F(1, 10) = 0.486$, NS). Figure 14 demonstrates the effect of kindling on premature responses.

Kindling also decreased choice latency in the risky, but not conservative, rats (all conditions: $F(2, 20) = 11.587$, $p < 0.001$; condition x risk group: $F(2, 20) = 16.602$, $p < 0.001$; $F(1, 10) = 9.277$, $p = 0.012$). Analysis of the different conditions and pairwise comparisons showed that, as noted above, risky rats were actually slower to choose an option than conservative rats during the pre-kindling baseline, but this difference was ameliorated by kindling (pre vs during kindling: condition: $F(1, 10) = 18.037$, $p = 0.002$; condition x risk group: $F(1, 10) = 25.692$, $p < 0.001$; risky- before vs kindling $p < 0.001$; conservative- before vs kindling: NS). This reduction in choice latency in the risky rats was still evident after kindling had ceased, as indicated by a significant difference in speed of decision-making when comparing the pre- and post- kindling periods (pre vs post-kindling- condition: $F(1, 10) = 11.609$, $p = 0.007$; condition x risk group: $F(1, 10) = 17.089$, $p = 0.002$; risky- kindling vs after: $p < 0.001$; conservative- kindling vs after: NS). Figure 15 shows the effect of kindling on choice latency.

Across conditions, the risky rats performed less trials per session compared to the conservative rats, but this effect does not appear to be due to the effect of kindling (all condition: $F(1.312, 13.125) = 2.603$, NS; condition x risk group: $F(1.312, 13.125) = 0.378$, NS; risk group: $F(1, 10) = 5.389$, $p = 0.043$). Although this was not observed prior to start of stimulation, this difference may be due to the capacity of the conservative rats to perform more trials as the punishment periods were shorter. Risky rats also made considerably more premature responses during kindling, which would impact the number of trials completed. There was, however, no overall effect of kindling on trials, or on choice omissions and collection latency (all Fs < 2.603, NS). Table 7 shows the data for the various parameters assessed in the risky and conservative rats.

3.2.4 Kindling—Carbamazepine challenge

Since two groups of rats were kindled at two different time points, the first group of rats to be kindled underwent a longer period following the last stimulation prior to the single stimulation (4 weeks) compared to the second group to be kindled (2 weeks). However, comparison between these two groups did not show differences on any of the behavioural parameters assessed (all Fs < 2.768, NS). Also, the extended period when rats were not stimulated prior to start of the carbamazepine challenge did not affect the degree of seizure elicited with a single stimulation regardless of the stimulation group, with all rats reaching a stage five seizure. Contrary to the effect of kindling on choice behaviour, a single stimulation did not affect choice of the different options, regardless of whether it was preceded by saline or carbamazepine (condition: $F(2, 20) = 0.625$, NS; condition x risk group: $F(2, 20) = 0.152$, NS; condition x option: $F(6, 60) = 0.464$, NS; risk group: $F(1, 10) = 1.463$, NS). Figure 16 shows the effect of carbamazepine on choice of the different options.

Furthermore, a single stimulation did not increase the number of premature responses made by the rats, regardless of the agent administered prior to the stimulation (condition: $F(1.237, 12.373) = 3.338$, NS; condition x risk group: $F(1.237, 12.373) = 2.120$, NS; risk group: $F(1, 10) = 0.783$, NS). However, we observed an effect of stimulation on the time to collect a reward, which was qualified by an interaction with rats' preference for the risky or safe options (condition: $F(2, 20) = 10.080$, $p = 0.001$; condition x risk group: $F(2, 20) = 6.671$, $p = 0.006$; risk group: $F(1, 10) = 1.107$, NS). Pairwise comparisons showed that the latency to collect a reward increased in risky rats with a single stimulation regardless of whether it followed saline ($p = 0.004$) or carbamazepine ($p = 0.002$) administration. Although not significant, risky rats were faster to collect reward than conservative animals during the post-kindling baseline, and this difference appeared to be reversed by a single stimulation. Figure 17 shows the effect of carbamazepine administration prior to a single stimulation on collection latency. There was no other effect of single stimulation in the carbamazepine on omission made, number of trials performed or choice latency (all Fs < 3.390). Table 8 shows the data for the various parameters assessed in the carbamazepine followed by a stimulation challenge for both groups of rats.

Figures

Figure 1: Schematic of the rat Gambling Task

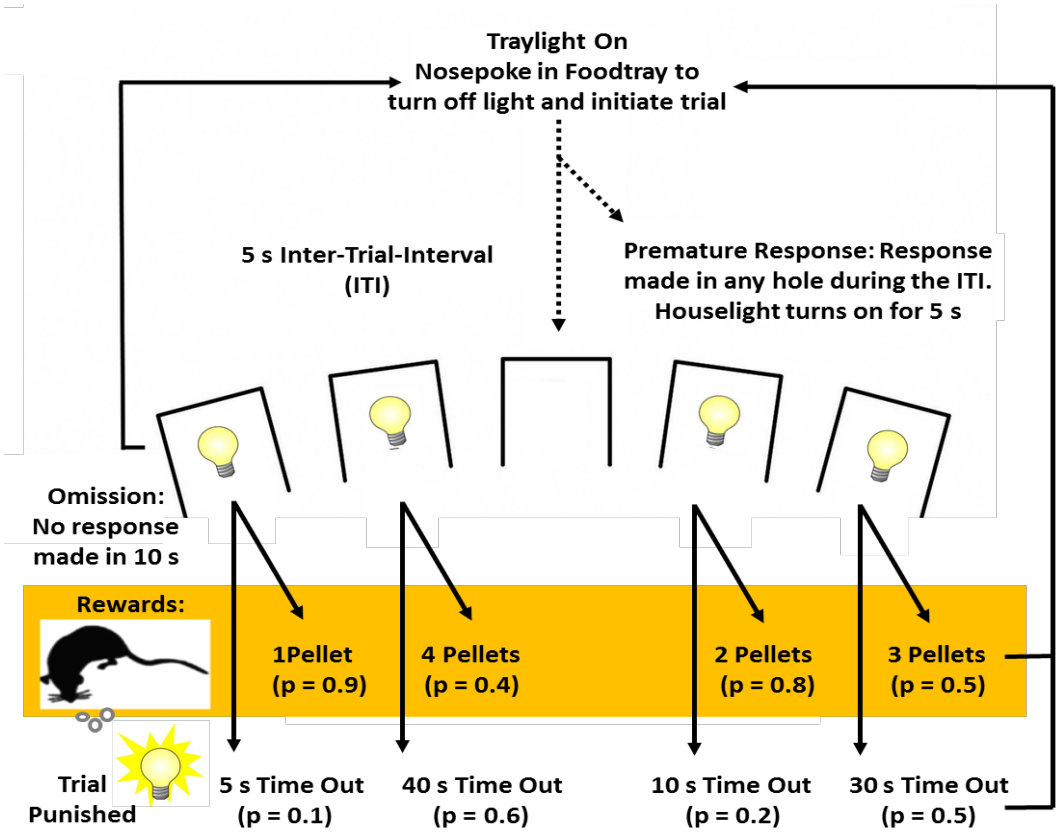

Figure 1: The task began when the animal made a nose-poke response in the food tray. The animal then needed to withhold responding for a 5 sec inter-trial interval (ITI) after which 4 holes were illuminated. Responding during the ITI was considered a premature response. In this task, each hole was associated with a different number of sucrose pellets (1-4), as well as a different frequency and duration of punishment "time-out" periods during which reward could not be earned. The most advantageous option, the option that gave the most pellets over a 30 min session, was the 2-pellet option (P2), whereas the most disadvantageous option was P4.

Figure 2: Baseline choice behaviour prior to the anticonvulsant drug challenge

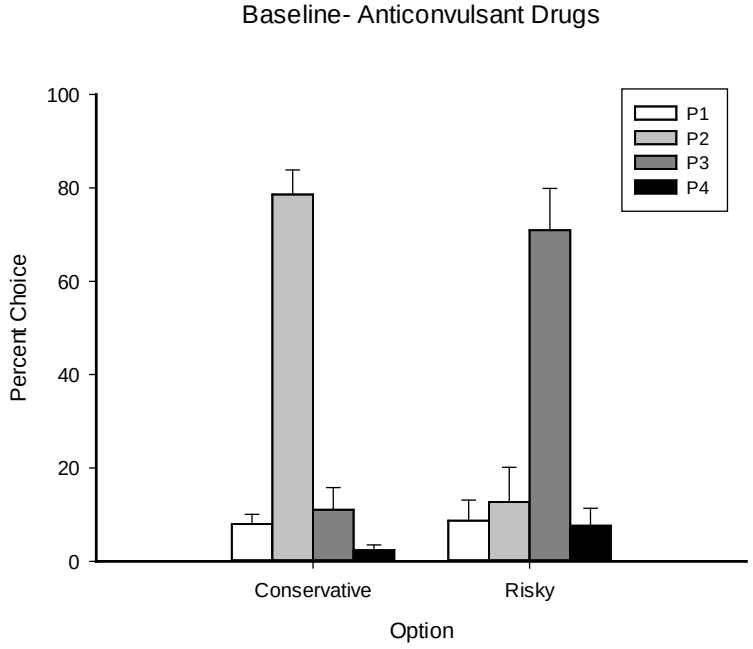

Figure 2: Percentage choice of the different option made by the conservative and risky rats prior to start of the anticonvulsant challenge. The conservative rats showed preference in the order of P2 > P3 > P1 > P4 whereas the risky rats showed preference in the order of P3 > P2 > P1 > P4. Data shown are mean ± SEM.

Figure 3: Effect of valproate on choice behaviour

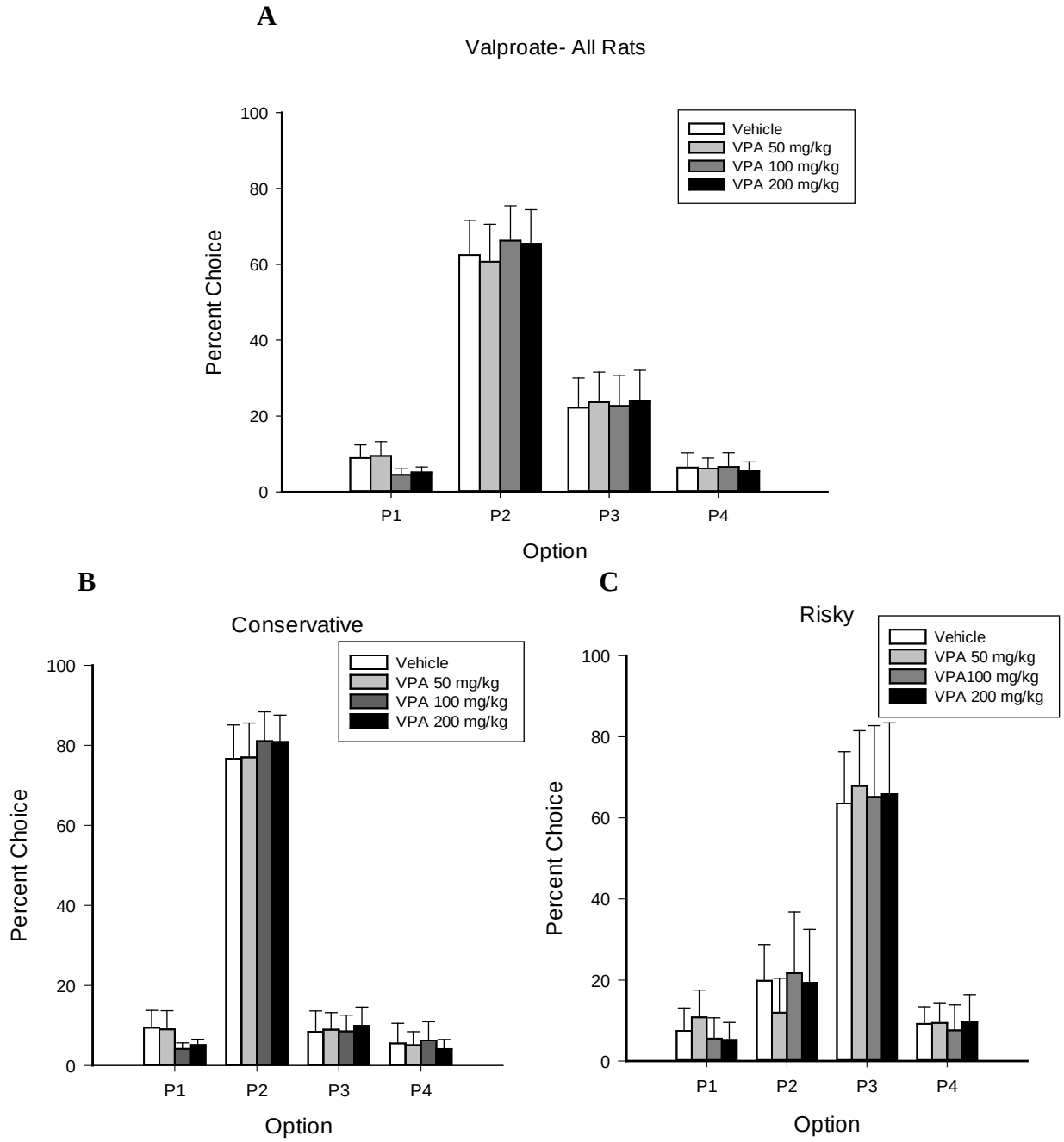

Figure 3: Percentage choice of the different option following administration of valproate. A: Percent choice including all rats. B: Choice in the conservative rats. C: Choice in the risky rats. VPA: valproate. Data shown are mean ± SEM.

