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IMPAIRED REINFORCEMENT LEARNING & BAYESIAN INFERENCE IN PSYCHIATRIC DISORDERS: FROM MALADAPTIVE DECISION MAKING TO PSYCHOSIS IN SCHIZOPHRENIA

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Impaired reinforcement learning & Bayesian inference in psychiatric disorders: from maladaptive decision making to psychosis in schizophrenia

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QUOTES

"The brain does much more than just recollect, it inter-compares, it synthesizes, it analyses, it generates abstractions. ... [It] is the realm both, of intuition and critical analysis. It is here that we have ideas and inspirations, here that we read and write. ... The cortex regulates our conscious lives, it is the distinction of our species, the seat of our humanity. Art and science live here. Civilization is the product of the cerebral cortex. [It] is in a way a liberation. We need no longer be trapped in the genetically inherited behavioural patterns of [our ancestors]. ... [It] may be the means of ensuring human survival, if we have the wisdom to pay attention."

— Carl Sagan

"Everything we do, every thought we've ever had, is produced by the human brain. But exactly how it operates remains one of the biggest unsolved mysteries, and it seems the more we probe its secrets, the more surprises we find."

— Neil deGrasse Tyson

"I think the brain is essentially a computer and consciousness is like a computer program. It will cease to run when the computer is turned off. Theoretically, it could be re-created on a neural network, but that would be very difficult, as it would require all one's memories."

— Stephen Hawking

"Pure mathematics is, in its way, the poetry of logical ideas."

— Albert Einstein

"I had to make sense, any sense, out of all these uncanny coincidences. I did it by radically changing my conception of reality."

— Peter Chadwick,
describing his experiences during an episode of paranoid schizophrenia.

"In madness, I thought I was the most important person in the world."

— John Nash

ABSTRACT

Computational modelling has been gaining an increasing amount of support from the neuroscience community as a tool to assay cognition and computational processes in the brain. Lately, scientists have started to apply computational methods from neuroscience to the study of psychiatry to gain further insight into the mechanisms leading to mental disorders. In fact, only recently has psychiatry started to move away from categorising illnesses using behavioural symptoms in an attempt for a more biologically driven diagnosis. To date, several neurobiological anomalies have been found in schizophrenia and led to a multitude of conceptual framework attempting to link the biology to the patients' symptoms. Computational modelling can be applied to formalise these conceptual frameworks in an effort to test the validity or likelihood of each hypothesis. Recently, a novel conceptual model has been proposed to describe how positive symptoms (delusions, hallucinations and thought disorder) and cognitive symptoms (poor decision-making, i.e. *"executive functioning"*) might arise in schizophrenia. This framework however, has not been tested experimentally or against computational models. The focus of this thesis was to use a combination of behavioural experiments and computational models to independently assess the validity of each component that make up this framework.

The first study of this thesis focused on the computational analysis of a disrupted prediction-error signalling and its implications for decision-making performances in complex tasks. Briefly, we used a reinforcement-learning model of a gambling task in rodents and disrupted the prediction-error signal known to be critical for learning. We found that this disruption can account for poor performances in decision-making due to an incorrect acquisition of the model of the world. This study illustrates how disruptions in prediction-error signalling (known to be present in schizophrenia) can lead to the acquisition of an incorrect world model which can lead to poor executive functioning or false beliefs (delusions) as seen in patients.

The second study presented in this thesis addressed spatial working memory performances in chronic schizophrenia, bipolar disorder, first episode psychosis and family relatives of DISC1 translocation carriers. We build a probabilistic inference model to solve the working memory task optimally and then implemented various alterations of this model to test commonly debated hypotheses of cognitive deficiency

in schizophrenia. Our goal was to find which of these hypotheses accounts best for the poor performance observed in patients. We found that while the performance at the task was significantly different for most patients groups in comparison to controls, this effect disappeared after controlling for IQ in one group. The models were nonetheless fitted to the experimental data and suggest that working memory maintenance is most likely to account for the poor performances observed in patients. We propose that the maintenance of information in working memory might have indirect implications for measures of general cognitive performance, as these rely on a correct filtering of information against distractions and cortical noise.

Finally the third study presented in this thesis assessed the performance of medicated chronic schizophrenia patients in a statistical learning task of visual stimuli and measured how the acquired statistics influenced their perception. We find that patient with chronic schizophrenia appear to be unimpaired at statistical learning of visual stimuli. The acquired statistics however appear to induce less expectation-driven *'hallucinations'* of the stimuli in the patients group than in controls. We find that this is in line with previous literature showing that patients are less susceptible to expectation-driven illusions than controls. This study highlights however the idea that perceptual processes during sensory integration diverge from this of healthy controls.

In conclusion, this thesis suggests that impairments in reinforcement learning and Bayesian inference appear to be able to account for the positive and cognitive symptoms observed in schizophrenia, but that further work is required to merge these findings. Specifically, while our studies addressed individual components such as associative learning, working memory, implicit learning & perceptual inference, we cannot conclude that deficits of reinforcement learning and Bayesian inference can collectively account for symptoms in schizophrenia. We argue however that the studies presented in this thesis provided evidence that impairments of reinforcement learning and Bayesian inference are compatible with the emergence of positive and cognitive symptoms in schizophrenia.

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DECLARATION

I declare that this thesis was composed by myself, that the work contained herein is my own except where explicitly stated otherwise in the text, and that this work has not been submitted for any other degree or professional qualification except as specified.

Edinburgh, Scotland, 2015

Vincent Valton, February 6, 2015

CONTENTS

ABBREVIATIONS

a.k.a. also known as

c.f. confer — compare with

e.g. exempli gratia — for example

etc. et cetera — and so forth

i.e. id est — that is

ADHD Attention Deficit Hyperactivity Disorder

AFC Alternative Forced Choice

AMPA α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

ANCOVA Analysis of Covariance

ANOVA Analysis of Variance

APA American Psychological Association

APD Anti-psychotic drug

BIC Bayesian Information Criterion

BPD Bipolar Disorder

CANTAB Cambridge Neuropsychological Test Automated Battery

CPT Continuous Performance Task

CPZ Chlorpromazine

DA Dopamine

D2r Dopamine D2 receptors

D1r Dopamine D1 receptors

DDT Delay Discounting Task

DISC1 Disrupted in Schizophrenia 1 gene

dlPFC Dorsolateral Prefrontal Cortex

DM Decision Maker

DMm Decision Maker modelled

DSM Diagnostic and Statistical Manual of Mental Disorders

FAM Family member of DISC1 translocation carrier

FCN Fixed Consecutive Number

1ST First Episode Psychosis

FI-EXT Fixed Interval / Extinction schedules

fMRI Functional Magnetic resonance imaging

GABA Gamma-AminoButyric Acid

GAF Global Assessment of Functioning

HAM-D Hamilton Depression Rating Scale

HR High Risk of developing psychosis

ICD International Statistical Classification of Diseases and Related Health Problems

IGT Iowa Gambling Task

IQ Intelligence Quotient

JND Just Noticeable Difference

JTC Jumping To Conclusions

KDE Kernel Density Estimation

LTP Long Term Potentiation

MC Monte Carlo method

MSN Medium Spiny Neurons

MSNI Minimum of Standard deviation and interquartile range Improved

NAcc Nucleus Accumbens

NART National Adult Reading Test

NIMH National Institute of Mental Health

NMDA N-methyl-D-aspartate

NRG1 Neuregulin 1 gene

OCD Obsessive Compulsive Disorder

PANSS Positive And Negative Symptom Scale

PCP Phencyclidine

PDF Probability Density Function

PE Prediction Error

PET Positron Emission Tomography

PFC Prefrontal Cortex

PSY Psychotic

RDoC Research Domain Criteria

RGT Rat Gambling Task

SANS Scale for the Assessment of Negative Symptoms

SCZ Schizophrenia

SNR Signal to Noise Ratio

SWM Spatial Working Memory task

TD-learning Temporal Difference learning

UHR Ultra High Risk of developing psychosis

VTA Ventral Tegmental Area

WCST Wisconsin Card Sort Test

WHO World Health Organisation

WM Working Memory

YMRS Young Mania Rating Scale

LIST OF FIGURES

1 INTRODUCTION

1.1 SCHIZOPHRENIA

Schizophrenia is a devastating psychiatric disorder with a lifetime prevalence of 0.3-0.66% (van Os and Kapur, 2009; Bhugra, 2005). This condition manifests itself through a variety of symptoms across patients, classified into three distinct categories: positive, negative and cognitive symptoms. Positive symptoms refer to hallucinations (i.e. visual or auditory) and delusions (i.e. usually involving a bizarre or paranoid content); negative symptoms include flattened affect, social withdrawal, apathy, poverty of speech, and anhedonia. Cognitive symptoms cover decreased memory performance, attentional and reasoning deficit, which is usually associated with an average IQ drop of 10 points following the disease onset (van Os and Kapur, 2009; McIntosh et al., 2005; Bhugra, 2005; Frith et al., 1991; Johnstone et al., 1991). Schizophrenia is highly debilitating, leading to an average loss of 15 to 20 years of life expectancy in comparison to the general population (Mangalore and Knapp, 2007; Andrew et al., 2012). It is argued that unhealthy lifestyles and increased suicidal rates (found to be about 12 times higher in the schizophrenia; Caldwell and Gottesman, 1990) might account for this general reduction in life expectancy (World Health Organisation, 1996).

Besides this devastating prospect for patients and their relatives, schizophrenia has been found to generate a high economical burden on society (Knapp et al., 2004; Serretti et al., 2009; Mangalore and Knapp, 2007). Recently, the total societal cost of schizophrenia has been estimated to be around £6.7 to £11.8 billion per year for England alone (Mangalore and Knapp, 2007; Andrew et al., 2012). This is including direct treatment costs and indirect societal costs such as loss of employment. In fact, it has been estimated that around 80% to 93% of patients with schizophrenia remain unemployed, leading to large societal costs due to loss productivity (Mangalore and Knapp, 2007; Andrew et al., 2012). Lack of employment is argued to result largely from cognitive deficits, problems of attention and working memory (Insel, 2010).

There is currently no cure for schizophrenia, mainly due to a poor understanding of the causes and mechanisms of the disorder. The best treatment to date consists of managing everyday symptoms through a combination of psychosocial treatments and anti-psychotic medications. This therapy aims to minimize symptoms, potential

risks to the patient or others (e.g. hallucinations/delusions leading to self-neglect or harm), and to avoid the relapse of psychosis. It is estimated that about 45% of patients recover after one or more episodes, 20% show a gradual worsening of symptoms and a final 35% exhibit a mix of remission with a worsening of some of the symptoms (relapsing-remitting; World Health Organisation, 1996).

1.1.1 *Debated origins of the disorder*

Several studies have identified neuroanatomical differences in patients (e.g. Seeman, 1994; Kreczmanski et al., 2007; Lawrie et al., 2008) as well as susceptible genes increasing the risk of developing psychiatric disorders (e.g. Chubb et al., 2008). However, while it is well established that high genetic risk factors alone are not sufficient to account for the development of the disorder (Lawrie et al., 2008); it is widely accepted that an interaction between genetic (Berry et al., 2003; Chubb et al., 2008; Bertolino and Blasi, 2009) and environmental risk factors (i.e. stress, traumatic experiences, etc. Jones et al., 1994; Mortensen et al., 1999; McDonald and Murray, 2000) is necessary to lead to the emergence of schizophrenia. So far, research in this field has identified various anomalies in patients, which has led to divergent hypotheses about the origins of the disorder. First, the Dopamine (DA) hypothesis was established through the observation of alleviated positive symptoms upon treatment with typical antipsychotic drugs (APD), which block dopamine receptors D2 (D2r). Consistent with this hypothesis, subsequent imaging studies found elevated dopaminergic signalling (Meyer-Lindenberg et al., 2005; Murray et al., 2008; Waltz et al., 2009), elevated presynaptic striatal DA synthesis and release, and increased striatal D2 receptor densities (Howes and Kapur, 2009). More recently studies have also found deregulated D1 receptor densities in the pre-frontal regions of patients (Howes and Kapur, 2009). The second hypothesis, the Glutamate (Glu) hypothesis emerged from the observation of induced psychosis in healthy subjects when exposed to psychoactive drugs, such as Ketamine and Phencyclidine (PCP), which acts primarily by blocking the glutamate binding sites of NMDA receptors (Corlett et al., 2007a; van Os and Kapur, 2009). Post-mortem studies also identified reduced glutamate levels in the pre-frontal areas of patients (Sherman et al., 1991). It is therefore assumed that reduced NMDA receptor densities or receptor hypo-function can account for the symptomatology observed in patients (Javitt and Zukin, 1991; Olney et al., 1999; Gilmour et al., 2012). The third hypothesis, the GABAergic hypothesis is supported by experimental studies reporting reduced cortical GABA, dysfunctional activity and reduced markers of inhibitory inter-neurons in the pre-frontal areas of patients (Lewis and Hashimoto, 2005; Tanaka, 2008; Nakazawa et al., 2012). Finally, the disconnection hypothesis stemmed from

several findings of reduced cortical volume, abnormal pre-frontal cortical folding, enlarged ventricles, abnormal synaptic connectivity (Harrison, 1999; Lawrie et al., 2008) and increased cortical activation during cognitive tasks (Manoach et al., 1999; Winterer and Weinberger, 2004). This increased activation is thought to be the result of a reduced synchrony or disconnection between different cortical areas, therefore requiring exaggerated efforts for completion (Friston, 2005a; Stephan et al., 2009).

As one can probably infer from the short description of the existing hypotheses of schizophrenia, the origins of the disorder are highly debated. However, researchers and practitioners alike tend to agree that until reliable biological markers are found, which can robustly and reliably predict the emergence of schizophrenia and its symptoms, the best course of action for current diagnostic purposes is to rely on clinical interviews and an interpretation of symptoms by trained professionals.

1.1.2 *Diagnosis: categorical vs dimensional classification*

In the absence of reliable biological markers, diagnosis of mental disorders is produced from a clinical examination of the symptoms and behaviours expressed by the patients (World Health Organisation, 1996). Using the diagnostic and statistical manual of mental disorders (DSM; DSM-IV-TR, 2000) or the international statistical classification of disease and related health problems (ICD; World Health Organization, 2009), psychiatrists can diagnose a patient's illness as a function of the number of symptoms present and the extent to which those have been present. Specifically, for schizophrenia, the current DSM (DSM-5, 2013) diagnosis is met when two or more criteria are present continuously for a period of one month or more, and had an impact on the patient's functioning for at least 6 months. The first criteria has to be either a delusion, hallucination or disorganised speech, while the second criteria can be negative symptoms, severely disorganised or catatonic behaviour. That is, positive symptoms are the predominant criteria necessary for the diagnosis of schizophrenia.

Recently however there has been an attempt to bridge the gap between categorical diagnoses based on the clinical consensus of symptoms and the identification of potential biological markers identified by neuroscience research (Insel et al., 2010). For example, the research domain criteria (RDoC), aimed to develop a precision (or personalized) medicine approach to mental disorders based on behavioural and neurobiological markers (Insel et al., 2010; Cuthbert and Insel, 2013). More importantly, the RDoC proposed to cut across the typical categorical boundaries delineating current mental disorders and instead investigate the variations present in mental illness as

belonging to dimensional continuum (Cuthbert and Insel, 2013). For example, using the Peters delusion inventory (Peters et al., 2004), delusions have recently been found to be present in the general population (Freeman et al., 2008; Corlett and Fletcher, 2012; Schmack et al., 2013), albeit to a milder degree than those present in patients with schizophrenia. This growing body of evidence has led to suggest that psychotic experiences might lie on a continuum (van Os et al., 2000; Allardyce et al., 2007; Linscott and van Os, 2010; David, 2010; Corlett and Fletcher, 2012). It is argued however that such a continuum would be impractical for clinical diagnosis (Lawrie et al., 2010). Particularly, a recent joint consortium between the American Psychological Association (APA), the National Institute for Mental Health (NIMH) and the World Health Organisation (WHO) agreed that while neurobiological parameters are of high importance for future diagnostic systems, according to the current state of knowledge, it seems more appropriate for use in research than for immediate clinical use (Insel et al., 2010).

1.2 COMPUTATIONAL MODELLING

While experimental studies provide valuable information to understand the abnormal biological and cognitive processes in schizophrenia, experimental work alone is often limited by ethical, economic or practical factors. Recently, computational and mathematical models have shown to be very useful research tools for the exploration of neural computation, and the understanding of the interaction between neural systems and functions (Montague et al., 2004, 2012). Specifically, Marr (1982) proposed that computational models may be used to investigate three distinct although complementary levels of analysis, namely the computational level (*"What"* does the brain compute, and *"why"*?), the algorithmic level (*"Which"* representations and algorithms can describe these computations?) and the physical level (*"How"* are these algorithms implemented neurally?; Dayan and Abbott, 2005). By integrating data from diverse experimental studies, models can offer a concise and formal description of a phenomenon, shed light on the underlying mechanisms and make predictions leading to novel experimental tests and hypotheses (Huys et al., 2011).

1.2.1 *Computational psychiatry*

Computational psychiatry is a young field in expansion at the intersection between computational neuroscience and psychiatry (Huys et al., 2011; Montague et al., 2012; Huys, 2013). This discipline builds on the initial efforts in the 80's using connec-

tionist models, but has also evolved to get closer to the physiological substrate and to more testable predictions (Montague et al., 2012; Huys, 2013). Although psychiatric disorders are characterised essentially by their high-level symptoms, following Marr's principles, computational models can help formalise symptoms and hypotheses to bridge the gap between neurobiology and psychiatry (Huys et al., 2011). That is, computational models are able to provide a normative framework to explicitly define and rigorously test competing hypotheses of mental disorders (Huys et al., 2011), while providing a link between different levels of descriptions (Huys, 2013).
For example, Maia and Frank (2011) illustrated how modelling using a deductive or abductive approach can lead to different predictions for psychiatry. That is, using a deductive approach scientists can start from the premise of known neurobiological deficits observed in mental disorders, and implement these deficits in a computational model. The performance of the model is then compared to this of patients. If the model can account for the performance observed in patients, it provides a mechanistic account to bridge biological abnormalities to behaviour or neural activity (Maia and Frank, 2011). Using the abductive approach on the other hand, scientists can start from the premise of a model of normal behaviour and alter the model in multiple ways to generate distinct novel hypotheses of brain dysfunction. All these models are then fitted to the performances of patients to find which hypothesis (different models) accounts best for the performance observed in patients (Maia and Frank, 2011). The winning hypothesis can then be refined in an attempt to explain the deficits at lower levels of description, or used to devise new experimental tests that will precisely assay the dysfunction suggested by the winning hypothesis.

Using these methods, Stephan and Mathys (2014) recently argued that computational modelling could potentially lead to "model-based assays" used to diagnose mental disorders (Stephan and Mathys, 2014).

1.3 ORGANISATION OF THE THESIS

The aim of this thesis is to use computational modelling to investigate the possible mechanisms leading to generalised cognitive deficits and psychotic symptoms in schizophrenia. Specifically, a growing body of evidence suggest that associative learning, statistical learning and working-memory deficits are associated with positive symptom severity in schizophrenia, implying that a potential link might exist between cognitive impairments and delusions. Using reinforcement learning and Bayesian inference we propose to assess whether these models could collectively account for the cognitive and positive symptoms observed in the disorder.

First, we propose to study whether erroneous prediction-error signalling could lead to maladaptive decision making in complex cognitive tasks, and potentially illustrate the acquisition of inaccurate internal models of the world leading to false beliefs (delusions). Secondly, we wish to address which of the most likely hypotheses of general cognitive dysfunction in schizophrenia accounts best for working memory deficits observed in patients. Finally, using a psychophysical task known to assay statistical learning and perceptual inference in healthy controls, we will investigate whether schizophrenia patients appear to be impaired in the acquisition of expectations (statistical learning) or in their perceptual inference mechanisms (integration of expectations and sensory evidence).

1.3.1 *Questions and aims*

Particularly in this thesis, we present independent projects performed through multiple collaborations over the years that investigated independently associative learning, working-memory deficits, statistical learning and perceptual inference. Using these independent projects we will attempt to address the following questions:

A. What predictions have computational models have been able to achieve in terms of explaining the mechanisms of psychosis and cognitive dysfunction in schizophrenia? Are there specific hypotheses that have been left relatively under-investigated?

B. Could deficits in prediction-error signalling lead to maladaptive decision-making in complex tasks such as the Iowa Gambling Task? Could false beliefs stem from the incorrect acquisition of an internal model of the world?

C. Can we differentiate working memory deficits in populations that exhibit psychotic symptoms but have different psychiatric diagnoses (i.e. First episode psychosis, chronic schizophrenia, bipolar disorder, Family relatives of DISC1 translocation carriers)? Using computational models, which of the most commonly debated hypotheses of cognitive dysfunction accounts best for deficits of working-memory in these populations?

D. Can patients with chronic schizophrenia perform statistical learning of visual stimuli? How do these acquired expectations about the visual stimuli affect their perception?

A chapter will be devoted to each of these questions. In chapter 2, we present a comprehensive survey of the computational literature of schizophrenia. In chapter 3, we use a reinforcement model of a rodent analogue of the Iowa Gambling Task to address

whether maladaptive decision-making can arise from abnormal prediction-error signalling. In chapter 4 we use an optimal inference model of spatial working memory in an (abductive) attempt to find which hypotheses are most likely to account for a generalised cognitive deficit in psychosis. In chapter 5, using a novel psychophysics tasks and Bayesian model of perceptual inference, we investigate whether chronic schizophrenia patients are impaired in statistical learning or perceptual inference. Finally, in chapter 6 we discuss whether this thesis support the idea that impairments of reinforcement learning and Bayesian inference can account for the cognitive and positive symptoms observed in schizophrenia.

2

LITERATURE REVIEW: COMPUTATIONAL MODELS OF SCHIZOPHRENIA & PSYCHOSIS

Schizophrenia is a psychiatric disorder with a debated aetiology. While the age-related incidence of the disorder and biological evidence point toward the hypothesis of a developmental disorder, genetic risk factors alone are not sufficient to account for the aetiology of the disorder. Computational modelling has been used to address: 1) the variety of symptoms observed in schizophrenia using high-level descriptive models of behaviour; 2) The causes of these symptoms using low-level modelling of neuromodulation and receptor imbalance in connectionist models. These studies mostly support competing hypotheses of schizophrenia's pathophysiology, resulting in a literature that is not always expanding coherently. The work presented in this chapter presents a review of the literature of computational modelling for schizophrenia and psychosis. This work was performed by myself under the supervision of Dr. Peggy Seriès and Prof. Stephen Lawrie. The resulting work has been assembled into a draft for publication as a first author (not included in appendix).

2.1 METHODOLOGY

To extract an exhaustive bibliography of the computational models in schizophrenia, our approach was to search within the PubMed and Web of Science databases using the following search criteria:

Title and/or abstract including: (*"schizo*"* or *"psychos*"*) and (*"neural?network*"* or *"model*"*).

where the '*' sign denotes the joker symbol used in regular expressions to search for a combination of possible word endings, such that: *"comput* model*"* searches for *"computer model"*, *"computational models"*, *"computational modelling"*, etc.

Exclusion criteria: We excluded papers that were not in English or peer-reviewed journals. Conference abstracts and animal models were discarded from this analysis, as well as computational models used for diagnostic purposes, data analysis or medication interactions. This resulted in a list of articles ranging from 1968 to 2014,

comprising all levels of description to the psychopathology of schizophrenia (i.e. the what? how? and why? of Marr's computational levels of description; Marr, 1982; Dayan and Abbott, 2005).

2.2 THE DOPAMINE (D2) HYPOTHESIS

2.2.1 *Experimental evidence*

The dopamine hypothesis has been popular in the search for aetiological factors of schizophrenia. This hypothesis emerged from the discovery of first generation of anti-psychotic drugs (APD) that tend to relieve patients from positive symptoms by blocking dopamine D2 receptors (D2r). Consistent with this findings, further support originated from the discovery of several psychotomimetic drugs (i.e., such as amphetamines) that can induce psychotic-like episodes in healthy individuals by increasing sub-cortical DA levels (Grace, 1991; Jentsch and Roth, 1999; Corlett et al., 2009a). Over the past decade, the dopamine hypothesis has been supported by various neuroimaging studies reporting increased pre-synaptic dopamine synthesis and storage in the striatum of acutely psychotic patients (Howes and Kapur, 2009; Fusar-Poli and Meyer-Lindenberg, 2013b; Howes and Murray, 2013). These dopamine levels were found to directly correlate with the degree of their symptoms (i.e., Cognitive and Positive; Howes and Kapur, 2009; Howes and Murray, 2013). Additionally, increases in D2 dopamine receptors densities have been identified in the striatum of patients, together with reduced receptor densities in the thalamus and the anterior cingulate cortex (Howes and Kapur, 2009), although these effects appear to be relatively small (Howes and Murray, 2013). Recent reviews suggest that the influence of striatal D3 receptors in schizophrenia are not significant (Howes and Kapur, 2009; Howes and Murray, 2013), further supporting the role of D2 receptors in psychosis. Consistent with the DA hypothesis, many of the top genetic risk factors of developing schizophrenia involve genes directly interacting with the dopaminergic pathways (Winterer and Weinberger, 2004; Howes and Kapur, 2009; Frank, 2008; Hall et al., 2009). While it is likely that excessive D2r-activation is directly involved in psychosis, scientists are still attempting to explain the mechanisms linking dopaminergic dysfunction to positive symptoms (i.e. linking molecular level anomalies to behaviour and symptoms). It appears however that an increase in striatal dopaminergic D2r and decline in frontal D1r densities, might more easily transpose to cognitive and negative symptoms rather than to the positive symptoms of the disorder (Maia and Frank, 2011).

2.2.2 *Models and support*

In the computational literature supporting the dopamine hypothesis, we identified four main categories of models that support a deficit in dopaminergic transmission, namely a: decreased signal-to-noise ratio (SNR), inappropriate sensory gating, aberrant salience and abnormal prediction error (PE).

2.2.2.1 *Signal-to-noise ratio (SNR) models*

Early computational models attempted to explain cognitive symptoms in schizophrenia through a generalised decline of the signal-to-noise ratio in cortical neurons. Specifically, in these models DA was thought to function as a signal-to-noise enhancer that modulates neuronal activity by amplifying the neurons' signal while reducing distortions induced by cortical noise.

SNR in connectionist Frameworks

In artificial neural networks (i.e., interconnected feed-forward networks of simple units), the signal-to-noise ratio can be altered by changing the gain or bias parameter of neurons (Aakerlund and Hemmingsen, 1998). This directly influences the activation pattern and the stochastic activity of the units (neurons) in the system. SNR models traditionally focused on modelling cognitive symptoms using connectionist frameworks to model the performance of patients in tasks where they usually show deficits (i.e., Continuous Performance Task, Stroop Task, Rorschach inkblots, Wisconsin Card Sort Test (WCST), Facial Affect — (Cohen and Servan-Schreiber, 1992, 1993; Jobe et al., 1994; Peled and Geva, 2000; Amos, 2000; Monchi et al., 2000; Carter and Neufeld, 2007)). In these models, poor performance on cognitive tasks stem from working-memory deficits in the units representing the prefrontal cortex (PFC).

In such connectionist frameworks, the working-memory of patients is assumed to be deficient due to a low signal-to-noise ratio, modelled by altering the gain or bias of the working-memory units. Through a complete exploration of the parameter space from low to high gain modulation (i.e. hypo-dopaminergic to hyper-dopaminergic states), the models addressed the validity of different dopamine dysfunctions leading to the observed reduced performance on cognitive tasks. All these models reached the same conclusions, namely that prefrontal DA hypo-function was responsible for the deficient cognitive performances observed in patients (Cohen and Servan-Schreiber, 1992, 1993; Jobe et al., 1994; Peled and Geva, 2000; Amos, 2000; Monchi et al., 2000; Carter and Neufeld, 2007). With respect to working-memory, low DA levels are thought to result in a signal that is easily corrupted by internal cortical

noise which in turn becomes incapable of transmitting and maintaining meaningful contextual information about the ongoing task (Cohen and Servan-Schreiber, 1992, 1993). Another theory suggests that DA hypo-function results in a failure to update task relevant information into WM (Amos, 2000). A deficit in WM updating would then result in a failure to switch to new contextual information, and lead to perseverative behaviour (Amos, 2000). That is, in switching-tasks such as the WCST where participants are required to infer a sorting rule that changes once it has been correctly acquired, patients are usually able to infer the first initial rule but consistently fail to flexibly update these rules once they have been changed (i.e. perseverative behavior). A possible criticism of these models is that they can only account for poor cognitive performances following a hypo-dopaminergic state (low SNR). In these models, increasing the gain of neuronal units so as to model hyper-dopaminergic state would lead to a high SNR, which would not result in a deterioration of cognitive performances. While it is consistent with neuroimaging findings in schizophrenia (frontal hypo-dopaminergia, Howes and Kapur, 2009), it has been shown experimentally that weak or excessive frontal D1r activation lead to poor working-memory performances (Vijayraghavan et al., 2007). As a result, these models would normally fail to account for working-memory deficits following frontal hyper-dopaminergia.

SNR in attractor networks (cortical stability)

Hopfield or attractor networks have also been used to model patients' behaviour by adding SNR perturbations. During training, these networks learn specific patterns of activation (memories) by updating the weights of connections between neuronal units. After training, the network can recover an entire memory from a degraded or partial memory input by gradually letting the network flow into the closest pattern of activation (attractor). All the attractors learnt by that network (memories) collectively form the attractor landscape. Such models have usually been used to explain the occurrence of spurious memories (hallucinations; Chen, 1994, 1995; Rolls et al., 2008) or to explain specific aspects of positive symptoms such as the perseverance of delusions (Rolls et al., 2008).

Early on, Spitzer (1995) argued that in cortical networks a hyper-dopaminergic state results in a high SNR, leading to strongly anchored activation of high-level constructs such as "ideas/concepts/meanings" (Spitzer, 1995). Consistent with this hypothesis, Rolls et al. (2008) argued that the perseverance of delusions could be explained in terms of deep basins of attractions in the attractor landscape of the network, where attractors would represent conceptual states, ideas, meanings or an interpretation of the environment. That is, the depth of the basins of attraction (strongly anchored state) would prevent unlearning or switching to new attractors (new interpretation),

leading to a perseverance and an inability to adapt to novel cues from the environment (Rolls et al., 2008). In Hopfield networks, the SNR is modulated by changing the temperature parameter of the neurons, which in turn alters their firing probabilities. A low SNR leads to the inability for the network to recover learnt memories due to a high amount of noise. A high SNR instead results in recurrent patterns of activation (irrespective of the original input) or non-existent spurious memories, assumed to be similar to delusional thoughts or hallucinations (Chen, 1994, 1995). When studying the whole spectrum of temperature changes in these models, Chen (1994; Chen, 1995) predicted an inverted-U response profile, whereby intermediate temperature levels induced normal behaviour and memory retrieval. High temperature resulted in positive symptoms (i.e., parasitic foci/spurious attractors: hallucinations, delusions), while low temperature impeded memory retrieval (i.e., cognitive symptoms). This is interestingly at least at the physiological level, since the model predicted an inverted-U response profile with working-memory performance, which was later validated experimentally by electrophysiological recordings of primates' PFC neurons during working-memory tasks (Vijayraghavan et al., 2007; Cools and D'Esposito, 2011).
Recent implementations of attractor networks have reached a high level of biological and physiological detail using integrate-and-fire spiking neurons together with realistic AMPA, GABA, NMDA and DA pathways (D1r vs. D2r mediated SNR; Rolls et al., 2008). In these studies GABAergic interneurons inhibit the activity of excitatory neurons that are not encoding the current memory (so as to keep the activated memory pattern stable), while NMDA receptors modulate the stochastic firing probabilities of the pyramidal cells. DA modulates the SNR by stabilizing the firing patterns of NMDA and GABA activity, whereby a D1-dominated state increases excitatory and inhibitory activity leading to deeper basins of attraction, while D2-dominated states flatten the energy landscape and facilitates jumps from one attractor to the other. The reduction of excitatory (NMDA) and inhibitory (GABA) activity leads to an impossibility for the network to keep the firing patterns stable, resulting in random jumps between attractors. These random jumps have been argued to be responsible for the positive and cognitive symptoms observed in schizophrenia (Loh et al., 2007; Rolls et al., 2008).
While these models make interesting predictions regarding the global inhibitory and excitatory activity of the network, these predictions are difficult to test and validate using present neuroimaging tools.

2.2.2.2 *Sensory Gating Models*

Sensory Gating was the very first theory of dopamine function that was tested using computational models to study schizophrenia (Callaway and Naghdi, 1982; Carr and

Wale, 1986). This theory postulates that the brain has to gate relevant information to working-memory and filter-out irrelevant stimuli from all modalities. In these models, the DA signal is assumed to perform this role (Cohen et al., 1996). This framework would theoretically enable subjects to flexibly adapt their behaviour to the demands of particular tasks, favouring the processing of task-relevant information over other sources of competing information. This process, also known as cognitive control (Cohen et al., 1996), is thought to be automatic. In schizophrenia, sensory gating would be disrupted due to inappropriate phasic and tonic dopaminergic signalling, leading to deficits in attention and cognition (Grace, 1991). The gating process works by preventing the access to working memory by task-irrelevant stimuli, while maintaining task-relevant information against distractors. Biologically, the gating of relevant information is thought to occur through the simultaneous phasic burst of DA neurons to the presentation of relevant stimuli, while tonic DA is though to be responsible for the maintenance and protection of working-memory (Tretter and Albus, 2007). In schizophrenia, this DA gating mechanism is hypothesized to be noisier, leading to incorrect updates (intrusion of irrelevant stimuli) and maintenance of information (perseveratory behavior).

Gating models traditionally used connectionist frameworks to reproduce the performances of healthy controls or the perseveratory behavior of patients at the WCST and CPT, CPT-X tasks (Braver et al., 1999; Braver and Cohen, 1999). In these models, the DA signal exerts a top-down influence on behaviour by gating task-relevant information, allowing update, maintenance and protection against distracting stimuli (Braver et al., 1999; Braver and Cohen, 1999). These models of working-memory gating converged to similar conclusions, namely that DA hypo-function was most likely to be responsible for the cognitive deficits observed in schizophrenia (Braver et al., 1999; Braver and Cohen, 1999). Several descriptive models (i.e. not formalised using computational simulations; Javanbakht, 2005, 2006) also argued that a DA hypo-function would lead to positive symptoms due to a weakened top-down behavioural control (Javanbakht, 2005, 2006). Finally, using a connectionist framework of facial affect recognition Carter and Neufeld (2007) attempted to explain a recurrent finding that is often neglected in the literature, namely: Why are patient with schizophrenia constantly found to exhibit reaction-time deficits in cognitive tasks? In this model, inefficient gating of information, led to an overflow of incoming stimuli, resulting in additional processing for task completion. The increased amount of processing leads to an escalation of reaction-time, consistent with those observed in patients during facial affect recognition (Carter and Neufeld, 2007). It is worth noting however that in-

creased reaction-times are not specific to schizophrenia and have also been observed in other psychiatric conditions such as depression.

2.2.2.3 *Aberrant Salience Model*

The aberrant 'motivational salience' hypothesis stems from a recent interpretation of the role of DA as signalling rewards associated to stimuli so as to guide behavior (Berridge, 1998). An aberrant 'motivational salience' is an incorrect assignment of motivational salience to innocuous stimuli, where DA acts as an indicator of motivation, desire, or attention attributed to a stimulus (Howes and Kapur, 2009). The theory of incentive or 'motivational salience' was first used to explain drug addiction, where inappropriate rewards for drug intake gradually increase the motivational drive to relapse and repeat behavior (Berridge, 1998; Redish et al., 2008; Torregrossa et al., 2011). In schizophrenia, scientists have posited that an aberrant DA signaling would result in incorrect stimulus-reinforcer associations, attributing inappropriate salience to innocuous stimuli (Howes and Kapur, 2009; Roiser et al., 2009; Anticevic et al., 2011; Roiser et al., 2013). This inappropriate salience attribution is hypothesized to lead to an increase and perseverance of delusional thinking, even in the face of opposing evidence (Howes and Kapur, 2009; Corlett et al., 2009b; Anticevic and Corlett, 2012). Recent behavioural and neuroimaging experiments appear to confirm the link between aberrant salience and DA signalling to the strength of delusions in schizophrenia patients (Roiser et al., 2009) and patients at ultra-high risk (UHR) of psychosis (Roiser et al., 2013).

Grasemann et al. and Hoffman et al. (2009; 2011) adapted the aberrant salience framework using a connectionist model of story learning and recall to study thought disorder (namely delusions and derailments). This model mimics the multiple stages of syntax processing, where in each processing stage, artificial neural networks are trained to recall chains of words and sentences to reproduce a previously learnt story from a partial original input. The model is trained to learn the sequences of words and sentences through back-propagation. Excessive DA signaling during learning (termed hyperlearning by Grasemann et al., 2009; Hoffman et al., 2011), was modelled by increasing the learning rate of the last 500 training cycles of the model. This manipulation was argued to be consistent with the aberrant salience hypothesis. That is, since increased DA transmission would lead to an aberrant assignment of salience, it should eventually result in excessive learning. The authors also implemented various alternative mechanisms such as working memory disconnection (loss of synaptic connections) and hypo-dopaminergic states (as in sensory gating) by altering the gain and bias of the response curve of neurons. When comparing the performance

of each model to that of controls and schizophrenia patients, only the hyperlearning (aberrant salience) and disconnection models provided satisfactory fit to the data. However, the aberrant salience model (hyperlearning) achieved the best fit to the experimental data. The hyperlearning model could account for derailments from the original story through a confusion between the characters of different stories (agent-slotting errors) leading to delusion-like ideas (Grasemann et al., 2009; Hoffman et al., 2011). The authors argued that this is similar to what is observed experimentally in the deluded portion of the schizophrenia subgroup. These studies suggest that fixed delusions could stem from contaminated memories (e.g. due to misappropriated agents/characters between stories). However, it is difficult to verify whether 'agent-slotting errors' genuinely lead to false beliefs (delusions) as the authors argue. That is, a falsely reconstructed story within the model can stem from an incorrect recombination of memories during recall, but we believe that this is in contrast with the idea that delusions are false beliefs strongly anchored in memory. However, it is interesting that out of all types of story recall errors that were possible, agent slotting errors were the most frequent, as was observed experimentally in the deluded subgroup of patients.

Other studies used connectionist frameworks to describe how the aberrant salience hypothesis might lead to cognitive and negative symptoms (Grossberg, 1999, 2000). Particularly, these models were interested in investigating how these symptoms might arise from impaired amygdala circuits and abnormal arousal levels in schizophrenia patients (Grossberg, 1999, 2000). In these studies, the arousal level of subjects is assumed to be driven by dopamine and to follow an inverted-U response profile. Specifically, DA release was postulated to drive the amygdala circuits, where hypo-dopaminergic or hyper-dopaminergic activation would lead to a reduced top-down control resulting in an inability to block incentive stimuli (Grossberg, 1999, 2000). These models were solely descriptive and were not tested using computer simulations, making it difficult to draw testable predictions.

2.2.2.4 *Prediction Error*

The prediction error (PE) hypothesis is the most recent interpretation of dopamine function in the brain. The theory dates back to the 60's when Sokolov (1960) proposed that our internal representation of the environment should be updated as a function of a mismatch between the predicted and actual stimuli (Schmajuk, 2005). This theory was later supported by clinical studies in animals and humans revealing that the dopaminergic signal was consistent with the expected reward signal of the Temporal Difference Learning (TD-learning) algorithm (Schultz et al., 1997). We want to men-

tion however, that the previous class of models supporting the dopamine hypothesis do not compete against more recent accounts for the role of dopamine in the brain. In fact, most of the connectionist models supporting the sensory gating and signal-to-noise mechanisms pre-dates the finding of associative learning through dopaminergic prediction-error signaling and focused almost exclusively on modelling prefrontal cortices. This explains why early computational studies did not discriminate direct and indirect dopamine pathways (D1r vs D2r) or tonic vs. phasic activity of dopaminergic neurons. Interestingly, the predictions made by these early computational studies of DA function (SNR, attractors, sensory gating) are still valid. These supported the idea that cognitive deficits stem from low prefrontal dopamine (D1r) activation, which could explain working-memory deficits. In contrast, recent studies (aberrant salience or prediction error) tend to account for the role of dopamine in the basal ganglia to reveal how abnormal learning signals due to increased limbic DA levels lead to positive symptoms and cognitive deficits.

In associative learning experiments, the DA signal originating from the Ventral Tegmental Area (VTA) is found to be similar to the prediction error signal used to drive learning in the TD-learning algorithm (Schultz et al., 1997; Smith et al., 2005). The DA signal is interpreted as the biological substrate of the prediction error, where an expected outcome leads to tonic DA release, unexpected positive outcome (say an expected reward following a lever press) leads to phasic DA release and unexpected negative outcome are represented by dips of DA release below the tonic baseline (lack of expected reward; Grace, 1991). Consistent with these findings, Smith et al. (2003, 2004, 2007) successfully modelled patients' cognitive deficits in associative learning tasks by modelling aberrant DA prediction-error that disrupts learning. The results and predictions of these models successfully matched the behavioural performance of rodents in experimental studies using amphetamines and anti-psychotics as pharmacological models of schizophrenia (Smith et al., 2003, 2004, 2007). Recent computational models from Frank & colleagues (O'Reilly and Frank, 2006; Frank and Claus, 2006; Waltz et al., 2007; Frank, 2008; Maia and Frank, 2011), also provide a very detailed mechanistic account of the direct and indirect pathways of the basal ganglia and how these interact with the frontal cortex. These cortico-basal-thalamo-cortical models have been able to provide a detailed account for motor and cognitive deficits in patients with Parkinson's disease (Frank et al., 2004; Moustafa et al., 2008a,b; Maia and Frank, 2011). Investigating the indirect and direct pathways modulated by D2r and D1r (indirect/NoGo and direct/Go pathways) could lead to novel predictions regarding D2r vs. D1r mediated cognitive deficits in schizophrenia (i.e. impairment

in positive vs negative reinforcers; Frank, 2008).

Recent neuroimaging techniques provide new tools to assay whether prediction error signals are impaired in schizophrenia. Using associative learning and functional magnetic resonance imaging (fMRI), multiple studies have identified strong distortions in the expected prediction error signal of patients (Corlett et al., 2007b; Murray et al., 2008; Roiser et al., 2009; Gradin et al., 2011; Roiser et al., 2013). Interestingly, the distortion magnitude of the prediction error signal was highly predictive of positive symptom severity (delusions; Murray et al., 2008; Roiser et al., 2009, 2013; Corlett et al., 2007b; Gradin et al., 2011). These findings led to suggest that incorrect prediction-errors are consistent with the aberrant salience hypothesis. That is, delusions might stem from faulty PE that fails to discriminate between logical, rational or adaptive associations in the environment such that patients would attend to stimuli they should normally ignore (Frank, 2008).