Figure 4: Effect of lamotrigine on choice behaviour

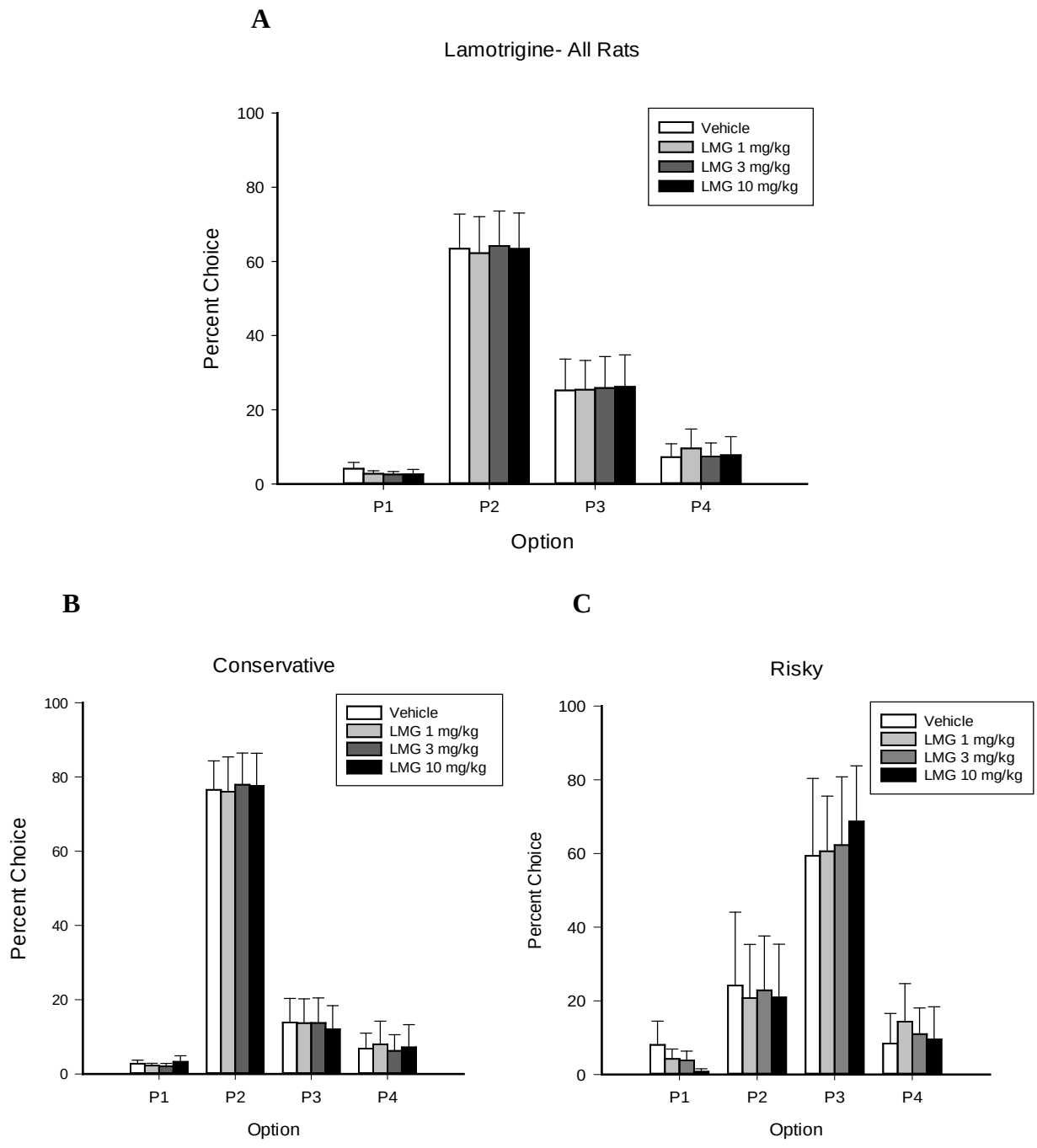

Figure 4: Percentage choice of the different option following administration of lamotrigine. A: Percent choice including all rats. B: Choice in the conservative rats. C: Choice in the risky rats. LMG: lamotrigine. Data shown are mean ± SEM.

Figure 5: Effect of carbamazepine on choice behaviour

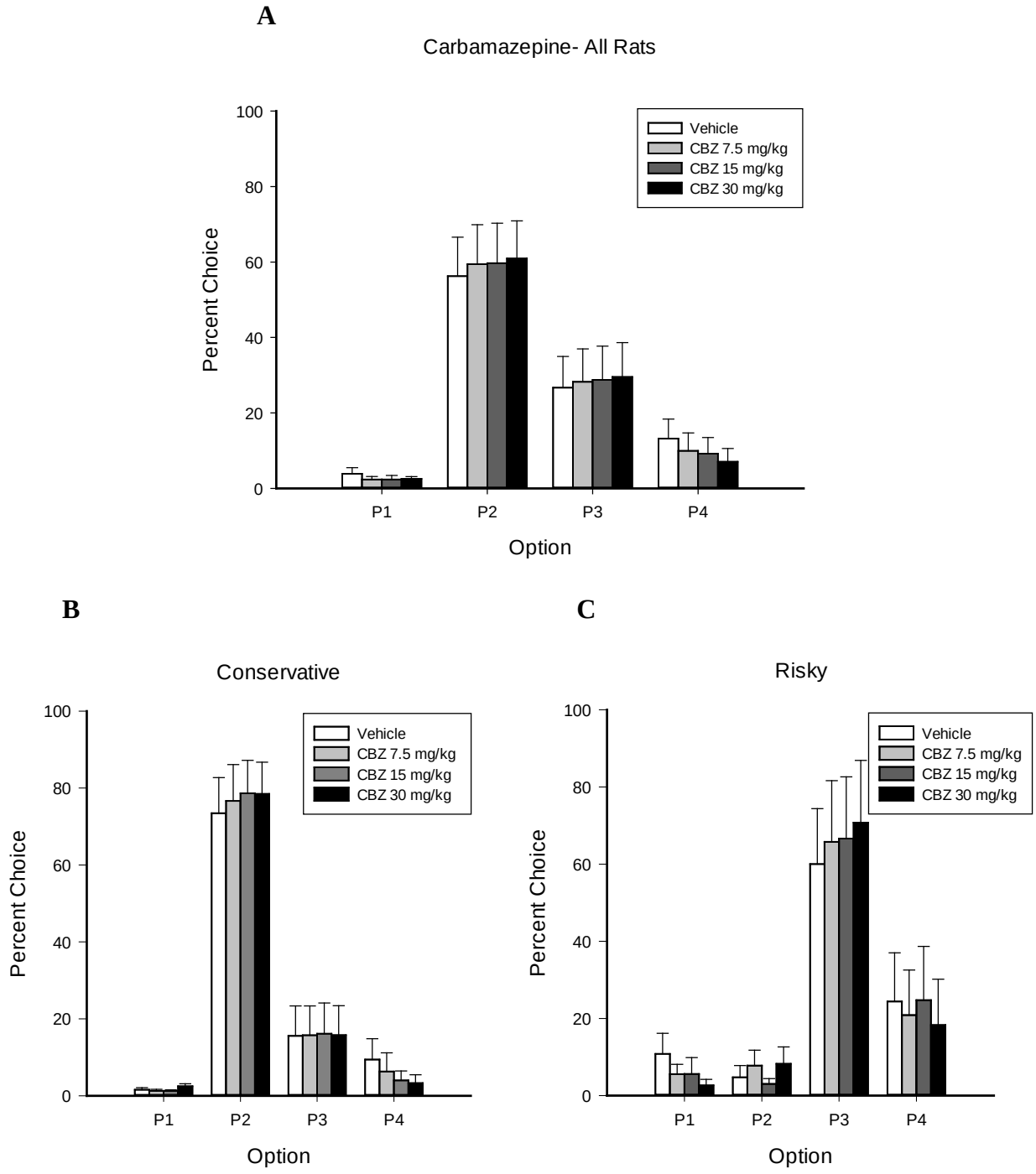

Figure 5: Percentage choice of the different option following administration of carbamazepine. A: Percent choice including all rats. B: Choice in the conservative rats. C: Choice in the risky rats. CBZ: carbamazepine. Data shown are mean ± SEM.

Figure 6: Effect of carbamazepine on premature responses

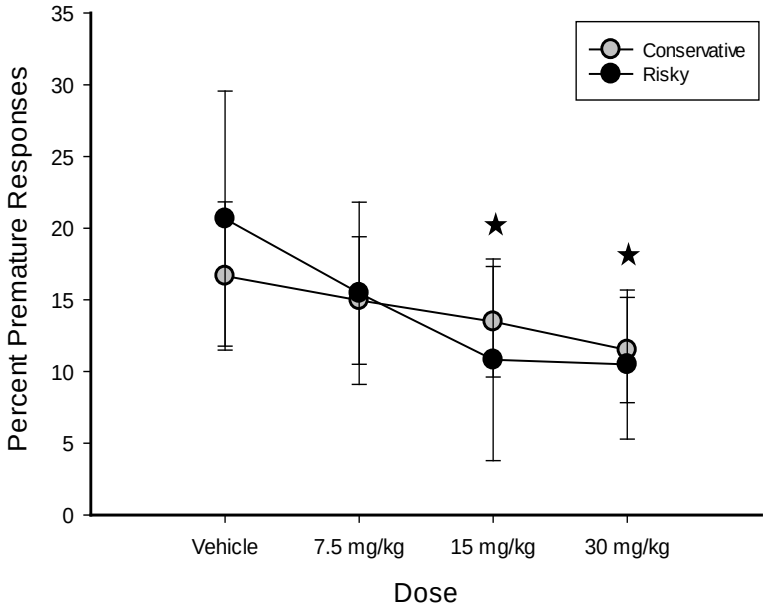

Figure 6: Percentage of premature responses made by the conservative and risky rats at each dose of carbamazepine. A moderate and higher dose of the drug reduced premature responses in all rats. Data shown are mean ± SEM.