2.3 THE GLUTAMATE HYPOTHESIS

2.3.1 *Experimental Evidence*

The glutamate hypothesis refers to the theory that glutamatergic signaling might be disrupted in schizophrenia. N-methyl-D-aspartate (NMDA) receptors are glutamatergic receptors known to be essential for synaptic plasticity and learning through the stabilization of synaptic connections (long term potentiation (LTP); Kandel et al., 2013). Consistent with this hypothesis, increases in the expression of NMDA receptors of subtype NR2A were identified in the prefrontal regions of schizophrenia patients (Akbarian et al., 1996). Secondly, psychotomimetic drugs such as Phencyclidine (PCP) and Ketamine that block NMDA receptors (NMDAr antagonists) lead to negative, cognitive and delusion-like symptoms in healthy individuals (Javitt, 1987; Javitt and Zukin, 1991; Jentsch and Roth, 1999). As a result, Ketamine has been widely used as a pharmacological model of schizophrenia (Javitt, 1987; Javitt and Zukin, 1991; Honey et al., 2006; Corlett et al., 2011; Moore et al., 2011; Anticevic et al., 2012; Corlett et al., 2013). This led to the widely accepted hypothesis that schizophrenia patients might suffer from deficient NMDA receptors (NMDA receptor hypo-function; Javitt, 1987; Javitt and Zukin, 1991; Jentsch and Roth, 1999; Honey et al., 2006). Finally, genetically modified NRG1 mice (NRG1 encodes the neuregulin protein, essential to NMDA receptor maturation) display abnormal behaviours similar to that of schizophrenia patients: abnormal social interactions, increased anxiety, abnormal lev-

els of DA release and hypersensitivity to amphetamines, all of which can be reversed with anti-psychotics (Powell et al., 2009).

2.3.2 *Models and support*

While Dopamine is widely accepted as playing a major role in psychosis, the glutamate hypothesis remains a strong potential candidate to explain the aetiology of schizophrenia. One reason for this is that the glutamate hypothesis can account for a wider range of symptoms, inducing positive, cognitive and negative symptoms when using Ketamine or PCP in healthy controls (Javitt, 1987; Javitt and Zukin, 1991; Jentsch and Roth, 1999). However, it is worth noting that no pharmacological treatment affecting glutamate has been found to be effective to date in schizophrenia (Papanastasiou et al., 2013).

The glutamate hypothesis is relatively recent in comparison to the DA hypothesis, and as a result fewer computational models have been developed to assay its validity. Such models (e.g. Murray et al., 2012) consist mostly of biophysical models using integrate-and-fire neural networks that simulate memory or working-memory storage and retrieval through attractor networks. These networks provide realistic simulations of the interactions between excitatory and inhibitory (E/I) activity in cortical areas relevant to the task being modelled (e.g. hippocampus and/or prefrontal cortex). That is, making a number of assumptions regarding the topology of the network (e.g. Mexican hat), these models can predict the E/I balance within cortical areas that is necessary for memory storage and retrieval. While these realistic neural networks provide very detailed predictions at the biophysical level, these predictions are difficult to validate experimentally. In fact, most of the data and measurements acquired in schizophrenia comes from neuroimaging or behavioural experiments, and are thus difficult to relate to predictions regarding precise neural activity.

2.3.2.1 *NMDA receptor hypo-function - Cortical Stability*

Models supporting the glutamate hypothesis usually address cognitive and/or negative symptoms due to NMDA receptors hypo-function in the PFC (Hsu et al., 2008; Wang, 2006; Murray et al., 2012) or through a combination of NMDA receptors hypo-function in the PFC and the hippocampus (Diwadkar et al., 2008; Siekmeier et al., 2007). Wang (2006) simulated prefrontal networks of working-memory using integrate-and-fire neural networks. In this model, pyramidal cells (excitatory) and inhibitory interneurons are differently modulated by NMDA receptors. Wang (2006) then tested whether such biophysically realistic attractor networks can simulate the sustained activity of PFC neurons observed during delayed-response tasks in pri-

mates. The author found that realistic models of WM maintenance can be instantiated by attractor networks, but that a precise E/I balance is critical in order to filter out distracting stimuli (Wang, 2006; Murray et al., 2012). A second class of models also addressed NMDA receptor hypo-function in the hippocampus (Diwadkar et al., 2008; Siekmeier et al., 2007). For example, Siekmeier et al. (2007) used a connectionist model of the hippocampus to simulate associative learning and context-dependent retrieval of verbal stimuli. The model predicted that NMDA receptor hypo-function in the hippocampus would result in poor memory retrieval (Siekmeier et al., 2007). Interestingly, the authors argue that a hyper-dopaminergic activation of the hippocampus would also result in NMDA receptor hypo-function, again leading to poor memory retrieval.

A possible criticism of this study is that patients seem to usually display memory encoding deficits rather than memory retrieval, and that a memory retrieval deficit would normally stem from a cortical deficit rather than from the hippocampus. It is important to note however that the different models presented here investigated different types of memory (Baddeley, 1987). Siekmeier (2009) was modelling deficits in verbal short-term memory, while Wang (2006); Murray et al. (2012) were investigating spatial working-memory networks. These two types of memory are assumed to involve different cortical processes and memory systems.

2.3.2.2 *Realistic Biophysical models - Cortical stability & Signal-to-Noise ratio*

Earlier attractor network models were the precursors of the latest biophysical models, which use AMPA, NMDA and GABA receptors to model working-memory (Loh et al., 2007; Rolls et al., 2008). In these models, the balance between inhibitory (GABA) and excitatory signals (AMPA/NMDA) is critical. First, in a combined experimental and computational setting, Wolf et al. (2005) studied the bistability (i.e. the switching between an up or down state) of medium spiny neurons in the Nucleus Accumbens (NAcc), which has been proposed to serve for gating purposes in working-memory (Gruber et al., 2006). Their model predicted that the medium spiny neurons (MSN) would require sustained excitatory inputs (from about 1000 afferent) in order to maintain a stable depolarized (up) state. In this model, NMDA receptors hypo-function is predicted to lead to an inability for MSN to express bistable activity and to impede gating or integration of information. Another study by Loh et al. (2007) addressed the interactions between inhibitory (GABA) and excitatory (NMDA/AMPA) activity on the dynamics of a working-memory attractor network. The authors found that an imbalance in excitation or inhibition led to the instability of the whole system, resulting in unstable working-memory. This instability resulted in changes in the attractor landscape. Decreased excitatory activity led to jumps from one attractor to another due to

an increased stochastic firing of the neurons in combination with shallower attractor states. As a result, memories were unstable. In this model, a decrease in both excitation (NMDA) and inhibition (GABA) results in a flat attractor landscape. The authors argue that a flat attractor landscape in temporal areas (short & long-term memory) would lead to jumps between trains of thoughts. This prediction is also in line with previous experiments showing excessive amounts of noise in the temporal (auditory) cortices of patients, especially during auditory hallucinations. Interestingly, although supporting the glutamate hypothesis, the authors managed to adapt the model using the work from Durstewitz and Seamans (2008), so as to account for the role of DA modulating network activity. The authors found that intermediate levels of DA modulate the SNR in frontal areas. That is, D1 receptor activation enhance both excitatory (NMDA) and inhibitory (GABA) activity resulting in an increased stability of the network (increase in SNR), while D2 receptor activation has the opposite effect and reduce the signal-to-noise ratio. The authors argue that this mechanism could potentially explain the effects of anti-psychotic medications by stabilizing deficient attractor networks through a decrease in D2 receptors activity.
It is worth noting however, that the majority of dopaminergic receptors in the frontal cortex seem to be of the D1r subtype (Howes and Kapur, 2009), and that D2r activation have previously been found to have no effect on WM networks (Wang et al., 2004). Again, while these studies provide interesting insights on the possible link between DA, SNR and attractor dynamics in schizophrenia, the model predictions are difficult to relate to experimental data, which mostly consists of behavioral and/or imaging data.

2.4 THE GABA HYPOTHESIS

2.4.1 *Experimental evidence*

Lewis and Hashimoto (2005) observed abnormalities of GABAergic interneurons in schizophrenia patients. Namely, they found that GABA synthesis and re-uptake was altered and diminished in the dlPFC leading to disrupted gamma oscillations and de-synchronization. Also, DA neurons appear to provide direct synaptic input to some (i.e. parvalbumin-expressing GABA) interneurons in the dlPFC of primates, suggesting a possible modulation of GABAergic inhibition through DA activation (Lewis and Hashimoto, 2005).

2.4.2 *Models and support*

Very few computational models support the GABAergic hypothesis alone, but rather integrate GABAergic inhibition with NMDA hypo-function to model biologically realistic simulations of cortical function, stability and synchrony (Loh et al., 2007; Rolls et al., 2008; Murray et al., 2012).

2.4.2.1 *Cortical stability*

Of the models investigating the GABA hypothesis, each of these studies explored different aspects of inhibitory dysfunction in schizophrenia (Tanaka, 2008; Akbarian et al., 1996). In Tanaka (2008), the effects of GABAergic activation through dopamine D1r modulation were investigated using a pure mathematical model of balanced inhibitory and excitatory activity. The author established through parameter exploration that for intermediate levels of D1r activation, GABA inhibits noise in the dlPFC circuitry of working-memory (increased SNR). The model of Spencer (2009) investigated the link between the GABA and disconnection hypothesis. Their integrate-and-fire model suggests that a deficient inhibition would lead to disrupted γ-rhythms as observed in schizophrenia. γ-rhythms, if disrupted, would disturb cortico-cortical synchrony and eventually result in a functional disconnection syndrome.

2.5 THE DISCONNECTION HYPOTHESIS

2.5.1 *Experimental evidence*

The disconnection hypothesis states that schizophrenia is associated with reduced synaptic connectivity (disconnection) or dysfunctional connectivity (i.e. disconnection) primarily in the mesocortical pathway (i.e. midbrain dopamine and serotonin afferent to the PFC) and between cortical areas such as the frontal cortex and the temporal lobes (Stephan et al., 2009; Friston, 1996; Pettersson-Yeo et al., 2011). This theory is supported by several post-mortem and neuroimaging studies revealing anatomical (Kubicki et al., 2005, 2007; Samartzis et al., 2014) and functional disconnection (Dima et al., 2010; Dauvermann et al., 2013) in patients. First, it was found that the normal developmental course of the mammalian brain begins with an over-elaboration of neuritic processes, which is then followed by a gradual reduction of synaptic density during adolescence, reaching about 60% of maximum levels in early adulthood (McGlashan and Hoffman, 2000). Interestingly, the end of this developmental timeline coincides with the age of onset of psychotic symptoms (first episode), suggest-

ing a late neurodevelopmental dysfunction during adolescence. Several post-mortem examinations later found reduced spine densities and smaller dendritic arbors on prefrontal pyramidal cells of schizophrenia patients (Stephan et al., 2009). Additionally, decreased synaptic protein messengers and synaptophysin were found in the dlPFC of patients. Together these findings provide a possible explanation for the observed decreased neuropil without neural loss found previously in schizophrenia (McGlashan and Hoffman, 2000). It is worth noting however, that decreased neuropil appears in other mental disorders and is not specific to psychotic-illness.

2.5.2 *Models and support*

2.5.2.1 *Cortical stability*

Computational models of the disconnection hypothesis can be classified into three subcategories. In the first group, simple Hopfield networks were used to study positive symptoms (Hoffman, 1987; Hoffman and Dobscha, 1989; David, 1994; Seeman, 1994). In these models, a disconnection is usually implemented by *'pruning'* the synaptic connections between the units of the networks after training. The pruning strategy adopted is a Darwinian *'evolutionary'* process, which eliminates weak and spatially distant connections by setting their weights to zero. This eventually results in an inability for the network to flow into previously learnt patterns of activation and recover memories. When excessive pruning is performed two types of behaviours emerge. First, the network produces generalizations or *'loose associations'*, by merging parts of distinct memory patterns into a single one, which was interpreted as a potential explanation for bizarre trains of thoughts (thought disorder). Secondly, the network could elicit spontaneous patterns of activations, that is, relentlessly recovering the same memory output irrespective of the input presented or recovering new memory patterns unknown to the model. The authors argued that the spontaneous emergence of new memories was homologous to hallucinations. Hoffman was the main instigator of this hypothesis in the field of schizophrenia. His early models qualitatively supported the hypothesis of an excessive pruning or memory overload in the disorder (Hoffman and Dobscha, 1989; Hoffman, 1987). However, the simulations of these effects were quantitatively unrealistic as up to 80% of *'evolutionary'* pruning was required for hallucinations to emerge. This specific hypothesis was later disputed by David (1994), which instead proposed that positive symptoms may emerge from an hyper-connectivity due to a deficit of the neurodevelopmental pruning process. However, these conclusions appears to be contradicted by experimental findings of reduced grey matter and connectivity in schizophrenia. Following Hoffman's sug-

gestions, other researchers sought to expand the model to account for the effects of environmental stress and dopamine modulation (Chen, 1994, 1995; Seeman, 1994). These effects were expressed in terms of memory overload and increased network temperature. The models provided a possible link between the positive and cognitive symptoms by incorporating dopamine as a signal-to-noise enhancer, where too little or too much dopamine was detrimental to the signal. In the mid 90's, computational studies started investigating the disconnectivity hypothesis from a different perspective such that positive symptoms might stem from secondary self-repairing properties of the brain following cortico-cortical synaptic pruning. When the cortico-cortical inputs connecting to the working-memory units of the network were degraded, the PFC tended to compensate by updating its local weights in order to recover memory patterns. This, in turn, led to increased WM noise resulting in the spontaneous retrieval of memories in the absence of external inputs (Ruppin et al., 1996; Horn and Ruppin, 1995; Ruppin, 1995).

The second group of disconnection models used three-layer perceptrons to study hallucinated voices in patients with schizophrenia (Hoffman and McGlashan, 1993b,a; Hoffman, 1997; Hoffman and McGlashan, 1997, 1999; McGlashan and Hoffman, 2000; Hoffman and McGlashan, 2001; de la Fuente-Sandoval et al., 2005; Hoffman and McGlashan, 2006). These networks were trained in an ad-hoc manner to associate inputs (phonemes) and outputs (words) using back-propagation. The network then relied on an intermediate layer representing verbal working-memory to disambiguate current phonemes. In the first implementations of this model, the working-memory module was only a delayed copy of the hidden layer (i.e. temporary buffer) used to bias and compute temporally successive inputs (Hoffman and McGlashan, 1993b,a; Hoffman, 1997; Hoffman and McGlashan, 1997, 1999; McGlashan and Hoffman, 2000; Hoffman and McGlashan, 2001; de la Fuente-Sandoval et al., 2005). Later models modified the working-memory so as to use a Hopfield network within the hidden layer (Hoffman and McGlashan, 2006). To account for the disconnection syndrome, synaptic connections were removed following an *'evolutionary'* approach as described previously. These models generated interesting results, whereby synaptic pruning improved the performance of word recognition by 50% when pruning up to 64% of the connections. However, above 77% of pruning, hallucinated words — i.e. words detected without input — started to occur and performance decreased drastically. The authors suggested that synaptic pruning during the neurodevelopmental stage of late adolescence might actually be beneficial as it would improve recall performances while reducing energetic costs. The model also suggests that a failure to stop normal synaptic pruning in early adulthood could account for the onset of the disorder. Neuronal loss

(Hoffman, 1997) and deregulated hypo-dopaminergic modulation (McGlashan and Hoffman, 2000; Hoffman and McGlashan, 2006) were also addressed in this framework. However, both failed to initiate so-called "hallucinations". Hypo-dopaminergic modulation was implemented in this model as a shift of the bias to each neural unit in WM (i.e. hidden layer), which protected over-pruned networks against hallucinations (Hoffman and McGlashan, 2006). Interestingly, assuming that dopaminergic modulation can realistically alter the bias of WM units, the model could successfully account for the effects of anti-psychotics and protected against positive symptoms.

Other models studied schizophrenia impairments at specific cognitive tasks such as facial affect recognition using a three-layer perceptron (Johnston et al., 2001), episodic memory deficits using a connectionist framework (Meeter et al., 2002), and semantic priming using interconnected Hopfield networks (Siekmeier and Hoffman, 2002). All these studies converged to similar conclusions, namely that synaptic pruning was found to degrade the performance of the network. However, the causes of an excessive pruning mechanism remains unknown and was largely left untouched in these studies. While genetic factors could be at play, no experimental study has found a common genetic component that would be responsible for this developmental deficit.

It is important to mention that while R.E. Hoffman was the most prominent scientist defending the disconnection hypothesis through models of excessive pruning processes (10 out of the 15 published modelling studies on disconnection), in later studies the author tested other competing hypotheses of schizophrenia including the disconnection hypothesis in a story-recall task (Grasemann et al., 2009; Hoffman et al., 2011). There, the authors found that only the disconnection and aberrant salience hypotheses could account for positive symptoms, but that the aberrant salience hypothesis accounted best for the performance of deluded schizophrenia patients at story learning and recall task. Finally, recent work from Whitford et al. (2012), hypothesized that frontal myelin damage in schizophrenia would lead to delays in the transmission of efference copies & corollary discharge (copies of motor commands & predicted sensory feedback). This delay would result in an asynchrony between proprioception (sensory feedback) and corollary discharge leading to sensory discrepancies. In such cases, a subject would perceive these sensory discrepancies as-if their own actions were not self-generated. This would result in delusions of control, that is, the false belief that an external force controls one's thoughts and behaviour.

2.6 THE BAYESIAN HYPOTHESIS

Recently the brain has been viewed as a complex processing machine used to interpret sensory inputs in order to make sense of the environment (Friston, 2005a, 2010; Franklin and Wolpert, 2011; Wolpert et al., 2011). According to this theory, the brain evolved to interpret and infer the cause and consequences from the environment in order to predict future outcomes in the environment and minimize surprises. This framework assumes that cognition can be described in terms of Bayesian inference, where subjects combine optimally sensory evidence (the "likelihood", for e.g. sensory inputs about a visual scene, say a face looking like Elvis Presley) and prior knowledge or expectations (the "prior", for e.g. knowledge about the frequency of certain objects in the environment) so as to form probability distributions relevant to the task at hand (e.g. how likely is it that I've just seen Elvis?). It is argued that using this framework, illusions would lead to an effect of surprise. This surprise would then require to logically explain these abnormal percepts by updating the internal model of the environment, resulting in false beliefs akin to delusions (Corlett et al., 2007b,a, 2009a,c; Fletcher and Frith, 2009). Delusional content, would in turn bias expectations of future outcomes in the environment resulting in stronger perceptual biases (i.e. illusions or hallucinations). This spiralling effect would gradually result in stronger and more salient illusions & false-beliefs, eventually leading to full-blown complex hallucinations and deeply anchored delusions.

2.6.1 *Experimental evidence*

The Bayesian brain hypothesis of psychosis has received relatively little support experimentally, with the exception of studies investigating illusions (Tschacher et al., 2006; Dima et al., 2009, 2010; Crawford et al., 2010; Williams et al., 2010; Horton and Silverstein, 2011; Silverstein and Keane, 2011b,a; Keane et al., 2013) or explicit statistical learning (Huq et al., 1988; Freeman et al., 2008; Speechley et al., 2010; Averbeck et al., 2011; Evans et al., 2012; Joyce et al., 2013; Garety et al., 2013; Garety and Freeman, 2013; Freeman et al., 2014). Such studies however, tend to investigate either illusion or learning in isolation (i.e. not attempting to study first the acquisition of expectations and then the influences of these expectations on perception).
For illusory perception, patients with schizophrenia have been found to be less susceptible than healthy controls at the hollow mask illusion (Dima et al., 2009, 2010; Keane et al., 2013), motion-induced blindness (Tschacher et al., 2006), illusory motion (Crawford et al., 2010), the size-weight illusion (Williams et al., 2010), and the Ebbinghaus illusion (Horton and Silverstein, 2011), for a review of perception in schizophre-

nia see (Silverstein and Keane, 2011b,a). In healthy controls, Schmack et al. (2013) recently demonstrated that the magnitude of expectation-driven illusions correlated with delusional ideation in these subjects. That is, in line with previous studies on perceptual illusions in schizophrenia (Tschacher et al., 2006; Dima et al., 2009, 2010; Crawford et al., 2010; Williams et al., 2010; Keane et al., 2013), the authors found that the stronger the delusions of healthy controls, the less likely these were to have their percepts affected by expectations (Schmack et al., 2013). This is consistent with the idea that patients with schizophrenia (or controls with mild forms of delusions) might have a deficit of perceptual inference or acquisition of expectations and outcomes.

2.6.2 *Models and support*

While there are a couple of descriptive models that attempt to account for a problem of Bayesian inference in schizophrenia (Corlett et al., 2009a; Fletcher and Frith, 2009; Frith and Friston, 2012; Jardri and Cachia, 2013), relatively few computational models have been implemented to provide a quantitative and mechanistic account of delusions and hallucinations using this framework (Adams et al., 2013; Jardri and Deneve, 2013).

In Adams et al. (2013), the authors argue that psychosis may stem from an abnormal encoding of the *'precision'* of prior beliefs relative to sensory evidence. That is, the expectations (prior beliefs) of the patients are weaker than they ought to be, resulting in too much emphasis on sensory evidence. This leads to a high state of surprise since sensory observations are not expected. The authors then argue that so as to minimise surprise a secondary reduction in the *'precision'* of sensory evidence follows. Using their model, the authors then demonstrate how such a model could explain deficits in tasks such as in the oddball stimuli, smooth eye-pursuit and the force-matching task. However the computational models presented in Adams et al. (2013) were not fitted to the experimental data of patients performing similar tasks. Instead the parameters of the models were manipulated in an ad-hoc manner so as to illustrate how a reduction in the *'precision'* of prior beliefs could lead to deficits in the tasks modelled (synthetic data). Future work should attempt to fit such models to real data-sets and test multiple hypotheses using model comparison, as it may yield different results.

Similarly to Adams et al. (2013), Jardri and Deneve (2013) proposed a hierarchical Bayesian model where each level of the hierarchy produces inference and abstraction over lower levels. In this model, the authors argue that bottom-up sensory evidence and top-down predictions could be reverberated throughout the hierarchy due to poor GABAergic inhibition. Particularly, the authors make the predictions that an

impairment in inhibition of both bottom-up and top-down signals would lead to no impairments in inference. However a selective impairment of inhibition of upward loops (bottom-up, sensory evidence), would result in sensory evidence being reverberated throughout the hierarchy as if it were prior beliefs. This would result in an over-estimation of sensory evidence (overconfidence). That is, consistent with Adams et al. (2013), the authors argue that delusions and hallucinations stem from an underweighting of the prior (decreased *'precision'* of the prior) and an over-estimation of the strength of sensory evidence (i.e. increased *'precision'* of sensory evidence). The authors call for experimental investigations to be carried in order to measure how patients weight their expectations and sensory evidence during perceptual or decision tasks.

2.7 DISCUSSION

In this review, we described promising models, which support various hypotheses of schizophrenia's aetiology. While, none of these computational studies could account for the variety and complexity of symptoms found in the disorder, most studies focusing on cognitive symptoms appear to support the dopaminergic hypothesis. Computationally, cognitive symptoms appear to stem from:

1. A weak frontal dopaminergic D1r activation (dlPFC), resulting in a decreased frontal SNR and deficient working memory.

2. Excessive striatal D2r activation, leading to impairments in prediction-error signalling, essential for associative learning and goal-directed behaviour.

Schizophrenia is an heterogeneous disorder, expressing itself through unique combinations of symptoms in every patient. Therefore, we do not exclude the possibility that several of the current hypotheses discussed in this review might jointly be responsible for the wide variety of behaviours and symptoms observed in the disorder. For example, biophysically realistic models of working-memory elegantly demonstrated how the balance between inhibitory GABAergic and excitatory glutamatergic activity is crucial to the proper functioning of realistic attractor networks (cortical stability). In these models, a deficit in either excitatory glutamate or inhibitory GABAergic activity led to impaired working-memory dynamics, cognitive impairments and arguably to some form of positive symptoms. Alternatively, models supporting a disconnection syndrome were able to successfully demonstrate how excessive pruning in cortical networks could lead to positive symptoms (spurious attractors), as well as predicting the neurodevelopmental timeline of schizophrenia, providing for the first time an explanation for the late adolescence onset of the disorder (McGlashan

and Hoffman, 2000; Hoffman and McGlashan, 2006). Less experimental evidence was found to support an association between neurotransmitter dysfunctions and cortico-cortical disconnection. However, we would argue that both the glutamate and GABAergic hypothesis could lead to a disconnection syndrome. Specifically, weaker synapses could emerge following a prefrontal NMDA receptor hypo-function. Such synapses could then be pruned away during the Darwinian *'evolutionary'* neurodevelopmental process proposed by (McGlashan and Hoffman, 2000; Hoffman and McGlashan, 2006). That is, weaker synapses would lead to an over-pruning of frontal cortices, resulting in a *'physical disconnection syndrome'*, as presented by the synaptic runaway model of Greenstein-Messica and Ruppin (1998). Alternatively, GABAergic inhibition appears to be essential to the generation of γ-band rhythms. Aberrant γ-oscillations, is argued to result in an asynchrony between cortical regions (Spencer, 2009), leading to a reduced ability to transmit information between cortical regions, (*'functional disconnection'*). As a result, we argue that a disconnection syndrome might be secondary to an incorrect balance between excitatory and inhibitory activity in cortical regions, leading to either excessive synaptic pruning during adolescence (*'physical disconnection'*) or an impossibility to synchronize information across cortical regions (*'functional disconnection'*). Finally, it is worth mentioning that NMDA receptor blockade has been found to result in strong changes of dopaminergic midbrain neurons (Jentsch and Roth, 1999). It is therefore possible that the dopamine dysfunction observed in schizophrenia could be secondary to a generalised NMDA receptor hypo-function.

2.8 AFTERWORD & CONCLUSIONS

In a recent review of computational studies in schizophrenia research, Rolls and Deco (2011) called for further investigation using bottom-up modelling approaches. The authors argued that using realistic biophysical models of attractor network and cortical dynamics, one could explore in much detail the interactions between neurotransmitter functions and produce precise predictions about the states of the neural networks in schizophrenia. We agree with the authors that the abstract modelling of decreased signal-to-noise ratio in schizophrenia can successfully give place to more refined biophysical models in order to account for our current knowledge of network dynamics and neurotransmitter function. However, Rolls and Deco (2011) argue that high-level, abstract, behavioural or descriptive models (i.e. phenomenological models) have no construct validity since these do not map to realistic brain function and as a result fail to produce testable predictions. In this thesis, we take a different standpoint. We would argue that since cognitive, positive and negative symptoms are the most sta-

ble, salient and measurable effect of the disorder across patients, high-level descriptive models can result in strong testable predictions at the behavioural level. That is, first, using high-level models, one can attempt to validate and refine the array of possible hypotheses down to those that are most likely to account for the symptoms and behaviours observed in patients. Once a subset of hypotheses has been identified, scientists will have a better chance to devise biophysically realistic models and predictions that are testable using current neuroimaging tools. Particularly, in light of the findings highlighted in this review, we found that the Bayesian brain hypothesis of psychosis has received relatively little investigation in comparison to the other hypotheses. This novel approach to schizophrenia is promising and deserves further theoretical and experimental investigation. In fact, in comparison to the models supporting the GABAergic, glutamate or dopamine hypothesis, the Bayesian brain hypothesis provides a high-level construct that makes strong testable predictions that can be validated experimentally at the behavioural level. That is, we could potentially test the predictions of this framework, and if proven successful, start to investigate the underlying neural processes that may have gone awry in this framework. Specifically, we propose to use a psychophysical task that has been validated in healthy controls to assay learning and perceptual inference (Chalk et al., 2010; Gekas et al., 2013). Using this task, we propose to investigate whether learning and perceptual inference mechanisms appear disrupted in schizophrenia.

3

RAT GAMBLING TASK (RGT): MALADAPTIVE DECISION MAKING, A CONTINUUM BETWEEN HEALTHY AND PSYCHIATRIC POPULATIONS

The work presented in this chapter is the result of a close collaboration with behavioural experimentalists at the National Centre for Scientific Research (CNRS - Bordeaux 2). Marion Rivalan and Dr. Françoise Dellu-Hagedorn designed and performed the behavioural experiments. The computational modelling and analysis was performed by myself under the supervision of Dr. Peggy Seriès and Dr. Alain Marchand. The resulting findings have been published in PLoS ONE as a shared first co-authorship (Rivalan et al., 2013; see Appendix A).[1]

3.1 BACKGROUND

3.1.1 *Iowa Gambling Task: Maladaptive decision making in humans*

Humans often face complex and conflicting choices and have to refrain from immediate gratification in order to select options with the best long-term pay-offs. The Iowa Gambling Task (IGT) is a cognitive test developed by Bechara and Damasio in (1994), with the aim to devise a neuropsychological test that simulates this *"complex"* and *"conflicting"* decision-making process in a laboratory. The task was originally constructed to study deficits of decision-making in patients with frontal lesions (particularly ventro-medial PFC lesions;Bechara et al. 1994, 1996, 1997, 1999, for review see Dunn et al. 2006). While these patients displayed no impairments in IQ, reasoning, comprehension and learning relative to healthy controls, they displayed specific deficits for decisions that involves conflicting factors and necessitate to plan and foresee long term benefits (Bechara et al., 1994, 1996, 1997, 1999; Dunn et al., 2006). In the IGT, participants are required to pick a card in one of four decks available (A,B,C or D) for 100 trials. After a deck is selected, the participant receives an immediate reward materialised as a gain of fictive money, sometimes followed by a penalty (loss of fictive money; Figure 3.1). Unknown to the participant, there are two advantageous (C-D) and two disadvantageous decks (A-B) of cards. Using trial-and-error,

1 The work presented in this chapter is largely adapted from (Rivalan et al., 2013; Valton, 2010). The dataset presented in this chapter is different from this presented in (Valton, 2010), where methods have been largely modified or extended.

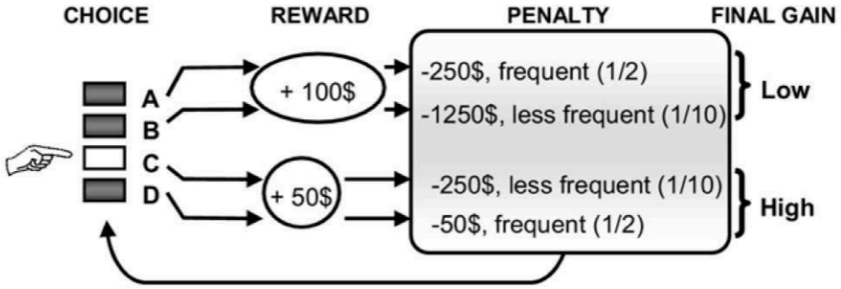

Figure 3.1: Principle of the Iowa Gambling Task. Participants can choose among four different decks of cards (deck A, B, C and D) to earn as much money as possible within one session (100 trials). The selection of an option is immediately rewarded ($50 or $100), but can also be followed by a penalty (loss of money) of variable amounts and frequency depending on the option chosen. The options (C, D) are equally advantageous in the long term in comparison to options (A, B) which are equally disadvantageous, leading to long term losses. The figure was included with permission from (Rivalan et al., 2009a)

participants are required to infer the optimal decision strategy by picking as often as possible from the advantageous decks. Advantageous decks provide small immediate rewards (+50$) usually followed by infrequent small losses leading to an overall net gain of +250$ every ten trials. On the other hand, disadvantageous decks result in a large immediate reward (+100$) followed by frequent large losses leading to an overall net loss of -250$ every ten trials. As a result, participants should gradually learn to forgo short-term benefits for long term profits. The decision-making performance is extracted by measuring either the total number of optimal deck selections at the end of the task or the ratio of advantageous to disadvantageous deck selections every 20 trials.

Uncertainty in the task is warranted by the immediate variability of gains (+50$ vs +100$) and the probability of punishments assigned to each deck. Conflicting decisions are warranted by the trade-off between the immediate gains and long-term consequences of each option. To-date, the IGT is the most commonly used tool to address decision-making deficits in a clinical setting (Bechara et al., 1994; Dunn et al., 2006; de Visser et al., 2011), particularly for disorders such as addiction, obsessive compulsive disorder (OCD), attention-deficit hyper-activity disorder (ADHD) and pathological gambling (Dunn et al., 2006; Buelow and Suhr, 2009).

3.1.1.1 *Performance in healthy population*

Most healthy participants successfully deduce that small but frequent payouts are beneficial in the long term (Bechara et al., 1994; Dunn et al., 2006). Starting with an

initial preference for disadvantageous decks (due to their high immediate reward), participants gradually learn to favour advantageous decks once they have been exposed to large penalties (Bechara and Damasio, 2002; Dunn et al., 2006). By the end of the task, healthy individuals display a strong preference for advantageous choices (Bechara and Damasio, 2002; Dunn et al., 2006).

Inter-individual differences in IGT performances within the healthy control group are generally overlooked. Some studies, however, report finding a strong dichotomy within healthy controls in terms of performances (Bechara et al., 1999, 2001; Petry, 2001; Bechara and Damasio, 2002; Bolla et al., 2004; Denburg et al., 2005, 2006; Glicksohn et al., 2007; Davis et al., 2007). These studies found that about 35% of healthy controls (reported range: 23-57%) preferentially choose immediate pay-offs and persevere to select disadvantageous options throughout the task (Bechara et al., 1999, 2001; Petry, 2001; Bechara and Damasio, 2002; Bolla et al., 2004; Denburg et al., 2005, 2006; Glicksohn et al., 2007; Davis et al., 2007). Further to this initial sub-division of poor and good DM within the healthy control group, studies also appear to find significant gender (Bolla et al., 2004; Glicksohn et al., 2007; Davis et al., 2007) and age-related effects (Denburg et al., 2005, 2006) to poor DM performances in these healthy individuals. It is worth noting, however, that healthy individuals that perform poorly at the IGT appear to be spared from impediments in everyday decision-making but report themselves as preferring *"sensation seeking"*, akin to risky situations, in everyday life (Bechara et al., 1999, 2000). Further to this finding, studies have found a link between poor performances at the IGT in healthy controls and traits such as risk-seeking (Bechara et al., 1999; Crone et al., 2003; Davis et al., 2007), reward sensitivity (Suhr and Tsanadis, 2007) and impulsivity (Crone et al., 2003; Davis et al., 2007). Risk-seeking and impulsivity are behavioural traits that are reminiscent of a variety of psychiatric conditions (DSM-IV-TR, 2000) such as ADHD (Moeller et al., 2001), pathological gambling and substance abuse (Jentsch and Taylor, 1999; Volkow and Fowler, 2000). If these traits are central to poor decision-making performances, both in healthy individuals and psychiatric conditions, it is conceivable that such psychiatric conditions might be better explained in terms of a continuum together with healthy individuals, rather than a clear-cut dichotomy separating the two (see Section 1.1.2) . In fact, healthy poor decision-makers appear to support the hypothesis of a spectrum of decision-making deficits, where healthy good decision-makers would lie at one end and psychopathologies would lie at the other extreme of this spectrum (see Section 1.1.2; Cuthbert and Insel, 2013).

Studying the influence of these behavioural traits on decision-making could help

understanding the variability observed in decision making performances and potentially help identifying the underlying neurobiological processes involved in these traits. Most importantly, these investigations could pave the way for a more biological-driven diagnosis of psychiatric conditions (Insel et al., 2010) that may exhibit extreme manifestations and combinations of these traits (DSM-IV-TR, 2000; DSM-5, 2013).

3.1.1.2 *Psychiatric population*

Impaired decision making is a core deficit of many psychiatric disorders (for overall review see Dunn et al., 2006) such as substance abuse (Bartzokis et al., 2000; Bolla et al., 2003; Monterosso et al., 2001; Stout et al., 2004; Yechiam et al., 2005), pathological gambling (Cavedini et al., 2002b; Goudriaan et al., 2004), OCD (Cavedini et al., 2004, 2002a; Lawrence et al., 2006), ADHD (Ernst et al., 2003a,b; Toplak et al., 2005, 2010), but is also found in schizophrenia (Beninger et al., 2003; Ritter et al., 2004; Shurman et al., 2005; Kester et al., 2006; Bark et al., 2005; Kim et al., 2009; Sevy et al., 2007), huntington's disease (Stout et al., 2001; Campbell et al., 2004), Parkinson's disease (Thiel et al., 2003) and anti-social behaviour such as psychopathy (Schmitt et al., 1999; Blair et al., 2001; Mitchell et al., 2002). Most particularly, the IGT is a highly sensitive tool to measure impaired decision-making in psychiatric conditions that are known to be characterized by poor decision-making such as pathological gambling, substance abuse, and OCD (Dunn et al., 2006).

While the list of psychopathologies associated with poor IGT performances is quite heterogeneous, common features such as impulsive or compulsive behaviours can be identified in a variety of these conditions (Suhr and Tsanadis, 2007; Buelow and Suhr, 2009; Rivalan, 2010). OCD, for example, is characterized by extreme anxiety (e.g. mysophobia - phobia for germs) leading individuals to perform compulsive behaviours (e.g. extreme hand-washing) and can be found to a lesser extent in other conditions like bulimia and pathological gambling (Hollander et al., 1996; Stein, 2000); Impulsivity, on the other hand, appear to be a core deficit of ADHD, substance abuse and anti-social behaviour (Hollander et al., 1996). While both compulsion and impulsivity exhibit a similar stereotypical behaviour, namely the inability to delay or inhibit behaviour, these behaviours have different causes. In compulsion, individuals attempt to minimise stress or anxiety, while impulsivity is characterised as an attempt to maximise *"pleasure"* or rewards (Hollander et al., 1996; Stein, 2000). This has led researchers to argue for a reclassification of mental disorders that display poor decision-making as the core symptom of the pathology (Hollander et al., 1996; Stein, 2000), in favour of a continuum-based classification where impulsivity and compulsivity act as extreme endpoints of this spectrum.

Schizophrenia: Historically, differences between schizophrenia patients and healthy controls at the IGT has been mixed. Early evidence suggested that patients did not show impairments at the IGT (Wilder et al., 1998), and subsequent studies generally replicated this finding (Cavallaro et al., 2003; Evans et al., 2005; Rodríguez-Sánchez et al., 2005). Other studies, however, found subtle effects (Beninger et al., 2003; Ritter et al., 2004; Shurman et al., 2005; Bark et al., 2005; Turnbull et al., 2006; Kester et al., 2006), showing that all patients or a sub-group of patients tend to prefer disadvantageous choices. In an early review of the IGT by Dunn et al. (2006), the authors argue that differences exist between the two groups, I quote:

> *"For example, of six studies examining schizophrenia, one found no deficit (Wilder et al., 1998), one found a disadvantageous deck preference (Ritter et al., 2004), one found deficits were dependent on medication type (Beninger et al., 2003), one found preference for the infrequent punishment decks (Shurman et al., 2005), and two found only sub-types of schizophrenia patients were impaired on the task (Bark et al., 2005; Turnbull et al., 2006)."*

A later review by Sevy et al. (2007) added further studies to the analysis and found methodological differences that might explain the lack of consistency across IGT studies in schizophrenia. The authors (Sevy et al., 2007) argue that several confounding factors such as small sample sizes, comorbidity (i.e. co-occurring conditions) such as substance abuse, IQ and education differences, as well as heterogeneous samples of patients (i.e. having different diagnosis) might account for the differences observed. The review concludes that although results are generally mixed, patients with schizophrenia tend to be generally impaired at the IGT and suggests to control for these confounding variables in future studies (Sevy et al., 2007). A recent IGT study appear to close this gap (Kim et al., 2009). The study used a relatively large sample size (n=52 patients, n=55 controls), controlled for IQ, comorbid substance abuse and finally used an homogeneous sample of chronic & stable schizophrenia patients (Kim et al., 2009). In this study, the authors confirm a strong preference for disadvantageous decks in the schizophrenia patient group. Nonetheless, the study found that patients appear to gradually learn to switch to advantageous choices, albeit at a much lower rate than controls. Patients manage to reach chance level (i.e. an equal ratio of advantageous to disadvantageous choices) in the last 20 trials of the task, while starting with a net negative score at the beginning of the task (Kim et al., 2009).

Overall, the literature tend to suggest that schizophrenia patients are impaired relative to controls at the IGT (Dunn et al., 2006; Sevy et al., 2007; Kim et al., 2009); However, patients do display a slow but profitable shift from disadvantageous deck

to advantageous ones over time (Kim et al., 2009). As a result, Kim et al. (2009) argue that patients with schizophrenia should either be less sensitive to both reward and punishment or hyper-sensitive to rewards and hypo-sensitive to punishments. Generally, patients also appear to prefer less frequent but larger penalties (decks B and D), suggesting that they are sensitive to the frequency but not the magnitudes of these penalties (Wilder et al., 1998; Shurman et al., 2005; Kim et al., 2009). With regards to the real outcome of the IGT, preferring smaller frequencies of penalties might appear as risk-averse. However, omitting to integrate the magnitude of rewards and punishments together with the frequency of penalties is risk-prone behaviour. Finally, schizophrenia patients appear to be impaired in reversal-learning tests such as the Wisconsin Card Sort Test (WCST) suggesting a relative inflexibility to changes of contingencies in their environment. However, patients performances at the IGT are not correlated with the measure of flexibility extracted by the WCST (Ritter et al., 2004; Kim et al., 2009; for review see Dunn et al., 2006; Sevy et al., 2007).

3.2 RGT: ANIMAL MODEL OF THE IOWA GAMBLING TASK

Animal research possess valuable advantages when compared to human experimentation. First, using animal models, scientists can control for confounding factors such as genetic variability or environmental factors that might affect behaviour. Secondly, experimenters can use a wide variety of invasive techniques that would not be practical with human participants for ethical reasons (i.e. pharmacological manipulation, direct cortical stimulation, lesions studies, *etc.*). Such tools, enable to manipulate and alter the behaviour of subjects by targeting specific neuro-anatomical or neurochemical pathways. These manipulations, in turn, induce changes in the performance or behaviour of the animals, shedding light on the pathways at play in decision-making or behaviour (Rivalan, 2010).

The Rat Gambling Task (RGT) developed by Rivalan et al. (2009a) is one of many rodent analogues of the Iowa Gambling Task (de Visser et al., 2011). The version of the RGT that we present in this chapter has been evaluated in a recent review (de Visser et al., 2011) as the best rodent analogue to the IGT. In this task, rats are required to select among 4 options (i.e., 2 advantageous, 2 disadvantageous) to collect an immediate reward (i.e., appetitive food pellets). Following the delivery of rewards, time-outs can occur with different probabilities and magnitude so as to model the penalty system of the IGT. Similarly to the IGT, during this task the rats have to infer that small but regular pay-outs (i.e. food pellets) are more beneficial in the long term. The performance at the task is extracted by monitoring the number of optimal

choices made by the animal every 10 minutes. Similarly to human studies using the IGT, Rivalan et al. (2009a) found that while most healthy rats learn to choose advantageous options, about 1/3rd of healthy rats preferentially choose immediate pay-offs and persevere to select disadvantageous options throughout the task. The authors found a link between risk-seeking and poor performances at the RGT, but this trait alone could not explain the entire variability of performances observed (Rivalan et al., 2009a). The authors argued that, as in humans, a combination of behavioural traits might jointly contribute to poor performances at the RGT, and that these traits need to be identified.

3.3 AIMS

3.3.1 *Inter-individual behavioural traits, a dimensional approach*

Several mental disorders related to poor executive functioning, such as substance abuse, pathological gambling, attention-deficit hyperactivity-disorder or mania, share common deficits and behavioural traits. Impulsiveness, risk taking (DSM-IV-TR, 2000) or inflexible behaviour (Goudriaan et al., 2006; Rubia et al., 2010; van der Plas et al., 2009; Walshaw et al., 2010), are often present, suggesting that they may jointly contribute to pathological behaviour. Poor decision making is a hallmark of these mental disorders and these patients are commonly impaired in the Iowa Gambling Task (IGT). This task measures the capacity to balance risks and gains and to resist immediate gratification in order to receive a larger long-term gain (Bechara et al., 1994). Interestingly, within a healthy population, a subset of individuals described as impulsive and sensation seekers display poor decision making in this task (Bechara and Damasio, 2002), supporting the notion that a continuum may exist between normality and pathological conditions. Accordingly, neuropsychological characteristics leading to poor decision making in healthy individuals are probably shared by clinical poor decision makers, and could be a potential risk factor for developing related mental disorders (Rivalan et al., 2009b; Hayton et al., 2012).

Our collaborators developed a single-session Rat Gambling Task (RGT) that reproduces the IGT principles (de Visser et al., 2011; Rivalan et al., 2009a, 2011). In this uncertain and conflicting situation, individuals without prior knowledge of the outcomes must gradually learn that the less immediately rewarding options are also less risky and more advantageous in the long term.

Using lesion studies, they have recently shown that good performances in the RGT

depend of the functional integrity of several areas of the prefrontal cortex (Rivalan et al., 2011). Like humans, a majority of rats are good decision makers (good DM) and choose the best options, whereas a minority prefers the worst options. These inter-individual differences are stable over time, specific to decision-making processes and reproducible across groups (Rivalan et al., 2009a). They also showed that, like humans, rats that are poor decision makers (poor DM) are risk-prone and more sensitive to reward than good DM (Rivalan et al., 2009a). However, although these traits were clearly associated with poor decision making in the RGT, they were not sufficient to dissociate good from poor performers individually. Therefore, Rivalan et al. (2009a) argued that additional behavioural trait, such as inflexibility and impulsivity, could also jointly contribute to poor decision-making.

Here, we present an analysis showing how inter-individual differences in clinically relevant behavioural traits may contribute to poor and good decision making in the RGT. Experimentally, we show that a combination of several independent behavioural and cognitive characteristics in one individual, namely risk-proneness, motivation for reward, motor impulsivity and behavioural inflexibility, have a cumulative effect and is highly predictive of performance in the RGT.

To quantitatively explore the impact of these traits on learning and decision-making, we developed a computational model of the RGT based on the Temporal Difference (TD) learning algorithm (Schultz et al., 1997; Bayer and Glimcher, 2005; Maia, 2009). The basic TD framework was extended to take into account these behavioural traits (i.e. risk seeking, reward seeking and cognitive inflexibility) and to estimate the influence of these traits in each rat. The extended model was used to address the following questions:

1. Can behavioural traits jointly contribute to poor performances in the RGT?
2. If they can, how do these traits alter learning and decision-making?

First our model suggests that behavioural traits can collectively account for good and poor decision making performances. Secondly, the model provides a quantitative explanation for the interactions between the behavioural traits and how these might impact learning and decision-making performances in the RGT.

3.4 METHODS

The RGT requires successive choices among four options in an operant cage (de Visser et al., 2011; Rivalan et al., 2009a). Two of the four options are associated with a higher

immediate gain, but are disadvantageous in the long run due to higher unpredictable penalties (time-outs). The experiments were performed in twelve polyvalent conditioning boxes (Imetronic, Pessac, France; 28x30x34 cm). Boxes were equipped with four nose-poke holes, dimly illuminated within the hole with a white LED. These holes were located on a curved wall on one side of the box, equidistant to a food magazine situated on the opposite wall. Each hole was equipped with an infra-red detector connected to an external dispenser delivering food pellets (45 mg, formula P, Sandow scientific, USA). Data collection was automated using a control software (Imetronic, Pessac, France) running on a computer outside the testing room. At least thirty minutes before each session, the rats were placed in the experimental room.

Training: During the training phase, the rats learned to associate two consecutive nose-pokes in one of the four illuminated holes with the delivery of one or two food pellets in the magazine. First, the rats had to associate a single nose-poke in any of the four illuminated holes with the delivery of one food pellet in the magazine. After a nose poke, only the selected hole remained illuminated, but all were inactivated until the rat collected the food reward. This procedure continued daily until rats obtained 100 pellets within a session (30 min cut-off). Then two consecutive nose-pokes in the same hole were required to obtain food, to ensure that the selection of the hole was a voluntary choice. After reaching the same criterion, rats were submitted to two final 15 min training sessions. In the first session, two pellets were delivered after a choice was made (maximum 30 pellets). This session habituated the rats to the quantity of pellets which could be obtained during the test. A second session followed, delivering only one pellet at a time (maximum 15 pellets). The number of reward deliveries was reduced to avoid reduction of sampling and the development of a preference for an option. The training phase usually lasted 5-7 days and tests were performed the following day.

Test: Rats could freely choose between four nose-poke holes (A-D) during a one-hour test session (or max. 250 pellets obtained). Choices C and D vs A and B led to the immediate delivery of one vs two pellets, but choices A and B could be followed by longer, unpredictable penalties (222 s and 444 sec time-outs) compared to choices C and D (12 sec and 6 sec). Penalties occurred at a low probability $(1/4)$ for choices B and C, and at a high probability $(1/2)$ for choices A and D (Figure 3.2). During the penalty, all lights were switched off and nose-poke holes were disabled, but the chosen hole remained illuminated to facilitate association between each choice and its consequences. A brief extinction of this light (1 sec) signalled the end of the time-out. The theoretical maximum gain was the same for advantageous choices C and D, and

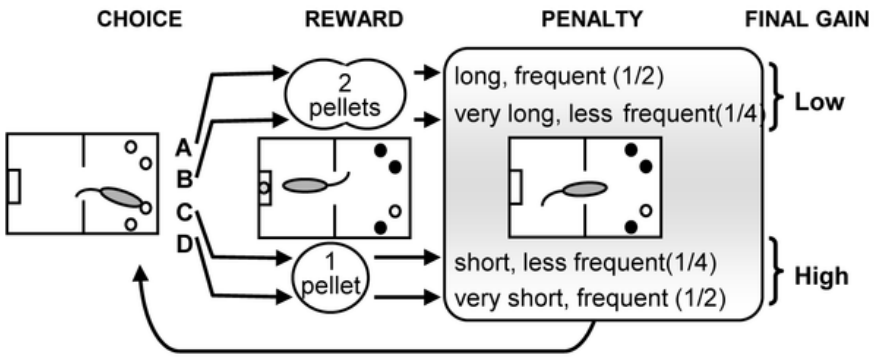

Figure 3.2: Principle of the Rat Gambling Task. Rats can nose-poke among four different holes (A, B, C and D) in an operant cage, to earn food reward (1-hour test). The selection of one option is immediately rewarded, but can also be followed by a penalty (time-out) of variable duration, according to different probabilities. Two options (C, D) are equally more advantageous than the other two (A, B), which are equally disadvantageous in the long term. The figure was included with permission from (Rivalan et al., 2013)

five times higher than for disadvantageous choices A and B.

Good and poor decision makers were differentiated on the basis of the percentage of advantageous choices (>70% and <30% respectively) during the last 20 minutes of test. The remaining rats were undecided with intermediate scores (between 30% and 70% advantageous choices — de Visser et al., 2011; Rivalan et al., 2009a, 2011). The mean latency to collect food pellets after a choice was taken as an indicator of the rats motivation for the food reward (Rivalan et al., 2009a).

3.4.1 *Scientific validity*

Since this chapter builds upon previous findings from Rivalan et al. (2009a), we briefly introduce analyses that successfully demonstrated the face and construct validity of the RGT (Rivalan et al., 2009a).

Reproducibility and stability of performances: Rivalan et al. (2009a) tested the same rats repeatedly at every 2-3 months interval to ensure that choice preferences were stable over time. The distribution of individuals into good and poor decision makers remained stable during repeated testing over a period of at least 6-9 months.

Food deprivation: Rivalan et al. (2009a) tested whether food deprivation induced different intrinsic motivational state for some rats, which might have explained poor decision-making. The authors challenged the stability of motivation for rewards on

RGT performances by testing different levels of food restriction before the task (i.e. decreasing the animal's body weight from 0% to 20% of free feeding weight). Food restriction had no significant impact on either the proportions of good and poor decision-makers (χ^2 exact test, p = .673; ns) nor on the evolution of their behaviour over time (Rivalan et al., 2009a).

Task difficulty: Task difficulty could also explain population differences in the RGT. As a result, good decision-makers were challenged with an increased task difficulty by gradually reducing the relative gain between advantageous and disadvantageous options. Increasing the task difficulty had no consequences on the proportions of good and poor decision-makers (Rivalan et al., 2009a). Good decision makers took more time to show significant preferences for advantageous choices. Poor decision-makers remained as fast as before at selecting disadvantageous choices, even with the increased task difficulty. This suggests that poor decision-makers rapidly assign preference to disadvantageous choices, irrespective of the relative gain between advantageous and disadvantageous options.

Decision making bias: A modified RGT experiment was used to discriminate whether the different subgroups of good and poor decision-makers were equally sensitive to penalties. In this paradigm, all options led to one food pellet, while the penalties for each option remained the same as in the original RGT (Rivalan et al., 2009a). Within the first minutes, animals chose equally among the different options, showing no pre-existing biases or preferences. All rats then rapidly developed a marked preference for the shorter time-outs and, to a lesser extent, for the less frequent penalties (Rivalan et al., 2009a). The rats readily discriminated between different dimensions of the penalty (duration & probability), preferring the less punished options. The results show that all rats (good and poor decision-makers) were equally able to discriminate optimal actions between different post-reward time-outs penalties. First, these findings suggest that poor decision-makers are similar to good decision-makers in their valuation of penalties. Second, this analysis confirms that poor decision-makers are able to take optimal decisions, suggesting that their action-selection process (i.e. decision-making) is not different from this of good decision-makers.

3.4.2 *Subject sample*

Male Wistar Han rats (n = 29; Charles River, France) were 12-13 weeks old at the beginning of the experiment. They were housed in groups of four in a temperature

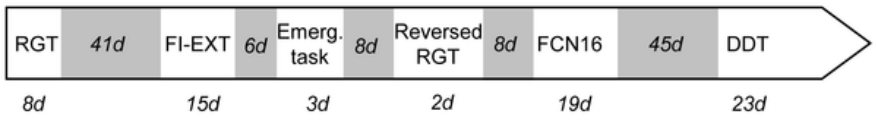

Figure 3.3: Order and duration of behavioural tasks. The number of days (d) of each behavioural testing phase (below arrow) and inter-test periods (grey zones) are indicated. RGT: Rat Gambling task, FI-EXT: multiple fixed-interval/extinction schedules, Emerg. Task: Light-dark emergence task, FCN16: Fixed consecutive number 16 cue schedule, DDT: Delay discounting task.

(23°C) and humidity-controlled room (60%) on an inverted 12 hr light/dark cycle (lights on at 20:30). Tests were conducted during the dark phase of the cycle. A week before the beginning of the experiments, animals were handled every day. Rats had free access to food and water except during impulsivity and decision-making tests during which they were moderately food deprived (95% free feeding weight). The configuration of the apparatus and the order of testing were chosen to minimize any possible interference between protocols (see Figure 3.3 for order and duration of tests). The whole behavioural testing phase lasted 6 months (178 days).

3.4.3 *Results*

The RGT measures, across successive trials, the ability to make the most advantageous choices. In this task, the contingencies associated with a higher immediate gain are disadvantageous in the long run due to higher unpredictable penalties. Decision-making could not be properly measured in six rats because they immediately demonstrated a preference without sampling the different options at the beginning of the test. These rats were discarded from the analysis. Three rats did not display preference for any particular option (undecided subgroup). Because of the small size of this group they were also discarded from our analyses. Among the remaining rats (n = 20), behaviour during the test was not influenced by prior spatial preference: proportions of individuals with analogous choices during training and testing did not significantly differ from chance (Chi-square test, χ^2 = .438; p = .33; ns).

As observed previously, typical good and poor decision makers (DM) can be distinguished within a normal group of rats. Because this task measures a preference between two kinds of options, two subgroups can be easily distinguished, as shown by the bimodal distribution of RGT scores (see meta analysis on Figure 3.4B). Good DM first choose randomly and then gradually orient most of their choices toward the advantageous options (Figure 3.4A). By contrast, poor DM sample the different

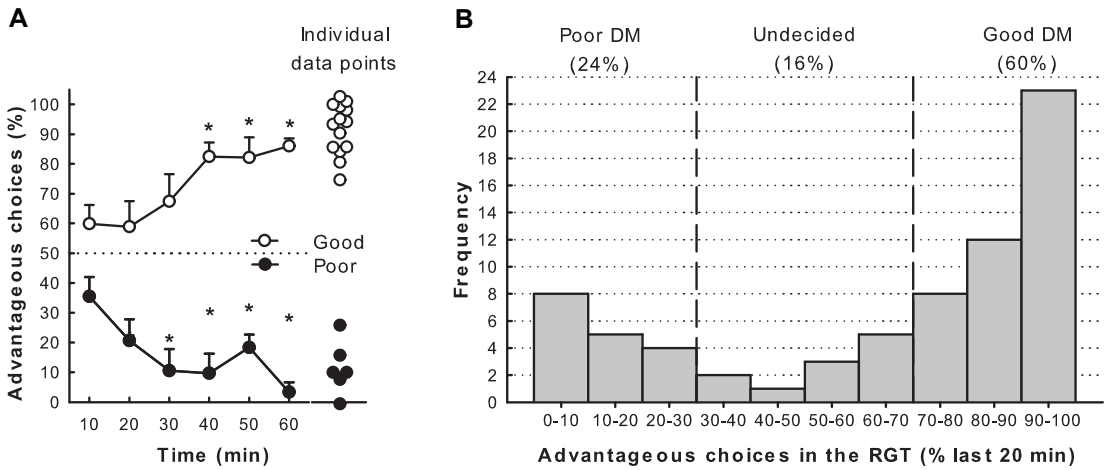

Figure 3.4: Animals' performance on the Rat Gambling Task (RGT). **(A)** Time-course of advantageous choices (%) of good and poor DM on the RGT and individual scores during the last 20 min of good (n = 14) and poor (n = 6) DM. Comparison with the indifference level, dotted line, t-test: * p<.05. **(B)** Meta analysis of the RGT data based on 12 distinct experiments (n = 228) using the same protocol. It reveals a bimodal distribution of RGT scores (% of favourable choices during the last 20 min) with a majority of good decision makers (good DM, with scores above 70%), a minority of poor decision makers (poor DM, with scores below 30%) and the remaining, undecided rats with intermediate scores.

options and rapidly orient their choices toward the disadvantageous options (within 10 minutes). During the last 20 minutes, percentages of choices for advantageous options could be divided into two main subgroups: a majority of good DM (n = 14; 61%, with scores above 70%) and a minority of poor DM (n = 6; 26%, with scores below 30%) that preferred the disadvantageous options (n.b. scores for the remaining undecided subjects were 38%, 54% and 63%).

3.4.4 *Measuring risk-seeking*

3.4.4.1 *Method*

The light-dark emergence test allows for the assessment of spontaneous risk taking behaviour in rats (Rivalan et al., 2009a). Exiting from a dark, safe compartment to a brightly illuminated one is a risky and stressful situation for a rat. This test was performed in a box (40x40x35 cm) with two small equal compartments that limit exploratory behaviour. An aperture (12x31 cm) enabled the rats to pass from one compartment to the other. One was completely enclosed by black opaque plastic sides, with a lid of the same material, while the other was white, had no lid, and was illuminated (560 lux). The rat was placed in the illuminated compartment facing the wall opposite the door. The rat was free to explore the two compartments of the

apparatus during a single 10 minute session. Rats were tested in the middle of the dark phase between 10:00a.m and 1:00p.m.

Data measures: From the rat first entrance in the dark box, the latency to emerge from this compartment to the illuminated one was recorded (600s cut-off). Risk assessments were evaluated by the number of body stretches and head protruding into the light compartment while the hind limbs remained in the safe compartment. Because these two parameters are correlated with the number of visits of the extremity of the open arms of an elevated plus-maze, which is the more risky area of this task (see Rivalan et al., 2009a), we considered these as a measure of risk-taking. Proportions of visits and time spent in the dark compartment (%) were also measured.

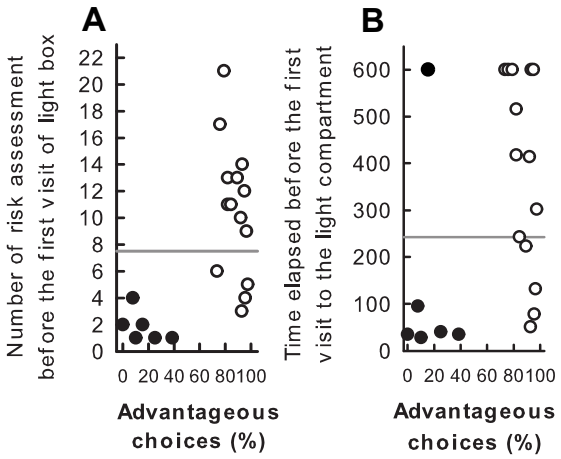

Figure 3.5: Rats' performances at the light-dark emergence test. Grey lines represent the median used to compute proportions of high and low scores in good and poor decision makers (open and black circles respectively). **(A)** The number of risk assessments before the first emergence in the risky compartment. **(B)** Time elapsed until the first visit to the risky compartment.

3.4.4.2 *Results*

In the light-dark emergence test, poor DM took more risks than good DM. They emerged more rapidly from the dark compartment than good DM (medians, 35 and 416 sec respectively; U = 13.5, p<.02). A majority of poor DM 83% vs 36% of good DM had a score below the median (Figure 3.5B). Poor DM also made much fewer risk assessments than good DM before the first exit (100% vs 29% below the median; Fisher exact test, p = .0007; Figure 3.5A). The median number of risk assessments were 1.5 and 11.2 for poor vs good DM respectively (U = 1.5, p<.001). Poor DM also tended to make more visits to the bright compartment than good DM (U = 20.5, p<.07).

3.4.5 *Cognitive Inflexibility*

3.4.5.1 *Method*

To assess behavioural flexibility, the contingencies for choices A-B and C-D were spatially reversed (Rivalan et al., 2009a) such that disadvantageous choices during

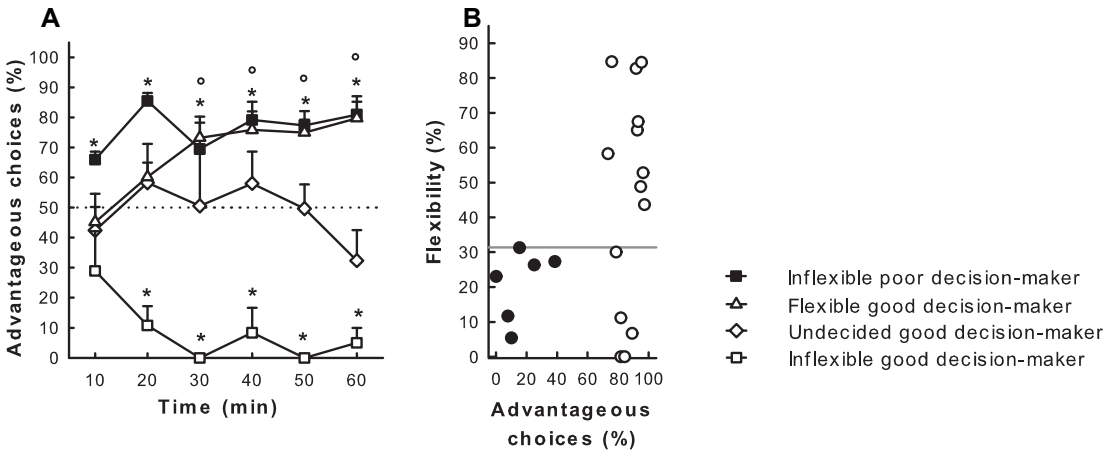

Figure 3.6: Animals' performance on the Reversal-Rat Gambling Task (Reversal-RGT). Grey lines represent the median used to compute proportions of high and low scores for good and poor decision makers (open and black circles respectively). **(A)** Time-course of advantageous choices (%) for flexible good DM, undecided good DM, inflexible good DM, flexible good DM and inflexible poor DM groups on the RGT-reversed version. Comparison with the indifference level, dotted line, t-test: * and °p<.05 at least. **(B)** Relationship between individual RGT scores and flexibility (final scores in the RGT-reversed version).

the RGT were now advantageous and *vice-versa*. To reduce spatial preferences related to the previous experience in the RGT, animals were first given a new training session (100 pellets or 30 min cut-off) during which only one hole at a time, pseudo-randomly, was illuminated and operating at a time, each nose-poke delivering 1 pellet. The test in reversed condition was done the following day, in the same conditions as the RGT, except that options A-B and options C-D were spatially exchanged.

Data measure: Performances were calculated as the mean percentage of choices for the preferred contingency during the RGT. Behaviours were differentiated on the basis of the time course of choices and flexibility. The observed behaviours were classified into three categories: flexible behaviour, with progressive reversion towards the new location of their favourite options (>60% of choices during last 20 min), undecided behaviour (choice between 40% and 60%) and inflexible behaviour with perseveration to previously learned choices (<40% of choices).

3.4.5.2 *Results*

Reversing contingencies in the RGT measures the rats' adaptation when advantageous/disadvantageous outcomes are spatially exchanged. Persistence to choose the same location reveals cognitive inflexibility (flexibility <35%), whereas shifting choices reflects detection of the change and behavioural flexibility. All poor DM vs only a third (36%) of good DM were inflexible (Fisher exact test, p = .014; Figure 3.6B).

Among the remaining good DM, 36% gradually reoriented their choices toward the new location of advantageous options, and 28% distributed their choices between all options (Figure 3.6A).

3.4.6 *Reward Seeking*

Method

Reward seeking was measured in this experiment using the latency to collect rewards (food pellets) during the RGT session. Previously, the runway paradigm had been used to measure to the latency for a rat to run along a straight alley in order to collect a food reward (Rivalan, 2010; Valton, 2010). This measure represented the intrinsic motivation for each rat to seek food rewards. This paradigm was found to be analogous to extracting individual latencies for reward collection during the RGT, so the latter measure has been used for this experiment (Rivalan et al., 2013). The number of visits to the nose-poke apertures was also monitored as a potential measure of reward-seeking behaviour.

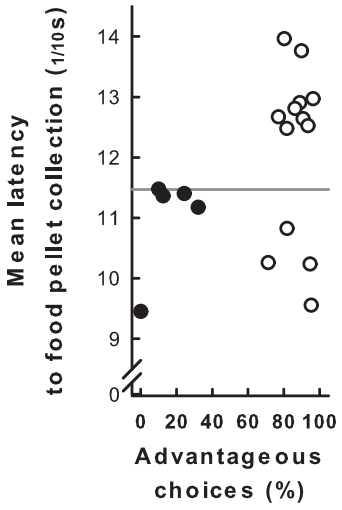

Figure 3.7: Animals' reward-sensitivity measure at the Rat Gambling Task (RGT). **(A)** Relationship between individual RGT scores and the mean latency to collect food pellets (one missing value) during the RGT.

Results

Poor DM showed a shorter latency to collect their reward than good DM, as previously observed (Rivalan et al., 2009a — Figure 3.7). All poor DM scores (100%) were below the median vs 36% for good DM (Fisher exact test, p = .032; group medians, 1.12 and 1.26 s respectively; U = 16, p = .07). However, the global activity of the two groups, reflected by the total number of visits to the nose poke holes, did not statistically differ (median scores: 1025 and 857 for good vs poor DM respectively; U = 20, ns).

3.4.7 *Motor Impulsivity / Perseverance*

Impulsivity is a multi-factorial trait encompassing both impulsive actions and impulsive choices (Dalley et al., 2011). Impulsive actions refer to an inability to delay a response (i.e., premature responses, or an inability to withhold a response; i.e. antici-

patory hyperactivity and perseveration) while impulsive choices refer to an inability to wait for a delayed greater benefit.

3.4.7.1 *Methods*

3.4.7.2 *Impulsive actions: anticipatory hyperactivity and perseveration*

The multiple Fixed-Interval/Extinction schedules of reinforcement (FI-EXT) was performed during a single session in operant chambers equipped with one lever. The chambers used for this test were different from the ones used in the RGT (Dellu-Hagedorn, 2006). Two periods of fixed-interval schedule of reinforcement (FI) alternated with two periods of extinction (EXT) (FI-EXT-FI-EXT). Impulsive responses corresponded to lever presses during frustrating periods where no reward was available (that is, during the FI delay or the EXT extinction phase).

The apparatus consisted of eight sound-insulated light-tight outer chambers each containing a lever conditioning box (Imetronic, Pessac). The boxes (32x32x22 cm) were constructed from white plastic panels with a Plexiglas door. They were equipped with a fan providing background noise. Each box was permanently illuminated by a diffuse 2 lux light source located in the middle of the ceiling (box light) and another light above the lever (cue light). The floor consisted of 5 mm diameter stainless steel bars spaced 1.5 cm apart. One stainless steel lever protruded horizontally 1 cm from the wall situated at the left of the door. A tray was situated centrally on the opposite wall. Food pellets (45 mg, formula P, Sandow scientific, USA) were delivered in the tray by a food dispenser. A program (Imetronic, Pessac) controlled the chambers and collected the data on a computer situated outside the testing room.

Training and test: During the FI, the box light was *'on'* and the first lever press after a designated time-interval was reinforced by a food pellet. The cue light above the lever was *'on'* when the pellet was available until the rat visited the tray. During the EXT (5 min), the box light was *'off'* and no pellet was delivered. During each session, the FI and EXT components operated twice in alternation. Rats were first trained for four sessions with a 30s FI-EXT schedule. Then, rats were trained for four sessions on a 1 min FI-EXT schedule followed by three sessions with a 2 min FI-EXT schedule. A maximum of 7 pellets per FI (14 pellets in total) were delivered during the 1 and 2 min FI conditions. Finally, rats were tested for four sessions on a 1 min FI-EXT schedule to assess adaptability to a change for a shorter FI phase. This latter condition has been chosen for analysis.

Data measure: The mean number of lever presses during each FI and each EXT conditions was recorded. As previously described (Dellu-Hagedorn, 2006), data from the initial FI after the start of the session, as well as that from the first interval following the first EXT were excluded because the behaviour during these intervals might deviate from those during the other intervals. The total mean number of lever presses, the number of visits to the empty tray as well as the speed at collecting food pellets were also measured for the FI and EXT schedules.

3.4.7.3 *Impulsive actions: premature responses*

The Fixed Consecutive Number of 16 lever press schedule (FCN16) measures behavioural inhibition in operant chambers by testing the rat's ability to carry out a long chain of sequential lever presses before obtaining a reward (Rivalan et al., 2007). The schedule required a fixed minimum number of 16 responses on one lever (FCN lever), signalled by a cue light, before a response on the second lever (Reinforcement lever) resulted in the delivery of one food pellet. Impulsivity was reflected by the proportion of prematurely ended chains of presses on the FCN lever. These chains reset the count and were not rewarded. Chains longer that 16 responses were scored as perseveration.

The operant chambers used for FCN16 testing were similar to the ones used for the FI-EXT schedule, except that they had two levers situated on the wall opposite to the food magazine instead of one. A cue light above the second (right) lever was also added. The reinforcement lever, much less used than the FCN lever, was the one previously used in the FI-EXT schedule.

Training: On the first day, only the reinforcement lever was available and every press resulted in the delivery of a food pellet in the tray. The rats quickly obtained at least 100 pellets within 40 min (criterion). The following days, both levers were available and the light above the FCN lever was turned on and rats were required to press the FCN lever first and then to press the Reinforcement lever to obtain food (FCN1). The cue light was switched off when the rats had completed the number of consecutive presses required on the FCN lever to obtain food. The cue light signalled the completion of the response requirement to avoid confounds related to time estimation (Rivalan et al., 2007). This cue light was turned on again when rats visited the tray. If the chain was shorter than the number required, the rat had to start a new chain. If the chain was longer, it had no consequence, and the pellet was delivered when the rat pressed the reinforced lever. When 100 pellets were obtained within a session (40 min cut-off), the FCN requirement was progressively increased to 2, 3, 5, 8

and 12 using a less strict criterion (45-min cut-off and at least 70 pellets) to avoid over-training. Rats that failed to reach the criterion in FCN5 after 20 training sessions were excluded from this task. Training under FCN12 lasted a minimum of two consecutive 30-min sessions until rats had reached a stable level of performance.

Test: Rats were tested using the same procedural conditions as in training but with a FCN requirement of 16 lever presses (FCN16) during three consecutive sessions (30 min or 100 pellets cut-off). A rewarded chain of lever presses corresponded to 16 or more lever presses executed on the FCN lever before pressing the reinforced lever.

Data measure: Only data from the third session of FCN16 were analysed as they revealed the largest inter-individual behavioural differences between good and poor decision makers. Impulsivity in this task is reflected by a low percentage of rewarded chains (<70%). Among rewarded chains, some were just as long as necessary (16 presses) and reflect high response efficiency, whereas some others exceeded the number of presses required and reflect low response efficiency. Thus, response efficiency was estimated by the number of FCN lever presses divided by the total number of food pellet consumed. The number of sessions needed to reach the test phase (learning score) and response rate (total number of each lever responses per min) were also considered. The distribution of the mean number of chain of lever presses according to their length was analysed.

Impulsive choice: delay discounting

The Delay Discounting Task (DDT) measures impulsive choices in an operant chamber by assessing the preference for an immediate small reward (one pellet, when pressing one of the levers) over a larger one delivered after a delay (5 pellets, when pressing the other lever). The delay preceding the delivery of the larger reinforcement was progressively increased between sessions.

The operant chambers were the same as those used for the RGT, except that the curved wall was replaced by a straight one equipped with two levers facing the food magazine on the opposite wall. The box light, two cue-lights above the two levers and one cue light in the tray of the food magazine were available and could be turned *'on'* and *'off'* depending of the procedure.

Training: During training, a press on the right lever (L1) resulted in the immediate delivery of one food pellet whereas a press on the left lever (L5) readily delivered five pellets. Given that the rats were previously trained in the FCN16 schedule that also

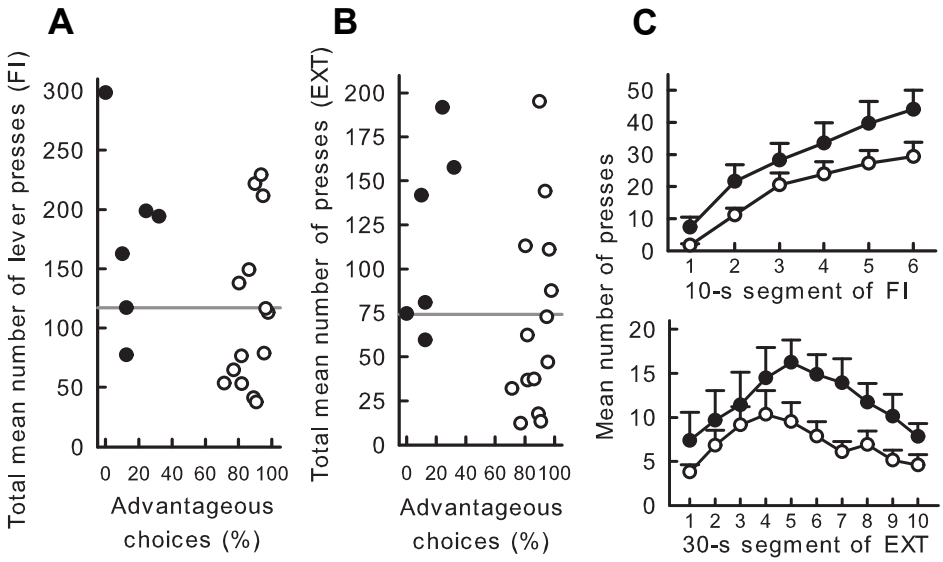

Figure 3.8: Good and poor decision makers (DM) performances in the multiple fixed-interval (FI) and extinction (EXT) schedules. Relationship between individual scores in the RGT and **(A)** the mean number of lever presses during the 1-min FI or **(B)** during the 5-min EXT. **(C, top panel)** Mean number of lever presses of good and poor DM during one 1-min FI component as a function of time. **(C, lower panel)** Mean number of lever presses during the 5-min EXT component as a function time. Grey lines represent the median used to compute proportions of high and low scores for good and poor DM.

used two levers (the previous FCN lever being now the L1 lever), a training period was conducted in order to obtain stable performances with no interference from previous requirements. This training period lasted until the rats made more than 70% L5 selections with less than 15% variation in this score on 2 consecutive sessions (in total, 3 sessions were necessary). Whenever an operant lever press was made, a light above this lever was switched on for 1 sec. Three seconds after food delivery, the magazine light was turned on for 60 sec, during which time additional presses were without consequence (time-out). The end of this time-out and the beginning of a new trial was signalled by turning off the food magazine light as well as the box light. The duration of the time-out was adjusted such that the duration of each trial was the same whichever lever was chosen.

Test: During the test phase, a press on L1 immediately delivered one food pellet, and was followed by a 60 sec time-out, whereas a delay was inserted between L5 pressing and the delivery of the five pellets. During this delay, the light above L5 lever remained on until the pellets were delivered, then a time-out (60 sec minus the length of the delay) immediately followed food delivery. The delay was fixed for a given daily session and increased progressively over the days by 10 sec intervals

from 0 to 40 sec according to a criterion of stability (i.e. scores over two consecutive sessions should not vary by more than 10%). All sessions ended when 100 pellets had been delivered.

Data measures: Percentage of L5 choice, total mean number of lever presses, and presses during the delay and time-out periods were measured. These parameters were calculated for each delay as the mean of the last two stable sessions.

3.4.7.4 *Results*

Impulsive actions using FI-EXT: Impulsive actions here denote anticipatory hyperactivity and perseverance. The FI-EXT task assesses reward anticipation and sensitivity to context during frustrating periods without reinforcement (Rivalan et al., 2007; Grégoire et al., 2012). Lever press activity is measured either during a delay before a lever press can deliver the reward (FI) or during an extinction phase (EXT) where no reward can be obtained (light house off). During the 1-min FI and 5-min EXT, 83% of poor DM had a motor activity equal to or higher than the median score, vs 43% for the good DM (Figure 3.8A,B). Overall, poor DM tended to perform more lever presses than good DM both during FI, (medians, 178 and 98 respectively; U = 23, p = .1) and during EXT (medians, 111 and 55; U = 21, p = .08), suggesting both anticipation and perseverance. Both groups exhibited the typical pattern of activity during each interval of the FI, namely a progressive increase in response rate as reinforcement availability approached, with poor DM reaching a score 1.5 times higher than good DM. During EXT, poor performers exhibited both a larger and longer episode of increased activity (Figure 3.8C). The latency to collect rewards did not significantly differ between groups (U = 31.5), nor did the number of visits to the empty tray (U = 35 and 30, ns). The mean number of lever presses during FI and EXT were positively correlated (r = .69, p<.001).

Impulsive actions using FCN16: Impulsive actions here denote premature responses and compulsive-like behaviour. The FCN16 measures response inhibition through the ability to complete a long sequence of lever presses on a first lever (FCN lever) before moving on to another lever (reward lever) that provides a reward (Rivalan et al., 2007; Grégoire et al., 2012). Both groups learned the task at the same rate (learning scores, U = 36, ns). Poor DM did not exhibit any deficit in inhibitory control (i.e. premature switches to the reward lever). The chain length distribution curve of both good and poor DM showed a peak for the optimal chain length (Figure 3.9A). Both groups predominantly performed rewarded chains (i.e. of length > = 16, Figure 3.9A-insert). However, poor DM made a higher proportion of long chains of

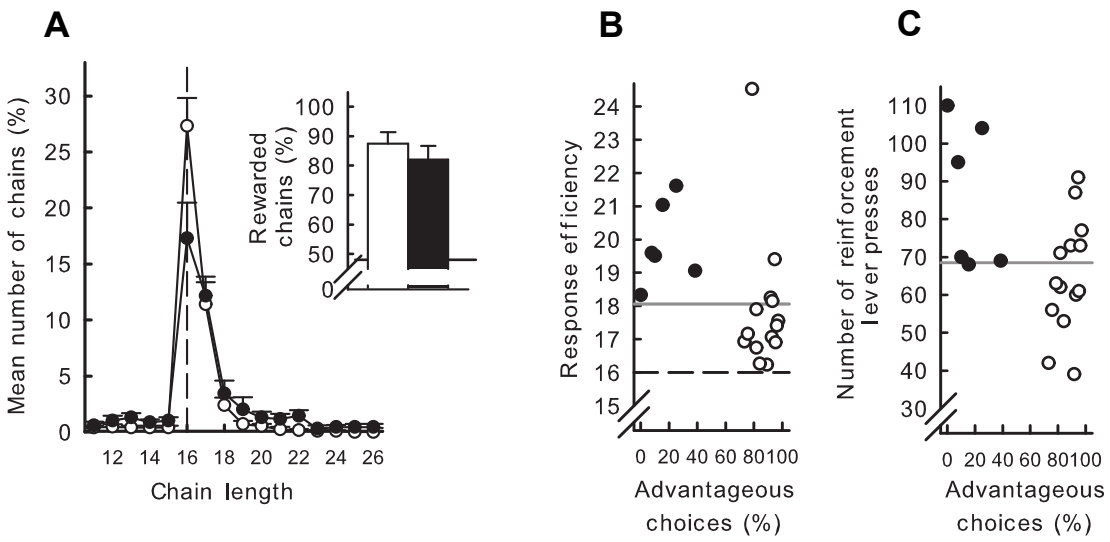

Figure 3.9: Good and poor decision makers (DM) performances in the (FCN16) Fixed Consecutive Number of 16 lever press schedule. **(A)** Frequency distribution (%) of chain length in the two groups. Optimal chain length (16) is indicated by the vertical dotted line. Inset: Percentage of rewarded chains for good and poor DM (Mean +SEM). **(B,C)** Relationship between individual scores in the RGT and **(B)** response efficiency or **(C)** the number of reinforcement lever presses. Grey lines represent the median used to compute proportions of high and low scores in good and poor DM.

responses (>16), leading to a lower response efficiency (Figure 3.9B; U = 8, p<.01). The occurrence of very long chains of presses was occasional. For instance, the number of chains longer than 22 presses was 1% of the total number of chains for good DM, and 3% for poor DM. However, all poor DM displayed at least one such very long chain during the test vs only 6 out of the 14 good DM. Moreover, whilst the number of presses on the FCN lever did not differ between groups (U = 28, ns), poor DM were more active on the reinforcement lever (U = 18, p<.05), making short bursts of presses instead of a single press. These perseverative behaviours, not accompanied by an attempt to collect the reward even when a clear signal announces its availability, are reminiscent of excessive and compulsive behaviour. All poor DM had scores on or above the median vs 43% for the good DM, which had scores below the median (Fisher exact test p = .018; Figure 3.9C).

Impulsive choices using DDT: Impulsive choice here refer to delay discounting. The DDT assesses the ability to tolerate a delay when a choice between an immediate small reward and a delayed larger reward is given. It indicates for each individual the subjective value of the large reward as a function of the delay and the delay at which both rewards are perceived to be of equal value. Under the no-delay condition, good and poor DM preferentially chose the larger reward (Figure 3.10A) and poor DM overall performed more lever presses than good DM (U = 16, p<.05; Figure 3.10B).

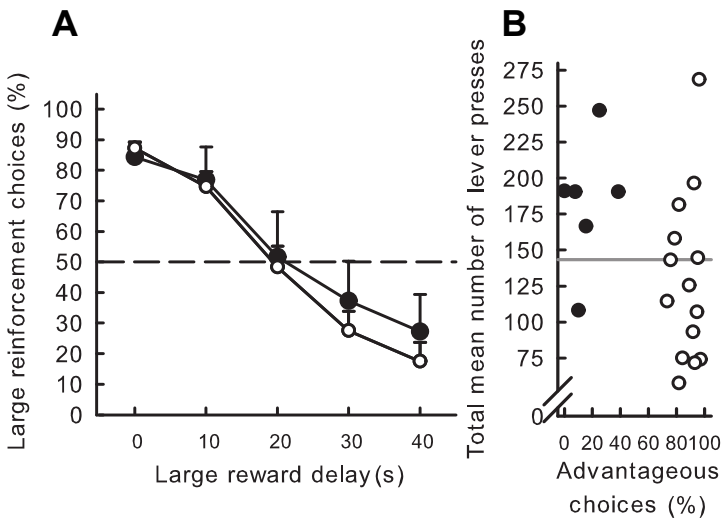

Figure 3.10: Good and poor decision makers (DM) performances in the in the (DDT) delay-discounting task. **(A)** Percentage of choices for the large, delayed reinforcement as a function of delay in the two groups. **(B)** Relationship between individual scores in the RGT and the mean number of lever press during DDT training. Dotted line represents chance level. The grey line denotes the median used to compute proportions of high and low scores in good and poor DM.

When the delay increased, both groups shifted to the immediate reward at the same delay, suggesting that they displayed similar reward discounting and tolerance to delay (Figure 3.10A).

	Poor decision makers							**Good decision makers**														
Rats	3	8	32	15	28	9	%	2	4	24	33	6	31	1	17	19	29	12	30	27	26	%
Motor impulsivity	✓	✓	✓	✓	✓		83	✓	✓	✓			✓			✓	✓			✓		43
& perseverance	✓	✓	✓	✓	✓			✓	✓	✓			✓			✓	✓					
Risk-seeking	✓	✓	✓	✓		✓	83	✓		✓	✓			✓		✓						14
	✓	✓	✓	✓	✓	✓	100		✓	✓	✓				✓							
Reward-seeking	✓	✓	✓	✓	✓	mis.	100		✓		✓	✓	✓		✓							36
Inflexibility	✓	✓	✓	✓	✓	✓	100	✓				✓		✓				✓	✓			36
Nb. of high scores	4	4	4	4	3			2	2	2	2	2	2	1	1	1	1	1	1	0	0	

Table 3.1: Motor impulsivity/perseverative responses correspond to high activity scores in both fixed-interval (FI) and extinction (EXT) schedules of reinforcement. Risk taking is indicated by a short latency to emerge and a low number of risk assessment in the dark-light box test, reward seeking by a short latency to collect food in the RGT, and inflexibility by performance in the RGT reversed condition. A tick indicates a high score (with respect to the global group median) for a given parameter. The last line shows the total number of high scores displayed by each rat. Proportions of subjects demonstrating high score in each group are also given. Mis. : missing value.

3.4.8 *Combination of traits*

A combination of behavioural traits is highly predictive of poor decision-making. Poor DM consistently displayed above median scores for each of the following behaviours (Table 3.1), except one poor DM missing motor impulsivity): motor impulsivity/perseveration, risk proneness, reward seeking and behavioural inflexibility. They obtained a lower global index when these behavioural traits were combined (sum of the ranks) compared to good DM (Figure 3.11). By contrast, no good DM ever expressed high scores for more than two of these particular behaviours. Thus, in healthy individuals, the combination of these traits more than any one in particular was highly predictive of poor decision making in the RGT. The association of cognitive inflexibility and risk taking behaviour or motor impulsivity was never observed in good DM and thus may be a particularly relevant combination of risk factors for impaired decision-making.