Figure 7: Effect of carbamazepine on choice latency

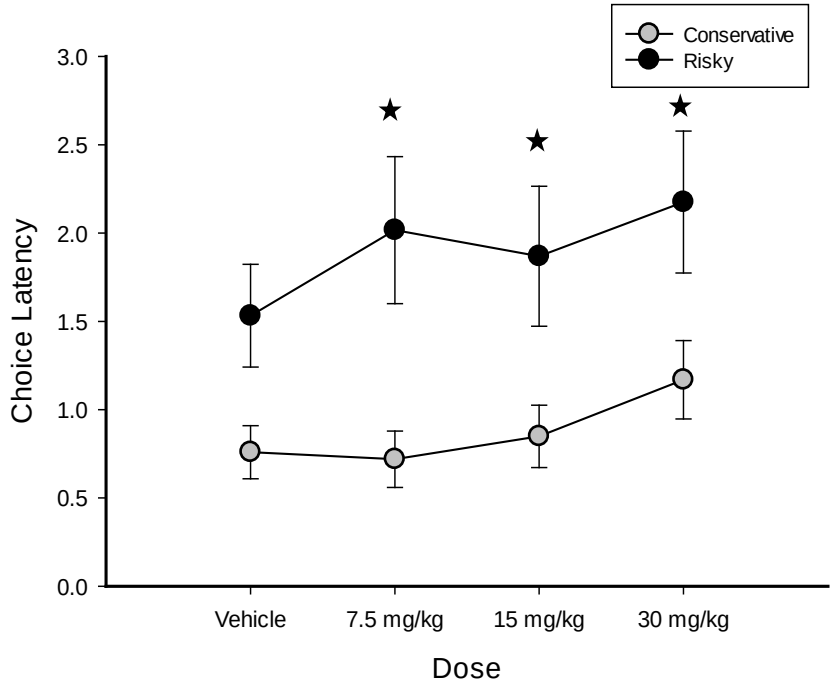

Figure 7: Latency to choose an option in the conservative and risky rats at each dose of carbamazepine. Each dose of the drug increased choice latency in all rats. Data shown are mean ± SEM.

Figure 8: Effect of carbamazepine on collection latency

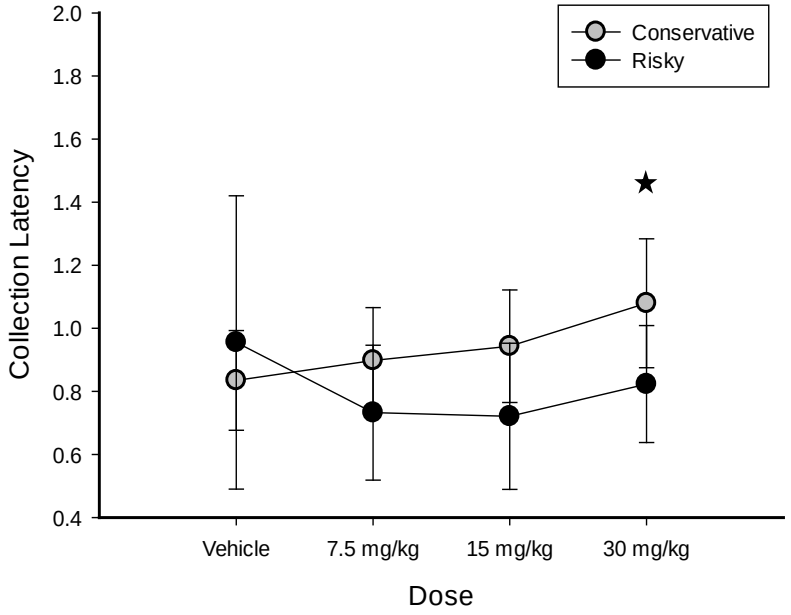

Figure 8: Latency to collect a reward in the conservative and risky rats at each dose of carbamazepine. The highest dose of the drug increased collection latency in the conservative rats. Data shown are mean ± SEM.

Figure 9: Effect of the various anticonvulsant drugs on choice behaviour in the amphetamine challenge

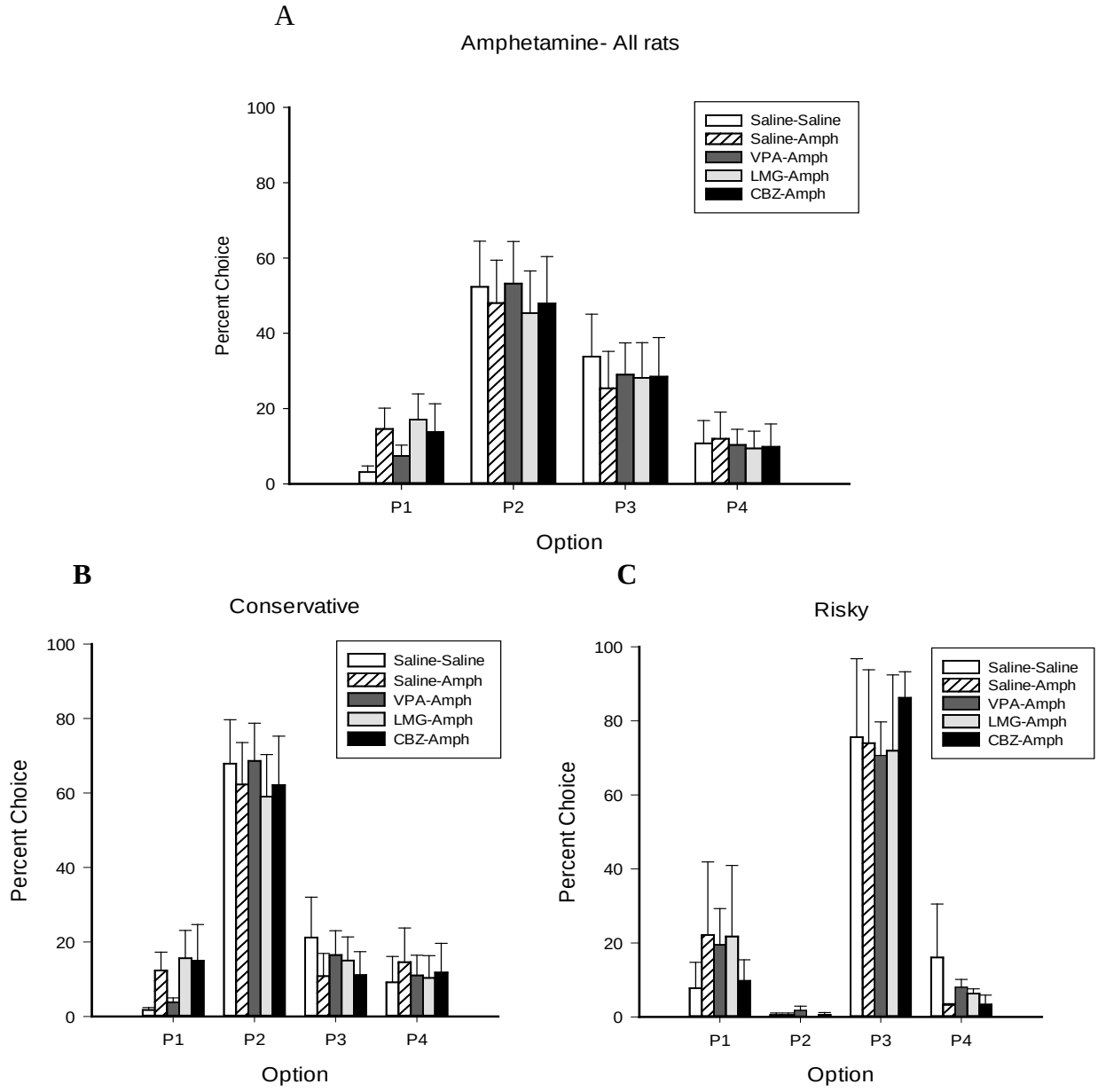

Figure 9: Percentage choice of the different option following administration of amphetamine and the various anticonvulsant drugs. A: Percent choice including all rats. B: Choice in the conservative rats. C: Choice in the risky rats. Amph: 1 mg/kg amphetamine, VPA: 200 mg/kg valproate, LMG: 10 mg/kg lamotrigine, CBZ: 15 mg/kg carbamazepine. Data shown are mean ± SEM.

Figure 10: Anticonvulsants efficacy in blocking the effect of amphetamine administration on premature responding

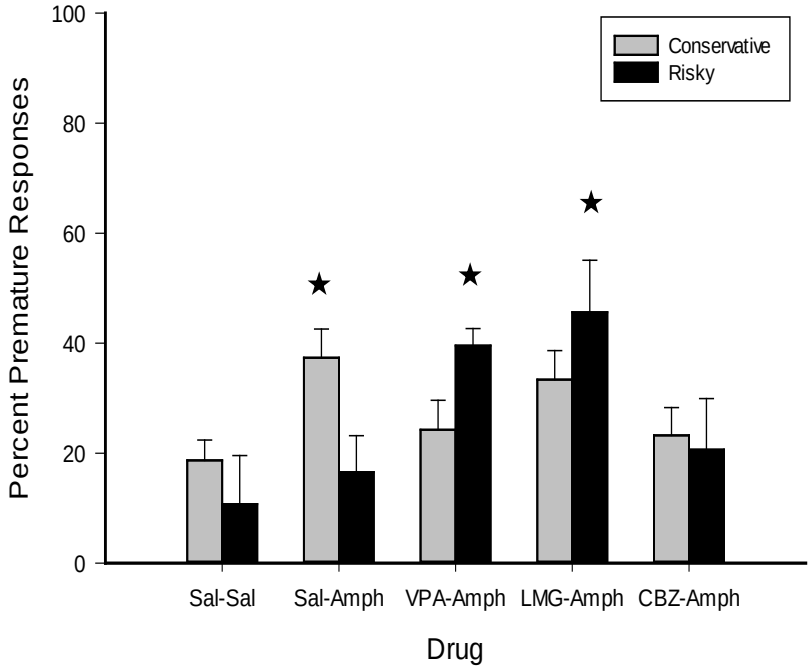

Figure 10: Effect of anticonvulsant drugs in blocking the ability of amphetamine to increase premature responding in conservative and risky rats. In the conservative rats, amphetamine increased premature responses, an effect which was attenuated by valproate and carbamazepine but not lamotrigine. In the risky rats, amphetamine did not increase premature responses, but such responses were increased when valproate or lamotrigine preceded amphetamine administration. Sal: saline solution, Amph: 1 mg/kg amphetamine, VPA: 200 mg/kg valproate, LMG: 10 mg/kg lamotrigine, CBZ: 15 mg/kg carbamazepine. Data shown are mean ± SEM.

Figure 11: Baseline choice behaviour prior to kindling

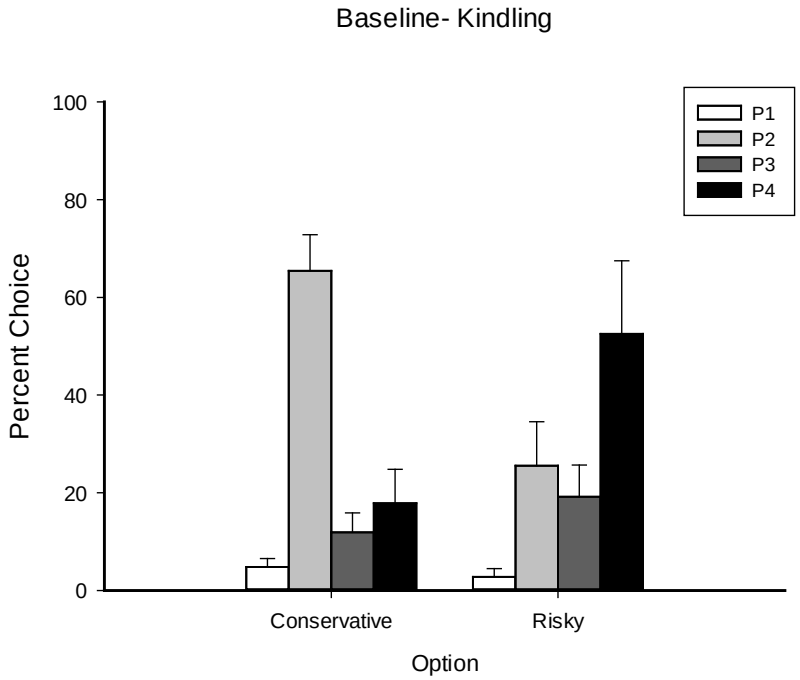

Figure 11: Percentage choice of the different option made by the conservative and risky rats prior to start of kindling. The conservative rats showed preference in the order of P2 > P4 > P3 > P1 whereas the risky rats showed preference in the order of P4 > P2 > P3 > P1. Data shown are mean ± SEM.

Figure 12: Placement of bipolar stimulating electrodes

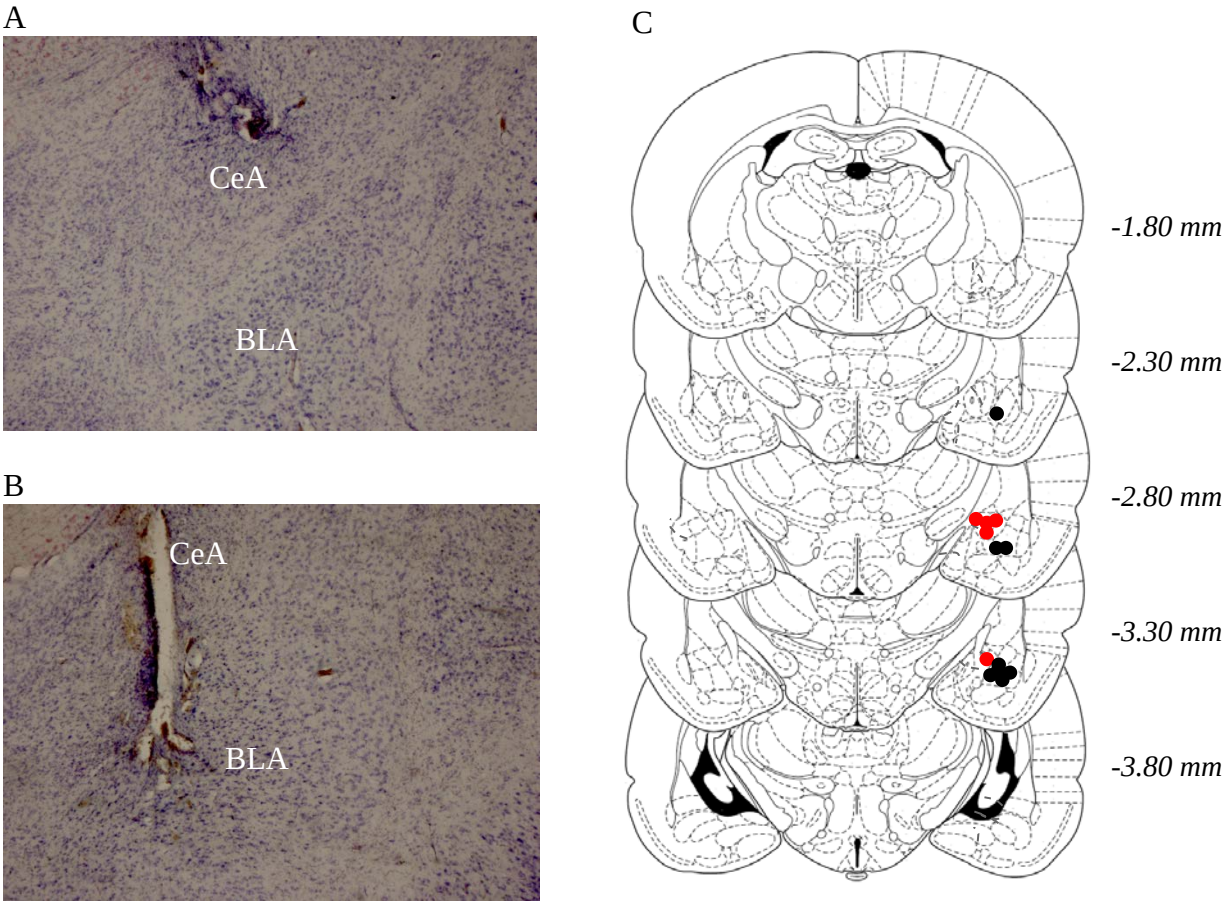

Figure 12: (A-B): Photomicrograph of placement of the bipolar stimulating electrodes. A: Electrode placed in the central nucleus of the amygdala (CeA). B: Electrode placed in the basolateral amygdala (BLA). C: Illustration of the placement of the bipolar electrodes in all rats. Red dots demonstrate CeA locations. Black dots demonstrate BLA locations.

Figure 13: Effect of kindling on choice option

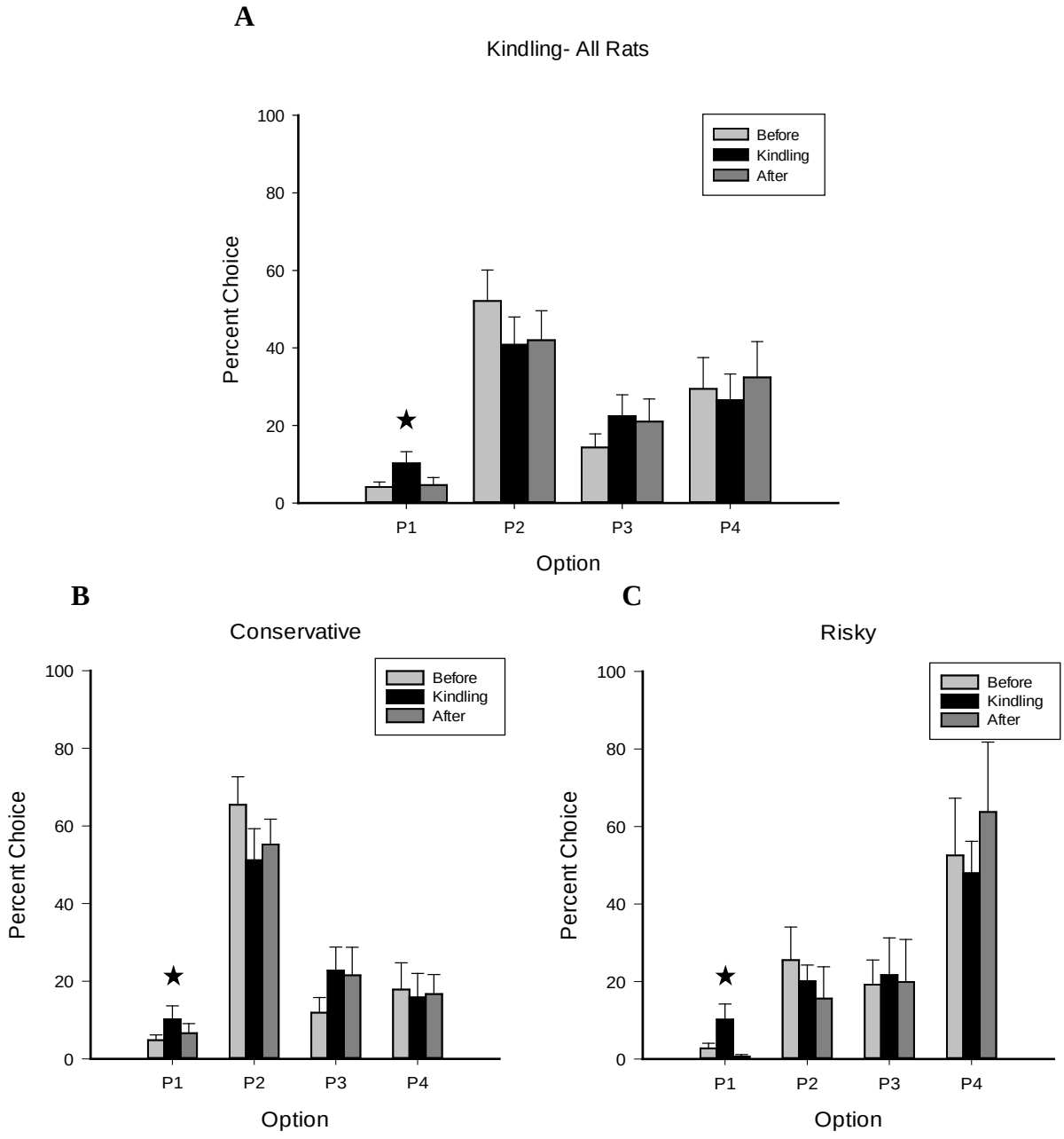

Figure 13: Percentage choice of the different option in the kindling experiment prior to, during, and following kindling. A: Percent choice including all rats. B: Choice in the conservative rats. C: Choice in the risky rats. All rats increased their choice of the option P1 during kindling but choice of the other options was not affected. Data shown are mean ± SEM.

Figure 14: Effect of kindling on premature responses

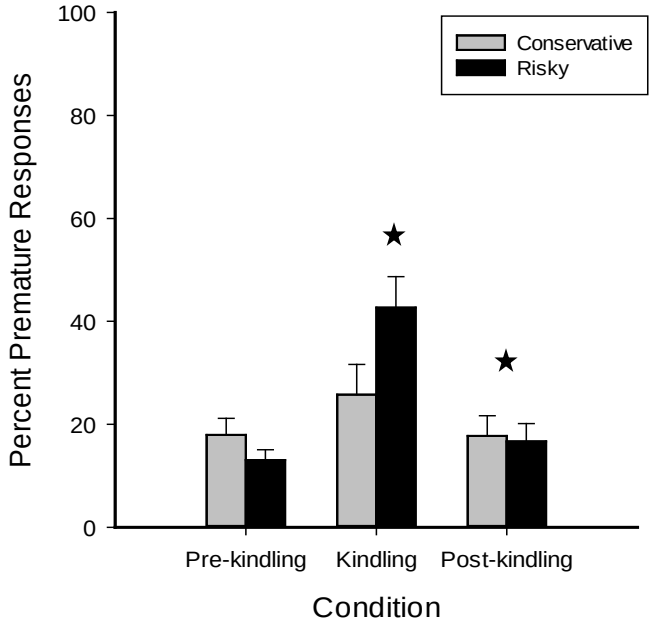

Figure 14: Percent premature responses made by the conservative and risky rats prior to start of stimulation, during kindling, and after stimulation ended. Kindling increased premature responses in the risky, but not the conservative rats. Premature responses returned to baseline after stimulation ended. Data shown are mean ± SEM.

Figure 15: Effect of kindling on choice latency

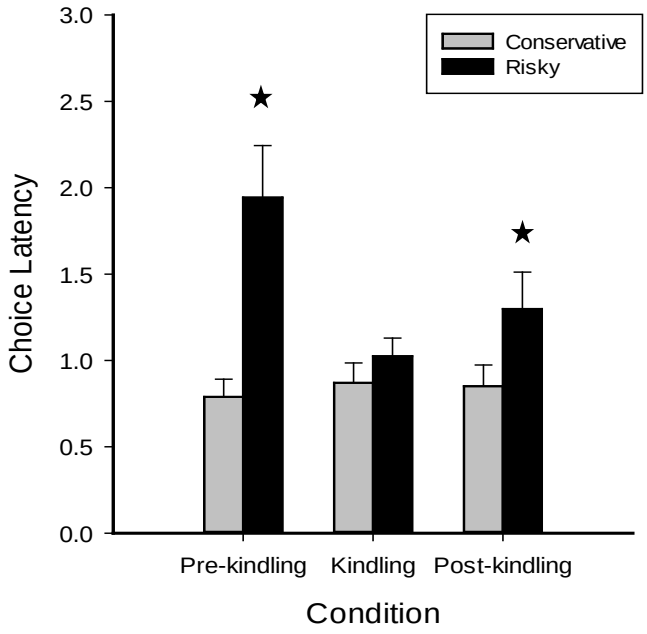

Figure 15: Latency to choose an option in the risky rats prior to start of stimulation, during kindling, and after stimulation ended. Kindling reduced choice latency in the risky rats, but did not affect the conservative rats. Choice latency increased in the risky rats after end of stimulation, but did not return to baseline. Data shown are mean ± SEM.