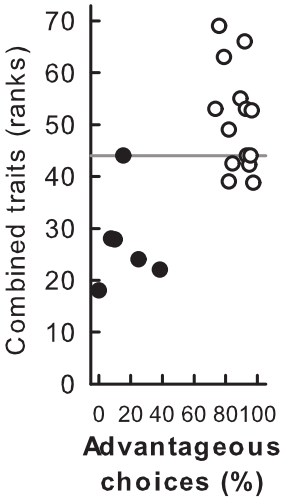

Figure 3.11: Animals' combined score (i.e. sum of ranks for each trait) for all the behavioural traits measured.

3.4.9 *Discussion and limitations of behavioural results*

As shown in Table 3.2, no correlation was observed between reward-seeking, risk seeking and behavioural flexibility. A positive correlation was found between all impulsive actions and perseverative responses in different experimental contexts. These parameters (except FI activity) were positively correlated with risk taking, and were independent from inhibitory control capacities (FCN schedule) and impulsive choice (DDT). We decided to model all independent traits (risk, reward and flexibility) excluding motor impulsivity since impulsivity/perseverance measures were correlated with the risk seeking trait (see Table 3.2).

3.5 MODELLING INDIVIDUAL RGT PERFORMANCES WITH BEHAVIOURAL TRAITS

3.5.1 *Temporal Difference learning model*

The environment of the RGT was modelled using a Markov decision process. The four possible choices (actions) in the task lead to different rewarded states s (i.e. high

			Reward	Flexibility	Risk		Inhib.cont.	Motor impulsivity & perseverance			
			1	2	3	4	5	6	7	8	9
Reward-seeking	RGT	1									
Behav. flexibility	Reversal	2	0.09								
Risk-seeking	Emergence	3	0.11	0.22							
	Emergence	4	-0.24	0.11	**0.69** ***						
Inhibitory control	FCN16	5	-0.27	0.00	-0.35	0.22					
Motor impulsivity	FCN16	6	0.14	-0.36	**-0.51** **	**0.45** *	-0.10				
& perseverance	FI	7	0.22	0.02	-0.28	-0.34	0.09	**0.68** ***			
	EXT	8	-0.08	-0.07	**-0.50** **	-0.52	0.07	**0.53** **	**0.69** ***		
	DDT	9	0.20	-0.18	**-0.61** ***	-0.53	0.22	**0.50** **	0.40	**0.57** **	
Impulsive choices	DDT	10	-0.23	0.12	-0.26	-0.22	**0.50** **	-0.10	-0.056	-0.19	0.07

Table 3.2: The three behavioural processes included in the model, reward and risk seeking, behavioural flexibility, were unrelated. Impulsive actions and perseverative responses in different experimental contexts were positively correlated. These parameters (except FI activity) were positively correlated with risk taking, and were independent from inhibitory control capacities (FCN schedule) and impulsive choice (DDT). Significant correlations are shown in bold. RGT: rat gambling task; FCN16: fixed consecutive number schedule of reinforcement; FI: fixed- interval; EXT: extinction: DDT: delay discounting task. Pearson's correlation test; *, p,.05; **, p,.01; ***, p,.001.

reward *'r = 2 food pellets'* for choices A & B or a low reward *'r = 1 food pellet'* for choices C & D). Each of these states is then followed by a probabilistic transition to the penalty associated with the reward state s (penalty transition probabilities are $1/2$, $1/4$, $1/4$, $1/2$ for the A, B, C and D states respectively). Penalties correspond to time-outs during which no food can be obtained. In the absence of penalties, rats obtain and consume on average one food pellet in nine seconds ($\delta_{episode} = 9$ sec). Therefore, time-outs of duration $\delta_{timeout(s)}$ can be expressed in terms of a gain loss (in units of food pellets) equivalent to an immediate penalty defined as:

$$plty(s) = \frac{\delta_{timeout(s)}}{\delta_{episode}} \tag{3.1}$$

This results in penalty values of -50, -25, $-4/3$, $-2/3$ food pellets for the states A, B, C, and D respectively.

The reward received after taking action a in state s is described by a state-action pair value $Q(s,a)$, which gradually comes to reflect the 'goodness' of selecting action a when in state s (Sutton and Barto, 1998; Doya, 2009; Maia and Frank, 2011). In this framework, the agent learns the value corresponding to each state-action pair $Q(s,a)$ by updating its expectations of the reward $Q(s,a)$ towards the reward received the last time action a was chosen in state s. This updating is based on the prediction error between the predicted reward for the state-action pair $Q(s,a)$ and the reward actually received r:

$$Q(s_t, a_t) \leftarrow Q(s_t, a_t) + \alpha(r_{t+1} - Q(s_t, a_t)) \tag{3.2}$$

where α is the learning rate parameter, r_{t+1} is the reward received after choosing action *a*, $Q(s_t, a_t)$ is the current estimate of the value of choosing action *a* in state *s* at time *t* (Sutton and Barto, 1998). This learning process causes *Q(s,a)* to gradually approach the real value of choosing action *a*. No temporal discounting parameter was introduced in this model as individual trials were considered to be independent, each leading to immediate reward consumption as well as possible penalties.

3.5.2 *Learning model with behavioural traits*

We then extended this basic framework to account for reward seeking, risk seeking and cognitive inflexibility.

3.5.2.1 *Reward Sensitivity*

The reward seeking trait is introduced as a modulation of the magnitude of the actual rewards r_t by a multiplicative weight:

$$r_t \leftarrow \omega \cdot r_t \tag{3.3}$$

Values of $\omega > 1$ correspond to the agent representing the reward values as higher than they really are. It was shown experimentally that poor decision makers were able to perform optimally, similar to the good decision makers, in a penalty-only version of the RGT. Therefore, sensitivity to penalty was left constant across animals. In the RGT, rewards are equal to either one or two. Therefore, modelling reward seeking as a multiplicative weight on the true reward provides the simplest way to describe the transformation from objective to subjective reward values (Niv et al., 2006).

3.5.2.2 *Risk Seeking*

Following previous work (Li and Chan, 2006), the behavioural trait of risk seeking (or risk aversion) is implemented by adding a positive (or negative) component to the reward that is proportional to the risk level of the action. We define the risk level associated with an action *a* as the standard deviation of penalty values experienced by the agent each time it has taken action *a*:

$$\sigma_{plty}(s_t, a_t) = \left(\frac{1}{n-1} \sum_{i=1}^{n} \left(plty(s_i, a) - \overline{plty(s, a)} \right)^2 \right)^{\frac{1}{2}} \tag{3.4}$$

where n denotes the number of times the action a was taken from the start of the session and $\overline{\mathrm{plty}(s,a)}$ is the average of past penalties:

$$\overline{\mathrm{plty}(s,a)} = \frac{1}{n}\sum_{i=1}^{n}\mathrm{plty}(s_i,a) \tag{3.5}$$

Therefore, the combination of reward seeking and risk seeking is modelled replacing the reward by:

$$r_t \leftarrow \omega \cdot r_t + \rho \cdot \sigma_{\mathrm{plty}}(s_t,a) \tag{3.6}$$

where ρ controls the strength of the risk seeking trait and is unique to each individual rat. A positive value denotes risk-seeking while a negative value corresponds to risk aversion. We choose to model risk in this form, in contrast to some other methods (Mihatsch and Neuneier, 2002; Niv et al., 2012), as the present form requires only one parameter and allows learning to reach larger asymptotic values in risky situations.

3.5.2.3 *Cognitive Inflexibility*

The cognitive inflexibility trait is modelled for simplicity by adjusting the learning rate parameter α: α is split into two separate components, an initial learning rate parameter α_0 and an exponential decay with time constant τ_0, which gradually reduces the learning rate across the session:

$$\alpha \leftarrow \alpha_0 \cdot e^{-\frac{t}{\tau_0}} \tag{3.7}$$

Parameter α_0 is comprised between 0 (no learning) and 1. Parameter τ_0 determines how quickly the agent stops learning and becomes insensitive to the reward prediction error. Each rat is described by particular values of α_0 and τ_0 and is thus characterised by a unique learning rate profile. Individuals with low α_0 and/or low τ_0 describe rats that are inflexible. A further global index of flexibility is given by the integration of α over time. We are aware that recent modelling studies have suggested using a state-splitting mechanism (Gershman et al., 2010a; Redish et al., 2007) to account for the commonly observed rapid recovery of performances during reinstatement of learned contingencies after extinction. However, our experiments did not address the recovery of the initial RGT conditions after the reversal. Therefore, implementing the state-splitting mechanism would have greatly increased the model complexity (i.e. number of free parameters) without improving the fit to the data.

3.5.3 *Combined model*

The resulting model is a TD learning algorithm (SARSA-λ) where risk seeking and reward seeking traits affect the value of rewards, while cognitive inflexibility controls the rate of learning. Putting all the traits together, the learning rule is:

$$Q(s_t, a_t) \leftarrow Q(s_t, a_t) + \underbrace{\alpha_0 \cdot e^{-\frac{t}{\tau_0}}}_{\text{inflexibility}} \left[\left(\underbrace{\rho \cdot \sigma_{plty}(s_t, a_t)}_{\text{risk}} + \underbrace{\omega \cdot r_t}_{\text{reward}} - plty(s_t, a_t) \right) - Q(s_t, a_t) \right] \tag{3.8}$$

3.5.4 *Decision Making*

Actions are selected according to a Softmax process, by assigning a probability of selection to each available action *p(s_t,a)* depending on the value of all available states:

$$p(s_t, a) = \frac{exp\frac{Q(s_t,a)}{\varepsilon}}{\sum_i^n exp\frac{Q(s_t,i)}{\varepsilon}} \tag{3.9}$$

where ε is a temperature parameter which controls the amount of exploration. A high level of exploration is imposed to all subjects during the first 10 min of simulation to ensure that all the options are initially sampled (by analogy with the behavioural procedures).

3.5.5 *Model fitting*

The performance of this model during the RGT is fitted to the performance profile of each individual rat using Maximum Likelihood, in order to extract a set of parameters that best describes the rat's behaviour (i.e. a set of four parameters influencing learning α_0, τ_0, ω, ρ and one parameter influencing the exploration/exploitation trade-off ε):

$$\hat{\theta}_{MLE} = \arg\max \mathcal{L}(\theta \mid x_{10} \cdots, x_{60}) \tag{3.10}$$

where $\mathcal{L}(\theta \mid x_{10} \cdots, x_{60})$ denotes the likelihood of the data under the model, θ are the model parameters, and x_{10} to x_{60} are the experimental performance levels (percentage of advantageous choices) of the rat over successive 10 min blocks. The likelihood is computed by running the RGT model 50 times for a given set of parameters. Using the performance profiles extracted for each model iteration, we calculate the probability distribution of getting an advantageous choice at every 10 minutes

time-bin. The maximum likelihood is the set of parameters that gives the highest probability of resulting in the observed rat performance profile at each of the 10 minutes time-bin.

3.5.6 *Model comparison*

We used the Likelihood Ratio Test and the Bayesian Information Criterion (Daw, 2011) to test whether simpler models including only 1 or 2 behavioural traits could be as predictive of poor decision making as the full model.

3.5.7 *Correlation analysis*

The significance of the observed correlation coefficient between the experimental measures and the modelled behavioural traits was tested using Monte Carlo permutation tests. This method performs random permutations to mix the paired values (i.e. modelled trait parameter values and the experimental analogue values) and measure the new correlation coefficients for each new permutation. Doing so a large number of times (i.e. 100,000 iterations) provides a distribution of correlation coefficients for random permutations of values so as to test the null hypothesis.

3.6 RESULTS

3.6.1 *RGT and Reversal*

The TD model was fitted to each rats' performances in the RGT to estimate the five free parameters describing each rat: two parameters for cognitive inflexibility, one for risk seeking, one for reward seeking and one for the exploration of the environment (see Methods). Partial models with fewer parameters were also tested (see below).

The model was able to reproduce the distinct performance profiles observed during the RGT session for poor and good DM (Figure 3.12A). This suggests that differences in risk-proneness, reward seeking behaviour and cognitive inflexibility can collectively account for the variability of performance profiles observed experimentally. Moreover, based on the performance of the rats during the RGT, the model could successfully predict the performance profile of all poor DM and of half of the good DM during reversal conditions (Figure 3.12B).

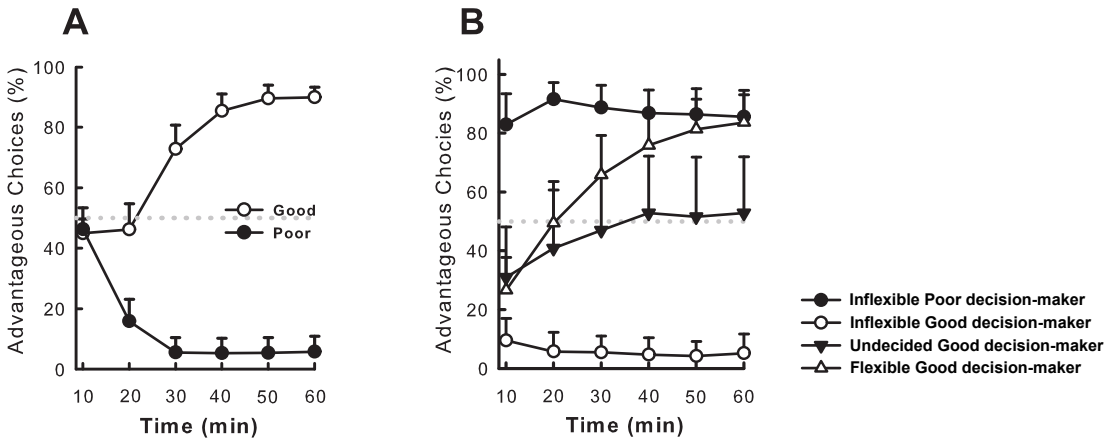

Figure 3.12: Model's performance on the RGT & Reversal-RGT. **(A)** Simulated time-course of advantageous choices (%) of good and poor DM on the RGT. **(B)** Simulated time-course of advantageous choices for flexible, undecided, inflexible good DM and inflexible poor DM groups on the RGT-reversed version. Dotted line represents chance level.

3.6.2 *Cognitive Inflexibility*

Cognitive inflexibility was implemented as a gradual decrease of the learning rate over the course of the experimental session controlled by two parameters α_0, the initial learning rate and τ_0 the decay (see Methods). The initial learning rate parameter α_0, extracted from a fit of the RGT session alone was positively correlated with the experimental measure of flexibility during reversal (r = .3303, group correlation MC permutation test p = .0266). The model predicted an inflexible learning behavior in all modelled poor DM (poor DMm; Figure 3.13A), as observed experimentally (Figure 3.6B). When both the RGT and reversal conditions were used to estimate all model parameters, all flexibility parameters (α_0, τ_0 and the area under α) correlated positively with the experimental measure of flexibility (e.g. for α, r = -.73, MC permutation test p = .0002, see 3.13B).

3.6.3 *Risk Seeking*

Risk seeking was implemented by adding a risk-related reward contribution (Li and Chan, 2006) to the actual rewards (see Methods). In the model (Figure 3.14A), as in the experiments (Figure 3.5A,B), poor DMm were characterized by higher levels of risk sensitivity than good DMm. The risk parameter extracted from the model significantly correlated with the two behavioural measures of risk seeking (i.e. mean latency for the first visit in the light compartment and risk assessments, r = -.5370 and -.5555; MC permutation test p = .0043 and p = .0051 respectively, see Figure 3.14B).

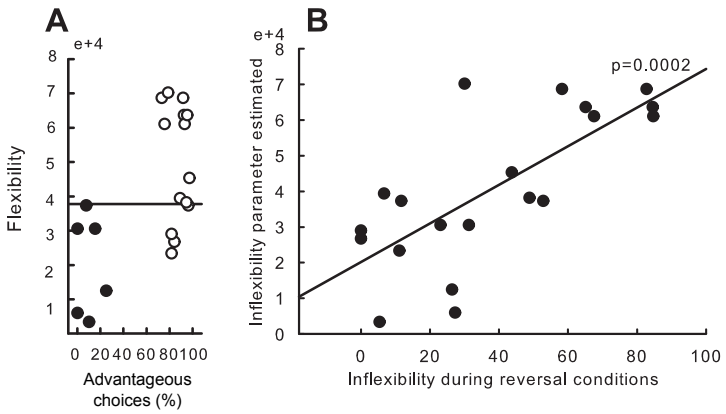

Figure 3.13: Estimated learning rate parameter, modeling cognitive flexibility. **(A)** Relationship between simulated individual RGT scores and the estimated flexibility parameters affecting the learning rate. **(B)** The measure of cognitive inflexibility (x-axis) and the estimated inflexibility parameter (area under α; y-axis). Grey lines represent the median used to compute proportions of high and low scores in good and poor DM.

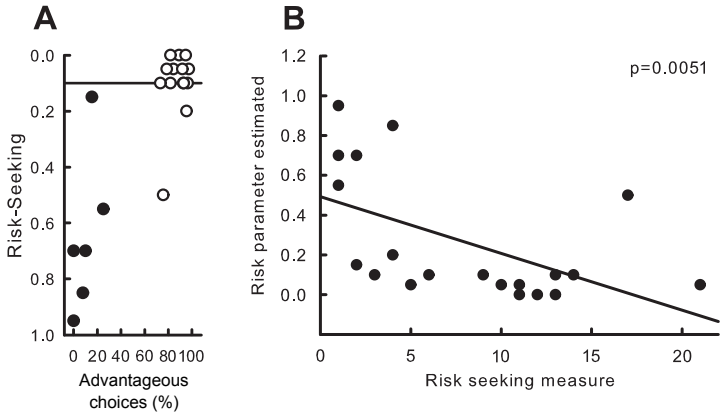

Figure 3.14: Estimated ρ parameters modeling the risk-seeking behavioral trait. **(A)** Relationship between simulated individual RGT scores and the estimated risk seeking parameters. **(B)** The measured risk seeking (number of risk assessments; x-axis) and the estimated risk-seeking parameter (y-axis). Grey lines represent the median used to compute proportions of high and low scores in good and poor DM.

3.6.4 *Reward Seeking*

Reward seeking behaviour was modelled by allowing the perceived magnitude of the rewards to be greater than the actual reward. In the model, consistent with experimental data (Figure 3.7), all poor DMm except one showed high reward seeking, whereas less than 29% of modelled good DM (good DMm) showed this trait (Figure 3.15A). The reward seeking parameter estimated from the model correlated significantly with the corresponding behavioural measure of reward sensitivity (r = -.4014, MC permutation test p = .0479, see Figure 3.15B).

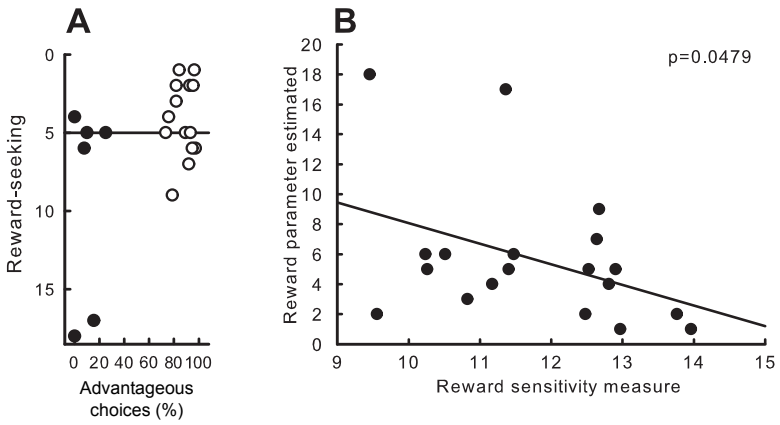

Figure 3.15: Estimated ω parameters modeling the reward-seeking behavioral trait. **(A)** Relationship between simulated individual RGT scores and the estimated reward seeking parameters during the RGT + Reversal. **(B)** The measured reward sensitivity (x-axis) and the estimated reward sensitivity (y-axis). Grey lines represent the median used to compute proportions of high and low scores in good and poor DM.

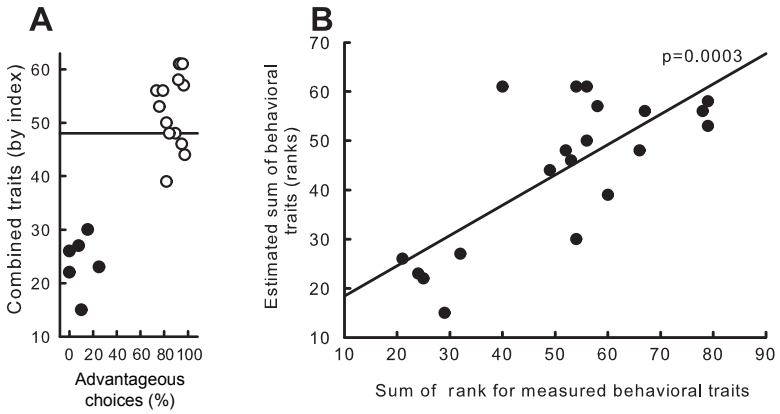

Figure 3.16: Estimated individual rank scores when combining all the behavioral traits modelled. **(A)** The sum of the simulated score ranks for each modelled behavior. **(B)** The sum of ranks for all the behavioral traits measured experimentally (x-axis) and those estimated by the model (y-axis). Grey lines represent the median used to compute proportions of high and low scores in good and poor DM.

3.6.5 *Combination of traits*

Finally, when all the different behavioural traits are taken into account (Figure 3.16A), poor DMm exhibited a combination of high levels for the modelled behavioural traits as observed in behavioural measures. The global index (sum of the ranks for each behavioural trait) of each modelled rat was highly correlated with the global index derived from experimental measures (r = .7420, MC permutation test p = .0003, see Figure 3.16B). Furthermore, similarly to the experimental data (Table 3.1 and Figure 3.11A), the model showed that the combination of high cognitive inflexibility, reward and risk seeking is particularly discriminative of poor DMm, since good DMm almost

never expressed more than one of those traits (Table 3.3).

	Poor decision makers							Good decision makers														
Rats	3	8	32	15	28	9	%	2	4	24	33	6	31	1	17	19	29	12	30	27	26	%
Risk-seeking	✓	✓	✓	✓	✓	✓	100			✓	✓				✓	✓	✓	✓		✓		50
Reward-seeking	✓		✓	✓	✓	✓	83		✓				✓	✓	✓		✓		✓		✓	50
Inflexibility	✓	✓	✓	✓	✓	✓	100	✓				✓				✓		✓				29
Nb. of high scores	3	2	3	3	3	3		1	1	1	1	1	1	1	2	2	2	2	1	1	1	

Table 3.3: Same representation as in Table 3.1 for modeled behavioral traits: risk taking, reward seeking and inflexibility parameters.

3.6.6 *Influences of combined behavioural traits on learning*

To understand why good and poor DM show different choice preferences, we analysed how well good and poor DMm evaluated advantageous and disadvantageous actions. The Q-values representing the valuation of each choice at the end of the RGT session were extracted for all rats, using the TD-learning model.

Figure 3.17B illustrates the mean Q-values assigned to the disadvantageous choices (A & B) and advantageous choices (C & D) by poor and good decision makers. Poor DMm vastly over-estimated the value of all states rather than just disadvantageous options. The over-estimation was more important for disadvantageous choices in comparison to the advantageous ones. By contrast, good DMm stopped exploring disadvantageous choices early in the RGT session due to their negative value.

In the model, high scores in risk seeking, reward seeking or inflexibility lead to an altered estimation of the true value of all states. High scores in a combination of traits lead to a shift in the valuation of the state-action pairs, where disadvantageous choices appear to be more valuable than advantageous ones.

Comparison with simpler models: Model comparison was also performed in order to address whether simpler models with fewer behavioural traits could have accounted just as well for the experimental data. We tested simpler versions of our model with either only one or two behavioural traits and compared the fit of these models to the experimental data. We used the Likelihood Ratio Test and the Bayesian Information Criterion to assess the fit of the models while penalizing for added complexity. The likelihood ratio test revealed that the full model (including reward sensitivity, risk seeking and cognitive inflexibility) was significantly better ($p<0.0001$) than any other simpler model, suggesting that all behavioural traits are necessary to describe

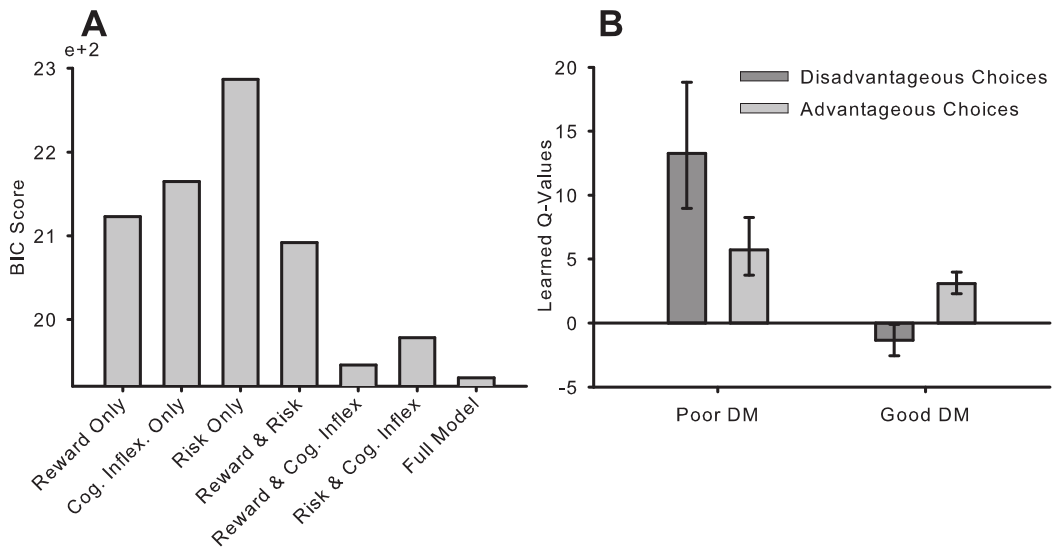

Figure 3.17: Model comparison and impact of behavioural traits on learning and decision-making. **(A)** Bayesian Information Criterion scores for each model (a low score is better). Models based on two traits fare uniformly better than models based on a single trait. Models with two traits including cognitive inflexibility have better scores than equivalent or simpler models. The model with all three simulated traits provides the best fit to the data even when penalizing for the increased model complexity (number of free parameters). **(B)** Learned Q-Values for advantageous and disadvantageous choices by both Good and Poor DM. Bars represent the mean Q-values assigned to the disadvantageous choices (A & B; dark-grey) and advantageous choices (C & D; light-grey) averaged over all poor or good decision makers at the end of an RGT session. Error bars represent 95% CI around the mean Q-value for all the rats of the population of interest. Poor decision makers vastly over-value disadvantageous choices in comparison to advantageous choices.

the experimental data. Similar results were obtained using the Bayesian Information Criterion (see Figure 3.17A).

3.7 DISCUSSION AND LIMITATIONS

Like the IGT in humans, the RGT probably involves a number of cognitive processes, and separating their relative contribution is a challenge. However, our purpose was not to focus on one specific executive function involved in choice, but rather to identify the whole complex phenotype sustaining poor decision making in conflictual and risky situations, as observed in real life. Indeed, a complex interplay between independent behavioural domains is more likely to reflect the complexity of human phenotype and disorders (Kalueff et al., 2008; LaPorte et al., 2010; Robbins et al., 2012).

In the present study, we confirm this hypothesis as we establish a clear link between

separate behavioural traits in a normal sample of rats and decision-making in the RGT. Although each trait considered separately has a poor predictive value, both the behavioural and the modelling analyses indicate that poor decision making can be accurately predicted when these traits are considered in combination.

3.7.1 *Behaviour & decision-making*

While integrating multiple cognitive abilities, the RGT offers the advantage to assess the time-course of the decision making process within a single session. It is particularly suitable for identifying inter-individual differences in decision making, and notably for identifying poor decision-makers because choices are made readily and lead to two opposed decisions: either a preference for advantageous options or a preference for the disadvantageous ones (Rivalan et al., 2011). As shown by the meta-analysis of several experiments in the RGT (de Visser et al., 2011), these behaviours are reproducible. Importantly, poor decision-making does not result from a slower learning. We have previously shown that repeating the RGT on three consecutive days does not change the rats' preferences (data not shown). Additionally, acquiring information about the value of the options separately before the test does not change the proportions of poor and good decision-makers, nor does it change their behaviours (Rivalan et al., 2011).

We show that poor decision making is expressed by individuals presenting excessive scores for a combination of behavioural and cognitive traits: risk taking, higher reward seeking behavior, motor impulsivity and behavioural inflexibility, expressed simultaneously. This contrasts with good DM which present a wider range of scores and only express up to two of these characteristics (Table 3.1). The various traits that we examined were largely independent from one another. A noteworthy exception was the relationship between motor impulsivity/perseveration and risk taking (see Table 3.2).

Link to psychiatry: Poor DM are characterized by risk and reward seeking, which have been found to be associated with trait dominance in rats and humans, and could be necessary for the development and maintenance of social structure (Davis et al., 2009; Demaree et al., 2009). Interestingly, risk and reward seeking, in combination with impulsivity, are hallmarks of poor decision making related mental disorders such as ADHD (Drechsler et al., 2008), personality disorders, substance abuse (Ernst et al., 2003a; Mazas et al., 2000), pathological gambling (van Holst et al., 2010) or ma-

nia (Kathleen Holmes et al., 2009). Poor DM are also characterized by behavioural inflexibility as well as perseverative and compulsive-like behaviours. Their inflexibility was particularly noticeable in the RGT reversal procedure, which requires redirecting choices on the basis of new response-reward contingencies (Granon and Floresco, 2009), but also in the FCN schedule with perseverative responses. Indeed, perseverative responses in the FCN have similarly been observed following amphetamine administration (0.8 mg/kg), in a similar procedure (Evenden and Ko, 2005). These effects of the psychomotor stimulant are likely to reflect compulsivity, especially at this dose, given that only low doses of amphetamine (0.25 mg/kg) are known to reduce impulsivity in this task (Rivalan et al., 2007; Grégoire et al., 2012), whereas higher doses (0.5 mg/kg or above) increase impulsive responses. Perseverative behavior, typically observed after acute administration of psychostimulants (Evenden and Ko, 2005), inflexible and compulsive behavior can be seen in drug addiction (Calu et al., 2007; Jentsch et al., 2002), pathological gambling (Goudriaan et al., 2006) and in obsessive-compulsive disorder (OCD) (DSM-IV-TR, 2000). Inappropriate compulsive behaviours (Dalley et al., 2011) may result from attributing excessive incentive value to reward associated stimuli (Berridge, 1998; Flagel et al., 2009). This could explain bursts of activity on the reinforcer level in the FCN schedule, as well as hyperactivity in the FI-EXT schedule. Compulsive behavior could also result from a quicker switch from initial voluntary goal-directed behavior to an habitual, automatic process with loss of control, as observed in drug addiction and OCD (Everitt et al., 2008; Gillan et al., 2011). Interestingly, poor decision-makers do not have more impulsive tendencies compared to good DM in terms of intolerance to delayed gratification and of inhibitory control. Still, we cannot exclude that more demanding tasks (e.g. the stop-task; Feola et al., 2000) could reveal differences in inhibition between both phenotypes. Moreover, the higher sensitivity of poor DM may have influenced the performance in this task. However, a recent meta-analysis also concluded that inhibition and decision-making in the IGT are dissociated (Toplak et al., 2010).

Previous studies have shown that individual behavioural traits can be related to maladaptive behavior in animal models of mental disorders (i.e. novelty-seeking in depression (Stedenfeld et al., 2011); impulsivity, novelty preference in drug self-administration (Molander et al., 2011; Dalley et al., 2007; Diergaarde et al., 2008). However, the cumulative effect of several symptoms in one individual, as systematically observed in mental disorders (DSM-IV-TR, 2000), has rarely been considered in an animal model (Kalueff et al., 2008). Here, we show that a complex phenotype is highly predictive of poor decision-making, since it only describes poor performers. Each of the traits identified participates to this phenotype that leads to the in-

ability to adapt to the situation because of a distorted representation of the balance between reward and risk, and an inflexible/compulsive behavior precluding readjustment of behavior. This complex phenotype reflects well the relevance of the concept of *"domain-interplay"* to explore the basis of maladaptive behavior (Kalueff et al., 2008; LaPorte et al., 2010). Although we cannot conclude that the different observed phenotypes represent innate or acquired differences, it is noteworthy that dominant rats are natural risk takers and display increased motivation for food reward (Davis et al., 2009; Demaree et al., 2009), two characteristics of poor decision makers in the RGT. This social parameter could be well related to performance in the RGT, a hypothesis that remains to be elucidated.

3.7.2 *Learning & decision-making*

Building on the expanding literature indicating that behavioural traits such as risk seeking affect learning and the prediction error signal (Niv et al., 2012; Schultz, 2011), we used a reinforcement learning model of the RGT to investigate the relationship between the traits and the decision making performances. First, we used the model to address whether the behavioural traits could collectively account for the variety of performances observed in the decision-making task (i.e. Can excessive behavioural traits lead to poor and/or undecided decision-making?). Secondly, we used the model to explore the interaction between the behavioural traits on learning and decision-making (i.e. How and why do excessive traits lead to poor decision-making?). The computational model, based on a TD-learning algorithm, was modified to include the behavioural traits of risk seeking, reward sensitivity and behavioural inflexibility.

The model reveals how risk seeking, reward sensitivity and behavioural inflexibility jointly contribute to the learning and the decision-making process. The model of the RGT fits the experimental data very closely, and demonstrates that traits such as high risk seeking, high reward seeking and cognitive inflexibility can be derived from the performance of individuals in the RGT. Importantly, all the parameters used to model the behavioural traits successfully correlated with the experimental measures for each trait, validating the assumptions made during the implementation. This suggests that the mathematical formalization of all the behavioural traits and their independent influence on learning in the RGT were valid. Interestingly, we found that individual traits were insufficient to lead to poor performances at the task (Table 3.3). Rather, poor decision-making required specific combinations of at least two of the behavioural traits, namely inflexible learning and risk seeking or inflexible learning and

reward seeking. This suggests that single excessive behavioural traits may be compensated for in good decision makers. Yet, such potential compensatory processes may fail when a combination of traits are involved.

Importantly, the computational study is based on the assumption that a failure in decision-making occurs through an altered internal representation of the values in the environment (Figure 3.17B), as is customary in computational modelling of psychopathology (Redish, 2004; Redish et al., 2008). We investigated the difference in valuation of the different choices by poor and good decision makers. Surprisingly, we found that poor DMm vastly over-estimate the value of all choices, but especially those corresponding to disadvantageous options. According to their inflated valuation of disadvantageous choices, poor DM appear to behave optimally according to their subjective & inaccurate value-map of the environment, rather than sub-optimally according to the objective outcome of the task. Our findings are in line with recently suggested mechanisms of psychopathology such as addiction (Schultz, 2011).

Our model accounts for the role of behavioural traits in learning and decision-making, using a basic TD-learning framework using minimal assumptions. Other formalisms such as win-stay loose-shift, Bayesian models or more elaborate TD models could also be explored (Mihatsch and Neuneier, 2002; Williams and Dayan, 2005; Niv et al., 2006; Redish et al., 2007; Gershman et al., 2010a; Niv et al., 2012). However, the present model offers a straightforward way to implement the traits of interest and allows a quantitative assessment of the impact of individual differences on the overall decision-making performances. In particular, we show that simple models incorporating fewer discriminative traits have less predictive value than the full model. More biologically targeted versions of this model could be developed (Bogacz and Larsen, 2011; Cohen and Frank, 2009; Potjans et al., 2009) and investigated with regard to the cortical-subcortical interplay specific to good and poor DM.

3.8 CONCLUSIONS

In conclusion, poor decision making in the RGT is predicted by a complex phenotype of cumulated behavioural and cognitive characteristics including risk seeking, reward seeking, inflexibility, possibly combined with motor impulsivity and perseverative / compulsive-like behaviours. This approach, based on the identification of high scores for these behavioural traits expressed spontaneously and in a comparable way as to those observed in the clinic, demonstrates that rat behavior can reliably model dimensions found in humans (Rivalan et al., 2009b; Matzel and Kolata,

2010). This work emphasizes the need to use *"integrative"* animal models to mimic the complexity of the clinically relevant phenotype (LaPorte et al., 2010). Our findings are also in line with the recent proposal by Robbins et al. (2012) to undertake a more objective description of psychiatric disorders through predisposing traits and neurocognitive endophenotypes, thereby explaining the high level of comorbidities between mental disorders. By integrating multiple behavioural measures, combined with computational modelling, our work provides a promising framework for revealing the neuropsychological determinants of poor decision-making as a potential risk factor for developing related mental disorders (Rivalan et al., 2009b; Hayton et al., 2012) and for exploring its neurobiological substrates.

4

COGNITIVE DEFICITS & WORKING MEMORY

Working memory has been identified as the strongest and most stable neuropsychological impairment present in schizophrenia (Lee and Park, 2005; Forbes et al., 2009). It has been hypothesised to be the leading cause of the generalised cognitive symptoms observed in the disorder (McKenna et al., 1990; Goldman-Rakic, 1994). Recently however, researchers have found that the degree of WM impairments both in schizophrenia and healthy controls were predictive of delusional ideation (Garety et al., 2013; Garety and Freeman, 2013; Freeman et al., 2008) and might be involved in the processes leading to psychosis. The work presented in this chapter uses the Spatial Working Memory (SWM) task from the Cambridge Neuropsychological Test Automated Battery (CANTAB) developed by Cambridge Cognition Ltd. It is one of several experimental paradigms that tests the retention and manipulation of visuospatial information over increasing memory load. The data acquired and presented in this chapter is part of a wider research study (i.e. the Grand Challenge study) investigating cognitive and functional differences in first episode psychosis, chronic schizophrenia, bipolar disorder and family members of Disrupted-In-SChizophrenia 1 translocation carriers (DISC1; known to be a risk factor for developing major mental illness — Chubb et al., 2008). The recruitment and testing of participants was performed by Barbara Duff. The implementation of a novel data extraction tool, analysis of the behavioural results, computational modelling of the SWM task, model fitting and analysis was performed by myself under the supervision of Dr. Peggy Seriès and Prof. Stephen Lawrie.

4.1 BACKGROUND

4.1.1 *Working memory in psychosis*

Working memory is the memory system used for the short term storage and manipulation of information (Baddeley, 1987). Impairments of working memory have been described as a recurrent feature of schizophrenia (Park and Holzman, 1992; Gold et al., 2003; Lee and Park, 2005; Forbes et al., 2009). Recent reviews have identified that WM deficits are probably the most stable neuropsychological deficit observed in schizophrenia (Lee and Park, 2005; Forbes et al., 2009), which could not be ex-

plained by differences in current IQ between samples (Forbes et al., 2009; Gray et al., 2013). Authors (Green and Nuechterlein, 1999) have suggested that working memory deficits in schizophrenia might be the leading cause of the array of symptoms observed in patients. However there is an ongoing debate as to whether the neuropsychological impairments stem from a generalised cognitive deficit (Blanchard and Neale, 1994; Johnston et al., 2001; Lencz et al., 2006; Fioravanti et al., 2012; Joyce, 2013; for a review see Reichenberg and Harvey, 2007) or from selective impairments. Several impairments of specific domains have been proposed, such as increased distractibility (Oltmanns, 1978), attention deficit (Nuechterlein and Dawson, 1984; Kenny and Meltzer, 1991) memory impairments (McKenna et al., 1990; for reviews see Aleman et al., 1999; Lee and Park, 2005; Forbes et al., 2009) or executive dysfunction (Weinberger et al., 1988, 1992).

Goldman-Rakic (1994) a leading scientist in the field of working memory argued that working memory dysfunction could explain some of the positive symptoms observed in schizophrenia such as thought disorder. In line with Goldman-Rakic's suggestions, Wood et al. (2003) found that spatial working memory impairments were predictive of psychosis in a Ultra High Risk (UHR) sample. Specifically, patients that subsequently became psychotic in this UHR group performed generally worse in working memory than those who did not (Wood et al., 2003). Multiple studies have since investigated working memory in schizophrenia, where robust deficits were demonstrated (Lee and Park, 2005; Forbes et al., 2009).

Other psychiatric disorders also appear to be affected by working memory deficits. For example, in a study involving 200+ participants, McIntosh et al. (2005) found that memory was impaired in schizophrenia, bipolar disorder, and patient's relatives. Working memory was significantly affected across all groups (bipolar, schizophrenia, family members) when compared to controls, suggesting that impaired memory might be predictive of an increased liability to psychosis (McIntosh et al., 2005). Reviews of neuropsychological impairments in bipolar disorder (Quraishi and Frangou, 2002) and schizophrenia (Aleman et al., 1999; Lee and Park, 2005; Forbes et al., 2009) suggest that both groups are significantly impaired in working memory and display a similar magnitude of impairment when compared to controls (Seidman et al., 2002; McClellan et al., 2004; McIntosh et al., 2005). Although it is worth noting that some studies found that bipolar patients displayed milder impairments than that of schizophrenia patients (Glahn et al., 2006; Badcock et al., 2005; Pirkola et al., 2005). A recent meta-analysis involving more than 17,000 working memory tests performed in patients with schizophrenia (Forbes et al., 2009), found that first episode patients were less affected than chronic patients in working memory, and argue that the disorder might accelerate the age-related decline of working memory performances. However

it is worth noting that some early studies identified significant deficits of working memory in first episode psychosis (Hutton et al., 1998; Joyce et al., 2002). In DISC1 translocation carriers, an increasing number of studies have found evidence for an association or a linkage between the DISC1 locus and impaired working memory function (Gasperoni et al., 2003; Porteous et al., 2006).

4.1.1.1 *Working memory, positive and cognitive symptoms*

Consistent with suggestions from Goldman-Rakic (1994) that working memory impairments in schizophrenia might lead to a subset of positive symptoms (thought disorder), recent studies (Broome et al., 2007; Garety et al., 2013; Freeman et al., 2014) have found that WM appear to be involved in probabilistic learning deficits and associated with delusional ideation in schizophrenia and healthy controls using the beads task (Huq et al., 1988). In this task, participants are presented with two jars of beads, one containing substantially more blue than red beads while the other jar contains opposite amounts of red and blue beads. Beads are taken one by one from a hidden jar and participants are required to guess which jar the beads originated from. Patients with schizophrenia appear to require significantly fewer draws of beads before they can make a firm decision, and report stronger beliefs about the origin of the beads than they ought to (Averbeck et al., 2011). Rapid decisions without careful sampling of the environment lead to early decision errors known as the jumping to conclusion bias (JTC). Particularly, probabilistic learning deficits as measured by the beads task (Huq et al., 1988) have been found to be linked to delusional ideation both in schizophrenia (Speechley et al., 2010) and in the general population (Freeman et al., 2008), suggesting that there is a continuum of severity for delusions (for a review see Garety and Freeman, 2013). That is, both in patients with schizophrenia and to a certain degree healthy controls, the jumping-to-conclusions (JTC) bias traditionally observed with the beads task is predictive of the intensity of delusional ideation. Interestingly, Broome et al. (2007) recently identified in a high-risk (HR) group that working memory deficits were also associated to the jumping to conclusion (JTC) bias. Specifically, the authors tested whether the JTC bias was associated with impaired working memory and found a significant association suggesting that a failure to hold information in memory might lead to deficiencies in probabilistic learning. Follow-up studies have since confirmed these results in schizophrenia spectrum psychosis (Garety et al., 2013), and in patients with persecutory delusions (Freeman et al., 2014). Particularly, Garety et al. (2013) argue that WM manipulation was particularly predictive of the JTC bias and poor probabilistic learning rather than WM span. While relatively few studies have demonstrated this effect to date, the accumulating evidence of a possible relationship between working memory, the JTC

bias and delusions suggest that these should be investigated systematically (Garety et al., 2013; Garety and Freeman, 2013).