Figure 16: Effect of carbamazepine prior to a single stimulation on choice behaviour

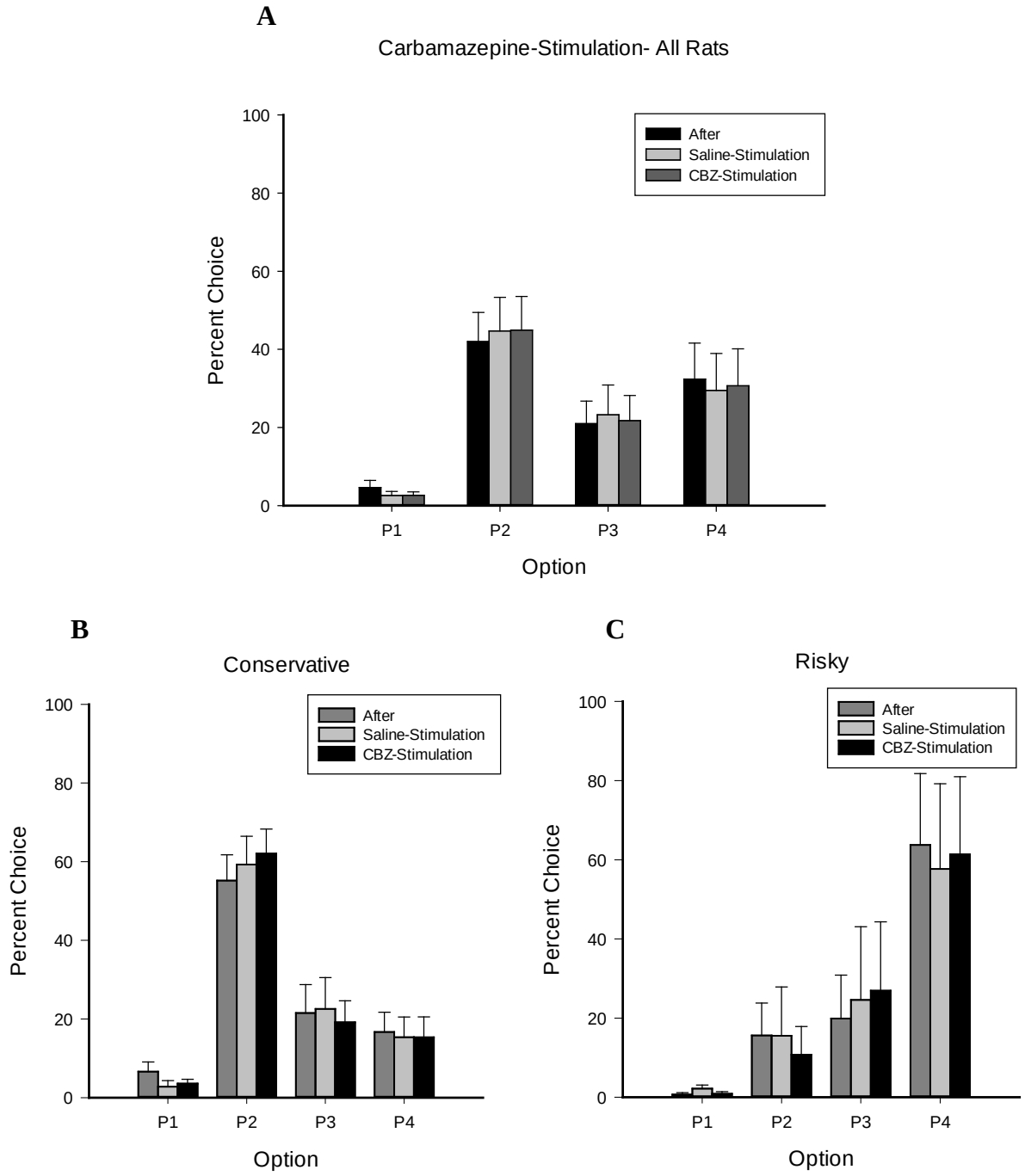

Figure 16: Percentage choice of the different option in the carbamazepine followed by stimulation. A: Percent choice including all rats. B: Choice in the conservative rats. C: Choice in the risky rats. Data shown are mean ± SEM.

Figure 17: Effect of carbamazepine prior to a single stimulation on collection latency

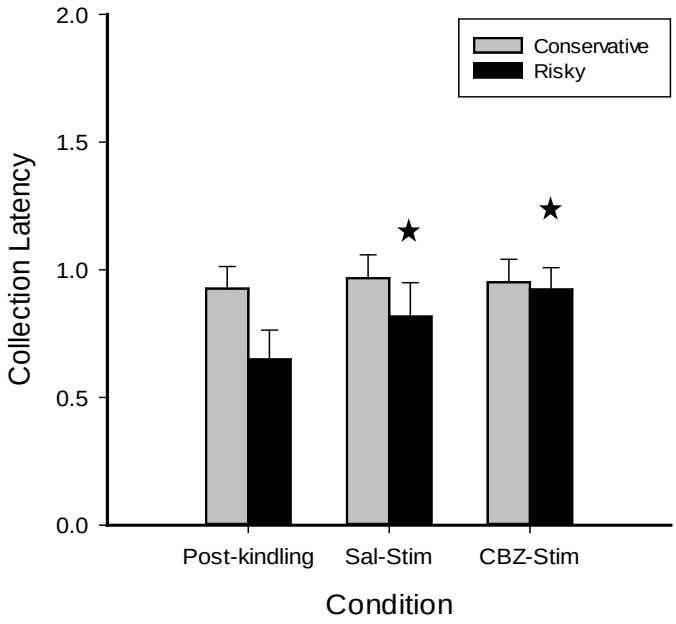

Figure 17: Collection latency following saline or carbarbamazepine and a single stimulation in previously kindled rats. Collection latency increased in the risky rats following single stimulation, regardless of the agent previously administered to make them more similar to the conservative rats. Single stimulation did not affect collection latency in the conservative rats. Sal: saline solution, Stim: stimulation, CBZ: carbamazepine. Data shown are mean ± SEM.

Tables

Table 1: Convulsion class monitoring sheet

	Rat #:					
	Date:					
	Stimulation number:	**1**	**2**	**3**	**4**	**5**
Stage:	**Symptoms**					
	Immobility					
	Twitching of the whiskers					
	Chewing movements of the jaw					
1	Eye closure					
	More severe facial clonus					
2	Head nodding					
3	Unilateral forelimb clonus					
	Bilateral forelimb clonus					
4	Rearing					
	Loss of balance					
5	Falling once					
	Multiple rearings					
6	Multiple fallings					
7	Running fits					
8	Periods of tonus					
Exclusion criteria:	Complete immobility					
	Rapid respiration					
	Squealing					
	Flight					
Overall health:	Class #					
	Need for exclusion?					

Table 1: Convulsion stage was assessed using this convulsion class monitoring sheet during each stimulation, which occurred twice daily.

Table 2: Effect of valproate on the various parameters of decision-making

		Trial	Premature	Omission	Choice Latency	Collection Latency
Vehicle	Conservative	114.17 ± 10.31	24.11 ± 3.67	0.33 ± 0.14	0.88 ± 0.08	0.82 ± 0.10
	Risky	74.00 ± 4.02	23.84 ± 4.18	0.00 ± 0.00	1.42 ± 0.28	0.71 ± 0.10
VPA 50 mg/kg	Conservative	111.67 ± 11.52	23.77 ± 2.93	1.50 ± 0.95	1.08 ± 0.20	1.04 ± 0.20
	Risky	70.00 ± 3.70	25.69 ± 8.03	0.00 ± 0.00	1.42 ± 0.29	0.73 ± 0.13
VPA 100 mg/kg	Conservative	115.67 ± 10.16	26.57 ± 4.16	0.08 ± 0.08	0.83 ± 0.10	0.78 ± 0.09
	Risky	78.25 ± 8.98	16.67 ± 3.99	0.25 ± 0.25	1.60 ± 0.37	0.70 ± 0.10
VPA 200 mg/kg	Conservative	124.17 ± 10.03	20.44 ± 4.09	0.33 ± 0.19	1.10 ± 0.14	0.93 ± 0.08
	Risky	73.00 ± 7.01	19.51 ± 6.10	0.25 ± 0.25	1.88 ± 0.32	0.73 ± 0.11

Table 2: Various parameters of decision-making following valproate administration in the conservative and risky rats. Valproate at any dose did not affect decision-making. VPA: valproate. Data shown are mean ± SEM.

Table 3: Effect of lamotrigine on the various parameters of decision-making

		Trial	Premature	Omission	Choice Latency	Collection Latency
Vehicle	Conservative	115.75 ± 11.93	23.24 ± 4.96	0.33 ± 0.14	1.23 ± 0.24	0.82 ± 0.09
	Risky	81.50 ± 11.83	15.59 ± 4.08	1.00 ± 0.71	0.80 ± 0.18	0.76 ± 0.12
LMG 1 mg/kg	Conservative	116.00 ± 12.69	24.00 ± 4.60	0.33 ± 0.25	1.23 ± 0.19	0.82 ± 0.10
	Risky	73.00 ± 10.65	17.46 ± 10.46	0.00 ± 0.00	0.70 ± 0.22	0.70 ± 0.18
LMG 3 mg/kg	Conservative	116.08 ± 11.17	21.78 ± 3.79	0.50 ± 0.29	1.20 ± 0.21	0.84 ± 0.10
	Risky	71.50 ± 11.88	24.07 ± 12.47	0.50 ± 0.50	0.67 ± 0.14	0.66 ± 0.09
LMG 10 mg/kg	Conservative	124.50 ± 11.22	18.36 ± 3.94	0.33 ± 0.14	1.34 ± 0.18	0.93 ± 0.10
	Risky	76.75 ± 11.12	14.66 ± 5.99	0.50 ± 0.29	0.92 ± 0.19	0.75 ± 0.14

Table 3: Various parameters of decision-making following lamotrigine administration in the conservative and risky rats. Lamotrigine at any dose did not affect decision-making. LMG: lamotrigine. Data shown are mean ± SEM.

Table 4: Effect of carbamazepine on the various parameters of decision-making

		Trial	Premature	Omission	Choice Latency	Collection Latency
Vehicle	Conservative	116.67 ± 12.95	16.67 ± 2.99	0.08 ± 0.08	0.76 ± 0.09	0.83 ± 0.09
	Risky	61.25 ± 4.21	20.67 ± 8.90	0.25 ± 0.25	1.53 ± 0.29	0.96 ± 0.47
CBZ 7.5 mg/kg	Conservative	123.17 ± 13.26	14.96 ± 2.57	0.25 ± 0.25	0.72 ± 0.09	0.90 ± 0.10
	Risky	65.25 ± 1.97	15.46 ± 6.35	0.75 ± 0.25	2.02 ± 0.42	0.73 ± 0.21
CBZ 15 mg/kg	Conservative	124.08 ± 10.97	13.47 ± 2.23	0.25 ± 0.13	0.85 ± 0.10	0.94 ± 0.10
	Risky	65.25 ± 2.78	10.82 ± 7.03	0.50 ± 0.29	1.87 ± 0.40	0.72 ± 0.23
CBZ 30 mg/kg	Conservative	127.42 ± 10.30	11.50 ± 2.12	0.50 ± 0.29	1.17 ± 0.13	1.08 ± 0.12
	Risky	66.50 ± 1.04	10.49 ± 5.20	1.25 ± 0.75	2.18 ± 0.40	0.82 ± 0.19

Table 4: Various parameters of decision-making following carbamazepine administration in the conservative and risky rats. A moderate and higher dose of the drug reduced premature responses in all rats. Each dose of the drug increased choice latency in all rats and only the highest dose of the drug increased collection latency in the conservative rats. CBZ: carbamazepine. Data shown are mean ± SEM.

Table 5: Effect of anticonvulsant drugs and amphetamine on the various parameters of decision-making

		Trial	Premature	Omission	Choice Latency	Collection Latency
Saline-Saline	Conservative	116.64 ± 12.39	17.28 ± 3.48	0.36 ± 0.27	0.67 ± 0.05	0.87 ± 0.13
	Risky	66.75 ± 2.17	12.43 ± 6.46	0.75 ± 0.75	1.41 ± 0.24	0.72 ± 0.17
Saline-Amph	Conservative	78.09 ± 11.97	41.22 ± 5.83	0.09 ± 0.09	0.66 ± 0.06	0.64 ± 0.07
	Risky	79.00 ± 11.17	16.54 ± 5.75	0.00 ± 0.00	1.24 ± 0.31	0.64 ± 0.07
VPA-Amph	Conservative	78.58 ± 10.88	28.23 ± 6.63	1.50 ± 0.89	1.32 ± 0.37	2.38 ± 1.55
	Risky	58.67 ± 3.25	39.56 ± 2.70	0.33 ± 0.29	1.30 ± 0.24	0.81 ± 0.20
LMG-Amph	Conservative	72.52 ± 8.23	39.57 ± 6.12	0.00 ± 0.00	0.70 ± 0.07	0.74 ± 0.14
	Risky	42.33 ± 11.06	45.63 ± 8.18	0.00 ± 0.00	0.93 ± 0.06	0.97 ± 0.27
CBZ-Amph	Conservative	107.67 ± 11.00	26.01 ± 5.46	0.33 ± 0.19	0.72 ± 0.07	0.86 ± 0.14
	Risky	65.33 ± 4.16	20.64 ± 8.05	0.33 ± 0.29	1.63 ± 0.80	0.85 ± 0.27

Table 5: Various parameters of decision-making in the conservative and risky rats. In the conservative rats, amphetamine increased premature responses, an effect which was attenuated by valproate and carbamazepine but not lamotrigine. In the risky rats, amphetamine did not increase premature responses, but such responses were increased when valproate or lamotrigine preceded amphetamine administration. Amph: 1 mg/kg amphetamine, VPA: 200 mg/kg valproate, LMG: 10 mg/kg lamotrigine, CBZ: 15 mg/kg carbamazepine. Data shown are mean ± SEM.