4.1.2 *Neural basis of working memory*

Goldman-Rakic (1987, 1995) pioneering work on working memory helped to identify neuroanatomical correlates of working memory. Using occulomotor delayed-response tasks in primates, the author demonstrated how neurons in the dorsolateral prefrontal cortex (dlPFC) are tuned to specific spatial orientations and display an increased discharge rate when a cue that match their preference is presented. The rate of these neurons was then sustained throughout the delay period until a response was made (Goldman-Rakic, 1987, 1995). That is, the author identified a neural biological basis for the encoding and maintenance of working memory in primates. Again in primates, Vijayraghavan et al. (2007) then demonstrated how the maintenance of information in working memory is critically dependent on the activation of dopaminergic D1 receptors (D1r) in the dlPFC (however not dependent on D2r; Wang et al., 2004, for a review see Cools and D'Esposito, 2011). Specifically, Vijayraghavan et al. (2007) found that the maintenance of information in dlPFC neurons was dependent on the level of dopamine present in the dlPFC. The response of dlPFC neurons followed an inverted-U dose-response profile, where moderate or excessive dopamine levels lead to suboptimal discharge rates during the maintenance of information in WM (Wang et al., 2004; Vijayraghavan et al., 2007; Cools and D'Esposito, 2011). That is, dopamine levels appear to modulate the robustness of the WM neural network to maintain information in memory against internal cortical noise or external distractor cues (Cools and D'Esposito, 2011).

Using neuroimaging tools in humans, studies (e.g. Braver et al., 1997; Cohen et al., 1997) have revealed that similar cortical structures to those found in primates were activated during working memory tasks (Fletcher and Henson, 2001; McNab and Klingberg, 2008). Particularly, McNab and Klingberg (2008) revealed that the basal ganglia along with the frontal cortex were concurrently responsible for filtering irrelevant information from entering WM and to gate relevant information into memory (Cools and D'Esposito, 2011). The activity of the basal ganglia and dlPFC in humans was predictive of the participants' WM capacity (McNab and Klingberg, 2008). Both the dlPFC and basal ganglia are known to be rich in dopamine afferent and receptor densities (Farde et al., 1987; Suhara et al., 1991), suggesting that dopamine might be critically involved in the encoding and maintenance of working memory in primates and in humans (Cools and D'Esposito, 2011).

4.1.2.1 *Neuroimaging of working memory in psychosis*

Dopaminergic transmission has been thoroughly documented as being significantly impaired in schizophrenia (Grace, 1991; Seeman et al., 1993; Howes and Kapur, 2009; Hall et al., 2009; Roiser et al., 2012; Howes and Murray, 2013; Fusar-Poli and Meyer-Lindenberg, 2013a,b) and is known to also be instrumental for learning and goal-directed behaviour (Schultz et al., 1997; Schultz, 2002; Montague et al., 2004; Schultz, 2007; Behrens et al., 2008). Specifically, positron emission tomography (PET) studies in schizophrenia (Abi-Dargham et al., 2002) have found elevated dopamine D1r availability in the dlPFC in comparison to controls. This increased availability was predictive of poor WM performance. Interestingly however, although first episode patients appear relatively spared from WM impairments (Forbes et al., 2009), a similar gain of D1r availability was also found in the dlPFC of these patients. In the striatum, meta-analyses of PET imaging for dopamine receptor densities found no evidence for increased D2/3 receptor densities in schizophrenia (Fusar-Poli and Meyer-Lindenberg, 2013a). However, the authors found large increases in dopamine synthesis capacity in comparison to controls (Fusar-Poli and Meyer-Lindenberg, 2013b). Recent reviews investigating dopaminergic signalling in schizophrenia (Howes et al., 2012; Howes and Murray, 2013) also identified that dopamine synthesis capacity, dopamine release and baseline synaptic concentrations were also elevated in schizophrenia (Howes and Murray, 2013). Early functional magnetic resonance imaging (fMRI) studies identified a reduced activation of the PFC of patients during WM tasks (*"hypofrontality"*; Yurgelun-Todd et al., 1996; Callicott et al., 1998; Carter et al., 1998), however these findings were disputed due to potential confounding factors such as a lack of motivation, inadequate strategy use of demanding task requirements (for review see Weinberger and Berman, 1996). Later studies addressed these issues (Manoach et al., 1999; Perlstein et al., 2001), and revealed that schizophrenia patients demonstrated an elevated activation of the left dlPFC, which was predictive of their deficits at the WM task. That is, the strongest the fMRI activation of the dlPFC, the more errors were being made. The authors argued that this over-activation of the dlPFC is the result of a prefrontal dysfunction, requiring exaggerated efforts in order to complete the task. Overall, the accumulating evidence suggests that abnormal dopaminergic transmission in schizophrenia could account for the working memory deficits identified in patients.

4.1.3 *Competing hypotheses*

While neuropsychological tests have generally revealed significant cognitive impairments in schizophrenia (Reichenberg and Harvey, 2007; Gold et al., 2009), there is clear lack of scientific consensus regarding the origins of those impairments. We have identified six major hypotheses of generalised dysfunction in schizophrenia that could lead to the generalised neuropsychological deficits observed in patients; namely a deficit in working memory encoding (Lee and Park, 2005; Mayer and Park, 2012), a deficit in working memory maintenance and/or manipulation (Reichenberg and Harvey, 2007; Fletcher and Honey, 2006), inflexible learning leading to perseverative behaviour (Goldberg et al., 1987; Morice, 1990; Ritter et al., 2004; Kim et al., 2009), an overconfidence and data gathering bias (Broome et al., 2007; Freeman et al., 2008; Speechley et al., 2010; Averbeck et al., 2011; Evans et al., 2012; Garety et al., 2013; Garety and Freeman, 2013; Joyce et al., 2013; Freeman et al., 2014), a deficit of attention (Nuechterlein and Dawson, 1984; Kenny and Meltzer, 1991; Gold et al., 2003) or distractibility (Oltmanns, 1978), and finally a failure to reduce the task complexity to a subset of relevant features for completion of the task (Gershman et al., 2010b). While these hypotheses are frequently debated in the literature of schizophrenia (Reichenberg and Harvey, 2007), no study has attempted to systematically test all these competing hypotheses simultaneously in a patient sample, as is now customary in computational modelling studies in psychiatry (Grasemann et al., 2009; Huys et al., 2011; Hoffman et al., 2011; Huys et al., 2012).

4.2 AIMS

Previous reviews have shown that patients with bipolar disorder, schizophrenia, and family relatives share similar working memory impairments (McIntosh et al., 2005). We hypothesize that rather than a common deficit across populations with different diagnoses, the measures extracted during working memory tasks might not have been specific enough to capture subtle differences in group performances.

In this study, we decided to use the spatial working memory task from the CANTAB that has been previously used in the literature to address spatial working memory deficits in schizophrenia (Pantelis et al., 1997; Hutton et al., 1998; Joyce et al., 2002; Wood et al., 2003; Badcock et al., 2005; Pantelis et al., 2009). However, we decided to expand the measures extracted from this task to identify whether subtle group differences in performance might exist. Additionally, by modelling the performance of participants at the CANTAB spatial working memory task, we wished to simul-

taneously test the six most commonly debated hypotheses of generalised cognitive deficits described in section 4.1.3. Using these models, we expect to detect whether the deficits observed in different groups stem from different generalised impairments or strategies. Formally, this study will attempt to address the following questions:

1. Can additional features (e.g. optimality score, time, etc.) be extracted from the raw performances at the spatial working memory task? If yes, can these additional features detect subtle differences in group performances and dissociate patients groups with different psychiatric diagnoses?

2. Which of the competing hypotheses presented in section 4.1.3 accounts best for the performance deficits observed in patients with first episode psychosis, chronic schizophrenia, bipolar disorder and family members? Are different groups better accounted for by different hypotheses?

To approach these questions, we built a computational model that uses probabilistic inference to solve the SWM task optimally. Using this model, we propose to test the validity of each hypothesis by comparing their ability to generate a performance similar to that of patients. To do so, each hypothesis will be implemented individually within our optimal inference model using the simplest assumptions. Then, the ability for each of these hypotheses to generate and fit patients' experimental data will be compared and analysed using the Bayesian Information Criterion. This comparison will enable to score and compare each hypothesis for every individual and group.

4.3 SAMPLE DEMOGRAPHICS

For this study, 43 healthy controls were recruited together with 5 first episode patients (1ST), 24 patients with chronic schizophrenia (SCZ), 15 patients with bipolar disorder (BPD), and 24 family members (FAM) with/without DISC1 translocation, for a total of 111 participants (see table 4.1). Recruitment and testing of participants was performed by Barbara Duff between 2010 and 2013. Translocation status of family members was unknown at the time of recruitment but following sequencing later revealed that 11 of the 24 family members were translocation carriers. Clinical diagnosis for translocation carriers was as follows: Major Depressive Disorder (Recurrent; n=3), Major Depressive Disorder (Single episode; n=3), Cyclothymia (n=3), Schizoaffective Disorder (n=1), Conduct Disorder (n=1). Clinical diagnoses were also established for three of the non-carriers: Major Depressive Disorder (Recurrent; n=1), Generalised Anxiety Disorder (n=2). One healthy subject requested to be withdrawn from the study and was therefore excluded from further analyses. One chronic schizophrenia

	CTR (n=42)	1ST (n=5)	SCZ (n=23)	BPD (n=15)	FAM (n=24)	Statistics	
Age	37.54 (2.14)	35.00 (3.22)	37.26 (2.25)	42.40 (3.66)	49.92 (3.70)	$\mathcal{F}$ =3.62	p<0.01
Gender (M/F)	25/17	3/2	18/5	11/4	8/16	χ^2 =11.38	p<0.05
NART IQ	110.98 (1.84)	113.60 (3.50)	109.57 (2.32)	113.07 (1.86)	105.04 (1.16)	$\mathcal{F}$ =3.47	p<0.05
current IQ	113.63 (1.84)	110.40 (6.24)	103.65 (3.54)	107.67 (4.21)	91.92 (2.24)	$\mathcal{F}$ =9.86	p<0.01
PANSS							
Total	31.56 (0.66)	52.60 (10.44)	54.30 (4.26)	45.53 (3.64)	37.83 (2.05)	$\mathcal{F}$ =12.61	p<0.01
Positive	7.18 (0.11)	11.20 (1.91)	12.57 (1.01)	9.87 (0.77)	8.04 (0.69)	$\mathcal{F}$ =12.10	p<0.01
Negative	7.31 (0.22)	12.60 (3.26)	14.43 (1.70)	10.40 (1.40)	7.12 (0.12)	$\mathcal{F}$ =10.89	p<0.01
SANS Total	1.15 (0.73)	23.40 (12.24)	28.48 (4.75)	18.40 (5.06)	0.00 (0.00)	$\mathcal{F}$ =18.65	p<0.01
GAF	86.84 (1.25)	46.40 (8.18)	50.65 (3.44)	61.07 (3.89)	83.17 (3.00)	$\mathcal{F}$ =37.54	p<0.01
YMRS	0.16 (0.14)	0.20 (0.20)	1.50 (0.33)	2.87 (0.81)	1.46 (0.88)	$\mathcal{F}$ =3.02	p<0.05
HAM-D	0.94 (0.50)	9.00 (4.49)	8.45 (1.75)	8.27 (1.95)	4.12 (1.19)	$\mathcal{F}$ =6.37	p<0.01

Table 4.1: Participants summary information. NART = *National Adult Reading Test*, PANSS = *Positive And Negative Symptom Scale (lower score is better)*, SANS = *Scale for the Assessment of Negative Symptoms*, GAF = *Global Assessment of Functioning (higher score is better)*, YMRS = *Young Mania Rating Scale*, HAM-D = *Hamilton Depression Rating Scale*. Values indicate mean and (standard error)

patient met exclusion criteria for substance abuse and was also excluded from further analyses.

Kolmogorov-Smirnov tests of normality revealed that age, premorbid-IQ (National Adult Reading Test — NART) and current IQ (Wechsler Abbreviated Scale of Intelligence) were normally distributed *(ks-test; p>0.05)*. Follow-up analysis of variance (ANOVA) revealed a significant difference across groups for age *(F(4,103)=3.62, p<0.01)*, pre-morbid IQ *(F(4,103)=3.472, p<0.05)* and current IQ *(F(4,103)=9.86, p<0.01)*. Post-hoc analyses revealed that family members (FAM) were significantly different to controls for age *(i.e. older; p=0.01)*, pre-morbid IQ *(i.e. lower premorbid IQ; p=0.036)* and current IQ *(lower current IQ; p<0.01)*. No significant differences were found for age, premorbid or current IQ between our the patients and control group (i.e. first episode, bipolar disorder, chronic schizophrenia; *p>0.05)*, suggesting that our patients groups were matched to controls for these variables. Bonferroni correction was applied to post-hoc tests to account for multiple comparisons.

4.4 SPATIAL WORKING MEMORY TASK (CANTAB)

The CANTAB spatial working memory (SWM) task requires participants to find a token in a series of boxes displayed on a computer screen (see figure 4.1). The participant, unaware of the location of the token, must initially search through the set of boxes until the token is found. Prior to the task, the participant is told that once a token has been found in a box, it will never re-appear in that box. A set finishes once the token has been found in each box present on the screen. The number of boxes displayed per set gradually increases over time (i.e. from sets of 3 boxes and up to 8 boxes) so as to challenge the participants' working memory maintenance, manipulation and capacity. Hence, in this task participants are required to keep track of the position of past tokens in order to apply an optimal search strategy (that is, searching exclusively in boxes that never contained a token). According to these rules, a subject can commit to four types of errors (see figure 4.1):

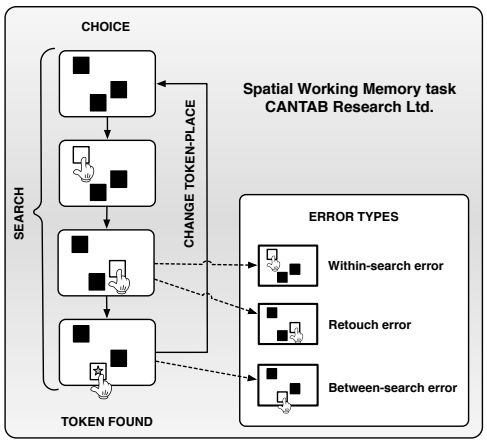

Figure 4.1: Illustration of the spatial working memory task. Using trial and error the subject attempts to find the location of the token (star) hidden in one of the boxes (black squares). Once the token is found, the search ends and a new one starts.

- Between-search errors: These errors happen when participants returns to explore a box that has previously contained a token (i.e. in a previous completed search[1] of that set[2]; see figure 4.1).
- Within-search errors: These errors arise when participants returns to a box previously explored (empty) during that search (see figure 4.1).
- Retouch errors: These errors occur when participants returns to explore the same box explored at time $(t-1)$. A retouch error will also be classified as a between or within-search error depending on whether the box was empty or contained a token at time $(t-1$; see figure 4.1).

1 A search is referred here as the explorations of boxes within the whole set of boxes to find the hidden token.
2 A set consists of multiple searches and ends once the token has been found in each box presented on screen.

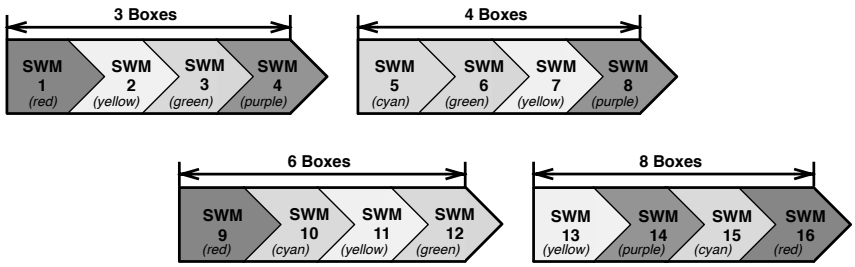

Figure 4.2: Sequence of spatial working memory sets given to each subject. The difficulty increased every four sets by increasing the number of boxes displayed on screen, so as to challenge that participants' working memory load.

- Double errors[3]: These errors appear when a participant makes an exploration-error that can be classified as both between and within-search error.

4.4.1 *Sequence*

The stimulus presentation sequence of the SWM task (shown in figure 4.2) was identical for every participant. It was composed of 4 sets per difficulty level (i.e. 4 sets of 3 boxes, 4 sets of 4 boxes, 4 sets of 6 boxes, 4 sets of 8 boxes) for a total of 16 sets. The colour of the boxes changed at the end of every set so as to observe whether colour affected the participants' performances.

4.5 METHODS: BEHAVIOURAL DATA ANALYSIS

The data analysis tools provided by Cambridge Research Ltd. enables to extract summary statistics about all the error types committed per difficulty level, for every participant. However, these are quite limited if one wishes to extract detailed information and summary statistics for every set or search throughout the task. We developed our own analysis tool to extract as much information and features as possible from the raw dataset of every participant (i.e. trial-by-trial actions). For each participant we extracted the following features:

- Between-search errors for each of the 16 sets presented.
- Within-search errors for each search of the 16 sets presented, for a total of 84 searches per participant.
- Retouch-error for each search of the 16 sets presented, for a total of 84 searches per participant.

3 Double errors were removed from the data-analysis framework provided by Cambridge Research Ltd. in recent versions of the SWM task.

- Double-errors for each search of the 16 sets presented, for a total of 84 searches per participant.
- The time required for solving a search for each 16 sets presented, for a total of 84 searches per participant.
- Time required for solving each of the 16 sets presented.
- An optimality score for each search of the 16 sets presented. The optimality score is defined as the number of unnecessary moves (i.e. explorations of boxes known not to hold the token — the sum of within-search, between-search and retouch errors). A score of zero on every set describes a participant that solved the task optimally, while a score below zero provides an estimation of the number of sub-optimal moves a participant has performed.

All the scores extracted from the raw participant data can also be summarized using conventional summary statistics at each of the four difficulty level (see figure 4.2). Participants' trial-by-trial analysis can then be used to fit our computational models and compare competing hypotheses for a given subject.

4.6 METHODS: COMPUTATIONAL MODELLING

We developed a series of computational models that replicate the the participants' performances at the spatial working memory task. A total of seven different models have been developed (one optimal model and six variants, one for each hypothesis).

4.6.1 *Optimal inference model*

The initial model uses optimal inference to solve the SWM task. In this framework, an optimal agent is required to find the target (token) while minimising the number of explorations (and errors) executed by making use of his current knowledge of the environment.

In probabilistic terms, this translates into computing the probability of finding the token '$r = 1$' (i.e. the token can either be present '1', or absent '-1') given that the agent selects the stimulus 's_i' (Box number 'i'), such that:

$$P(r_i = 1|s_i) = \begin{cases} 0 & \text{if } s_i \text{ was observed previously} \\ \frac{1}{n - |s\_observed|} & \text{otherwise} \end{cases} \tag{4.1}$$

where 'n' is equal to the number of boxes in the current set, '$s\_observed$' is the set of observed boxes (i.e. where the target cannot be found) and '$|s\_observed|$' defines the number of items in the set '$s\_observed$'.

For example, let's assume that 3 boxes are presented to the agent. The probability that each box holds the token is one over the total number of boxes available 'n'. That is, all the boxes have an equal probability to hold the token (e.g. $1/3$). Let's say that the agent then observes the box number 's_1', and finds the box to be empty. $P(r_1 = 1|s_1)$ is then equal to 0 and 's_1' is added to the set of observed boxes '$s\_observed$'. Since the probability $P(r = 1|s_1)$ is equal to zero, the total probability of finding the token is now one over the total number of remaining boxes (i.e. unobserved boxes s_2 & s_3). That is, the probability of finding the token is now $P(r_2 = 1|s_2) = P(r_3 = 1|s_3) = \frac{1}{n-|s\_observed|} = 1/2$ for each remaining box s_2 & s_3.

Boxes are then chosen using the Softmax function (see eq. 4.2), which defines the probability of choosing a stimulus as a function of the likelihood of finding the token $P(r = 1|s_i)$ and a temperature parameter 'ε' that controls the exploration and exploitation trade-off.

$$P(\text{Choose } s_i) = \frac{\exp\left(\frac{P(r_i=1|s_i)}{\varepsilon}\right)}{\sum_{x=1}^{n} \exp\left(\frac{P(r_x=1|s_x)}{\varepsilon}\right)} \tag{4.2}$$

4.6.2 *Modeling deficits*

In the following sections we alter the optimal inference model described above by introducing extra parameters that modify its performance at the SWM task. Each new computational model affects the SWM performance in different ways, leading to different types of errors.

4.6.2.1 *Model 1: Deficit of working-memory update*

In this model, we introduce a deficit in the update of working memory. In the initial optimal model, the information about the environment is held into working memory '$s\_observed$'. As the subject explores new boxes, the newly acquired information is updated into '$s\_observed$' to reflect the new probability of finding the token in the remaining boxes. We defined a deficit in the update of working-memory by introduc-

ing an extra parameter 'β_j' that controls whether novel information from a given trial (exploration of a box) is taken into account or dismissed:

$$P(r_i = 1|s_i) = \begin{cases} 0 & \text{if } s_i \text{ was observed} \wedge \forall x \in [0,1] > \beta_j \\ \frac{1}{n-|s\_observed|} & \text{if } \forall x \in [0,1] \leqslant \beta_j \end{cases} \tag{4.3}$$

where 'β_j' is the update threshold parameter of the individual 'j', and 'x' is a randomly generated value extracted on each trial within the range $[0, 1]$. If $x \leqslant \beta_j$, the stimulus observed 's_i' is not included in the list of observed stimuli '$s\_observed$'. That is, the working-memory is not updated with the newly acquired information gathered from the past exploration.

For example, let's assume that 3 boxes are presented to the agent, which chooses to observe the box 's_1'. This box is found to be empty. Before the agent updates this information a randomly generated value 'x' is drawn between zero and one. If this value 'x' is superior to the update threshold 'β_j' of that individual, then 's_1' is added to the list of observed stimuli '$s\_observed$' and '$P(r = 1|s_1) = 0$', as in the optimal inference model. However, if 'x' is inferior or equal to the update threshold of that individual 'β_j', then 's_1' is not added to the list of observed stimuli '$s\_observed$' resulting in all the stimuli 's_1,s_2,s_3' still being equally likely to hold the token on the next trial. This is equivalent to performing an action without taking the result into account, which would eventually lead to within-search errors.

4.6.2.2 *Model 2: Deficit of working-memory maintenance*

In this model we introduce a deficit in the maintenance of working memory. To model this deficit we decided to degrade the information held in memory as a function of the current working memory load of the participant. Specifically, the record of past observations $r_i = 1$ in this model decays exponentially to baseline (i.e. corrupted/lost information) as a function of memory load:

$$r_i(t+1) = \begin{cases} r_i(t) + \exp\left(-\frac{avail\_wm_j}{\omega_j}\right) & \text{if } s_i \text{ was found to be empty} \\ r_i(t) - \exp\left(-\frac{avail\_wm_j}{\omega_j}\right) & \text{if } s_i \text{ previously contained a token} \end{cases} \tag{4.4}$$

where '$avail\_wm_j$' defines the remaining number of items that can be stored in the working memory of the individual 'j', and 'ω_j' is the working memory maintenance parameter of this individual. Here we define the remainder of available memory '$avail\_wm_j$' as the difference between the minimum memory capacity required to complete the task (i.e. 8 items) and the current memory load of the individual '$|s\_observed|$'. The maintenance parameter 'ω_j', controls how rapidly the participants'

memory will degrade as a function of their current memory load (i.e. the larger 'ω_j' the faster the memory will degrade). When the reward value from an observed stimulus decays back to its original value (i.e. 0), the stimulus 's_i' is removed from the list of observed stimuli '$s\_observed$'. For a participant, this is equivalent to forgetting the result of previous explorations of that stimulus and will eventually lead to redundant explorations (i.e. between-search and within-search errors).

4.6.2.3 *Model 3: Inflexible learning*

A reminiscent component of learning deficits in psychotic patients, is their inability to flexibly adapt their behaviour to a changing environment (Goldberg et al., 1987; Morice, 1990; Ritter et al., 2004; Kim et al., 2009). We decided to model inflexible learning by introducing a learning rate parameter 'τ_j' that controls the amount of information that the participant takes into account on a given trial. That is, by gradually decreasing the learning-rate over time, the model will eventually become indifferent to novel information extracted from the environment:

$$P(r_i = 1|s_i) = \begin{cases} P(r_i = 1|s_i) + \alpha\,(0 - P(r_i = 1|s_i)) & \text{if } s_i \text{ is empty} \\ P(r_i = 1|s_i) + \alpha\left(\frac{1}{n-|s\_observed|} - P(r_i = 1|s_i)\right) & \text{otherwise} \end{cases} \tag{4.5}$$

and

$$\alpha = \exp\left(-\frac{t}{\tau_j}\right) \tag{4.6}$$

where 'τ_j' controls the gradient of the exponential decay. The smaller 'τ_j' the faster the model stops acquiring information, leading to between, within and retouch errors.

For example, let's assume that 3 boxes are presented to an inflexible agent ('$\tau_j = 0.01$') on trial 10. This agent chooses to observe 's_1', and finds an empty box such that '$P(r_1 = 1|s_1)$' should be updated to reflect the new probabilities of observing the token in that box from $1/3$ to 0. However, since the learning rate 'α' is equal to zero ($exp(-\frac{10}{0.01}) \approx 0$), the probabilities are not updated towards their new values, reflecting the relative inflexibility of the agent to take new information into account.

4.6.2.4 *Model 4: Overconfidence & data gathering bias*

In this model we introduce a data gathering bias such that the sampling is inappropriate for the task at hand, as is evidenced in the literature of *'jumping to conclusions'* (Broome et al., 2007; Freeman et al., 2008; Averbeck et al., 2011; Evans et al., 2012; Garety et al., 2013; Garety and Freeman, 2013; Freeman et al., 2014). For this hy-

pothesis, we decided to model the data gathering bias by increasing the temperature parameter 'ε_j' of the Softmax action selection process:

$$P(\text{Choose } s_i) = \frac{\exp\left(\frac{P(r_i|s_i)}{\varepsilon_j}\right)}{\sum_{x=1}^{n} \exp\left(\frac{P(r_x|s_x)}{\varepsilon_j}\right)}; \quad \varepsilon_j \to 1 \tag{4.7}$$

where a high 'ε_j' (i.e. 0.5 to 1) leads to sub-optimal action-selection. That is, participants will not rely on the information retrieved from the environment when deciding which novel stimuli to observe.

4.6.2.5 *Model 5: Attention & distraction*

This hypothesis suggest that patients with schizophrenia have a deficit of attention (Nuechterlein and Dawson, 1984; Kenny and Meltzer, 1991; Gold et al., 2003) and are often distracted (Oltmanns, 1978) during cognitive tasks. We implemented distractions by introducing a new parameter 'δ_j' that controls whether the participant was distracted on a given trial by assigning the value of a previously observed stimuli to the stimulus currently being observed:

$$r_i = \begin{cases} r_i & \forall x \in [0,1] > \delta_j \\ \forall s \in [1..n] \wedge s \neq n, r_s & \forall x \in [0,1] \leqslant \delta_j \end{cases} \tag{4.8}$$

where 'δ_j' is the distractibility threshold that controls whether the value of the stimulus 's_i' currently observed is correctly acquired. 'x' is a random generated value extracted on each trial within the range $[0, 1]$. When $x \leqslant \delta_j$, the value assigned to the currently explored stimulus will be this of another previously observed stimuli, as if the participant was distracted when presented the outcome of observing a box and confused it with another previously observed stimuli.

4.6.2.6 *Model 6: Failure to reduce task complexity*

Our last model tests the ability for patients to reduce the task complexity by only attending to features of the task that are relevant for its completion. This hypothesis comes from recent published literature (Gershman et al., 2010b) and meta-analyses of cognitive deficits in schizophrenia showing that patients are able to learn and solve simple tasks but tend to fail when the complexity of the task increases (Reichenberg and Harvey, 2007; Siegert et al., 2008; Gold et al., 2009). In the case of our spatial working memory task, the complexity of the task is reduced at each trial if the participant understands that each time a token is found the subsequent search for the new token will happen in a '$n - |s\_observed|$' subset. This strategy decreases efficiently

the size of the search by one for every token previously found. We implemented this in our model by introducing a new parameter 'κ_j' that controls whether the participant reduces their search to a subset of possible token positions known not to have previously held a token:

$$P(r_i = 1|s_i) = \begin{cases} 0 & \text{if } s_i \text{ was observed previously} \\ \frac{1}{n-|s\_observed|} & \text{otherwise, if } \kappa_j = 1 \\ \frac{1}{n} & \text{otherwise, if } \kappa_j = 0 \end{cases} \tag{4.9}$$

where 'κ_j' is a parameter that controls whether the participant 'j' does take previous observations into account to reduce the size of search space at time $(t+1)$. That is, performing a search on '$s\_unobserved$' rather than on the full set 'n' boxes. A subject not reducing the complexity of the task (i.e. $\kappa_j = 0$) will eventually re-explore previous stimuli known not to hold the token again and commit between-errors.

4.6.3 *Separability of hypothesis*

It is important that each of the hypotheses implemented by our computational models lead to different predictions in terms of performances at the task. In fact, if different models lead to the exact same performance profiles, all our models would fit equally well the performance of participants. That is, we would not be able to discern which hypothesis (i.e. computational model) is most likely to account for the performances observed in our patient groups. We performed a preliminary analysis of our models to test whether each implemented hypothesis leads to different performances at the task. To do so, each model was tested over a range of increasing parameter values so as to monitor how parameters influence performances as a function of the task difficulty (see figure 4.3). The results of this preliminary analysis demonstrate that each model lead to different performance profiles (i.e. the evolution of the number of errors as a function of the task difficulty and the number of errors achieved at each difficulty level). That is, each model lead to different predictions, which will later facilitate the distinction between competing hypotheses of cognitive dysfunction in schizophrenia (assuming participants make errors at the working-memory task).

4.6.4 *Model fitting*

For each of our six models (i.e. `WM update`, `WM maintenance`, `Inflexible learning`, `over-confidence`, `Distraction`, `Reduce complexity`), the performances of the model (i.e. between-search, within-search and retouch errors) are fitted to the performances

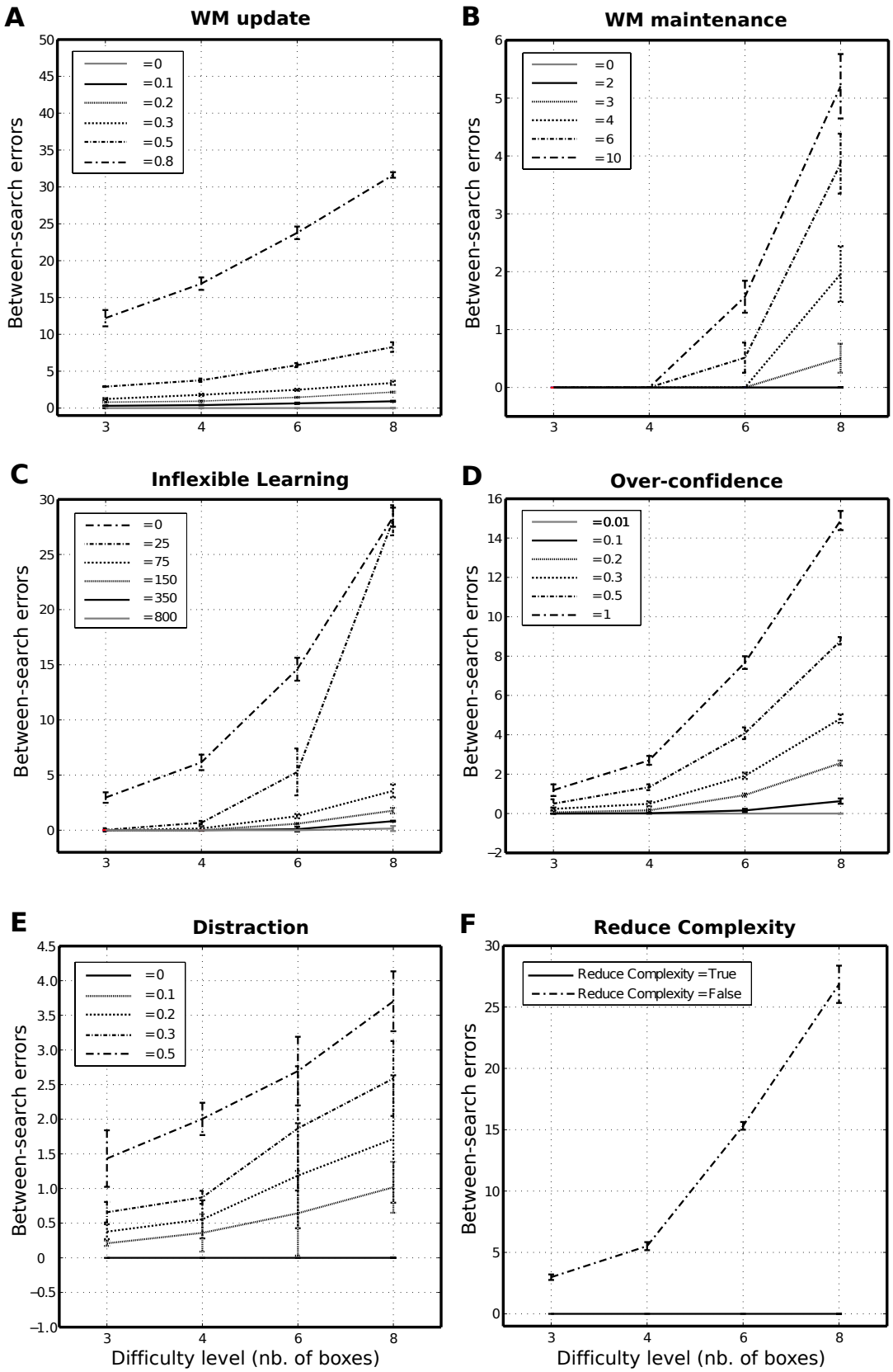

Figure 4.3: Preliminary analysis of separability between hypotheses. Each model was tested over a range of increasing parameter values to compare the performance profiles of different models. **(A)** Working Memory update model. **(B)** Working Memory maintenance model. **(C)** Inflexible learning model. **(D)** Over-confidence & gathering-bias model. **(E)** Distraction model. **(F)** Reduce complexity model.

of every individual participant. Using maximum likelihood, we find the parameters values of each model that best describes the participant's behaviour:

$$\hat{\theta}_{MLE} = \arg_{\theta} \max \mathcal{L}\left(\theta \mid Between_{Err(1:16)}, Within_{Err(1:16)}, Retouch_{Err(1:16)}\right) \quad (4.10)$$

where $\mathcal{L}\left(\theta \mid Between_{Err(1:16)}, Within_{Err(1:16)}, Retouch_{Err(1:16)}\right)$ denotes the likelihood of the data under the model, θ are the model parameters, '$Between_{Err(1:16)}$', '$Within_{Err(1:16)}$' and '$Retouch_{Err(1:16)}$'are the between-search, within-search and retouch errors performed at each of the 16 sets of the task. The likelihood is computed by running each model 800 times for a given set of parameter values. Using the performance profiles extracted after all the iterations, we calculate the probability distribution of getting an error (between, within or retouch error) at each set of the task. The maximum likelihood is then given by the parameters values that gives the highest probability of resulting in the observed participant performances (errors) at each of the 16 sets.

4.6.5 *Model comparison*

Since the models varied with respect to their implementation and their number of free parameters (one parameter for overconfidence and two parameters for every other model), we used the *'Bayesian Information Criterion'* (BIC) to compare different models and avoid choosing a model that over-fits the data. This technique allows to score the fit of a given model to the experimental data while penalising this score for added model complexity (i.e. number of free parameters). This enables us to compare different models and select those that explain the best our dataset. The BIC metric is given by:

$$BIC = -2 \cdot \ln(\mathcal{L}) + k \cdot \ln(n) \quad (4.11)$$

where $\mathcal{L}$ defines the likelihood of generating the experimental data from the model, *'k'* represent the number of free parameters in that model and *'n'* is the number of data points available when fitting the experimental data. The model resulting with the lower BIC metric is the one to be preferred as this model provides the best trade-off between the fit to the experimental data and the model complexity (i.e. less complex model avoid over-fitting and lead to better generalisation).

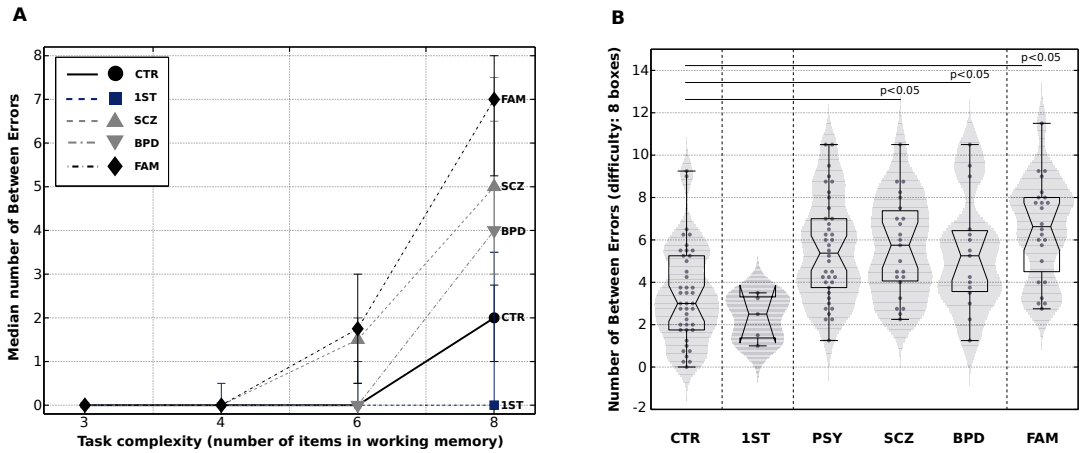

Figure 4.4: **(A)** Between-search errors at the SWM task for each group at increasing difficulty levels (i.e. 3, 4, 6 and 8 items). Error bars depict 95%-bootstrapped confidence intervals. **(B)** Boxplot representing the distribution of between-search errors made at the highest difficulty level (8 items) for each of our participant groups. Shaded area represent the smoothed distribution of between-search errors for the group and individual data points depict the mean number of between-search error for each individual of that group (i.e. mean number of errors of the last 4 sets). The *PSY* group is a composite group made from the chronic schizophrenia and bipolar disorder groups.

4.7 RESULTS

4.7.1 *Behavioural data*

We analysed independent measures of SWM performances using repeated-measures analysis of variance (repeated-measures ANOVA) for the 16 different sets displayed to the participants (i.e. 4 sets in each of the 4 difficulty levels). Mauchly's test of sphericity was performed prior to the repeated-measure ANOVA to check for sphericity assumptions. Greenhouse-Geisser correction was applied when assumptions were violated. Post-hoc tests and corrections were performed using 10,000 Monte Carlo permutations per statistical test.

4.7.1.1 *Error analysis*

Between-search errors: The Mauchly's test revealed that the sphericity assumption was violated for between-search errors ($\chi^2 = 352.149$, $p<0.001$). Corrected analysis revealed a main effect of difficulty on the number of between-search errors ($F(1.348,40.234) = 116.507$, $p<0.001$). Analysis of interaction between difficulty level and groups (difficulty × group) was significant ($F(5.394,140.234) = 4.141$, $p<0.005$), suggesting that the groups were affected differently by difficulty levels. Sets with similar difficulty were pooled to extract a single measure of between-search errors per difficulty level. A following

analysis was performed on this measure to identify which difficulty levels were significantly different between our participants' groups. The analysis revealed a significant mean difference across groups for the highest difficulty level (i.e. 8 items, see Figure 4.4A — $F(4,104)=4.919$, $p=0.001$). Figure 4.4A illustrates how increasing the working memory load affects the number of between-search errors for all groups.

Post-hoc analysis at the highest level of difficulty (i.e. 8 items — Figure 4.4B) revealed significant differences between groups for chronic schizophrenia *vs.* controls (2-tailed MC permutation tests: $p=0.0242$), bipolar disorder *vs.* controls (2-tailed MC permutation test: $p=0.0125$) and family relatives *vs.* controls (2-tailed MC permutation test: $p<0.01$). No significant difference was found between first episode psychosis and healthy controls nor between chronic schizophrenia *vs.* bipolar disorder (2-tailed MC permutation test: *p=n.s.*), or chronic schizophrenia *vs.* family members (2-tailed MC permutation test: *p=n.s.*). No significant difference in between-search error was found within the family member group for translocation carriers vs. non-carriers (2-tailed MC permutation test: *p=n.s.*).

Within-search errors: Analysis of within-search error using correction for sphericity violation (Mauchly's test $\chi^2 = 194.266$, $p<0.001$) revealed a significant effect of difficulty on within-search errors across groups *($F(1.587,165.044)=8.823$, $p=0.001$)*, but found no significant interaction between difficulty and groups ($\texttt{difficulty} \times \texttt{group}$; *$F(6.348,165.044)=0.659$, p=n.s.*). This suggests that difficulty affects the mean number of within-errors across all groups, but that the mean number of within-errors is not significantly different between our groups. Post-hoc analysis within family members revealed that the translocation-carrier status had no significant effect on the mean number of within-search errors *($F(3.176,318)=0.879$, p=n.s.)*.

Retouch errors: Analysis of retouch-errors using correction for sphericity violation (Mauchly's test $\chi^2 = 20.403$, $p<0.005$) revealed no significant effect of difficulty on the number of retouch errors *($F(2.619,272.395)=1.373$, p=n.s.)*. That is, retouch errors remained at similar levels throughout the task. No significant interaction was found between difficulty level and groups *($\texttt{difficulty} \times \texttt{group}$; $F(10.477,272.395)=0.797$, p=n.s.)*. Post-hoc analysis within family members revealed no translocation-carrier effect on the mean number of retouch errors *($F(5.11,318)=1.475$, p=n.s.)*.

Remaining variables: Since analyses of within-search and retouch errors revealed no significant difference between groups, no further analyses were performed on these variables. Double errors were removed from further analyses as these result from

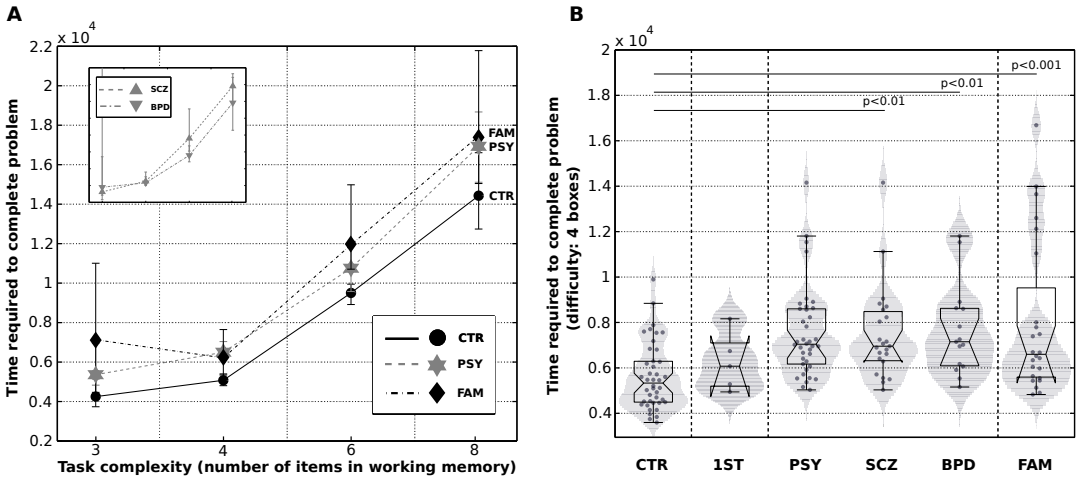

Figure 4.5: **(A)** Group response times at the SWM task for increasing difficulty levels (i.e. 3, 4, 6 and 8 items). Error bars depict 95%-bootstrapped confidence intervals. The *PSY* group is a composite group made from the chronic schizophrenia and bipolar disorder groups. **(B)** Boxplot representing the distribution of the time required to finish a set at the 2^{nd} difficulty level (4 items) for each group. The shaded area represent the smoothed distribution of required time to finish a set for each group. Individual data points depict the mean time required for each individual of that group (i.e. mean of the 4 sets with difficulty 4).

errors that can be categorised as both between and within-search error. Since within-search errors are not significantly different across groups, double errors would not have conveyed further information than between-search errors alone. The optimality measure was also excluded from our analysis as it is a compound feature resulting from participants' within-search, between-search and retouch errors. Since significant differences were observed only for between-search errors, the optimality measure would have been virtually identical to the number of between-search errors and lead to redundant analyses.

4.7.1.2 *Analysis of time variables*

Time required to solve a set per difficulty level: Analysis of the time required to solve a set using correction for sphericity violation (Mauchly's test $\chi^2 = 222.481$, p<0.001) revealed a significant effect of difficulty across all groups *(F(*1.346,140.007*)*= 41.366, *p<0.001* — see Figure 4.5A). Sets with similar difficulty were pooled to extract a single measure of the time required to solve a set at each difficulty level. A following analysis was performed on this measure to identify which difficulty levels were significantly different between our groups. This revealed that the mean time required to complete a set was significantly different across groups when 4 items were present (*F*(4,104)=2.707, *p=0.034*) and a trend towards significance when 3 items were displayed (*F*(4,104)=2.375, *p=0.057*). Post-hoc analysis using correction

for sphericity violation (Mauchly's test $\chi^2 = 228.036$, p<0.001) revealed a significant effect of difficulty within the family members on the time required to solve a set *(F(1.345,318)=38.82, p<0.001)*, but no interaction between difficulty and translocation carrier status ($\texttt{difficulty} \times \texttt{translocation}$ — *(F(2.69,318)=0.523, p=n.s.)*.

Post-hoc analysis on sets containing 3 items revealed significant differences between chronic schizophrenia *vs.* controls (2-tailed MC permutation tests: p=0.0046), bipolar disorder *vs.* controls (2-tailed MC permutation test: p=0.003) and family relatives *vs.* controls (2-tailed MC permutation test: p<0.001). Analysis of the time required to solve a set when 4 items were displayed (see Figure 4.5B) revealed significant differences between chronic schizophrenia *vs.* controls (2-tailed MC permutation tests: p<0.001), bipolar disorder *vs.* controls (2-tailed MC permutation test: p<0.001) and family relatives *vs.* controls (2-tailed MC permutation test: p<0.001). No significant difference was found between first-episode psychosis and controls (2-tailed MC permutation test: *p=n.s.*). With sets of 3 or 4 items, no significant difference were found between chronic schizophrenia *vs.* bipolar disorder (2-tailed MC permutation test: *p=n.s.*) or schizophrenia *vs.* family members (2-tailed MC permutation test: *p=n.s.*).

Time required for search completion: Analysis of the time required to solve a search was performed using a multivariate analysis of variance. This revealed no difference across groups *(F(68,364)=1.12; p=n.s.)*. Similarly, no significant differences were found between family members with and without translocation *(F(34,182)= 1.088; p=n.s.)*. These findings are in line with earlier analyses of within-search errors suggesting that patients do not make significantly more within-search errors than controls. That is, if patients performed more within-search errors than controls, the average time required to solve the task should have been proportional to the number of within-errors (i.e. extra trials resulting in more time spent to solve the search).

4.7.1.3 *Correlation with symptoms*

Significant correlations were found between the number of between-search errors of participants at the highest difficulty level and the PANSS total score ($\rho = 0.256$, p=0.008), and the PANSS negative scores ($\rho = -0.195$, p=0.045). No significant correlations were found between the number of between-search errors and GAF score ($\rho = -0.063$, *p=n.s.*), PANSS positive score ($\rho = 0.087$, *p=n.s.*), SANS score ($\rho = 0.059$, *p=n.s.*, YMRS score ($\rho = 0.111$, *p=n.s.*) or HAM-D scores ($\rho = 0.098$, *p=n.s.*).

Within family members, the translocation status was found to correlate with the GAF score ($\rho = -0.456$, $\rho = 0.025$), PANSS total score ($\rho = 0.466$, p=0.022), PANSS positive

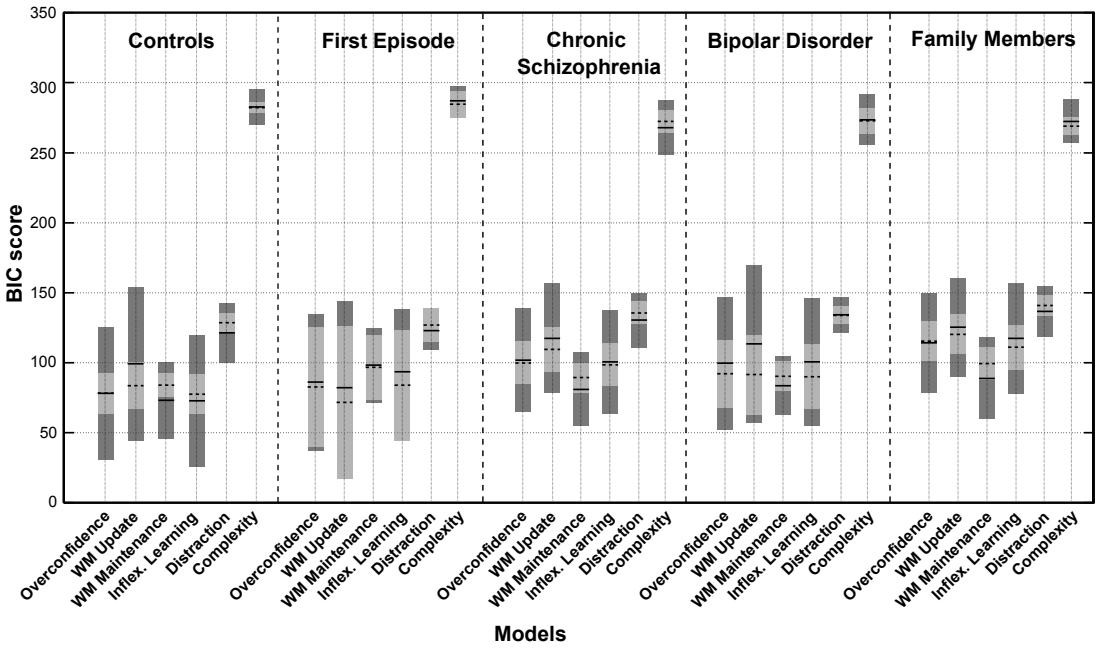

Figure 4.6: Comparison of models using the Bayesian Information Criterion for each group. For each group, the dashed-horizontal line and the plain horizontal line denote the mean and median BIC scores for the best fit of each model (lower is better). The standard error centered around the mean is denoted by the light-grey area, while the standard deviation (centered around the median) is denoted by the dark-grey shaded area. Within each group, the model with the lowest mean and median is the model that best captures the performances of the individuals of that group.

score ($\rho = 0.410$, p=0.047), YMRS score ($\rho = 0.553$, p=0.005).

In summary, we found that the chronic schizophrenia, bipolar disorder and family member groups were significantly impaired in working-memory when compared to healthy controls. This difference was most pronounced at challenging memory loads (i.e. 8 items). These groups were also found to be significantly slower than controls at the easiest memory loads (i.e. 3 & 4 items), which could not be accounted for by the number of errors made by the participants. Interestingly, the translocation status of family members was not found to predict working-memory performances at the task. Finally, the first episode group appeared to be relatively unimpaired at the working-memory task, and performed similarly to healthy controls throughout the task.

4.7.2 *Computational analysis*

Our models were then fitted to the experimental data of each individual participant. We present in this section the result of these analyses. It is worth mentioning that

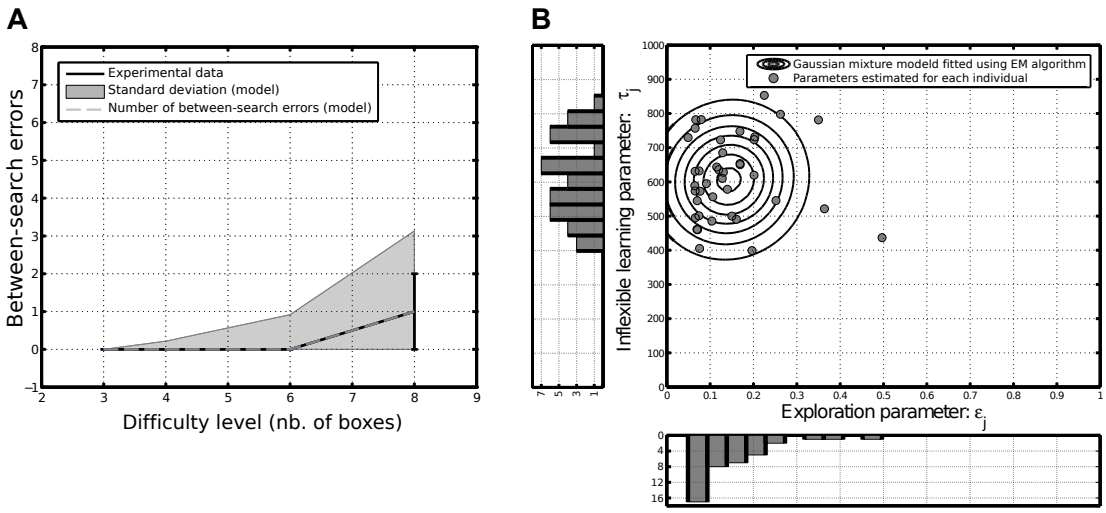

Figure 4.7: Model fit and estimated parameters for the healthy control group using the *"Inflexible Learning"* model. **(A)** The modeled group performance was generated from the individual performance profile of every subject using individually estimated parameter values. **(B)** Estimated parameter values for each healthy control subject (grey dots). Black elipses denote the contour of the probability density (gaussian mixture model) of the estimated parameters for the group. The smaller the radius of the elipse the higher the probability density.

while our models are fitted to the performance of every individual (i.e. between-search, within-search and retouch errors), the timing data extracted from the behavioural data was not used to fit our models since no timing components were accounted for in the model.

4.7.2.1 *Model fit and comparison*

Our six models were fitted to each of the 109 participants in this study in order to find the parameter values that best describe each individual performance profile. Once the parameters found for each model and individual, a complete model comparison was performed in order to assess which of the six hypothesis accounts best for the performance profiles of every group (see Figure 4.6).

Healthy controls: Analysis of the model fit for the healthy control group suggests that participants are best described by the *"Inflexible Learning"* model, (see figure 4.6). That is, although the mean BIC score is not significantly different between the two models (*"Inflexible Learning"* vs. *"WM Maintenance"*), on average the *"Inflexible Learning"* model was the hypothesis that could account best for the participant's performances (i.e. no errors or low amount of between-search errors). The fit of this model to the group's performance can be seen on figure 4.7A, where the performance profile of the model is made from the composite performance profile of all the individual

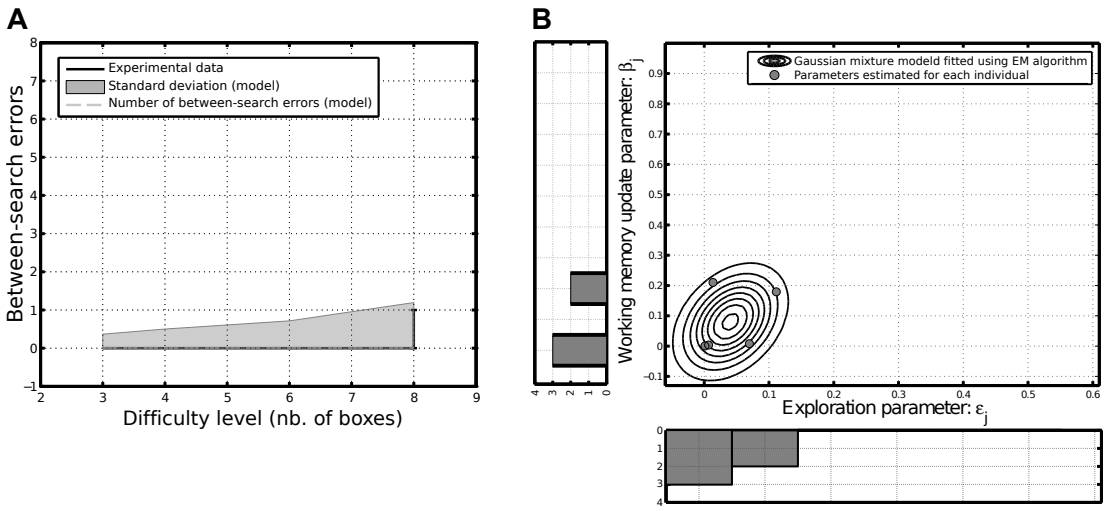

Figure 4.8: Model fit and estimated parameters for the first-episode group using the *"Working-memory update"* model. **(A)** The modeled group performance was generated from the individual performance profile of every subject using individually estimated parameter values. **(B)** Estimated parameter values for each healthy control subject (grey dots). Black elipses denote the contour of the probability density (gaussian mixture model) of the estimated parameters for the group. The smaller the radius of the elipse the higher the probability density.

participants of the group using each participants' estimated set of parameters. The figure demonstrates how closely the model can match the performance of the whole group, both in terms of median performance (number of between-search errors) and in terms of standard deviation over increasing difficulty levels.

We then analysed the distribution of parameter values for the *"Inflexible learning"* model in order to find whether the parameters of participants that made errors were significantly different from those who did not. The analysis revealed that parameter estimates were quite similar across participants. For example, parameter values of inflexibility 'τ_j' were clustered around intermediate-to-high levels of inflexibility for all subjects. That is, all participants were consistently acquiring information from the environment throughout the task. Healthy controls were represented by low temperature values 'ε_j', suggesting a relatively low exploration/exploitation trade-off. That is, participants were generally exploiting the information acquired from the environment. This exploration parameter 'ε_j' was found to correlate significantly with age (Pearson $r = 0.414$, $p = 0.007$), current IQ (Pearson $r = -0.415$, $p = 0.007$), PANSS negative scores (Pearson $r = 0.642$, $p < 0.001$) and the SANS (Pearson $r = 0.53$, $p = 0.001$).

First episode psychosis : Analysis of the model fit for the first episode group suggests that participants are best described by the *"Working-memory update"* model, (see figure 4.6). That is, on average the *"Working-memory update"* model was the hypothesis that explained best the participant's behaviour (i.e. no-errors or low amount of errors). The fit of this model to the group's performances can be seen on figure 4.8A, where the performance profile of the model is made from the composite performance profile of all the individual participants of the group using each participants' estimated set of parameters. The figure demonstrates how closely the model can match the group's performances, both in terms of median performances (number of between-search errors) and in terms of standard deviation over increasing difficulty levels.

Analysis of the distribution of parameter values for the *"Working-memory update"* model revealed that participants were clustered around low parameter values of WM update 'β_j'. That is, participants were updating their working-memory on the majority of trials using novel trial-by-trial information gathered from the environment (i.e. low 'β_j' threshold). First episode participants appear relatively well described by low temperature values 'ε_j', suggesting a relatively low exploration/exploitation trade-off. That is, participants were generally exploiting the information retrieved from the environment. The exploration parameter 'ε_j' was found to correlate significantly with pre-morbid IQ (Pearson $r = -0.972$, $p = 0.006$), but was not correlated with any of the clinical symptom scales (i.e. PANS, SANS, GAF, YMRS, HAM-D). The working-memory update parameter 'β_j' was found to correlate significantly with the PANSS positive symptom score (Pearson $r = -0.886$, $p = 0.045$).

Chronic schizophrenia, bipolar disorder and family members Analysis of the model fit for chronic schizophrenia, bipolar disorder and family members suggests that participants were best described by the *"Working-memory maintenance"* model, (see figure 4.6). That is, on average the *"Working-memory maintenance"* model was the hypothesis that explained best the participant's performances (i.e. moderate-to-high number of between-search errors). Chronic schizophrenia, bipolar disorder and family members groups were pooled together for this analysis since the behavioural analysis suggested that they all have similar performance profiles and that the model comparison suggest that the same hypothesis accounts best for their performance. The fit of the model to the group's performance can be seen on figure 4.9A, where the performance profile of the model is made from the composite performance profile of all the individual participants using each participants' estimated set of parameters. The figure 4.9A demonstrates how closely the model fits the behavioural data, both in terms of median performances (number of between-search errors) and in terms of

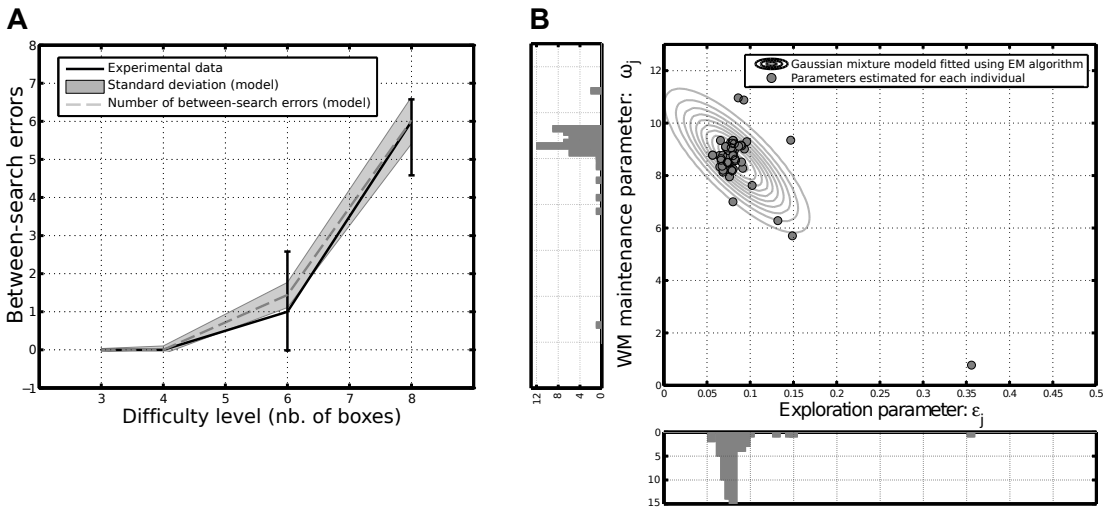

Figure 4.9: Model fit and estimated parameters for the chonic schizophrenia, bipolar disorder and family member groups pooled together using the *"Working-memory mainteance"* model. The three groups were pooled together since behavioural-analysis revealed these groups were similar in terms of between-search errors and since the same model was found to account best for these groups performance profiles. **(A)** The modeled group performance was generated from the individual performance profile of every subject using individually estimated parameter values. **(B)** Estimated parameter values for each healthy control subject (grey dots). Black elipses denote the contour of the probability density (gaussian mixture model) of the estimated parameters for the group. The smaller the radius of the elipse the higher the probability density.

variance over increasing difficulty levels.

Analysis of the distribution of parameter values for the *"Working-memory maintenance"* model revealed that most participants were clustered around intermediate-to-high parameter values of WM maintenance 'ω_j'. That is, working memory was degrading at a faster rate when working memory load was high (i.e. participants were forgetting earlier information rapidly on difficult sets). The participants were well modelled by low temperature values 'ε_j', suggesting a relatively low exploration/-exploitation trade-off. This suggests that participants were generally exploiting the information retrieved from the environment, but forgot earlier information as the task started to challenge working-memory load. The exploration parameter 'ε_j' estimated for each participant was found to correlate significantly with age (Pearson $r = 0.345$, $p = 0.005$) and current IQ (Pearson $r = -0.344$, $p = 0.005$) but was not correlated with any of the clinical symptom scales (i.e. PANS, SANS, GAF, YMRS, HAM-D).

4.8 DISCUSSION

4.8.1 *Behavioural results and intepretation*

In this chapter we studied the WM performances of a variety of patient groups in a spatial working memory task. The literature on spatial working memory in patients with first episode psychosis (Hutton et al., 1998; Wood et al., 2003; Joyce et al., 2002; Pantelis et al., 2009), chronic schizophrenia (Park and Holzman, 1992; Pantelis et al., 1997; Tek et al., 2002; Saperstein et al., 2006; Pantelis et al., 2009; for a review see Lee and Park, 2005; Piskulic et al., 2007), and bipolar disorder (Kéri et al., 2001; Pirkola et al., 2005; Badcock et al., 2005; Glahn et al., 2006), already identified that patients tend to show WM deficits when compared to healthy controls. Particularly, within the studies that used the same spatial working memory task presented in this chapter (i.e. CANTAB spatial working memory task — Pantelis et al., 1997; Hutton et al., 1998; Joyce et al., 2002; Wood et al., 2003; Badcock et al., 2005; Pantelis et al., 2009), researchers consistently found significant impairments in between-search errors when patients were compared to controls. The strategy scores provided by the CANTAB analysis tools were found to be correlated with between-search errors in two studies (Hutton et al., 1998; Joyce et al., 2002), but detailed analysis suggests that the difference in performance relies on spatial span rather than strategy use (Pantelis et al., 1997; Piskulic et al., 2007). In this study, we designed a refined data analysis tool to extract between-search, within-search, retouch, and double errors for every set and search of the task, as well as novel features such as response time and compound optimality scores. The aims of this detailed data extraction tool were two-fold: 1) To observe whether patients with different diagnoses could be dissociated by a specific subset of performance features that might have been overlooked using summary statistics; 2) To provide detailed experimental data to our computational model, thereby greatly improving the fit of the models to behavioural data, which would not have been possible with the summary statistics alone.

Similarly to previous studies using the CANTAB spatial working memory task (Pantelis et al., 1997; Hutton et al., 1998; Joyce et al., 2002; Wood et al., 2003; Badcock et al., 2005; Pantelis et al., 2009), we found significant impairments in between-search errors between groups, but no impairments were found for the remaining error types (i.e. within-search, retouch, double errors). Specifically, we found a significant increase in between-search errors for the highest difficulty level in chronic schizophrenia, bipolar disorder and family members when compared to healthy controls. However in contrast with previous work (Badcock et al., 2005), we found that these groups did

not differ from each other in terms of performances. That is, in our study bipolar patients were impaired to a similar degree with chronic schizophrenia patients and family members (irrespective of their translocation status). Also unlike previous studies (Pantelis et al., 2009), we found no significant impairment in SWM performances of first episode patients when compared to controls. We suspect that the relatively small sample-size of our first episode sample (n=5) might not have been sufficient to reveal significant impairments.

Further to the impairments observed in between-search errors, we found a significant difference between chronic schizophrenia, bipolar disorder, and the family member groups to that of controls at the time required by a participant to solve a set (one of our novel performance features). Specifically, we found that the chronic schizophrenia, bipolar and family members were significantly slower than healthy controls at the easiest sets of the task, when the working memory load was relatively low (3 & 4 items). Slower response times at the beginning of the task could result from an increased number of errors in this population, however the analysis of between-search errors reveals no differences in terms of errors at the early stages of the task. This suggests that the increase in response time does not stem from errors made by the participants. Intriguingly, this difference disappears at higher memory load, when participants do make significantly more errors than controls. This suggests that patients are slower at making decisions than controls at the early stages of the task, but then become faster than controls since patients make more errors but still manage to solve a set in the same amount of time than controls. In light of these findings, we posit that patients are slower in early stages simply due to being cautious until they are confident that they have correctly acquired the rules of the task. We hypothesize that three distinct mechanisms could explain why patients are responding faster than controls during later stages of the task:

1. Patients gradually become overconfident in later stages of the task, leading to faster but uncarefully planned decisions resulting in more errors.

2. Patients' attention level deteriorate due to the repetitiveness of the task, tiredness, or simply because the novelty of the task has worn. Reduced attention levels would lead to hasty responses and an increased amount of errors.

3. Patients start making errors at the task due to a more taxing load on working memory, resulting in an increased speed of execution due to frustration.

4.8.2 *Computational analysis*

In this chapter we assessed a variety of computational models to address which of many competing hypothesis of cognitive dysfunction in schizophrenia, is most likely to account for the performance deficits observed in a spatial working memory task. First we developed a computational model that uses probabilistic inference to solve the SWM task in an optimal manner and then introduced simple alterations to model the hypotheses of interest (i.e. overconfidence, WM update deficit, WM maintenance deficit, Inflexible learning, distraction to irrelevant stimuli, deficit in reducing the complexity of the task to the relevant components). Interestingly, each of these models led to highly dissociable performance profiles at the SWM task.

4.8.2.1 *Healthy controls & first episode psychosis:*

Both the healthy control and first episode groups made relatively few number of between-errors at the task. However, the model comparison suggests that the performance of the first episode group is best accounted for by a deficit of WM update, while healthy controls are best described by the inflexible learning model. That is, although the performance of first episodes was qualitatively similar to that of controls, different models were selected as more likely to account for their respective performances. However, we would advise caution while interpreting these results in healthy controls and first episode patients. In fact, while our models were able to make different predictions when working-memory performance was impaired, all our models could account equally well for performances when few or no errors were made by participants. We therefore suggest that our models are better suited to compare and explain performance deficits when participants do make errors at the task.

4.8.2.2 *Bipolar disorder, DISC1 family & chronic schizophrenia :*

Model comparison for the bipolar, family members and the chronic schizophrenia group revealed that their performances were better accounted for by the working memory maintenance model. This is in line with the conclusions reached by recent reviews and meta-analyses of generalised cognitive deficits in schizophrenia (Reichenberg and Harvey, 2007; Gold et al., 2009). These argued that memory maintenance and manipulation appear most likely to result in poor WM performances since working memory capacity is relatively spared in schizophrenia (Goldberg et al., 1993; Kolb and Whishaw, 1983; Park et al., 1995; Tamlyn et al., 1992 [4]), that memory encoding deficits could not account for poor performances (Tek et al., 2002) and that decreased

4 Although some authors disagree (Aleman et al., 1999; Dickinson and Ramsey, 2007; Gold et al., 2010)

attention was also unable to account for the generalised cognitive impairments observed in patients (Goldberg et al., 1987; Gold et al., 2009).

Maintenance of working memory has been thoroughly documented from the early work of Goldman-Rakic (1995) and more recently Vijayraghavan et al. (2007; for a review see Cools and D'Esposito, 2011) as requiring precise levels of dopamine to WM dlPFC neurons for correct WM maintenance. That is, too little or too much dopamine release to dlPFC WM neurons lead to incorrect updating or maintenance of information in memory (Vijayraghavan et al., 2007; Cools and D'Esposito, 2011). Interestingly, abnormal dlPFC activation has been found in schizophrenia during WM tasks (Manoach et al., 1999; Perlstein et al., 2001; Abi-Dargham et al., 2002; Rodríguez-Sánchez et al., 2005) and more recently impaired fronto-striatal prediction-error signals were also identified in patients (Corlett et al., 2007b). These appear to suggest that impaired DA signalling found in schizophrenia (Howes and Kapur, 2009) or bipolar disorder (Abler et al., 2008) may be able to account for their poor WM performances. Early computational studies have attempted to explain away the role of DA in WM as a gating mechanism (Cohen et al., 1996; Durstewitz et al., 1999; Braver et al., 1999; Braver and Cohen, 1999, 2000; Durstewitz et al., 2000a,b; Frank et al., 2001; Durstewitz and Seamans, 2002; Gruber et al., 2006; O'Reilly and Frank, 2006; Todd et al., 2008; Badre and Frank, 2012), whereby DA helps to *"gate"* relevant information to working memory through phasic activity during encoding of stimuli, while tonic DA activity *"locks"* the information in memory to prevent corruption from external distractors or internal cortical noise. However, recent computational studies now tend to approach WM maintenance deficits as a imbalance between excitation and inhibition (E/I) at the level of neuronal micro-circuits (Loh et al., 2007; Cano-Colino and Compte, 2012; Murray et al., 2012). For example, Murray et al. (2012) demonstrated that a cortical micro-circuit can accurately encode spatial information and sustain the activity of a pool of neurons (maintenance of information) over time, as observed experimentally (Goldman-Rakic, 1995). However when reducing inhibition (disinhibition), encoding of information was still possible but resulted in less accurate sustained activity that was prone to corruption by external distractors close to the originally encoded information. Disinhibition has been previously documented in schizophrenia by Lewis and Hashimoto (2005) and is thought to stem from NMDAr hypofunction of inhibitory interneurons (Murray et al., 2012). While these two types of models can equally account for the WM maintenance deficits observed in patients, both support different hypotheses of the aetiology of schizophrenia. Interestingly however, these hypotheses are not mutually exclusive (Jentsch and Roth, 1999). Earlier computational studies (Durstewitz et al., 1999; Brunel and Wang, 2001;

Durstewitz et al., 2000a,b; Durstewitz and Seamans, 2002, 2008; Seamans et al., 2001; Tanaka, 2006) suggest that DA can modulate inhibition through NMDA activation. Specifically, Durstewitz et al. (1999, 2000a,b) argue that DA can enhance NMDAr conductances, resulting in an increased robustness of the sustained activity to distracting stimuli or internal cortical noise. While, Murray et al. (2012) argue for decreased NMDAr conductances on inhibitory interneurons, both models could theoretically result in imbalanced E/I in cortical micro-circuits, leading to identical impairments during maintenance of WM information. These hypotheses deserve further investigation to identify which of those two E/I imbalances might be present in schizophrenia.

4.8.3 *Limitations*

While we did observe significant differences across groups in between-search errors, our participants demographics suggest a significant difference for age, gender ratio and IQ (both current and pre-morbid) in the DISC1 family member group. Further analysis within these covariates revealed that age was negatively correlated to current IQ in this subgroup (i.e. family members are on average 10-15 years older that the average participant of the other groups), which in retrospect could be explain part of the drop in IQ observed between family members and the control group. Age was removed as a covariate from further analysis as required per the rules of the analysis of covariance (ANCOVA) to avoid statistically redundant features. An ANCOVA was performed to control for current IQ, gender ratio and revealed that no significant difference in between-search errors between family members and healthy controls could be found once the covariates were included as regressors. Particularly, current IQ was found to account for all the performance differences between family members and healthy controls. This would tend to suggest that no significant difference in performance truly exist between family members and healthy controls, and that the difference reported in the result section stemmed from the lower current-IQ of family members. However, we want to express caution regarding the interpretation of this covariate analysis. In fact, measures of current IQ are computed from a composite of scores made in a battery of standardized cognitive tests used to assess independent processes, one of which being working memory. Furthermore, although tasks are designed in such a way as to test independent components, tasks that assess planning and reasoning will always require use of working memory to some degree. That is, to a certain degree, part of the IQ score of every participant will reflect their intrinsic performance in working memory. Therefore, using IQ as a covariate for a measure or performance in working memory would be inappropriate and similar to using working-memory performance as a regressor for itself. We believe, this could

explain why differences between family members and controls disappear when controlling for IQ. Further investigation is required to identify whether the effect we observed in family member is veridical. Ideally, future studies in DISC1 family members should attempt to carefully match the participants demographic variables to this of healthy controls. In schizophrenia, a meta-analysis of SWM performances (Piskulic et al., 2007) revealed similar limitations, namely a significant correlation between IQ of schizophrenia patients and SWM performances in 56% of the reviewed literature. In our case however, ANCOVA analyses were not performed for the first episode, chronic schizophrenia and bipolar disorder groups since post-hoc analyses revealed that pre-morbid IQ, current IQ and age were matched to those of healthy controls.

The original goal of this study was to identify which of the most commonly disputed set of hypothesis for cognitive dysfunction in schizophrenia is most likely to account for our patients' performances in a SWM task. As a result, hypotheses were tested independently of each other on all participants, one at a time. One possible extension of our computational analysis would be to test a combination of hypotheses on the participants' data. That is, in our current analysis, only one model at a time was fitted to the participant data, but it is possible that a combination of models (e.g. WM maintenance model with inflexible learning) might have improved the fit of the participants' data and yield novel predictions. None of our computational models challenged WM capacity as others have done previously (Collins and Frank, 2012). However reviews and meta analyses suggest that WM capacity is relatively spared or within normal range in patients with schizophrenia (Reichenberg and Harvey, 2007). Meta-analysis of neuropsychological impairment in schizophrenia and relatives found that relatives of schizophrenia and schizotypal patients show mild to moderate impairment at maintenance & manipulation of WM (Reichenberg and Harvey, 2007). This is in line with the findings of our model comparison for family members and chronic schizophrenia (Reichenberg and Harvey, 2007; Lee and Park, 2005), since deficits are still present when encoding of information is optimized (Tek et al., 2002).

4.9 CONCLUSION

Similarly to previous studies using the CANTAB spatial working memory task (Pantelis et al., 1997; Hutton et al., 1998; Joyce et al., 2002; Wood et al., 2003; Badcock et al., 2005; Pantelis et al., 2009), we found significant impairment of working memory in chronic schizophrenia, bipolar disorder and family members. Although in comparison with the previous literature (Gasperoni et al., 2003; Porteous et al., 2006), we did

not observe an association between translocation status and working memory performances. Interestingly however, our extended data analysis suggest that these groups require more time to solve a set in earlier trials when compared to controls and this difference cannot be accounted for by the number of errors performed by patients.

Our computational analysis reinforces previous suspicions that WM maintenance is probably responsible for the generalised cognitive deficits observed in schizophrenia (Reichenberg and Harvey, 2007). Further studies are now required to identify the mechanisms leading to poorer WM maintenance in these patients. Two theories prevail, the WM gating hypothesis (Cohen et al., 1996; Durstewitz et al., 1999; Braver et al., 1999; Braver and Cohen, 1999, 2000; Durstewitz et al., 2000a,b; Frank et al., 2001; Durstewitz and Seamans, 2002; Gruber et al., 2006; O'Reilly and Frank, 2006; Todd et al., 2008; Badre and Frank, 2012) and the cortical microcircuit imbalance (Loh et al., 2007; Cano-Colino and Compte, 2012; Murray et al., 2012). The former theory suggests that abnormal dopaminergic transmission to the dlPFC leads to a failure to gate and maintain information in memory when faced with distractors, while the latter suggests that excitatory/inhibitory imbalances at the level of cortical microcircuits lead to shallow bump-attractor states that are prone to disruption. Further investigation is required to identify the neural basis of WM maintenance deficits in schizophrenia.

5

BAYESIAN INFERENCE AND PERCEPTION: STATISTICAL LEARNING AND PERCEPTUAL INFERENCE IN CHRONIC SCHIZOPHRENIA

The work presented in this chapter uses an experimental paradigm that was initially developed by Chalk et al. (2010) in the laboratory of Dr. Peggy Seriès and in close collaboration with Prof. Aaron Seitz at the University of California Riverside. Modification of the behavioural paradigm, recruitment of participants, testing of patients as well as the analysis of results was performed by myself under the supervision of Dr. Peggy Seriès and Prof. Stephen Lawrie. The resulting findings are about to be submitted for publication as a first author (see Appendix B)[1]. This chapter builds on the assumptions that perception is a process of inference. Here we test statistical learning and inference in schizophrenia, and compare these to a control population. This chapter, however, does not aim to elaborate on the possible cortical implementations that might perform such computations (for reviews of this specific topic see: Knill and Pouget, 2004; Fiser et al., 2010; Series and Seitz, 2013)

5.1 INFERENCE AND PERCEPTION

While there is inherent structure, regularity and continuity within our sensory environment, sensory information is noisy and uncertain. In vision, physical limitations of the eye (e.g. retinal blind-spot, density of receptors on the retina, mapping of a 3D environment into a 2D image) or noise in the neural encoding of the stimulus induces uncertainty in the interpretation of sensory information. Nevertheless, the brain appears to deal effectively with this uncertainty such that we can plan and interact *"optimally"* within the environment (Knill and Pouget, 2004). Although Hermann von Helmholtz (1867) did not talk about optimality per se, he was first to outline the idea that perception might result from a process of *"unconscious inference"* (von Helmholtz, 1925). Namely that, in order to deal with the *"ambiguity"* of sensory information, the brain must use *"knowledge derived from the past"* or *"assumptions"* about the stimuli to resolve uncertainty. Interestingly, if perception results from a process of inference we should observe specific behavioural effects in perceptual tasks (Series

1 The work presented in this chapter is largely adapted from a draft of publication to be submitted. The computational methods have been altered or extended from previous work by Chalk et al. (2010) and the dataset presented consists of patients with chronic schizophrenia and healthy controls.

and Seitz, 2013). First, using previous knowledge about a stimulus should reduce the uncertainty about this stimulus, resulting in increased performances. That is, combining noisy sensory information with previous knowledge would essentially increase the precision of the resulting percept, leading to an increased speed and accuracy that would not have been possible from noisy sensory information alone. Second, previous knowledge should alter the subjective interpretation of the stimuli. For example, when sensory information is either exceptionally noisy, ambiguous or even non-existent, the resulting percept should mostly be driven by the knowledge of the participant, resulting in perceptions that conform to the subjects' expectations (i.e. illusions; Gregory, 1968, 1997).

Expectations (or *"knowledge"*) about the world can be manipulated by experimenters to assay how these interact with sensory information and contribute to perception. Expectations have been found to modulate and interact with a variety of sensory modalities such as vision (Sterzer et al., 2008; Chalk et al., 2010; Gekas et al., 2013; Series and Seitz, 2013), audition (Remez et al., 1981; Davis and Johnsrude, 2007), touch (Botvinick and Cohen, 1998) and even complex sensations such as such as pain (Voudouris et al., 1990; Colloca and Benedetti, 2005) and emotions (Petrovic et al., 2005).

5.2 BAYESIAN BRAIN HYPOTHESIS

The combination of expectations and sensory evidence can be formalised mathematically using Bayes theorem. Particularly, an increasingly popular idea in theoretical neuroscience is that perception and decision making can be well described using probabilistic inference (a.k.a. "Bayesian") models (Knill and Pouget, 2004; Friston, 2010, 2012). According to this "Bayesian Brain Hypothesis", the brain learns internal statistical models of the environment which are used in situations of uncertainty to disambiguate perceptual inputs and guide decisions. "Statistical and perceptual learning studies have repeatedly shown that the visual system continuously extracts and learns the statistical regularities of the environment, and can do so automatically and without awareness", for a review, see Series and Seitz (2013).
For example, Weiss et al. (2002) used this framework to successfully describe perceptual illusions in healthy individuals. In this study, illusions result from the brain's attempts to interpret sensory inputs based on its internal models and expectations. Specifically, Weiss et al. (2002) demonstrated that a large number of visual motion illusions could be explained in terms of an *'a priori'* expectation for "slow speeds". Multiple studies have since found that healthy subjects quickly learn the statistics of

their environment, and combine these statistics with sensory evidence resulting in behaviour akin to that of an ideal Bayesian observer (Weiss et al., 2002; Chalk et al., 2010; Gekas et al., 2013), for reviews see (Knill and Pouget, 2004; Fiser et al., 2010; Series and Seitz, 2013). This framework is known to result in optimal perception when the inputs match the environment statistics but can result in biases when the stimuli deviate from expected inputs (Series and Seitz, 2013). A famous example of such a bias is the *"hollow-mask illusion"*, where subjects perceive a face-mask as being convex, while it is in fact concave, presumably due to the very strong *'a priori'* expectation that faces are convex objects (Gregory, 1968, 1980, 1997).

This Bayesian framework can be extremely informative. For example, using well defined experimental conditions, scientists can precisely control the stimuli given to participants and manipulate the subjects' expectations to see how it affects their perception. Using these techniques, one can measure perceptual biases over multiple trials to estimate a participant's confidence in sensory information (i.e. sensory evidence), pre-existing expectations (Weiss et al., 2002), whether these expectations are immutable (Sotiropoulos et al., 2011), the time-frame required for the acquisition of new expectations (Chalk et al., 2010), or even assay the acquisition of increasingly complex expectations (Acerbi et al., 2012; Gekas et al., 2013), for a review, see Series and Seitz (2013).

5.3 BAYESIAN BRAIN HYPOTHESIS IN PSYCHOSIS

Interestingly, a wide variety of psychiatric conditions are characterised by experiences of abnormal percepts (i.e. hallucinations; Collerton et al., 2005) and delusions (van Os and Kapur, 2009). Relevant to delusions and perception, psychotic patients have been found to exhibit disturbed prediction-error signalling (Corlett et al., 2007b; Murray et al., 2008; Romaniuk et al., 2010; Gradin et al., 2013), which is known to be essential for learning stimulus-reward associations (Schultz et al., 1997; Schultz, 2002, 2010) and building internal models of the environment so as to guide behaviour (Dayan and Daw, 2008; Daw et al., 2011; Dolan and Dayan, 2013; Dayan and Berridge, 2014). The magnitude of prediction-error signalling anomalies have repeatedly been found to correlate with delusion severity (Corlett et al., 2007b, 2010), suggesting a possible link between abnormal prediction-error signalling and delusions. Further to deficits of prediction-error signalling, an increasing number of studies report that schizophrenia patients show a deficit in integrating probabilistic information resulting in faster responses than healthy subjects, an effect called the *'jumping-to-conclusions'* (JTC) bias (Huq et al., 1988; Speechley et al., 2010; Averbeck et al., 2011; Evans et al., 2012; Joyce

et al., 2013). This bias is often measured using the *'beads task'* (Huq et al., 1988). Although these findings have not always been replicated (McKay et al., 2007; Heerey et al., 2008), there is a growing body of evidence suggesting that schizophrenia patients are impaired in statistical learning and inference (Garety et al., 2013). Similarly to the observed link between prediction-error disturbance and delusion severity, patients with stronger delusional symptoms appear to fare worse at the task than those who do not, suggesting a potential link between delusions and statistical learning/probabilistic inference (Huq et al., 1988; Speechley et al., 2010).
This is critical since statistical learning is essential to Bayesian inference. To attain the performance of an ideal observer, a participant must be able to update its internal model of the world with every new piece of information (e.g. after every trial). Only by doing so, one can accurately represent the uncertainty for a given choice in the case of the *'beads task'*, or for a given stimulus in the case of perception. Impaired statistical learning would lead to incorrect or malformed expectations (internal model) that would ultimately result in sub-optimal performances.