Table 6: Effect of the placement of stimulating electrode

	Basolateral Amygdala	Central Nucleus of the Amygdala
Trial	80.80 ± 14.15	74.68 ± 8.37
Premature	30.90 ± 7.97	28.79 ± 5.72
Omission	0.46 ± 0.40	0.44 ± 0.33
Choice Latency	0.93 ± 0.13	0.95 ± 0.18
Collection Latency	0.90 ± 0.12	0.84 ± 0.04

Table 6: Various parameters of decision-making depending on the location of the stimulating electrode. Placement shown in the basolateral and central nucleus of the amygdala for the conservative and risky rats. Data shown during kindling. Data shown are mean ± SEM.

Table 7: Effect of kindling on the different parameters of decision-making

	Pre-Kindling		Kindling		Post-Kindling	
	Conservative	Risky	Conservative	Risky	Conservative	Risky
Trial	100.71 ± 13.08	62.58 ± 6.31	88.08 ± 10.85	54.33 ± 3.73	92.13 ± 9.32	59.42 ± 5.62
Premature	17.95 ± 3.20	13.04 ± 2.03	25.75 ± 5.89	42.66 ± 6.03	17.74 ± 3.93	16.66 ± 3.47
Omission	0.29 ± 0.10	0.50 ± 0.22	0.67 ± 0.40	0.08 ± 0.08	0.38 ± 0.33	0.08 ± 0.08
Choice Latency	0.79 ± 0.10	1.94 ± 0.30	0.87 ± 0.12	1.02 ± 0.11	0.85 ± 0.11	1.30 ± 0.21
Collection Latency	1.03 ± 0.08	0.82 ± 0.13	0.96 ± 0.90	0.71 ± 0.05	0.93 ± 0.09	0.65 ± 0.11

Table 7: Various parameters of decision-making in the kindling experiment for the conservative and risky rats. Kindling increased premature responses in the risky, but not the conservative rats. Kindling also reduced choice latency in the risky rats, but did not affect the conservative rats. Choice latency increased in the risky rats after end of stimulation, but did not return to baseline. Data shown are mean ± SEM.

Table 8: Effect of carbamazepine on the different parameters of decision-making

	Post-Kindling		Saline-Stimulation		CBZ-Stimulation	
	Conservative	Risky	Conservative	Risky	Conservative	Risky
Trial	92.13 ± 9.32	59.42 ± 5.62	93.63 ± 12.31	65.50 ± 7.42	95.88 ± 12.74	59.50 ± 8.57
Premature	17.74 ± 3.93	16.66 ± 3.47	16.83 ± 5.18	28.77 ± 9.61	17.77 ± 5.43	18.95 ± 7.35
Omission	0.38 ± 0.33	0.08 ± 0.08	0.13 ± 0.13	0.00 ± 0.00	0.38 ± 0.26	1.00 ± 0.71
Choice Latency	0.85 ± 0.11	1.30 ± 0.21	1.09 ± 0.23	1.49 ± 0.20	1.03 ± 0.17	1.26 ± 0.19
Collection Latency	0.93 ± 0.09	0.65 ± 0.11	0.97 ± 0.09	0.82 ± 0.13	0.95 ± 0.09	0.92 ± 0.09

Table 8: Various parameters of decision-making in carbamazepine followed by a stimulation for the conservative and risky rats. Collection latency increased in the risky rats following single stimulation, regardless of the agent previously administered to make them more similar to the conservative rats. Single stimulation did not affect collection latency in the conservative rats. CBZ: carbamazepine. Data shown are mean ± SEM.

4. Discussion

The first experiment in this thesis investigated the effect of three anticonvulsant drugs, and their interaction with amphetamine, on decision-making in normal animals. In the second experiment, the effects of kindling on choice behaviour were determined, and whether administration of one of the anticonvulsant drugs, carbamazepine, would alter the effects of amygdala stimulation. As expected from previous reports, rats were able to learn the task contingencies and to discriminate between advantageous and disadvantageous options on a rat Gambling Task (rGT), a task analogous to the Iowa Gambling Task (IGT) used in humans. These studies also demonstrated individual differences between rats such that a subgroup of animals showed a consistent preference for the disadvantageous options at baseline and these animals responded differently to some of the drug and kindling manipulations. The first study showed that anticonvulsant drugs differentially affected parameters associated with decision-making when administered in isolation and also when co-administered with amphetamine. More specifically, we observed that carbamazepine alone affected premature responses, choice latency and collection latency, whereas valproate and lamotrigine had no effect. When administered alone, amphetamine increased premature responses in the conservative, but not in the risky rats. Lamotrigine only failed to block this increase in responding. In the risky rats, we observed a synergistic effect of the anticonvulsants valproate and lamotrigine with amphetamine such that in combination, they increased premature responses in these rats. Carbamazepine did not show this effect. Kindling of the amygdala transiently and selectively increased choice of P1 in all rats, and also increased premature responding and speed of decision-making in risky, but not conservative, animals.

4.1 Anticonvulsant drug challenge

4.1.1 Effect of anticonvulsant drugs

Neither lamotrigine or carbamazepine altered animals' individual preference for the various options on the rGT. It appears that the drugs themselves may not influence decision-making under uncertainty once the contingencies have been learned. Valproate did appear to have some subtle effects on choice, depending on whether rats were conservative or risky in their choice, but further analyses could not identify any robust changes in preference caused by the drug in either subgroup.

Although valproate and lamotrigine had no effect on any other task parameters, higher doses of carbamazepine reduced the number of premature responses made in all rats, regardless of baseline preference for the advantageous and disadvantageous options. Premature responses in this task provide an index of motor impulsivity (Zeeb et al., 2009). All doses of carbamazepine also increased the latency to choose an option, whereas the highest dose only also increased the latency to collect reward in the conservative, but not risky, rats. The increase in choice and collection latencies observed with carbamazepine are consistent with the decrease in processing speed seen in the human population (B. Hermann, Meador, Gaillard, & Cramer, 2010). Increase in response latencies could also indicate a general motor slowing, suggesting that the decrease in premature responses observed following higher doses of carbamazepine are not truly reflective of improved impulse control, but simply reduced motor output. However, this drug did not increase trials omitted or reduce the number of trials completed, as would be expected if animals were experiencing motor problems. The concurrent improvements in behavioral inhibition, combined with slower latencies to choose an option and collect reward, may therefore indicate that a slower processing style contributed to improved motor inhibition.

As reviewed in the introduction, what is known regarding how these drugs exert therapeutic benefit suggests some potential differences in their mechanisms of action. For example, only carbamazepine appears to have significant activity as an adenosine receptor antagonist. It is increasingly recognized that the adenosine and dopamine systems interact, and that A_{2A} receptor antagonists can attenuate the effects of dopamine D_2 receptor antagonists in tests of motivated behaviour (Nunes, Randall, Podurgiel, Correa, & Salamone, 2013). The ability of A_{2A} antagonists to remediate the behavioural effects of low levels of dopaminergic activity is also an area of much research with respect to therapeutics for Parkinson's disease. However, A_{2A} antagonists act as stimulants, as exemplified by caffeine, and would therefore be expected to increase premature responding (Cocker, Hosking, Benoit, & Winstanley, 2012). It is therefore unlikely that this pharmacological property of carbamazepine resulted in the decrease in motor impulsivity and response speed observed here.

One obvious explanation is that the general slowing of cognitive processing and an increase in behavioral inhibition results from a decrease in neuronal excitability, as would be expected following administration of anticonvulsant drugs. However, while all the drugs used here can block voltage-dependent Na^+ channels, this blockade is itself voltage-dependent and should only occur during repeated discharges, as would be expected during a seizure. It is also valproate, rather than carbamazepine, that has the most robust ability to increase levels of GABA release. It is therefore unlikely that either of these mechanisms account for the decrease in premature responding caused by carbamazepine, as such effects should then be observed following administration of all the anticonvulsant drugs used in the case of the former, or primarily by valproate.

As noted in the introduction, carbamazepine is structurally similar to the tricyclic anti-depressant drug imipramine, and may therefore inhibit catecholamine uptake. Some findings indicate that carbamazepine can increase serotonergic neurotransmission, and global decreases in 5-HT can increase premature responding. However, whether decreases in 5-HT levels result in improved or impaired impulse control appears to depend critically on the type of 5-HT receptor most affected. For example, a 5-HT_{2A} antagonist reliably decreases premature responding on the 5CSRT, whereas a 5-HT_{2C} antagonist has the opposite effect (e.g. Winstanley et al., 2005). Carbamazepine has been found to potentiate the characteristic "wet-dog shakes" caused by administration of the 5-$HT_{2A/C}$ agonist (+/-) -1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI). This behavioural effect of DOI is thought to reflect 5-HT_{2A} agonism, implying that carbamazepine acts more as an agonist at this receptor class (Kitamura et al., 2008). However, carbamazepine reverses the increase in 5-HT_{2C} receptors in the hippocampus associated with the development of seizures following pilocarpine administration (Krishnakumar, Nandhu, & Paulose, 2009). This increase in 5-HT_{2C} receptors is thought to be compensatory, due to a decrease in 5-HT within this epilepsy model. It is therefore possible that carbamazepine can potentiate 5-HT's actions at 5-HT_{2C} receptors, which would be expected to result in a decrease in motor impulsivity. Such a hypothesis remains highly speculative, but could be empirically tested by determining whether carbamazepine's effects on premature responding can be attenuated by a 5-HT_{2C} antagonist.

4.1.2 Effect of anticonvulsant drugs combined with amphetamine

Individuals with BD showed deficits in decision-making on the IGT (Christodoulou et al., 2006). There are no ideal animals models of BD, but acute amphetamine injections are often used as a proxy for the manic state due to the increase in activity and impulsivity observed. We

therefore hypothesized that anticonvulsant drugs may be able to ameliorate the increase in motor impulsivity and changes in decision-making caused by amphetamine on the rGT.

Surprisingly, during the course of this series of drug challenges, we did not find any effects on choice behaviour caused by amphetamine, or when amphetamine was preceded by any of the anticonvulsant drugs. In contrast, previous work has reported significant effects of amphetamine on-task (Zeeb et al., 2009). At both the moderate and higher dose, amphetamine decreased choice of the optimal option P2 and increase choice of the small reward option P1. The highest dose of amphetamine also increased choice of the risky option P4. It is unclear why the current study did not replicate the effects of amphetamine on rGT choice behavior. It is worth noting that the current study found mean differences in a direction consistent with the effect of amphetamine noted previously, such that we observed an increase in choice of P1 and a decrease in choice of P2 when amphetamine was administered alone or when preceded by the anticonvulsant drugs. Given that 3 rats were excluded due to poor response to the anticonvulsant drugs, there were slightly fewer rats used here as compared to the Zeeb et al. (2009) study. Also, baseline variation was significantly greater in this cohort of animals, with the risky group failing to develop a preference for the best option. It is therefore possible that we could not detect significant differences in choice due to a lack of power.

Another possibility is that previous exposure to the anticonvulsant drugs during the Latin square drug designs caused some behaviourally-silent changes in brain function which dampened the effects of amphetamine on choice. As noted in the introduction, one of the many mechanisms of action attributed to valproate is an inhibitor of histone deacetylase (HDAC). HDAC inhibitors can have widespread influences on gene expression (see Machado-Vieira, Ibrahim, & Zarate, 2011 for review), though whether these could arise following the acute drug

regimen used here is not clear. Also, amphetamine did have the expected effect on premature responding on this task, increasing this measure of motor impulsivity. However, surprisingly, this change was only observed in conservative animals. The inconsistent nature of amphetamine's effects therefore does not definitively rule out the possibility that long-lasting changes were caused by the series of anticonvulsant drug challenges, even though baseline behaviour was not altered.