As a result, scientists have posited that the delusions and hallucinations, as seen in psychotic patients, may result from an incorrect Bayesian inference mechanism (Friston, 2005b; Corlett et al., 2009c,a; Frith and Friston, 2012; Adams et al., 2013; Jardri and Deneve, 2013). That is, from a cognitive perspective since patients with schizophrenia appear to be impaired in statistical learning and inference, their internal model of the world would be erroneous, resulting in abnormal beliefs or delusions. From the perception side, it is argued that hallucinations could be interpreted as a severe form of illusions. These would arise from either an incorrect mapping between the sensory information and expectations, an incorrect acquisition of these expectations, or an imbalance between learnt statistics and sensory information (for reviews see Fletcher and Frith, 2009; Corlett et al., 2011).

5.3.1 *Perception and illusions in schizophrenia*

Supporting the idea that psychosis might be explained in terms of deficient perceptual inference, patients with schizophrenia have been found to be less susceptible to a large variety of illusions such as: the hollow mask illusion (Dima et al., 2009, 2010; Keane et al., 2013), motion-induced blindness (Tschacher et al., 2006), illusory motion (Crawford et al., 2010), the size-weight illusion (Williams et al., 2010), and the Ebbinghaus illusion (Horton and Silverstein, 2011), for a review of perception in schizophrenia see (Silverstein and Keane, 2011b,a).
Building on the premise that perception is a process of inference, investigations of

illusions in schizophrenia tend to suggest that patients would either be deficient in terms of probabilistic learning, sensory integration or perceptual inference. However, these perceptual studies tend to measure a patients' susceptibility to illusions that are driven by pre-existing expectations (Tschacher et al., 2006; Dima et al., 2009, 2010; Crawford et al., 2010; Williams et al., 2010; Keane et al., 2013). Such expectations would most likely have been acquired by participants long before being exposed to the perceptual task (i.e. probably throughout their lifetime). As a result, these studies could not measure the shape of the participants' perceptual prior, before and after the task. This is important, as one needs to ensure that the statistics of the stimulus (i.e. perceptual prior) has been correctly acquired for all participants before measuring their susceptibility to these illusions. Otherwise, it is impossible to discriminate whether reduced illusory percepts stem from either: weaker expectations (sub-optimal learning), a failure to acquire the prior altogether (non-existent learning), or a decrease in the uncertainty of sensory information (increased likelihood).

Following earlier work from Sterzer et al. (2008), a recent study found that delusional ideation correlated positively with the magnitude of expectation-driven illusions in healthy controls (Schmack et al., 2013). That is, in contrast with previous studies on perceptual illusions in schizophrenia (Tschacher et al., 2006; Dima et al., 2009, 2010; Crawford et al., 2010; Williams et al., 2010; Keane et al., 2013), the authors found that the stronger the delusions of healthy controls, the more likely these were to have their percepts affected by expectations (Schmack et al., 2013). This would tend to suggest that there is an association between delusional ideation and expectation-driven illusions, although the direction of this association appears to be debated[2]. To our knowledge however, no study has looked simultaneously at the acquisition of expectations (i.e. probabilistic learning) and their influences on perception (i.e. perceptual illusions) in the context of a perceptual task in schizophrenia.

5.4 AIMS

The current study therefore investigates visual statistical learning and the influence of these expectations on perception in patients with schizophrenia. We used a previously developed motion task (Chalk et al., 2010) that is known to induce the rapid acquisition of the statistics of a motion stimuli. In this task, subjects need to report the direction of motion of a cloud of dots (estimation task) and whether they have perceived the dots or not (detection task; on some trials no stimulus are presented).

2 However, Schmack et al. (2013) also reported a negative correlation between delusional ideation and perceptual stability

Unknown to the participants, two directions of motion are more frequently presented than others. In healthy individuals, we found that subjects implicitly and unconsciously learn those stimulus statistics. This learning influenced perception such that: 1) motion stimuli were perceived as being more similar to the most frequently presented stimuli than they really were (i.e. estimation biases); 2) participants reported perceiving the most frequently presented stimuli in absence of visual stimuli (i.e. illusion/*'hallucinated'* dots). Bayesian modelling could be applied to individual performance to monitor the acquisition of the statistics of the stimuli (i.e. perceptual prior).

Using this task, we here aimed to address whether patients with schizophrenia can acquire correctly the statistics of the motion stimuli and to assay how those perceptual priors are used in perception.

5.5 SAMPLE DEMOGRAPHICS

Twenty-one male subjects (11 chronic patients with schizophrenia; 10 healthy controls) with normal or corrected-to-normal vision were recruited from the outpatient clinic of the Royal Edinburgh Hospital (Participants demographics – Table 5.1). Patients' diagnoses were assigned by experienced clinicians based on standardised interviews (Diagnostic and Statistical Manual of Mental Disorders; DSM-IV-TR, 2000). None of the control participants met the criteria for psychotic illness, schizotypal or schizoid personality disorder (DSM-IV-TR, 2000). All participants gave informed written consent and did not receive monetary compensation for participation. The study was approved by the Psychiatry and Clinical Psychology subcommittee of the Lothian research ethics committee.

The two groups did not differ in age, pre-morbid IQ or current IQ. All patients were medicated (90% on atypical anti-psychotics, 50% of these were also on mood stabilisers). Patients were well at the time of testing and did not differ from controls on the PANSS positive, general and total symptoms scale (PANSS = Positive and Negative Symptom Scale). Significant differences were found between the two groups on the negative symptom scale and the global assessment of functioning.

Characteristics	Healthy controls (n=10)	Schizophrenia Patients (n=11)	Significance level
Age	36.66 (3.85)	37.63 (3.40)	*n.s.*
Premorbid IQ	114.66 (1.86)	113.90 (2.75)	*n.s.*
Current IQ	118.11 (2.07)	109.09 (4.33)	*n.s.*
PANSS			
Positive Scale	7.77 (0.43)	10.27 (1.26)	*n.s.*
Negative Scale	7.44 (0.24)	11.45 (1.53)	****(p<0.05)**
General Scale	21 (2.45)	24.27 (2.71)	*n.s.*
Total	36.33 (2.53)	44.63 (4.78)	*n.s.*
GAF	75.55 (3.96)	58.63 (4.77)	*****(p<0.01)**
CPZ eq. (mg/day)	—	447.16 (60.30)	*N/A*
Illness duration yr.	—	14.72 (2.73)	*N/A*

Table 5.1: Participants summary information. PANSS=*Positive And Negative Symptom Scale (lower score is better)*, GAF = *Global Assessment of Functioning (higher score is better)*, CPZ eq. = *Chlorpromazine anti-psychotic equivalent dose in mg/day. Values indicate mean and (standard error)*

5.6 MOVING DOTS EXPERIMENT

5.6.1 *Apparatus & Stimuli*

Motion stimuli consisted of a field of dots with a density of 2 dots/deg^2, moving coherently (100%) at a speed of 9° s^{-1}. Dots were contained within a circular annulus with minimum and maximum diameter of 2.2° and 7° respectively. Using coherent motion direction and speed of 9° s^{-1} ensures that motion discrimination *per se* should not differ significantly between patients and control groups (Chen et al., 2005, 2006). Stimuli were generated using the Matlab programming language with the psychophysics Toolbox (Brainard, 1997), displayed on a Dell P790 monitor running at 1024×768 at 100 Hz. The display luminance was calibrated and linearised using a Cambridge Research Systems Colorimeter (ColorCal MKII). The background luminance was set to 5.2 cd/m^2. Participants viewed the display in a darkened room at a viewing distance of 100cm.

5.6.2 *Procedure*

Each trial was composed of two tasks arranged as follows (Figure 5.1a); First, participants were presented with a fixation point (0.5° diameter) for 400 ms. With the

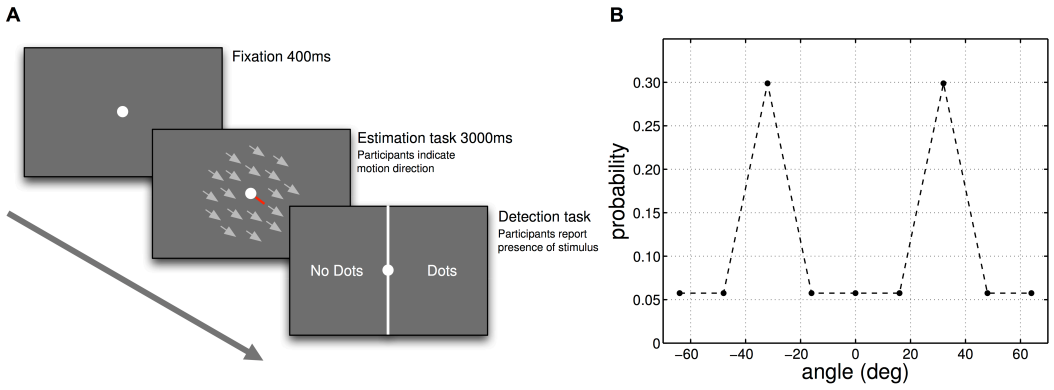

Figure 5.1: **(A)** Experimental procedure. Participants were presented with a fixation point followed by the motion stimulus and a response bar (red bar) that they were instructed to align to the perceived motion-direction. The screen was cleared either when participants clicked to validate their estimation or 3000 ms had elapsed. A new screen appeared with a two-alternative forced choice task (2-AFC), requiring participants to indicate whether they perceived dots during the estimation task. **(B)** Probability distribution of the motion directions. Unknown to participants, the distribution of motion direction was bimodal (i.e. stimuli appeared most often at $\pm 32°$ around a central direction). The central direction was randomised for each participant.

fixation point still on-screen, the motion stimulus (cloud of dots) was displayed along with a red bar extending from this fixation point. During the presentation of the field of dots, participants were required to estimate the direction of motion by aligning the red bar into the perceived direction of motion (*Estimation task*). The angle of this bar was randomized on each trial and participants were instructed to focus their gaze on the fixation point throughout the estimation task. The display then cleared when the participant either clicked the mouse to validate their choice (estimation) or when 3000 ms had elapsed. After the estimation, a 200 ms delay was enforced before the detection screen was presented. The new screen was divided in two equal areas reading "Dots" and "No Dots", giving the participants a two-alternative forced choice (2-AFC). Subjects were required to move the cursor to the right or the left to indicate whether they detected dots or not, and click to validate their choice (*Detection task*). The cursor flashed green or red for correct or incorrect responses respectively. No time-outs were enforced during the detection task. Finally, the screen was cleared for 400 ms before a new trial began. Every 20 trials, subjects were presented with feedback on their estimation performance in terms of average estimation error.

5.6.3 *Design*

The task structure repeated for 567 trials (i.e. lasting approximately 40 minutes instead of 60 minutes for 850 trials in Chalk et al., 2010) with opportunities for breaks every 170 trials (i.e. every 10 to 15 minutes) to prevent fatigue. Stimuli were presented at four different randomly interleaved contrast levels. The highest contrast level was 1.7 cd/m^2 above the 5.2 cd/m^2 background. There were 167 trials at zero contrast and 67 trials at high contrast. Contrasts of other stimuli were determined using a 4/1 and 2/1 staircase on detection performance (García-Pérez, 1998). Throughout the experiment, there were 90 trials with the 2/1 staircase and 243 trials with the 4/1 staircase. For the two stair-cased contrast levels, on a given trial, the direction of motion could either be 0°, ±16°, ±32°, ±48°, ±64°, with respect to a central reference angle. This central reference angle was randomised for each participant. To reduce potential biases in the population, we averaged results due to reference repulsion from cardinal motion directions.

Unbeknownst to the participants, we manipulated their expectations about which motion directions were most likely to occur by presenting stimuli moving at ±32° more frequently than others (resulting in a bimodal distribution, Figure 5.1b). At the highest contrast level, 50% of trials were at ±32° and 50% remaining trials at random directions (i.e. not just the predetermined directions).

5.7 METHODS

Data analysis on the estimation task was performed on confirmed trials only (i.e. trials where participants validated their choice with a click on both *detection* and *estimation* tasks). Since the presented directions were symmetrical around a central reference angle, results were averaged for stimuli moving on either side of this reference angle. The first 130 trials were excluded from the analysis to allow the staircases to converge to stable contrast levels (see Figure 5.3). Out of the original 21 participants, one subject had a mean absolute estimation error greater than 30° at the highest contrast levels and was therefore discarded from further analysis. Responses from high contrast stimuli were used as a performance benchmark to ensure that participants were performing the task. These trials were excluded from the analysis.

5.7.1 *Behavioural analysis*

In the estimation task, the variance of participants' direction-estimates was large. As in previous work (Chalk et al., 2010; Gekas et al., 2013), we hypothesized that these resulted from random estimations on a proportion of trials, thus increasing substantially the variance of motion direction estimates. To account for this, we fitted the estimation responses to the following distribution:

$$(1-\alpha)\cdot\mathcal{V}(\mu,\kappa)+{}^{\alpha}/_{2\pi} \tag{5.1}$$

where 'α' is the proportion of trials where the participant makes random estimates, and '$\mathcal{V}(\mu,\kappa)$' is the circular normal (i.e. von-Mises) distribution with mean 'μ' and width '$1/\kappa$', given by:

$$\mathcal{V}(\mu|\kappa)=\frac{e^{\kappa\cdot\cos(\theta-\mu)}}{2\pi\cdot I_0(\kappa)} \tag{5.2}$$

Parameters were chosen by maximising the likelihood of generating the data from the distribution. Participants' estimation means and standard deviation were taken as the circular mean and standard deviation of the von-Mises distribution. This parametric approach allows for more consistent and significantly smaller variances across participants, motion directions, and contrasts, than merely averaging over trials, without compromising the qualitative aspect of the results (Chalk et al., 2010; Gekas et al., 2013).

5.7.2 *Kernel density estimation*

In trials were no stimulus was presented, we reconstructed the probability distributions of participants' responses over motion directions using Kernel Density Estimation (KDE) across each group. The KDE is a non-parametric method used to estimate the probability density function from discrete measures of a random variable. To do so, a kernel that defines the form of the probability density function (e.g. Gaussian kernel) is placed at each of the observed measurement. Then, all the individual kernels are summed to create the probability density function of the random variable (motion direction). In our case, we used a circular normal kernel since our random variable is circular. As is customary for KDE, the variance of the kernel is estimated from the data using the minimum of standard deviation and interquartile range improved (MSNI) method. This method has proven to be robust against over-smoothing (Silverman, 1986) as well as providing adequate fit to skewed (Wand and Jones, 1994) and multi-modal distributions (Bowman and Azzalini, 1997).

5.7.3 *Computational analysis*

In Chalk et al. (2010), the authors compared two alternative classes of computational models to understand how the participants' expectations affect the estimation of motion-direction. The first class consists of *'response-bias'* models that attempt to replicate the observed behaviour using a response strategy unrelated to perceptual changes. The second class of models however, builds on the premise that perception results from an inference akin to a *'Bayesian strategy'* (Knill and Pouget, 2004; Series and Seitz, 2013), where participants combine their expectations about motion-direction with the sensory evidence available.

In studies by Chalk et al. (2010); Gekas et al. (2013), Bayesian models were found to account best for the behaviour of healthy participants. In this study, both classes of models were fitted to the behavioural data of patients to uncover whether different strategies might be used between groups.

5.7.4 *Bayesian models*

We used two Bayesian models in this study. First a simple model was used to study how expectations are combined with sensory evidence to produce the estimation of motion-directions. Then a refined version of that model was used to account for the detection phase of the task, and to address how expectations alter the detection of stimuli. Both Bayesian models start from the same premise, namely that participants combine their expectations about the stimulus (prior) with sensory evidence (stimulus) in a probabilistic manner. A diagram of the three different processing stages of the Bayesian model are shown in Figure 5.2. First, we assume that on every trial participants make noisy sensory observations of the motion-direction (stimulus). This effectively transforms the stimulus direction from a point-value ($\theta_{\theta\in[0,2\pi]}$) to a probability distribution ($p_{likelihood}(\theta_{observed}|\theta)$) defined as:

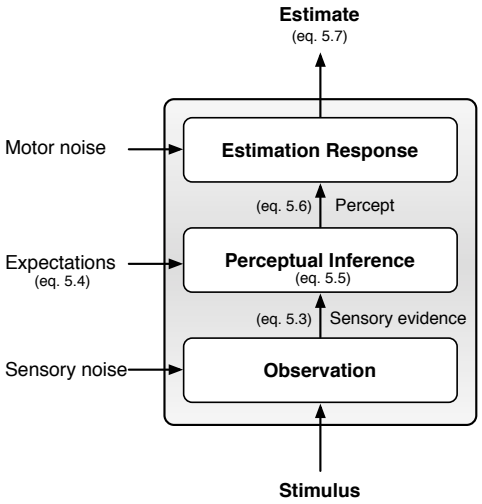

Figure 5.2: Diagram of the Bayesian model. This schematic depicts the three different processing stages of the stimulus, from sensory integration to perceptual inference and motor response (estimation).

$$p_{likelihood}(\theta_{observed}|\theta) = \mathcal{V}(\theta|\kappa_{sensory}) \tag{5.3}$$

where $\mathcal{V}(\theta|\kappa_{sensory})$ is a circular normal probability distribution (defined in eq. 5.2) centred on the point-value 'θ' with variance $1/\kappa_{sensory}$ that defines the participant uncertainty about the motion-stimulus. We name the resulting probability distribution *'sensory evidence'* or *'sensory observation'*. We then hypothesize that participants only acquire an approximation of the *'true'* prior probability $p_{prior}(\theta)$ representing the participants' expectations of motion-direction:

$$p_{prior}(\theta) = \frac{1}{2}\left[\mathcal{V}\left(-\theta_{expected}, \kappa_{expected}\right) + \mathcal{V}\left(\theta_{expected}, \kappa_{expected}\right)\right] \tag{5.4}$$

The prior is parametrised as the sum of two circular normal distributions centred on motion-directions '$-\theta_{expected}$' and '$\theta_{expected}$' with variance $1/\kappa_{expected}$. These parameters were estimated from the data of each participant. Following our premise, the posterior probability that the stimulus is moving in a particular direction 'θ', given a sensory observation $\theta_{observed}$ is obtained by multiplying the likelihood function $p_{likelihood}(\theta_{observed}|\theta)$ with the prior probability $p_{prior}(\theta)$:

$$p_{posterior}(\theta|\theta_{observed}) \propto p_{prior}(\theta) \cdot p_{likelihood}(\theta_{observed}|\theta) \tag{5.5}$$

The resulting percept is defined as the most likely motion-direction from the posterior distribution, such that:

$$\theta_{perceived} = \arg_{\theta\in[0,2\pi]} \max\, p_{posterior}(\theta|\theta_{observed}) \tag{5.6}$$

Finally, the Bayesian model accounts for the *'motor noise'* associated with the estimation response $\theta_{perceived}$ (i.e. aligning and clicking on the mouse), such that:

$$p\left(\theta_{estimate}|\theta_{perceived}\right) = (1-\alpha) \cdot \mathcal{V}\left(\theta_{perceived}, \kappa_{motor}\right) + \alpha/2\pi \tag{5.7}$$

where 'α' controls the proportion of random guesses on each trial, and the magnitude of the *'motor noise'* is determined by the variance $1/\kappa_{motor}$ of a circular normal (eq. 5.2) centred on the perceived stimulus $\theta_{perceived}$. The parameter κ_{motor} is estimated from the participants' estimation trials when the contrast is high, such that there is no (or relatively few) uncertainty about the sensory stimulus (i.e. $\kappa_{sensory}$ virtually equivalent to zero). Two alternative versions of the simple Bayesian model were tested, one where the sensory concentration parameter (i.e. $\kappa_{sensory}$) was kept constant across all motion-direction presented, and one where $\kappa_{sensory}$ was allowed to vary with the stimulus direction. We named the simple model with constant value `'Bayes'` and the later `'Bayes_var'`. The `'Bayes'` model has a total of four free parameters (i.e.: α, $\kappa_{sensory}$, $\theta_{expected}$, $\kappa_{expected}$) that were chosen so as to maximise the

fit of the model to the data of each individual participant. `'Bayes_var'` on the other hand required eight free parameters since it required a new $\kappa_{sensory}$ parameter for every motion direction presented.

5.7.4.1 *Bayesian model with detection*

The simple Bayesian model `'Bayes'` presented above ignored the detection phase of the moving-dots task, and relied exclusively on trials where participants correctly detected the stimulus. Here, still based on (Chalk et al., 2010), we describe a refined version of the simple Bayesian model that takes into account the participants' detection of the stimulus as well as their estimation of motion-direction. We named this model `'Bayes_full'`. On a single trial, stimuli moved in a direction 'θ', and could be either present ($s = 1$) or absent ($s = 0$), such that :

$$Stimulus = (\theta \in [0, 2\pi], s \in \{0 = absent, 1 = present\}) \tag{5.8}$$

As previously, we assume that participants made noisy sensory observations on each trial such that the motion direction presented is effectively transformed from point-values to probability distributions ($\theta_{observed}, s_{observed}$). For simplicity, we made the assumption that sensory observations '$s_{observed}$' and '$\theta_{observed}$' were made independently of each other. The resulting sensory likelihoods were parametrized as:

$$p_{likelihood}\left(s_{observed} = \{0,1\}|\theta, s\right) = \begin{cases} \left\{ \begin{matrix} 1-d \\ d \end{matrix} \right\}_{d\in[0,1]} & \text{if } s = 1 \\ \left\{ \begin{matrix} 1-c \\ c \end{matrix} \right\}_{c\in[0,1]} & \text{if } s = 0 \end{cases} \tag{5.9}$$

where parameters 'd' and 'c' represent the sensory likelihood that the participant detected a stimulus when it is presented ($s = 1$) or absent ($s = 0$) respectively. For trials where no stimulus were presented ($s = 0$), we assumed that participants picked a direction randomly from all the possible motion-directions, such that:

$$p_{likelihood}\left(\theta_{observed}|\theta, s\right) = \begin{cases} \mathcal{V}\left(\theta|\kappa_{sensory}\right) & \text{if } s = 1 \\ 1/2\pi & \text{if } s = 0 \end{cases} \tag{5.10}$$

where $\mathcal{V}\left(\theta|\kappa_{likelihood}\right)$ is the circular normal distribution (eq. 5.2) centred around 'θ' with variance defined by $1/\kappa_{sensory}$. The parameters $\kappa_{sensory}$, 'd' and 'c' were kept

constant across motion-directions as in the simple `'Bayes'` model. The participants' approximation of the *'true'* prior was defined as:

$$p_{prior}(\theta, s) = \begin{cases} b \cdot \frac{1}{2}\left[\mathcal{V}\left(-\theta_{expected}, \kappa_{expected}\right) + \mathcal{V}\left(\theta_{expected}, \kappa_{expected}\right)\right] & \text{if } s = 1 \\ (1-b) \cdot 1/2\pi & \text{if } s = 0 \end{cases} \tag{5.11}$$

where 'b' defines the participants' expectation of a stimulus being present. We assumed that participants' expectations were uniform when no stimulus was presented. On the other hand, when a stimulus was presented, the participants' expectations were parametrized as in the original `'Bayes'` model. As before, the posterior probability results from the multiplication of the likelihood function $p(\theta_{observed}, s_{observed}|\theta, s)$, with the prior probability $p(\theta, s)$:

$$p_{posterior}(\theta, s|\theta_{observed}, s_{observed}) \propto p_{prior}(\theta, s) \cdot p_{likelihood}(\theta_{observed}, s_{observed}|\theta, s) \tag{5.12}$$

We hypothesized that participants estimated the motion-direction and stimulus presence independently by taking the maximum of the posterior distribution on each trial:

$$\{\theta_{perceived}, s_{perceived}\} = \arg_{\theta,s} \max\, p(\theta, s|\theta_{observed}, s_{observed}) \tag{5.13}$$

As in the original `'Bayes'` model the last stage of the model accounts for the *'motor noise'* associated with the estimation response $\theta_{perceived}$, such that:

$$p\left(\theta_{estimate}|\theta_{perceived}\right) = (1-\alpha) \cdot \mathcal{V}\left(\theta_{perceived}, \kappa_{motor}\right) + \alpha/2\pi \tag{5.14}$$

where 'α' controls the proportion of random guesses on each trial, and the magnitude of the *'motor noise'* is determined by the variance $1/\kappa_{motor}$ of a circular normal (eq. 5.2) centred on the perceived stimulus $\theta_{perceived}$. The `'Bayes_full'` model has a total of seven free parameters (i.e.: α, $\kappa_{sensory}$, c, d, $\theta_{expected}$, $\kappa_{expected}$, and b) that were chosen so as to maximise the fit of the model to the data of each individual participant.

5.7.5 *Response-bias models*

While the previous models attempted to model estimation biases assuming that participants follow a *'Bayesian strategy'*, based on previous work (Chalk et al., 2010) we also decided to address whether this behaviour might result from a simple *'response bias'*. That is, participants might rely solely on either sensory information or on their expectations on a given trial. For example, a participant might estimate motion-direction as one of the most presented directions on a certain proportion of trials and estimate correctly motion-direction using sensory inputs on the remaining trials.

5.7.5.1 *Response bias* — ADD1 *model*

In this model we assumed that on a proportion of trials participants were unsure about the presented motion direction and as a result estimated close to one of the most presented direction (i.e. as if relying entirely on their expectations). We named this model `'ADD1'`. Similarly to the models following a *'Bayesian strategy'*, in this model participants also made noisy sensory observations such that the presented motion direction 'θ' was transformed from a point-value to a probability distribution $p(\theta_{observed}|\theta)$ to account for sensory uncertainty:

$$p\left(\theta_{observed}|\theta\right) = \mathcal{V}\left(\theta|\kappa_{sensory}\right) \tag{5.15}$$

On the majority of trials, we assume that participants make a perceptual estimate $\theta_{perceived}$ that is equal to the observed stimulus $\theta_{observed}$. That is, on most trials, participants rely exclusively on their sensory information during the estimation task. On the remaining proportion of trials, participants rely exclusively on their expectations and make perceptual estimates that are sampled from a learned distribution $p_{expected}(\theta)$, such that:

$$p_{expected}\left(\theta\right) = \frac{1}{2}\left[\mathcal{V}\left(-\theta_{expected}, \kappa_{expected}\right) + \mathcal{V}\left(\theta_{expected}, \kappa_{expected}\right)\right] \tag{5.16}$$

As in our previous Bayesian models, we add uncertainty around the perceived stimulus $\theta_{perceived}$ to account for *'motor noise'* during the estimation (5.2), and to allow for a proportion of trials where the participants make random guesses:

$$p\left(\theta_{estimate}|\theta_{perceived}\right) = (1-\alpha)\cdot\mathcal{V}\left(\theta_{perceived}, \kappa_{motor}\right) + \alpha/2\pi \tag{5.17}$$

Bringing these equations together, the estimation responses for a single participant are given by:

$$\begin{aligned} p\left(\theta_{estimate}|\theta\right) = (1-\alpha) \\ \cdot\left[\left((1-a\left(\theta\right)\right)\cdot p_{likelihood}\left(\theta_{observed}|\theta\right)\right) \\ + \left(a\left(\theta\right)\cdot p_{expected}\left(\theta_{estimate}\right)\right)\right] \\ * \mathcal{V}\left(0, \kappa_{motor}\right) + \alpha/2\pi \end{aligned} \tag{5.18}$$

where $*$ denotes a convolution and $a(\theta)$ determines the proportion of trials where participants sample from their expectations. The `'ADD1'` model has six free parameters ($\theta_{expected}$, $\kappa_{expected}$, $a(\theta)$, $\kappa_{sensory}$, κ_{motor}, and α) that were fitted to the estimation data of each individual participant.

5.7.5.2 *Response bias* — ADD2 *model*

The second response-bias model `'ADD2'` is identical to the `'ADD1'` model, with the exception that the strategy used to sample from expectations is now slightly more elaborate. In this model, we assume that on the proportion of trials were the participants sample from their expectations, they preferentially sample from the side of the distribution where the observed motion direction just occurred. That is, participants effectively truncate the probability distribution of their expectations on a trial by trial basis to sample only from the most *'relevant'* side of their expectations. For example, if the motion-direction presented on a given trial was 45°, participants would sample only from their expectations between 0-180° as opposed to −180°-180°. As a result $p_{expected}(\theta)$ was defined as follows:

$$p_{prior}(\theta) = \begin{cases} \mathcal{V}\left(\theta_{expected}, \kappa_{expected}\right) & \text{if } s = clockwise \\ \mathcal{V}\left(-\theta_{expected}, \kappa_{expected}\right) & \text{if } s = anticlockwise \end{cases} \tag{5.19}$$

As in the `'ADD1'` model, on the majority of trials participants made sensory estimates $\theta_{estimated}$ that were equal to their sensory observation $\theta_{observed}$. Now however, on the remaining proportion of trials, participants would make estimates that are sampled either from the distributions $p_{anticlockwise}(\theta)$ or $p_{clockwise}(\theta)$ depending on the actual stimulus motion-direction. As for all models, we also allowed for *'motor noise'* and for a proportion of random guesses during the estimation. The resulting distribution of estimation-responses is given by:

$$\begin{aligned} p(\theta_{estimate}|\theta) = (1-\alpha) \\ &\cdot [((1 - a(\theta) - b(\theta)) \cdot p_{likelihood}(\theta_{observed}|\theta)) \\ &+ (a(\theta) \cdot p_{anticlockwise}(\theta_{estimate})) \\ &+ (b(\theta) \cdot p_{clockwise}(\theta_{estimate}))] \\ &* \mathcal{V}(0, \kappa_{motor}) + \alpha/2\pi \end{aligned} \tag{5.20}$$

where $*$ denotes a convolution, $a(\theta)$ and $b(\theta)$ are free parameters that control the proportion of trials were participants sample from each distribution. Additionally, we considered variations to the `'ADD1'` and `'ADD2'` models (denoted `'ADD1_mode'` and `'ADD2_mode'` respectively). There, on trials where participants were unsure of the stimulus motion direction, they made perceptual estimates that were equal to the mode of their expectations. This is equivalent to the `'ADD1'` and `'ADD2'` models, with the concentration parameter $1/\kappa_{expected}$ being equal to zero.

5.7.6 *Model fitting*

As previously mentioned, one can estimate the *'motor noise'* inherent to each individual by fitting the participants' estimation-response at the highest contrast. At the highest stimulus contrast, we assumed that the stimulus was clearly visible such that the *'sensory noise'* is virtually non-existent. That is, uncertainty about the stimulus motion-direction is equivalent to zero ($1/\kappa_{sensory} = 0$). As a result, the *'motor noise'* could be estimated for each model using the equation (eq. 5.1) and using 'θ' in place of $\theta_{estimated}$.

For each of our seven models (i.e. `Bayes`, `Bayes_var`, `Bayes_full`, `ADD1`, `ADD1_mode`, `ADD2`, `ADD2_mode`), we calculate the probability $p(\theta_{estimate}|\theta; M)$ of making an estimate $\theta_{estimated}$ given the *'true'* motion-direction presented 'θ' and the set of free parameters 'M' of each model. We make the assumption that the participants' estimation responses are independent on each trial and calculate the likelihood of generating the observed experimental data given the model and its parameters 'M'. Model parameters are chosen so as to maximise the fit to the experimental data of each individual participant, resulting in a set of parameters unique to every individual. To find the parameters 'M' that maximise the fit to the data, we maximise the log of the likelihood function such that:

$$M = \arg_M \max \left[\sum_i^{n_{trials}} \log \left(p \left(\theta_{estimate} = \theta_{i,data} | \theta_i, M \right) \right) \right] \tag{5.21}$$

where 'θ_i' is the presented motion-direction and '$\theta_{i,data}$' the estimation-response on a given trial 'i'.

5.7.7 *Model comparison*

Since the models varied greatly with respect to the number of free parameters, we used the *'Bayesian Information Criterion'* (BIC) to compare different models and avoid choosing a model that over-fits the data. This technique allows to score the fit of a given model to the experimental data while penalising this score for added model complexity (i.e. number of free parameters). This enables us to compare the fit of widely different models and select those that explain the best our dataset. The BIC metric is given by:

$$BIC = -2 \cdot \ln(\mathcal{L}) + k \cdot \ln(n) \tag{5.22}$$

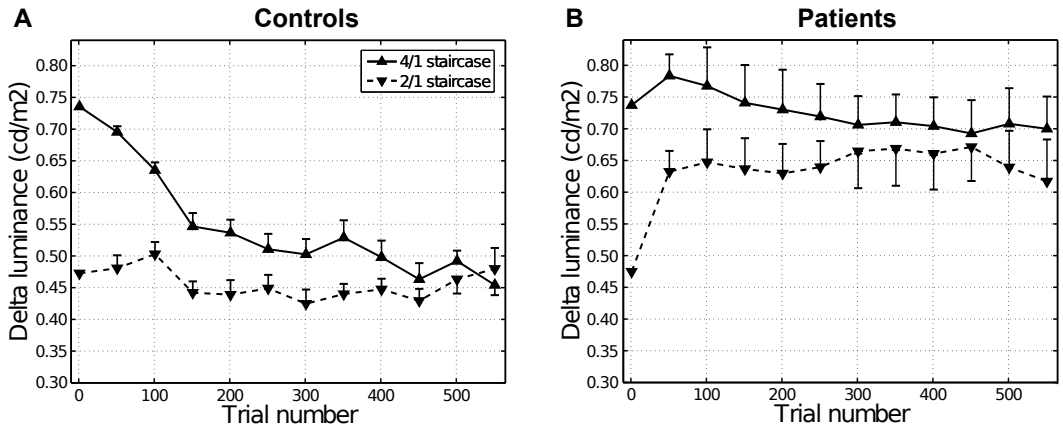

Figure 5.3: Comparison of contrast discrimination performances between the two groups. **(A)** Controls' averaged stimulus contrast, relative to background contrast for the 4/1 (plain line) and 2/1 (dashed line) staircased contrast levels. **(B)** Patients' averaged stimulus contrast, relative to background contrast for the 4/1 (plain line) and 2/1 (dashed line) staircased contrast levels. For all figures, results are averaged across all participants. Error bars denote standard error.

where $\mathcal{L}$ defines the likelihood of generating the experimental data from the model, *'k'* represent the number of free parameters in that model and *'n'* is the number of data points available when fitting the experimental data. The model resulting with the lower BIC metric is the one to be preferred as this model provides the best trade-off between the fit to the experimental data and the model complexity (i.e. less complex model avoid over-fitting and lead to better generalisation).

5.8 RESULTS

5.8.1 *General performance*

Participants' detection performance was monitored to adapt the stimulus contrast to each participant's just noticeable difference (JND – contrast sensitivity). Using 2/1 and 4/1 staircases, we ensured that the individual detection performances would converge to 70.4% and 84.1% respectively (Levitt, 1971).

Contrast staircases converged to stable luminance levels after about 130 trials for both groups (figure 5.3a-b); Controls converged to a stable luminance level of $0.48 cd/m^2$ (± 0.06) after 130 trials, while patients converged to $0.68 cd/m^2$ (± 0.07) after 51 trials. These results confirm previous findings (Skottun and Skoyles, 2007) suggesting that schizophrenia patients display significantly poorer contrast-sensitivity in comparison to controls ($t(18)=3.42$, $p<0.01$).

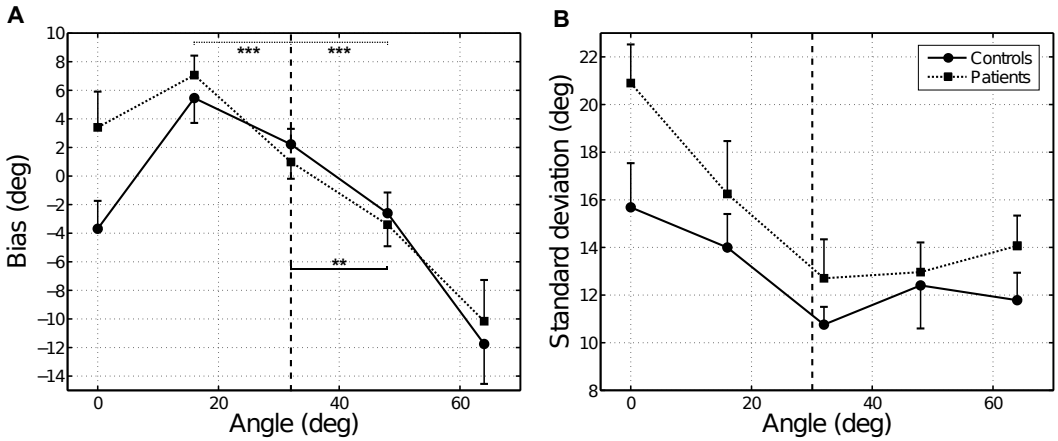

Figure 5.4: Effect of expectations on estimation biases between Controls (plain line) and Patients (dotted line). **(A)** Participants' mean bias in the perceived of motion-direction as a function of the true motion direction presented. **(B)** Standard deviation of participants' estimated motion-directions as a function of the presented of motion-direction. Results were averaged over all participants in each group; error bars represent within-subject standard error. The vertical dashed lines correspond to the most frequently presented motion-direction (i.e. $\pm 32°$). ** & *** denotes p<0.05 and p<0.01 respectively.

5.8.2 *Statistical learning*

First, we investigated whether participants acquired the statistics of the stimulus. To do so, we looked at patterns suggestive of statistical learning in each group, namely attractive biases towards the most frequent directions, decreased reaction times and improved detection performance for the most frequent directions (Chalk et al., 2010).

5.8.2.1 *Estimation performance*

To investigate whether the participants' perceived motion-directions were biased, we measured the difference between the true motion-direction and the motion direction reported by the participants. Figure 5.4a displays the average estimation bias plotted against the true motion-direction for each population (i.e. plain line for controls, dotted line for patients). Estimates at $\pm 16°$ and $\pm 48°$ were respectively positively and negatively biased towards stimuli moving at $\pm 32°$, while estimates at $\pm 32°$ (vertical dashed line) were unbiased. This indicates that for both groups, estimations were biased towards $\pm 32°$, the most frequent directions. These results replicate findings by Chalk et al. (2010) and Gekas et al. (2013) in control subjects. Overall, there was a significant effect of motion-direction on the estimation bias for controls ($F(1,4)=6.12$, $p<0.001$; *One-way ANOVA*) and patients ($F(1,4)=8.27$, $p<0.001$; *One-way ANOVA*). The estimation bias at $\pm 16°$ and $\pm 48°$ was significantly different from the bias at $\pm 32°$

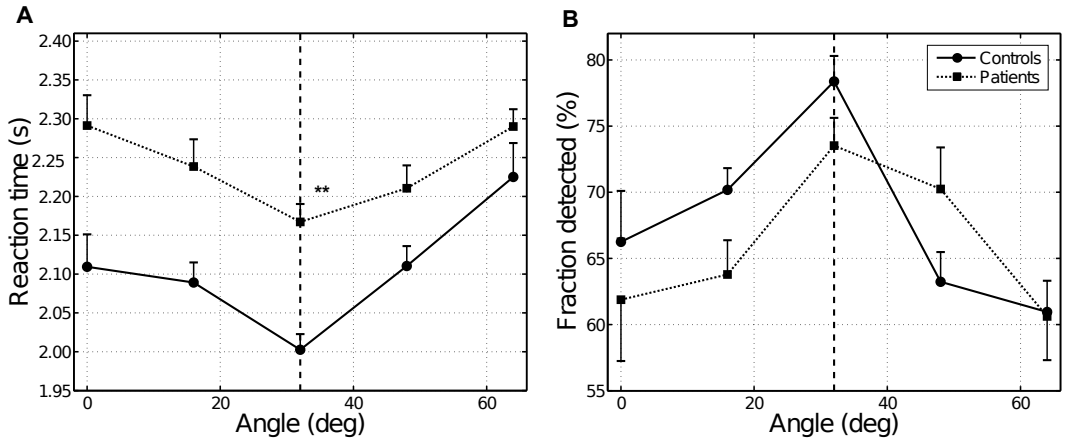

Figure 5.5: Effect of expectations on detection performance and reaction times between Controls (plain line) and Patients (dotted line). **(A)** Reaction times during the estimation task as a function of motion direction. **(B)** Proportion of motion directions that were detected by the participants as a function of the presented motion direction. Results were averaged over all participants in each group; error bars represent within-subject standard error. The vertical dashed lines correspond to the most frequently presented motion-direction (i.e. $\pm 32°$), **denotes p<0.05.

for patients ($p<0.001$ *and* $p<0.001$ *respectively, paired t-test*). Similarly, the estimation bias at $\pm 48°$ was significantly different from the bias at $\pm 32°$ for controls ($p<0.05$ *, paired t-test*). Together, these results confirm that participants perceived the most frequently presented motion-direction correctly but tended to perceive other motion directions as being more similar to the most frequent directions than they really were.

We also investigated whether the standard deviation of estimated motion-directions changed as a function of the presented motion-direction. In accordance with previous work (Chalk et al., 2010; Gekas et al., 2013), we found that the mean standard deviation was smaller at $\pm 32°$ than at other directions (figure 5.4b). Although there was no significant effect of motion-direction on the estimation standard deviation for both controls (*ns., Kruskal-Wallis H test*) and patients (*ns., Kruskal-Wallis H test*), the standard deviation at $\pm 32°$ was significantly lower than the median standard deviation at the other motion-directions (*Controls:* $p=0.033$, *Patients:* $p=0.046$*; one-tailed MC permutation test — difference of medians*). These results indicate that participants' estimations were more accurate for the most frequently presented directions than for other directions, consistent with the idea that participants had learned to optimise their performance for these most frequent directions.

5.8.2.2 *Detection performance*

Next we examined whether participants' expectations influenced their performances at the 2-AFC detection task. To do so, we measured the fraction of trials where participants' reaction times were shorter than the stimulus presentation (i.e. <3s during the estimation) and where they correctly responded "dots" during the detection task (figure 5.5d). We observed a common pattern across participants, whereby stimuli were more often detected at the most frequently presented directions than at other directions. Controls were more likely to detect stimuli moving in the most frequently presented motion directions: 78.1%±1.5 at ±32° versus 65.3%±1.4 detected for all other directions (p<0.001, *two-tailed paired t-test*). Similarly, patients were significantly more likely to detect stimuli moving at ±32° (73.2%±1.8) in comparison to all other motion-directions (64.2%±3.2; p<0.01, *two-tailed paired t-test*). Overall, there was a significant effect of motion-direction on the fraction detected, both for controls ($F(1,4)$=11.36, p<0.001, *one-way ANOVA*) and patients ($F(1,4)$=4.72, p<0.005, *one-way ANOVA*). Patients and controls did not differ at detecting motion-direction at the mostly presented direction (±32°; *ns., two-tailed independent samples t-test*). These results indicate that, in terms of detection responses (hit rates), similar benefits of statistical learning were present in both patient and control groups.