Risky animals showed similar levels of premature responding as conservative rats at baseline, therefore the differential effects of amphetamine on this form of motor impulsivity cannot be accounted for by a ceiling effect. In the conservative rats, carbamazepine and valproate significantly blocked the amphetamine-induced increase in impulsive action, whereas lamotrigine did not alter the response to amphetamine in these animals. Conversely, in risky animals, amphetamine increased premature responding compared to saline administration only when preceded by valproate or lamotrigine. It is interesting to note that carbamazepine did not have any such synergistic effect when administered with amphetamine, and premature responses did not differ from saline when these two drugs were administered together.

The effects of carbamazepine are somewhat consistent across both risky and conservative rats, in that they prevented any amphetamine-induced increase in impulsivity, and are in keeping with our observation that this was the only drug tested that affected premature responding when administered alone. The ability of carbamazepine to attenuate amphetamine's effects on premature responding may likewise result from the drug's actions on the 5-HT system. Even though amphetamine can increase 5-HT release throughout the brain, the selective 5-HT_{2C} agonist Ro60-0175 attenuates the increase in premature responding caused by this stimulant drug

(Fletcher, Rizos, Noble, & Higgins, 2011). Carbamazpine may therefore be modulating impulsivity by increasing serotonergic neurotransmission through 5-HT_{2C} receptors.

Given that valproate and lamotrigine are used successfully to treat BD, it is surprising that we observed an increase in premature responses when these drugs preceded amphetamine administration in risky rats. Although it has been reported that lamotrigine is more effective at treating depression rather than mania (Herman, 2004), valproate is highly efficacious and widely used as a first line treatment for manic and mixed episodes (Macritchie et al., 2003). Although serotonin clearly has a role to play in the ability of amphetamine to increase premature responding, this action of the stimulant also depends on its ability to potentiate the actions of dopamine (Cole & Robbins, 1989; Pattij, Janssen, Vanderchuren, Schoffelmeer, & van Gaalen, 2007; van Gaalen, Brueggeman, et al., 2006; van Gaalen, van Koten, Schoffelmeer, & Vanderschuren, 2006). Data from *in vivo* microdialysis suggest that, although 50 mg/kg of valproate alone did not increase dopamine release in the prefrontal cortex (PFC), this dose has synergistic effects when co-administered with typical and atypical antipsychotics, producing a larger increase in dopamine release within this area than antipsychotic administration alone (Ichikawa, Chung, Dai, & Meltzer, 2005). However, although prefrontal dopamine levels are thought to correlate with attentional performance (Puumala & Sirvio, 1998), no relationship between dopamine activity and premature responding has been reported in this region. Furthermore, direct administration of either D_1 or D_2 family receptor dopamine agonists into the medial prefrontal cortex (PFC) do not alter premature responding on the 5 Choice Serial Reaction Time Task (5CSRT; Granon et al., 2000). Instead, the majority of data to date indicate that the increase in premature responding caused by amphetamine depends on dopamine release in the NAc, rather than the cortex (Pattij et al., 2007; Pezze, Dalley, & Robbins, 2007), and

neither valproate or carbamazepine increased the level of dopamine in this region (Ichikawa & Meltzer, 1999). It is therefore unlikely that valproate and lamotrigine increased premature responding when combined with amphetamine due to potentiation of the stimulant's effects on prefrontal dopamine release.

Antimanic drugs including the anticonvulsant drugs require daily doses and often weeks before their full efficacy can be observed in reducing symptoms of mania (Müller-Oerlinghausen, Berghöfer, & Bauer, 2002). In our study, we only administered the anticonvulsants acutely, and these results may not reflect the effects of long-term administration of these compounds. This could explain our inconsistent results regarding the efficacy of the anticonvulsants in reducing premature responses alone, or in response to amphetamine. Exploring the effects of chronic administration of the various anticonvulsants could show cognitive effects not observed in the present study such as on choices of the different options, as well as on motor impulsivity.

4.1.3 Differential effect between the risky and conservative rats

We observed a different effect of amphetamine administration on the conservative and risky rats in our task, indicating that these baseline differences in choice may stem from differences in monoamine transmission. This is certainly not the first time that variations in baseline behaviour have been associated with differential response to drugs. The idea that cognitive functioning depends on optimal levels of neurotransmitter function, with either too much or too little resulting in impairments, is well-established in the field. This leads directly to the theory that individuals who perform less well on a particular cognitive task may have too little or too much neurochemical modulation at baseline, and may therefore react differently to pharmacological challenges. This has been particularly well documented with respect to

dopamine function in the prefrontal cortex and working memory. On the 5CSRT, the effect of microinfusions of a dopamine D_1 agonist into the medial PFC was dependent on baseline performance, such that a moderate dose increased accuracy of target detection in animals that showed poor attentional ability, but had no effect in high performers (Granon et al., 2000). Similarly, a low dose of a D_1 antagonist decreased performance in highly accurate rats, but did not affect the accuracy of poor performers.

With respect to gambling and impulsivity, in human pathological gamblers, the putative dopamine agonist modafinil increased motivation to gamble and risky decision-making in highly impulsive individuals, but had the opposite effect in less impulsive gamblers (Zack & Poulos, 2009). Our group has also observed that infusing either a D_1 or D_2 antagonist directly into the orbitofrontal cortex decreases premature responding in highly impulsive, but not less impulsive, animals (Winstanley et al., 2010). Highly impulsive animals also seem more sensitive to the rewarding or reinforcing properties of stimulant drugs, and self-administer cocaine more readily, an effect which could result from lower levels of D_2 receptor binding in the ventral striatum (e.g. Dalley et al., 2007). Further support for the association of dopamine and impulsivity comes from genetic studies of single nucleotide polymorphisms and more specifically, genes coding for the D_2 receptors which may be altered in individuals with addiction (Verdejo-García, Lawrence, & Clark, 2008).

In summary, individual differences in cognitive behaviour often result in differential responses to monoaminergic compounds, and this may reflect underlying differences in receptor density or frontostriatal function. We currently do not know the biological mechanism underlying individual differences in choice behaviour on the rGT, and this could be addressed in future studies. Finally, we can not exclude the possibility that the small number of risky rats

may account for our incapacity to obtain a significant effect of amphetamine on premature responses in this group.

4.2 Kindling experiment

4.2.1 Comparison between placement in the BLA or CeA of the bipolar electrode

Whether the electrode was placed in the BLA or CeA did not alter the effect of kindling on any behavioural measure. The number of rats in each of the BLA and CeA groups is quite small, which may have hampered our ability to detect a differential effect caused by stimulating either of these areas. However, a group size of between 5 and 7, although smaller than the ideal, is certainly not unacceptable in behavioural experiments of this kind (e.g. Zeeb & Winstanley, 2013). Although the BLA has strong reciprocal interconnections with the OFC and medial prefrontal cortex (mPFC), the CeA receives excitatory transmission from the BLA and has strong projections to other dopaminergic structures implicated in the reward system, such as the NAc (Sah, Faber, Lopez De Armentia, & Power, 2003). It is perhaps not surprising that stimulation of the BLA and CeA had similar effects on behaviour, as both of these structures, though functionally distinct, contribute to decision-making in risk-related tasks. Although the CeA was historically thought of as more of a relay station between the BLA and the hypothalamus concerned predominantly with the processing of sensory information, recent data suggest that this area has a more prominent role to play in cognition. For example, the CeA has been implicated in detecting the omission of an expected reward (Holland & Gallagher, 1993) and in tuning the strength of associations of conditioned stimuli with unconditioned stimuli (Holland & Kenmuir, 2005). Therefore, altering either BLA or CeA function may affect reward associations. In this sense, the BLA and the CeA may both be necessary for learning the contingencies associated with the different response options in the rGT, as these include both a

probability of reward delivery and the witholding of a reward on loss trials. In addition, a stage-5 seizure in kindling is associated with secondary generalized seizures where the entire brain enters a seizure state (Goddard et al., 1969). At this stage, the specific location of the stimulating electrode within the amygdala may be less important, as connectivity between numerous brain regions will be affected.

4.2.2 Effect of kindling on choice behaviour

Whereas bilateral lesions to the BLA increased choice of the high-risk, high-reward options on the rGT, amygdalar kindling lead to a transient increase in preference for P1 in both the risky and conservative rats. This choice results in the most frequent reward delivery and the shortest and least frequent penalty time-outs, but also the smallest unit of reward per win trial. Although this option delivers more reward than the classically "risky" P3 and P4 options, it is not as profitable as P2. An increase in choice of P1 has also been observed following administration of amphetamine (Baarendse & Vanderschuren, 2012; Zeeb et al., 2009; Zeeb & Winstanley, 2013) and in response to sensory specific satiety (Zeeb & Winstanley, 2013). Furthermore, bilateral lesions to either the BLA or OFC, or disconnecting the BLA and OFC, prior to acquisition of the task delays development of a robust preference for P2 due to increased choice of P1 (Zeeb & Winstanley, 2011, 2013).

The amygdala is thought to be strongly involved in the evaluation of the costs and benefits associated with a decision (Baxter & Murray, 2002; Floresco, St Onge, Ghods-Sharifi, & Winstanley, 2008). Lesions or inactivations of the amygdala have been shown to result in suboptimal choices across a range of behavioural paradigms. For instance, in a study using a delay discounting task, bilateral BLA lesions increased choice of a small immediate reward, interpreted as an increase in impulsive choice (Winstanley et al., 2004). This is somewhat

comparable to the choice bias observed during kindling, in that rats chose smaller immediate gains that accrued over the shortest time interval, even though this response did not maximise long term profit. Inactivation of the BLA also decreased choice of high-reward, high-effort options in two different tasks (Floresco & Ghods-Sharifi, 2007; Ghods-Sharifi et al., 2009). Rats also decreased their choice of a risky lever delivering a greater number of sugar pellets when the probability of reward diminished to or below 50% following BLA inactivation (Ghods-Sharifi et al., 2009). It is suggested that BLA lesion or inactivation did not alter preference for the high reward options in these tasks since increasing effort or equaling probability of reward with the lower reward option re-established preference for the high reward option. On the rGT, BLA lesions made prior to acquiring the task led to a slower acquisition of the optimal strategy, as rats chose the small option P1 more often during the early stages of training (Zeeb & Winstanley, 2011). However, rats eventually learned to choose the best option P2. In contrast, lesions to this area after task acquisition led to an increase in choice of the disadvantageous options P3 and P4.

Increased choice of P1 may reflect a bias towards more frequent or more certain rewards, a decrease in sensitivity to reward size, or a hypersensitivity to the longer penalties associated with the other options. As noted above, BLA lesions do increase choice of the smaller immediate reward in a delay discounting paradigm, but do not alter preference for larger over smaller rewards when neither is delayed. Hence, BLA lesions did not grossly alter reward magnitude judgements, despite increasing preference for an option which yielded smaller per trial rewards. It is therefore tempting to conclude that kindling of the BLA likewise did not affect discrimination between rewards of different sizes, but biased animals towards immediacy.

However, given that bilateral BLA lesions result in a very different pattern of behaviour on the rGT as compared to kindling, it is difficult to use findings from BLA lesions studies to aid

in the interpretation of the current dataset as clearly lesions and kindling are distinct phenomena. In addition to our observations that kindling did not induce neuronal damage, kindled rats that were stimulated to develop epileptogenesis also did not show signs of brain damage, suggesting that extensive neural damage is not required in order to develop epileptogenesis in animals (Michael et al., 1998). Nonetheless, kindling has been found to alter many components of neural networks. Although we can assume that lesions or inactivations of the BLA effectively silence the contribution made by this region to the cognitive process in question, we do not have such a clear understanding of how kindling may alter neuronal processing in a particular region. The output could be garbled, leading to confusion in areas which receive this information, or the signal could be fundamentally altered but still comprehensible to other structures.

Electrophysiological (EEG) data on the effect of kindling certainly supports the suggestion that neuronal connectivity is disrupted following amygdala stimulation. As behavioural seizure intensity increases, so does the extent of the spread of seizure activity, and the neural signature intensity in other brain areas such as the thalamus and the frontal lobe (Blumenfeld et al., 2007). During a seizure, the excitatory glutamate neurotransmitter increases in the amygdala whereas inhibitory GABA levels decrease (Kaura, Bradford, Young, Croucher, & Hughes, 1995). As mentioned in the introduction, an increase in GABA transminase has been associated with seizures. Kindling of limbic system structures has also been found to increase the number of excitatory post synaptic potentials (EPSPs), and an increase in the expression of the NMDA receptor subunit GluN1 was also observed weeks following amygdala kindling (Kikuchi, Iwasa, & Sato, 2000). It is possible that kindling also decreases synaptic GABAergic inhibitory transmission, but the data is unclear regarding a potential loss in GABA projections (Morimoto, Fahnestock, & Racine, 2004).

The effects of kindling observed here may therefore reflect changes in GABAergic or glutamatergic neurotransmission in the BLA. Unfortunately, the effects of systemic or intra-BLA administration of GABAergic or glutamatergic drugs have yet to be determined on performance of the rGT behaviour. However, the noncompetitive NMDA antagonist ketamine has been found to increase choice of the small immediate reward in a delay discounting task (Floresco, Tse, et al., 2008), similar to BLA lesions. Ketamine also increased choice of the smaller, less effortful reward in an effort-discounting task, although this change in behaviour was likewise attributed to intolerance of delay (Floresco, Tse, et al., 2008). Cost-benefit decision-making is therefore susceptible to changes caused by NMDA receptor antagonism, and such a mechanism may be relevant for the effects of kindling observed here.

4.2.3 Effect of kindling on motor impulsivity and response latencies

In addition to the effects on choice, kindling transiently increased premature responding and speed of decision-making, but only in animals that preferred the disadvantageous options at baseline i.e. the risky rats. Although the sample size for the risky rats is small, these data raise the intriguing possibility that poor decision-making may be a risk factor for impulse control deficits during periods of seizure activity. Whether this relates to the observation that epileptic patients with lower IQs show a more pronounced deterioration in executive function and processing speed over time remains to be determined, but could be an exciting avenue for future research.

As to why choice latency may be affected by kindling, an increase in response latencies have been observed following BLA inactivation when rats performed a risk discounting task (Ghods-Sharifi et al., 2009). However, BLA lesions did not affect premature responding or choice latency on the rGT (Zeeb & Winstanley, 2011). There was also no increase in choice

latency after BLA lesions on a delay discounting task (Winstanley et al., 2004). The changes observed in our study once again highlight the difference between the outcome of kindling and targeted neuronal damage.

As noted above, data from the 5CSRT has demonstrated that premature responding is sensitive to manipulations of the dopamine system. Response latencies can also be altered by dopaminergic agonists and antagonists. For example, systemic administration of higher doses of D_1 and D_2 agonists increased choice latency (Winstanley et al., 2010), as does infusion of a D_1 or D_2 antagonist into the NAc (Pezze et al., 2007). Given that psychotic symptoms are often observed in TLE, and that neuroleptic medications with D_2 antagonist properties are used to treat TLE (Koch-Stoecker, 2002), it is perhaps unsurprising that considerable research has focused on the impact of kindling on the dopamine system. For example, it has been reported that amygdala kindling in rats led to increased dopamine turnover in the prefrontal cortex, but decreased turnover of this same neurotransmitter in the NAc (Rada & Hernandez, 1990). Increased extracellular dopamine levels have also been observed in the amygdala following kindling (Shin, Anisman, Merali, & McIntyre, 2004) but so have long-lasting (more than a month) decreases, both in the amygdala (Engel & Sharpless, 1977) and mPFC (Mintz et al., 1992). Another study found a lasting decrease in tyrosine hydroxylase in the stimulated amygdala, but no effect of stimulation on this enzyme in other areas such as the striatum or the frontal cortex (Farjo & Blackwood, 1978).

To summarise, the exact way kindling affects dopamine neurotransmission is unknown, but kindling-induced changes in dopaminergic signaling may contribute to the increase in premature responding and choice latency observed here. Whether changes in dopaminergic activity could explain the changes in choice behaviour observed on the rGT after kindling is less

clear; although amphetamine has previously been reported to increase choice of P1, somewhat in parallel to the effects of kindling shown here, this change in decision-making (unlike the effects of amphetamine on premature responding) cannot be attenuated by co-administration of dopamine antagonists (Zeeb, Wong, & Winstanley, 2013). BLA stimulation was found to inhibit spontaneous firing of a population of dopamine neurons in the mPFC (Floresco & Tse, 2007). Nonetheless, researchers have demonstrated that tetanic stimulation of the BLA leads to increase in firing of dopamine neurons in the NAc, as well as increase extracellular dopamine levels for up to 25 min. This potentiation of activity in the NAc is believed to be due to glutamate transmission following BLA stimulation, and be mediated by both D_1 and NMDA receptors (Floresco, Blaha, Yang, & Phillips, 2001; Floresco & Tse, 2007; Floresco, Yang, Phillips, & Blaha, 1998). Given the involvement of the NAc in decision-making and impulsivity, it may be the case that the effect on choice behaviour and premature responding observed in this experiment could be explained by this mechanism.

4.2.4 Carbamazepine challenge in kindled rats

We had hoped to determine whether carbamazepine would reduce the increase in premature responding observed following kindling in risky rats, in an attempt to model whether anticonvulsants are useful in reducing any increase in impulsivity precipitated by seizures in TLE. Given that the effects of kindling on impulsivity were transient, but that increased sensitivity to seizures is permanent following kindling induction, we reasoned that a single stimulation session may be enough to reproduce the deficit in impulse control initially observed, and we could then test whether this increase in premature responding could be antagonised with carbamazepine. However, premature responding did not increase in risky or conservative rats following this stimulation session, therefore this experiment did not provide the opportunity to

test whether carbamazepine could attenuate deficits in impulse control induced by kindling. This issue would therefore have to be addressed in an additional study in which carbamazepine is administered either from the outset of kindling, or in the final 3 sessions once kindling has been established.

It is possible that the difference in the methodology used during the carbamazepine challenge may have hampered our ability to replicate the effect of kindling. For example, rats were stimulated twice daily during kindling, but only once during the carbamazepine challenge. It may be that the cumulative or long lasting effect of stimulation may have been necessary in order to replicate the effect of kindling on behaviour. Although this may be different from kindling in rats, human patients undergoing electroconvulsive therapy show cognitive deficits such as memory impairment during and shortly after end of treatment, but these effects mostly resolve as the time following end of treatment increases (Calev et al., 1991). In the current study, the period during which rats were not stimulated after the end of kindling may have similarly decreased the cognitive and behavioural changes observed during kindling. In this experiment, two groups of rats were stimulated at two time points. For this reason, the first group of rats to be kindled had a longer post-stimulation period (4 weeks compared to 2 weeks) prior to the single stimulation, which may have led to a differential effect of that single stimulation on behaviour between the groups. However, rats did not differ depending on the stimulation group they were in on any of the parameters during saline or carbamazepine followed by stimulation and therefore, the difference between these groups on the longevity of lack of stimulation may not explain our failure to replicate the effects seen during kindling. Nonetheless, as mentioned above, it is possible that even the shortest delay may have allowed recovery from the cognitive effect induced by kindling.

The dose of carbamazepine used may also need to be revised for any future experiments. We chose the highest dose of carbamazepine that did not affect rGT performance on its own, so that we could have observed whether any effects of the drug were genuinely due to a remediation of seizure-induced changes in impulsivity, rather than on impulsivity in general i.e. whether carbamazepine was blocking the effects of kindling on impulsivity via the same mechanism that it would reduce seizure intensity. However, this dose did not reduce the severity of the seizures and may therefore not be representative of therapeutic doses used to treat TLE (Albright & Burnham, 1980). Chronic administration of this drug may be necessary to assess its efficacy at reducing seizures, or we could use a higher dose.

The fact that kindling-induced changes in impulsivity and decision-making can be dissociated from changes in seizure severity also suggests that the neurobiological basis of these two phenomena is distinct. Future studies could aim to address this dissociation by seeking to identify changes in neuronal activity (e.g. cFos, or other molecular signaling markers) that are evident when cognitive behaviour is altered by kindling vs when the seizure threshold becomes established (Leussis & Heinrichs, 2007; Szyndler et al., 1999).

4.2.5 Comparison with the human data

As reviewed in the introduction, reports indicate that TLE patients are impaired at performing the IGT, either failing to develop a preference for the advantageous over the disadvantageous, or actually preferring the disadvantageous decks (Delazer et al., 2010; Yamano et al., 2011). Inasmuch as we had hoped to model these deficits in decision-making on the rGT using kindling to approximate TLE, our experimental findings do not seem representative of the clinical condition. However, it is worth noting that TLE patients are not impaired in tests of risky decision-making in which the odds of winning and losing are clearly signaled i.e. when the

patients are aware of the odds in play (Delazer et al. 2010). In the IGT, the odds associated with reward and punishment are not explicit- the subject must learn which decks are advantageous and disadvantageous through trial and error. Acquisition of the IGT therefore involves decision-making under ambiguity (or unexpected uncertainty) rather than just under risk (or expected uncertainty (see e.g. Yu & Dayan, 2005 for discussion). In contrast, the rats used in the current study had already acquired the rGT before experiencing seizures, thereby modeling the impact of seizure activity on decision-making under risk but not choice under ambiguity. A more appropriate experimental strategy to try and capture changes in choice behaviour observed in epilepsy may therefore be to investigate the effects of kindling on acquisition, rather than performance, of the rGT. However, it is worth noting that both performance and acquisition of the rGT are sensitive to lesions of the BLA (Zeeb & Winstanley, 2011), therefore it is somewhat surprising that kindling of the amygdala did not increase choice of the risky options. Again, such differences speak to the clear dissociations between the cognitive effects of lesions and kindling (see section 4.2.2).

As mentioned in the previous section, the effects of kindling on rGT behaviour were not permanent in this study, despite the fact that seizure vulnerability was maintained. In human patients suffering from epilepsy, epileptogenesis, the occurrence of spontaneous seizure, is a feature of the disease. In the kindling model in rats, development of epileptogenesis is rarely reached even after a very large number of stimulations have been administered (Goddard et al., 1969). Therefore, the kindling model is intrinsically different to the human disorder, which may explain why changes observed in this study were reversible unlike in the human population. Certainly, researchers have argued that chronic epilepsy models in which animals exhibit long-term enhancement of seizure susceptibility are preferable to some of the acute pharmacological

seizure models as well as the maximal electroshock and pentylenetetrazole models. It is worth noting that, although anticonvulsant drugs can control seizures in some patients and block seizures induced by kindling in rats, none of the compounds available to date can prevent the development of kindling in animals or cure epilepsy. The kindling model does at least capture the progressive nature of epilepsy, with seizures increasing in intensity over time, even though it does not map directly onto any form of the disorder. Animal models based on genetic mutations may lead to the development of a better model in the future (see e.g. Frankel, 2009).

4.3 Summary and conclusions

The aims of the studies in this thesis were to characterise the effects of 3 distinct anticonvulsant drugs- carbamazepine, valproate and lamotrigine- on performance of the rGT, and to determine whether kindling would produce impairments in choice behaviour or impulsivity similar to those observed in TLE that could then be attenuated by anticonvulsant administration. Even though the three anticonvulsants tested were those that have been found to be efficacious in the treatment of BD, and therefore judged most likely to have beneficial effects on the rGT given that this task measures motor impulsivity and decision-making under risk, none of these compounds reliably altered choice behaviour. However, carbamazepine did decrease premature responding- the index of motor impulsivity obtained from the rGT- perhaps via a serotonergic mechanism. This drug also appeared to slow processing speed, consistent with human literature, and block the pro-impulsive effect of amphetamine, although the response to amphetamine observed here was not as robust as that observed in previous studies.

Kindling increased choice of P1- the option associated with the smallest but most frequent reward. Although not indicative of an increased preference for risk, this change in strategy is nonetheless suboptimal, and may reflect some aspects of impulsive choice in that

smaller immediate rewards are preferred at the expense of longer term gain. Kindling also increased premature responses. However, neither the change in choice or disinhibition was permanent, and the attempt to attenuate these effects with carbamazepine was therefore unsuccessful. Although we did not perfectly reproduce the cognitive changes associated with TLE using the kindling model, we did see some evidence of increased impulsivity and impaired choice. Future studies in which kindling is performed during acquisition of the rGT may be more effective at modeling the decision-making deficits in TLE. Some of the effects observed were also dependent on whether rats favoured the risky or conservative options at baseline. Understanding the neurobiological mechanisms underlying these individual differences may also provide some insight into vulnerability to impairments in decision-making under uncertainty associated with TLE and other psychiatric disorders.

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