Another measure that reflects how easily participants detected stimuli is their response reaction time during the estimation task. To do so, we measured the elapsed time between the stimulus presentation and the estimation response of the participant (i.e. mouse click). A general pattern was observed across participants, whereby the mean reaction time at the most presented direction was shorter than at all other directions (figure 5.5c). For trials where controls correctly detected a stimulus, their reaction time was significantly reduced for the most frequently presented motion-direction relative to other motion directions (201±4.2 ms at ±32° versus 214±5.2 ms over all other motion-directions; p<0.005, *two-tailed signed rank test*). Similarly, patients were generally faster at detecting and responding to stimuli presented at the most frequented motion directions (217±7.4 ms at ±32° vs. 225±6.5 ms over all other motion-directions; p=0.019, *two-tailed signed rank test*). However, although patients were generally faster for the most presented motion direction in comparison to other directions, they were significantly slower than controls at the estimation of motion direction (p=*0.014; two-tailed ranksum test*). Slow reaction time is a hallmark of schizophrenia that has been documented thoroughly in the literature in simple reaction-time tasks using visual and/or auditory stimuli (Nuechterlein, 1977).

5.8.3 *Perceived motion in absence of visual stimuli 'hallucinations'*

Finally, we investigated whether the acquired statistics about the motion stimulus affected the participants' perception on trials where no stimulus was presented but where participants reported both a motion-direction and seeing a stimulus. We refer to this effect as *'hallucinations'*. The *'hallucinations'* in our perceptual task are of course different in terms of content and complexity to the visual hallucinations observed in psychosis (Collerton et al., 2005). However, studying these has the potential to shed light on perhaps similar perceptual mechanisms at play. On average participants *'hallucinated'* the stimulus on 17.9±4.77 trials for controls and 14.60±5.87 trials for patients, corresponding to 13.8±4% and 11.3±4% of trials where no stimulus were presented (*ns., two-tailed MC permutations test — difference of medians*). Interestingly, for this subset of trials, participants' estimation responses varied significantly with motion-direction, with a clear peak at the most frequently presented motion-directions (±32°; *Controls: p=0.002, Patients: p=0.019, two-tailed signed-rank test*). This suggests that participants did not make random *'hallucinations'* of the stimulus but rather preferentially hallucinated the most presented motion-directions.

To quantify the probability ratio that participants made estimates that were closer to the most frequently presented motion directions relative to other directions, we multiplied the probability that participants estimated within 8° of these motion-directions by the total number of 16° bins:

$$P_{rel} = p\left(\theta_{estimate} = \pm 32\,(\pm 8)\,\mathrm{deg}\right) \cdot N_{bins} \tag{5.23}$$

This probability would be equal to 1 if participants were equally likely to estimate within 8° of ±32° as they were to estimate within the other 16° bins. We found that the median value of 'P_{rel}' was significantly greater than 1 for both groups, indicating that participants were strongly biased to report motion in the most frequently presented directions when no stimulus was presented. That is, participants *'hallucinated'* significantly more stimuli at the most presented directions (figure 5.6a-b).

The fact that participants report perceiving dots that are not present, more often at the most frequently presented motion-directions provides strong evidence that the statistics of the task have been correctly acquired. Hallucinations of the most presented directions (i.e. hallucinations at ±32°±8°) appear significantly more often than at random directions after only 250 trials in controls (p=0.029, *two-tailed signed-rank test*) and 400 trials in patients (p=0.019, *two-tailed signed-rank test*). It is interesting to note however that while healthy controls and patients did not differ in the amount of

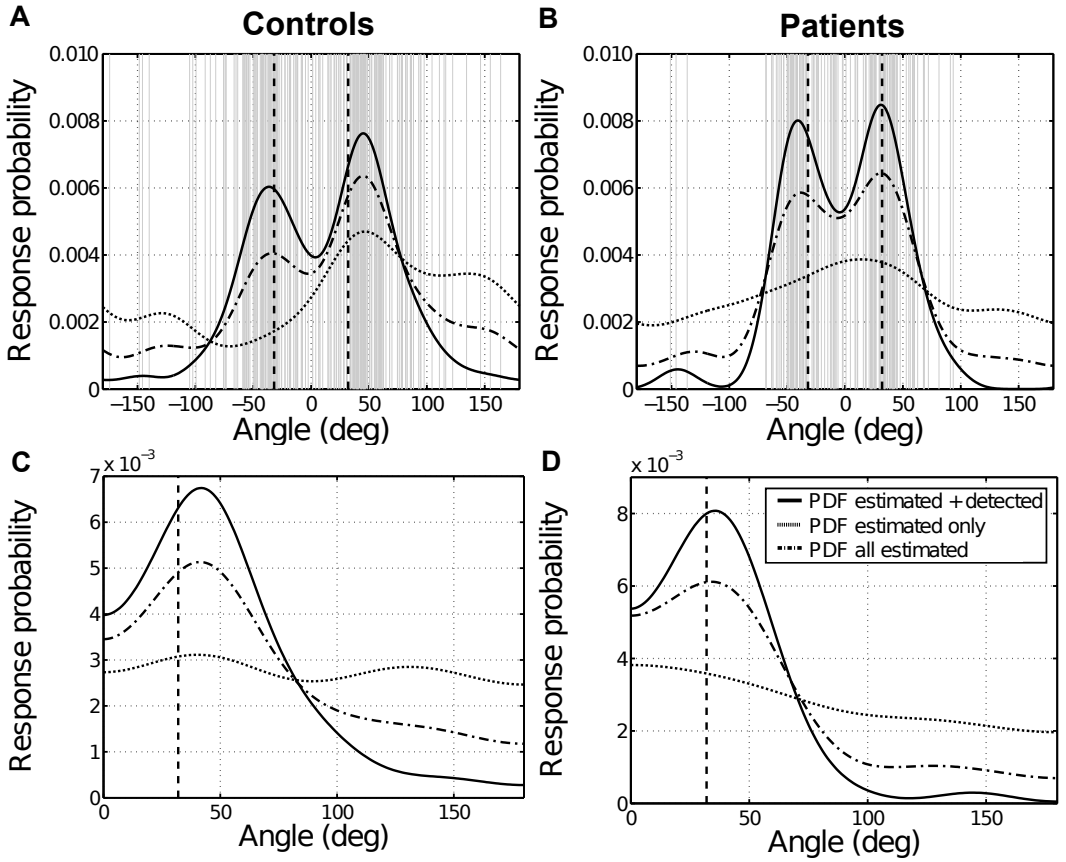

Figure 5.6: Estimation responses in the absence of stimulus for each group (Controls - A, C; Patients B, D). **(A, B)** The vertical grey lines correspond to all the estimated motion directions when no stimulus was present (i.e. *'hallucination'*) pooled across the whole group (A-controls, B-patients). The black line represents the fitted probability distributions of response for trials where participants report a seeing a stimulus. The dotted line represents the fitted probability distribution for trials where participants reported a motion direction during the estimation but did not confirm seeing a stimulus during the detection task. The dot-and-dash horizontal line depicts the fitted probability distribution for all trials where motion direction was reported. **(C-D)** Data from either side of the central motion are averaged together. The dashed vertical line signals the position of the mode of the prior (i.e. $\pm 32°$).

'random'-hallucinations (i.e. over all directions; *ns., two-tailed MC permutations test — difference of medians*), patients made significantly fewer hallucinations of the most presented direction than controls (p=0.0174, *two-tailed MC permutation test - difference of medians*). In fact, 66% of patients made 3 or less hallucinations of the most frequently presented directions, of which 50% made no hallucinations at all. By comparison, all controls hallucinated stimuli at the most presented directions (i.e. 90% of controls hallucinated between 3 to 14 times at $\pm 32° \pm 8°$).
To ensure that the stimulus hallucinations at $32° \pm 8°$ were not the result of a strategy, we analysed the subset of trials where participants made an estimation but did not report seeing a stimulus. That is, on a large proportion of trials the presented motion stimuli were moving in one of two directions. It is therefore possible that participants could have developed a strategy to move subconsciously the estimation bar towards one of these directions irrespective of their response in the detection-task. If this were the case however, we would also expect the *'no-stimulus'* estimation distributions to be biased towards the most frequently presented directions for trials were participants did not detect a stimulus. This response-bias could be ruled out since participants were not significantly more likely to move the estimation bar closer to the frequent directions on trials where they did not report seeing a stimulus (i.e. all except 1; figure 5.6a-d see "PDF estimated only"). These results largely replicate those of Chalk et al. (2010) and Gekas et al. (2013).

Finally, we found that the participants' hallucinations at $32° \pm 8°$ correlated significantly with the neuropsychological assessment of the GAF (r_2=0.532, p=0.0131, *MC permutation test*) as well as the PANSS total (r_2=−0.498 p=0.035, *MC permutation test*) and PANSS positive symptoms scores (r_2=−0.586 p=0.0077, MC permutation test). Together these findings suggest that the more severe their symptoms were (as measured with the GAF and PANSS), the less *'hallucinations'* participants made during the task. We found no relationship between the daily-dosage of anti-psychotics (Chlorpromazine equivalent; Andreasen et al., 2010) and the total amount of hallucinations at $32° \pm 8°$ (*ns.; MC permutation test*).

5.9 DISCUSSION AND INTERPRETATION

In summary, our results replicate previous findings of Chalk et al. (2010) both in the patient and control groups. The performance of both groups show that participants implicitly learn the statistics of the motion stimuli and that those expectations modify their perception. All participants display an attractive estimation bias towards the frequently presented directions and reduced estimation variability for these direc-

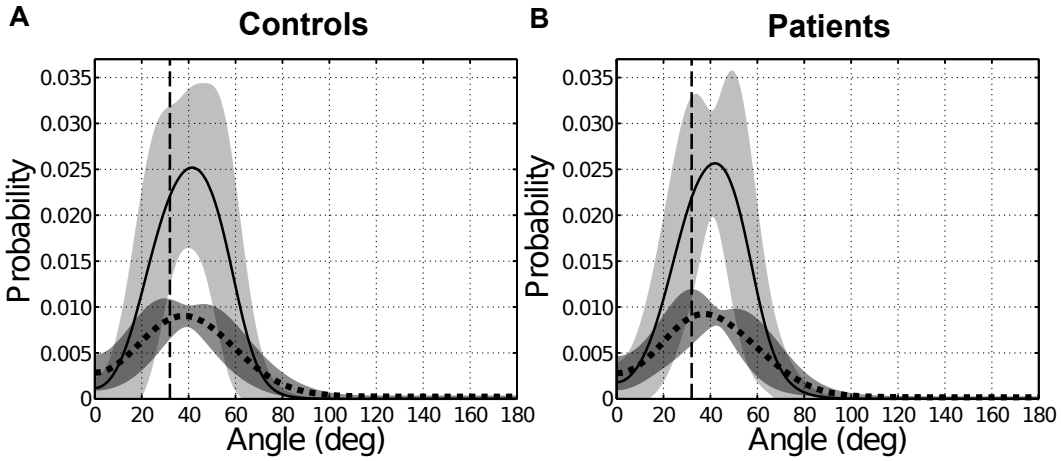

Figure 5.7: **(A, B)** Participants learned prior distribution of presented motion directions as predicted by the Bayesian model `'Bayes_dual'` (plain line and light-gray area). The probability distribution of perceptual hallucinations when simulating the task with the Bayesian model `'Bayes_dual'` (dotted line and dark-grey area).

tions. They also show faster reaction times and higher detection rates for the most frequently presented directions. Finally, they tend to *'hallucinate'* the expected directions in absence of stimuli.

Patients were not qualitatively, nor quantitatively different from controls in these measures used to assess learning of the task statistics. However, we found that patients and controls differed in two ways. First, patients with schizophrenia displayed significantly poorer contrast discrimination thresholds and slower reactions times than controls. Second, we found that patients reported significantly less *'hallucinations'* of the most frequently presented motion directions than healthy subjects. The amount of hallucinations of the most frequently presented directions correlated significantly with the GAF, PANSS total and positive scores, suggesting that the better they usually fare in neuropsychological tests, the more participants experience expectation-driven hallucinations at the task.

5.9.1 *Bayesian interpretation of 'hallucinated' dots*

An emerging conceptual model of schizophrenia suggests that the disorder would stem from deficits in Bayesian inference. For example, it has been proposed that the recurrent complex visual hallucinations (Collerton et al., 2005) seen in psychotic patients could be explained in terms of deficits in the Bayesian integration of perceptual priors and likelihoods (Fletcher and Frith, 2009; Corlett et al., 2009a; Adams et al., 2013).

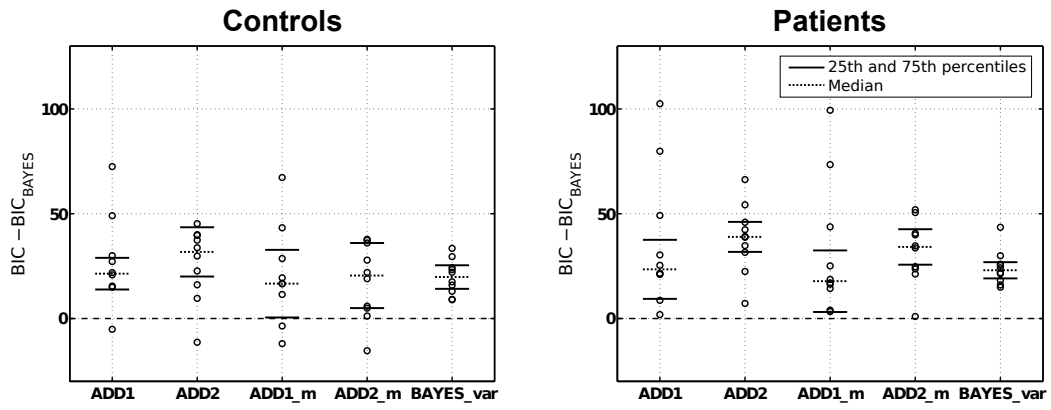

Figure 5.8: Model Comparison using the Bayesian Information Criterion (BIC). The BIC score is evaluated for each model and substracted by the BIC score evaluated for the simple `'Bayes'` for each participant. Values greater than zero indicate that the simple `'Bayes'` model was better at describing the behaviour of the participant.

Our paradigm is well suited to assess whether patients show deficits in probabilistic inference either due to deficits in acquisition of the sensory priors, deficits in the use of these priors, or due to less uncertainty in the encoding of sensory information. Indeed, we found that participants' performances at our task can be accurately described by a Bayesian model where participants learn an approximation of the stimulus statistics in the form of a perceptual prior and combine it with sensory information. Both the perceptual biases and *'hallucinations'* in absence of stimulus can be understood as the signature of this prior. Moreover, our paradigm allowed for the first time to directly measure the acquisition of a perceptual prior in individuals suffering from schizophrenia. Our results suggest that the perceptual priors acquired by our controls and medicated patients are identical (figure 5.7a,b).

However, while patients seem to have learnt the statistics of motion-direction just as well as controls, they reported fewer *'hallucinations'* of the most frequently presented directions. These results concur with previously reported findings suggesting that chronic schizophrenia patients are less sensitive to expectation-driven illusions (e.g. the Hollow-mask illusion) than controls (Tschacher et al., 2006; Dima et al., 2009; Crawford et al., 2010; Williams et al., 2010; Keane et al., 2013). Finally, we find that the strength of positive symptoms correlated negatively with the participants' sensitivity to hallucinations of the motion stimulus (i.e. the stronger the symptoms, the fewer the hallucinations). Similar findings have been reported in studies of the hollow-mask illusion in schizophrenia patients (Keane et al., 2013).

It is intriguing however that the influence of the prior is similar to that of controls for the estimation task but different for the detection task. To reconcile these results,

we considered different hypotheses:

First, it is possible that chronic patients might consistently use a model of the task that is simpler than the Bayesian model. We explored this possibility by assessing whether response-bias models could better account for the performance of patients that have fewer expectations-driven hallucinations. To do this, we used a systematic model comparison approach named the Bayesian Information Criterion (BIC). We found that patients were better described by the Bayesian model than by any other model (figure 5.8), suggesting that fewer hallucinations in our task are not due to the use of a different strategy by these patients.

Second possibility, chronic patients might overestimate the accuracy of their sensory integration (the likelihood), as described by (Adams et al., 2013). This would result in perception driven mostly by sensory information when no stimuli are present, therefore seeing no stimulus when nothing is presented. However, this model should result in weaker perceptual biases in patients compared to controls. This was not the case in our study.

Finally, we posit that chronic patients might have developed a heightened perception threshold requiring higher amount of evidence (i.e. stronger posterior) in order to perceive a stimulus or make a decision about the presence of a stimulus. In fact, patients require higher stimulus contrast and integrate information over longer periods of time before responding (slower reaction times during the estimation task). We hypothesize that it is a possible adaptation strategy used by patients to overcome responding to stimuli that are not truly present (i.e. recurrent complex hallucinations). That is, because patients have formerly been exposed to hallucinations, they might now demand heightened evidence to consciously report perceiving or perceive stimuli that might not truly be present.
This hypothesis deserves more investigation but at this stage it seems compatible with our results. This could be further explored using psychophysical tasks where the prior is given explicitly to the participants (Speechley et al., 2010; Wolpert et al., 2011). However, it is worth noting that this approach might prove difficult if patients are truly impaired when given explicit learning tasks (Gold et al., 2009).

5.10 LIMITATIONS AND FUTURE WORK

Our study was limited in a few ways. First, the sample size used in this chapter might appear relatively small (21 subjects) for an ordinary clinical study in psychia-

try, but it is actually quite typical for psychophysics. Second, the patient group that was presented in this chapter was relatively well at the time of testing (PANSS scores) and displayed IQ levels that are not typical of the general schizophrenia population (van Os and Kapur, 2009). Higher IQ levels have recently been shown to result in better performances in visual perceptual tasks (Melnick et al., 2013). As a result, it is possible that our sample might not be entirely representative of the general population of patients, or patients currently undergoing a psychotic episode. To palliate this limitation we are currently performing the same motion-task in first episode psychosis, chronic schizophrenia patients and healthy controls through a collaboration with Philip R. Corlett at Yale University.

At a later stage, it would be interesting to explore whether pharmacological models of schizophrenia (e.g. acute Ketamine or Amphetamine administration) yield similar results to those observed in first episode psychosis. We can only speculate, although according to the existing literature (Corlett et al., 2007b, 2011) we might expect learning to be altered in this population resulting in increased amounts of hallucinations that are not driven by expectations. It is also possible however that learning of visual statistics might be unscathed, in which case we would predict a large increase in the amount of expectation-driven hallucinations due to an increased top-down signalling of the prior on perception.

5.11 CONCLUSIONS

In line with studies finding no implicit learning deficit in schizophrenia (Kéri et al., 2000; Danion et al., 2001; Marvel et al., 2005; for review see Gold et al., 2009), we find that patients' performances suggest that they correctly acquired the statistics of the stimuli in our task. First, in contrast with studies that assay explicit statistical inference in context with cognitive symptoms such as learning and decision-making (i.e. usually believed to involve frontal regions), here we measured implicit statistical learning of visual stimuli that could be embodied in visual processing areas rather than frontal cortices (Kok et al., 2013). In fact it is worth noting that, while patients with schizophrenia are generally impaired in explicit learning, these appear relatively spared in implicit learning tasks that do not require integrating information after each trial (Gold et al., 2009). Secondly, our patient sample was relatively well at the time of testing and might not be representative of patients experiencing full-blown psychosis (i.e. chronic medicated schizophrenia; mean illness duration 14.72 ± 2.73 years). Our patient sample displayed no significant differences with the control group in terms

of positive-symptom scales and current IQ.

Finally, both patients and controls preferentially hallucinated stimuli at the most frequently presented directions when no stimulus were present, strongly suggesting that they correctly acquired the statistics of the task. Moreover, in line with recent studies (Keane et al., 2013), patients appeared to be less sensitive to expectation-driven perceptual *'hallucinations'* than controls, suggesting that they may have a normal top-down *vs.* bottom-up signalling but a heightened perceptual threshold, requiring higher amounts of evidence in order to perceive a stimulus. In agreement with Keane et al. (2013), we also found that the amount of expectation-driven perceptual *'hallucinations'* were predictive of positive-symptom severity or delusion ideation in chronic schizophrenia.

6

DISCUSSION

In this thesis we investigated whether impairments in reinforcement learning and Bayesian inference could explain the cognitive and positive symptoms observed in schizophrenia. In chapter 2, we first presented a comprehensive survey of the computational literature of schizophrenia, reviewed the advances and predictions made by computational models and highlighted potentially promising research avenues. In chapter 3, we used a reinforcement model of a rodent analogue of the Iowa Gambling Task (IGT) to assay whether maladaptive decision-making can arise from abnormal prediction-error signalling. In chapter 4 we used an optimal inference model of a spatial working memory in an (abductive) attempt to find which hypotheses are most likely to account for a generalised cognitive deficit in psychosis. Finally, in chapter 5, we used a psychophysical task and Bayesian model of perceptual inference to investigate whether chronic schizophrenia patients were impaired in statistical learning and perceptual inference. We first re-introduce briefly the results found in this thesis and elaborate on whether each study individually support the general hypothesis that cognitive deficits and positive symptoms could be explained by impairments in reinforcement learning and Bayesian inference.

6.1 MAIN FINDINGS & INTERPRETATION

First, in a comprehensive survey of the computational efforts made in the field of schizophrenia, we reviewed promising models supporting competing hypotheses of schizophrenia's aetiology, namely the dopamine hypothesis, the glutamate hypothesis, the GABAergic hypothesis, the disconnection hypothesis and finally the Bayesian Brain hypothesis. None of these computational studies could account for the whole range of deficits and symptoms observed in schizophrenia. However, models supporting the dopamine hypothesis were found to collectively account for the wide range of cognitive deficits observed in patients. Specifically, computational models of DA function were able to make relatively strong mechanistic predictions as to how a deficiency of DA signalling could lead to generalised cognitive deficits. Namely, these models suggested that cognitive deficits could stem from either:

1. A weak signal-to-noise ratio due to low D1r activation in prefrontal cortices (dlPFC) involved in working-memory.

2. Excessive striatal D2r activation leading to impairments in prediction-error signalling, known to be instrumental for associative learning, decision-making and goal-directed behaviour.

Both of these systems were investigated in this thesis using a spatial working-memory task known to assay working memory impairments in psychosis (Pantelis et al., 1997; Hutton et al., 1998; Joyce et al., 2002; Wood et al., 2003; Badcock et al., 2005; Pantelis et al., 2009), and a rodent analogue of the IGT (where schizophrenia patients have previously been shown to be impaired; Dunn et al., 2006; Sevy et al., 2007; Kim et al., 2009) that relies on associative learning for task completion.

However, two other types of models were able to make predictions that are worth mentioning here. First, a biophysically realistic model of working-memory using bump-attractors networks (Murray et al., 2012) recently provided compelling evidence that an imbalance between glutamate excitatory and GABAergic inhibition may lead to working-memory deficits. Specifically, the authors found that a disinhibition from GABAergic inhibitory neurons due to an NMDAr hypofunction lead to a less precise encoding of information and an increased susceptibility to corruption by distractor that is similar to the information already encoded. Secondly, computational models supporting the disconnection hypothesis were able to account for the late adolescence onset of the disorder (Hoffman and McGlashan, 1997; McGlashan and Hoffman, 2000). Specifically, this hypothesis argues that during the maturation of the PFC (late adolescence), weak synapses are pruned away to improve global efficiency. In schizophrenia, these models predicted that the maturation process lead to an over-pruning of frontal cortices, leading to both cognitive and positive symptoms. We suggested that both the glutamatergic and GABAergic hypotheses could account for this disconnection syndrome. Namely, that weaker synapses could emerge following a prefrontal NMDAr hypofunction, leading to an over-pruning during adolescence (Greenstein-Messica and Ruppin, 1998). Alternatively, since GABAergic inhibition is essential to γ-band rhythms, inefficient GABAergic inhibition in schizophrenia would result in an asynchrony between cortical areas (Spencer, 2009), leading to a long-range functional disconnection syndrome.
It becomes evident from this review however, that it is difficult to observe a coherent picture from this computational literature which could account for all the deficits and subtleties observed in schizophrenia. Especially, while we found that the glutamate and GABAergic hypothesis appear complementary and could potentially explain a disconnection syndrome, dopamine dysfunction still remains the most prevalent monoamine deficit leading the the positive symptoms observed in schizophrenia (Howes and Kapur, 2009; Howes et al., 2012; Howes and Murray, 2013). However,

pharmacological and behavioural studies investigating the effects of NMDA receptor blockade have suggested that it may lead to strong changes in midbrain DA neurons (e.g. Jentsch and Roth, 1999). It is therefore possible that an NMDAr hypofunction could account for the disconnection syndrome (late adolescence onset of the disorder) and secondary Dopaminergic dysfunction observed in schizophrenia, providing a over-arching theme throughout this literature.

Finally, we compared the empirical support gathered by each hypothesis and found that the Bayesian Brain hypothesis has received relatively little support and empirical investigation with the exception of studies investigating illusions (e.g. Dima et al., 2009; Keane et al., 2013) or explicit statistical learning (e.g. Huq et al., 1988; Speechley et al., 2010). This hypothesis is argued to be able to account for both cognitive and positive symptoms in schizophrenia. Specifically, it is thought that deficient probabilistic learning would lead to an incorrect acquisition of the statistics of the world resulting in deficits of cognition and delusion-like beliefs (Corlett et al., 2009a; Fletcher and Frith, 2009; Frith and Friston, 2012). In turn, these incorrect expectations would lead to deficits in perceptual inference, explaining away the hallucinations experienced by patients with schizophrenia. We investigated this hypothesis using a psychophysical task known to assay statistical learning and perceptual inference mechanisms in healthy controls.

6.1.1 *Associative learning & maladaptive decision making*

In our first study, we used a reinforcement model of a rodent analogue of the Iowa Gambling Task (IGT) to assay whether maladaptive decision-making could arise from aberrant prediction-error signalling. Particularly, in this study we found that in a healthy population of animals, one third of these would prefer the most disadvantageous option (Rivalan et al., 2013), similar to the preference of patients with schizophrenia at the IGT (Dunn et al., 2006; Sevy et al., 2007; Kim et al., 2009). Furthermore, it was found that these poor decision-makers exhibited behavioural traits such as risk-seeking, cognitive inflexibility and excessive reward sensitivity, suggesting that the traits might be responsible for the poor decision-making performances. We implemented an optimal reinforcement learning algorithm of the RGT, that we altered in an attempt to investigate whether these behavioural traits could be modelled as a disruption of the prediction-error signal and lead to the maladaptive decisions. In this computational study we found that:

1. An aberrant prediction error signalling may lead to maladaptive decision making in the proportion of healthy rats that are poor decision makers.

2. The formalism used to describe the behavioural traits appeared to be valid since the parameters implementing the behavioural traits correlated with their experimental counterpart.

Interestingly, when we investigated how the prediction-error disruptions led to maladaptive decisions, we found that abnormal prediction-errors led to the acquisition of incorrect values (over-valuation) for disadvantageous options. That is, abnormal prediction-error led to the acquisition of an incorrect model of the task outcomes, resulting in decisions that appeared optimal according to the agent internal model but were in fact maladaptive according to the real outcomes of the task.
In schizophrenia, patients have been shown to be impaired at the human equivalent of the task (IGT; Dunn et al., 2006; Sevy et al., 2007; Kim et al., 2009). Specifically, patients with schizophrenia appear to exhibit behavioural traits that are similar to these modelled in our task, namely inflexibility to changes in the environment (as measured by the WCST; e.g. Weinberger et al., 1988; Elliott et al., 1995) and reward sensitivity (Kim et al., 2009). Furthermore, patients have consistently been shown to display prediction-error signalling deficits (Corlett et al., 2007b; Murray et al., 2008; Romaniuk et al., 2010; Gradin et al., 2011). As a result we could argue that, similarly to the previous computational efforts of Smith et al. (2004, 2005, 2007) which illustrated how aberrant prediction-error signalling can lead to conditioned-avoidance or latent-inhibition deficits in animal models of psychosis (rats), our study illustrates how aberrant prediction-error signalling could lead to an incorrect acquisition of the values of the world (false task model/beliefs) resulting in maladaptive decision making. Although it might be incorrect to argue that rats have delusions, if we loosen the definition of a delusion to false or erroneous beliefs, then our model can illustrate how prediction-error disruptions eventually lead to the acquisition of false beliefs (incorrect values for the task at play). Specifically, the definition of a false belief in this context has some resemblance to delusions in that it is a belief that is not supported by objective logical evidence, but is nonetheless continuously pursued and reinstated due to a subjective erroneous internal interpretation of the agent, and as a result is relatively impermeable to contradiction (delusion; Corlett et al., 2009b).

6.1.2 *Working memory & cognitive deficits*

In our second study we assessed spatial working memory deficits in first episode psychosis, chronic schizophrenia, bipolar disorder and family relatives of DISC1 translocation carriers. First we wanted to investigate whether different working-memory impairments could be identified in this heterogeneous psychiatric population. Similarly to previous studies using the same spatial working memory task (Pantelis et al.,

1997; Hutton et al., 1998; Joyce et al., 2002; Wood et al., 2003; Badcock et al., 2005; Pantelis et al., 2009), we found significant impairment of working memory in chronic schizophrenia, bipolar disorder and family members. Although, we did not observe an association between translocation status and working memory performances in family members (Gasperoni et al., 2003; Porteous et al., 2006). Interestingly however, our extended data analysis suggested that these groups require more time to solve a set in earlier trials and that this difference cannot be accounted for by the number of errors performed by patients. A recent study using Ketamine (a NMDAr antagonist) in time perception tasks tend to suggest that glutamatergic processes might account for the increased reaction times observed in schizophrenia (Coull et al., 2011).

Secondly we used an optimal inference model of spatial working memory in an (abductive) attempt to find which most commonly debated hypotheses of schizophrenia were most likely to account for the generalised cognitive impairments observed in these groups. Interestingly, we found that our computational analysis reinforced previous suspicions, namely that working-memory maintenance was responsible for the generalised cognitive deficits observed in schizophrenia (Reichenberg and Harvey, 2007). Specifically, the same computational model was found to account for the poor performances of patients with bipolar disorder and family relatives of DISC1 translocation carriers. We suggest however that further investigations are required to identify the possible neurobiological substrates responsible for these working-memory deficits. Specifically, according to the existing computational hypotheses available, two theories prevail, namely the WM gating hypothesis (Cohen et al., 1996; Durstewitz et al., 1999; Braver et al., 1999; Braver and Cohen, 1999, 2000; Durstewitz et al., 2000a,b; Frank et al., 2001; Durstewitz and Seamans, 2002; Gruber et al., 2006; O'Reilly and Frank, 2006; Todd et al., 2008; Badre and Frank, 2012) and the cortical microcircuit imbalance (Loh et al., 2007; Cano-Colino and Compte, 2012; Murray et al., 2012). The former theory suggests that abnormal dopaminergic transmission to the dlPFC leads to a failure to gate and maintain information in memory when faced with distractors, while the latter suggests that excitatory/inhibitory imbalances at the level of cortical microcircuits lead to shallow bump-attractor states that are prone to disruption.

In light of recent findings suggesting that working-memory deficits are predictive of delusional ideation both in psychotic patients and in the general population (Broome et al., 2007; Freeman et al., 2008; Garety et al., 2013), scientists have posited that working-memory deficits could explain deficits in explicit statistical learning (Broome et al., 2007). That is, during explicit statistical learning, patient might require the use of working-memory in order to integrate information over time. Since working-memory appears to be deficient in schizophrenia, the explicit acquisition of statistical

information would in turn be impaired, as found in the beads task (Broome et al., 2007; Garety et al., 2013). It appear therefore possible, that working-memory impairments might be central to explicit statistical learning deficits, which have been linked to —and hypothesised to result in— delusional ideation (Broome et al., 2007; Garety et al., 2013).

6.1.3 *Statistical learning & perceptual inference*

Finally, in our third and last study we investigated implicit statistical learning and perceptual inference in schizophrenia. Specifically, scientists have posited that delusions and hallucinations might stem from an incorrect Bayesian inference mechanism (Friston, 2005b; Corlett et al., 2009a; Fletcher and Frith, 2009; Frith and Friston, 2012; Adams et al., 2013; Jardri and Deneve, 2013). In this framework, hallucinations are argued to arise from either an incorrect acquisition of expectations (statistical learning) or an imbalance between learnt statistics and sensory information (Fletcher and Frith, 2009). To test this hypothesis, we used a psychophysical task previously developed by Chalk et al. (2010) and known to induce the rapid acquisition of a motion stimuli. In this task, healthy individuals were previously found to implicitly acquire the statistics of the stimulus. This learning then influenced perception such that the motion stimuli were perceived as being more similar to the most frequently presented stimuli than they really were (i.e. estimation biases) and participants reported perceiving the most frequently presented stimuli in absence of visual stimuli (i.e. illusion/*'hallucinated'* dots). The goal of this study was to investigate whether patients with schizophrenia could implicitly acquire the statistics of a visual stimuli and to observe how these acquired expectations affected their perception.
Interestingly, consistent with previous studies (Kéri et al., 2000; Danion et al., 2001; Marvel et al., 2005; for review see Gold et al., 2009), we found that the patients' performances suggested that they correctly acquired the statistics of the stimuli in our task. That is, participants appeared not to be impaired in the implicit acquisition of visual statistics, and performed similarly to healthy controls at the task. This is in contrast with previous studies demonstrating impaired statistical learning in schizophrenia (Huq et al., 1988; Speechley et al., 2010; Averbeck et al., 2011; Evans et al., 2012; Joyce et al., 2013). However it is worth mentioning that these tasks typically assay explicit as opposed to implicit statistical learning. That is, in explicit learning tasks patients would be actively engaged in the acquisition of probabilistic information, which might involve cognitive processes such as working-memory to maintain and update information over time (Broome et al., 2007). In contrast, implicit statistical learning of visual stimuli could be embodied directly in visual processing

areas rather than frontal cortices (Kok et al., 2013), and therefore be void of deficits triggered working-memory. These findings are also consistent with reviews suggesting that while patients with schizophrenia are generally impaired in explicit learning, they appear relatively spared in implicit learning tasks that do not require integrating information after each trial (Gold et al., 2009).

Finally, we found that both patients and controls preferentially *'hallucinated'* stimuli at the most frequently presented directions when no stimulus were present, strongly suggesting that they correctly acquired the statistics of the task. Moreover, in line with recent studies (Keane et al., 2013), patients appeared to be less sensitive to expectation-driven perceptual *'hallucinations'* than controls.To explain this phenomenon, we speculated that patients might have developed a heightened perceptual threshold, requiring higher amounts of evidence in order to perceive a stimulus. This is consistent with our findings, namely that patients are generally slower during the estimation task, suggesting that they might integrate information over a larger period of time in order to reach a higher confidence in the perceived stimuli. This is only speculative however, and further investigation is required to replicate and confirm this effect. Interestingly however, in agreement with Keane et al. (2013), we also found that the amount of expectation-driven perceptual *'hallucinations'* were predictive of positive-symptom severity. This would tend to suggest that the perceptual mechanisms investigated in our task may be similar to those leading to hallucinations in schizophrenia. That is, although not directly supporting the hypothesis of a perceptual inference deficit in psychosis, our results appear at least compatible with previous studies suggesting that perceptual inference is different to that of controls in schizophrenia. Further work is required in order to investigate precisely how patients differ from controls. Specifically, using psychophysical tasks were the prior is explicitly given to the participants (Acerbi et al., 2014), one could investigate the suboptimal inference mechanisms that might be present in psychotic patients and are not dependent on prior statistical learning.

6.2 GENERAL LIMITATIONS

In this thesis, we identified some issues and limitations that are worth mentioning. First and foremost, we found that IQ levels were highly predictive of working-memory performances. This is an issue that is often mentioned in the working-memory literature (Piskulic et al., 2007). In our study, while we did observe significant differences in working-memory for the family members, current IQ was found to account for all the performance differences of that group. This would tend to suggest that no significant difference in performance truly existed between family

members and healthy controls, and that instead these difference stemmed from the lower current-IQ of the family members.
We want to express caution regarding this interpretation. In fact, measures of current IQ are computed from a composite of standardized cognitive tests used to assess "independent" cognitive processes, one of which being working memory. Furthermore, although these tests are designed so as to assess independent components, tasks that assay planning and reasoning will always require use of working memory to some degree. That is, part of the IQ score of every participant will be reflected by their intrinsic performances in working memory. We would argue as a result that using IQ as a covariate for a measure or performance in working memory might be inappropriate. To circumvent this issue, scientists typically attempt to match the demographic variables of the groups of interest in order to measure an effect between similar types of populations (IQ, age, education, etc.). However, since mental illnesses such as schizophrenia appear to result in an average IQ drop of about 10 points following the disease onset, one needs to be careful so as to select a sample that will be representative of the psychiatric population.
Secondly, it is worth mentioning that while there is a scientific consensus suggesting that working memory is deficient in schizophrenia (e.g. Gold et al., 2009; Forbes et al., 2009), the specificity of these memory impairments are highly debated (Kapur et al., 2012). For example, scientists argue for a deficit of working-memory capacity (e.g. Gold et al., 2009, 2010), others for deficits of encoding (e.g. Lee and Park, 2005), others suggest a deficit in memory manipulation (e.g. Fletcher and Honey, 2006) and also a deficit of memory maintenance (e.g. Reichenberg and Harvey, 2007). It appear therefore critical that future studies attempt to isolate and investigate systematically and independently the different aspects of working-memory that might be impaired.

6.3 FUTURE WORK

A couple of extensions from the studies presented in this thesis could potentially yield interesting insights on schizophrenia and its mechanisms. First, using the reinforcement learning model of the the rodent gambling task presented in Chapter 3, one could attempt to model the behaviour of patients with schizophrenia at the human equivalent of the task (IGT). Specifically, patients with schizophrenia appear to exhibit behavioural traits that resemble these modelled in our study, namely cognitive inflexibility, reward sensitivity and risk seeking. It would be interesting to test whether the behavioural traits formalised in the model for rodents translate to behavioural equivalents in humans. Particularly, using the IGT, one could use a questionnaire at regular intervals throughout the task (as has been done previously) to

investigate the subjective valuation of options by the patients. If the patients appear to incorrectly overvalue disadvantageous choices in the questionnaire (as predicted by the model), this would provide compelling evidence suggesting that a disruption of prediction-error lead to the acquisition of an incorrect internal model of the task. Such a study could also be performed using functional neuroimaging so as to provide a quantitative measurement of the impairment of prediction-error present in patients during the task. The degree of disruption of prediction-error measured at the task could then be compared to that predicted by the model.
Secondly, one could investigate the probabilistic inference mechanisms that are present in schizophrenia by removing the need for statistical learning. Particularly, using a psychophysical task such as in (Acerbi et al., 2014), where the prior is explicitly presented to the participants, one would be able to study how patients with schizophrenia combine probabilistic information. Specifically, one would be able to investigate whether patients with schizophrenia combine probabilistic information optimally, and whether this differs from that of healthy controls. Finally, one would be able to distinguish whether deficits of probabilistic inference in schizophrenia stem from impairments in the acquisition of statistical information or whether it results from a suboptimal combination of probabilistic information.

6.4 CONCLUSIONS

In this thesis, we investigated whether impairments in reinforcement learning and Bayesian inference could account for the cognitive and positive symptoms observed in schizophrenia. First, we illustrated that impairments in prediction-error signalling can lead to maladaptive decision making through an incorrect acquisition of the values of the environment. We further suggested that an aberrant prediction-error signalling led to the acquisition of an incorrect model of the task outcomes, resulting in decisions that appeared optimal according to the agent's internal model but were in fact maladaptive according to the real outcome of the task. We then argued that this has some resemblance to delusions, in that it is a false belief that is not supported by logical evidence but will be continuously pursued and reinstated due to an erroneous subjective internal model of the world. Secondly, our model comparison analysis suggested that a deficit of working-memory maintenance accounted best for the performance deficits observed at a spatial working memory tasks in patients with chronic schizophrenia, bipolar disorder and family relatives of DISC1 translocation carriers. As recently suggested (Broome et al., 2007; Garety et al., 2013), working memory appear to be linked with failures in statistical learning and delusional ideation. This has led scientists to suggest that working memory might be required in order

to perform explicit statistical learning (Broome et al., 2007), and that an impairment of working-memory maintenance could explain deficits in integrating explicit statistical information over time (Broome et al., 2007; Garety et al., 2013). Finally, we demonstrated that patient with chronic schizophrenia do not show implicit statistical learning deficits of a motion stimuli and established that patients have identical estimation biases and perceptual inference mechanisms to that of healthy controls. However, we found that patients appear to make less expectation-driven *'hallucinations'* of the motion stimulus when no stimulus was presented, and that the number of these *'hallucinations'* appear to correlate with positive symptom severity. This led us to suggests that positive symptoms in schizophrenia might be compatible with a deficit of perceptual inference, but that further work is required to investigate the implications of this finding. It is worth mentioning however that one might argue that since patients tend to *'hallucinate'* less than controls in our task, they are in essence more *'optimal'* in terms of perceptual inference than controls. However, as Teufel et al. (2013) recently argued, it is the combination of the prior and likelihood that lead to optimal perception so as to disambiguate noisy sensory evidence, even if this sometimes leads to perceptual illusions. As a result, a lack of illusions or *'hallucinations'* in our task should rather be seen as evidence for a deficit of perceptual inference rather than evidence for a more optimal inference than that of controls.

Finally we conclude that impairments in reinforcement learning and Bayesian inference appear to be able to account for the positive and cognitive symptoms observed in schizophrenia, but that further work is required. Specifically, while our studies addressed individual components such as associative learning, working memory, implicit learning & perceptual inference, we cannot conclude that deficits of reinforcement learning and Bayesian inference can collectively account for symptoms in schizophrenia. We argue however that our studies provided evidence that impairments of reinforcement learning and Bayesian inference are compatible with the emergence of positive and cognitive symptoms in schizophrenia.

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Part I

APPENDIX A

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PLOS ONE

Elucidating Poor Decision-Making in a Rat Gambling Task

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Abstract

Although poor decision-making is a hallmark of psychiatric conditions such as attention deficit/hyperactivity disorder, pathological gambling or substance abuse, a fraction of healthy individuals exhibit similar poor decision-making performances in everyday life and specific laboratory tasks such as the Iowa Gambling Task. These particular individuals may provide information on risk factors or common endophenotypes of these mental disorders. In a rodent version of the Iowa gambling task – the Rat Gambling Task (RGT), we identified a population of poor decision makers, and assessed how these rats scored for several behavioral traits relevant to executive disorders: risk taking, reward seeking, behavioral inflexibility, and several aspects of impulsivity. First, we found that poor decision-making could not be well predicted by single behavioral and cognitive characteristics when considered separately. By contrast, a combination of independent traits in the same individual, namely risk taking, reward seeking, behavioral inflexibility, as well as motor impulsivity, was highly predictive of poor decision-making. Second, using a reinforcement-learning model of the RGT, we confirmed that only the combination of extreme scores on these traits could induce maladaptive decision-making. Third, the model suggested that a combination of these behavioral traits results in an inaccurate representation of rewards and penalties and inefficient learning of the environment. Poor decision-making appears as a consequence of the over-valuation of high-reward-high-risk options in the task. Such a specific psychological profile could greatly impair clinically healthy individuals in decision-making tasks and may predispose to mental disorders with similar symptoms.

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Introduction

Several mental disorders related to poor executive functioning, such as substance abuse, pathological gambling, attention-deficit hyperactivity-disorder or mania, share common deficits and behavioral traits. Impulsiveness, risk taking [1] or inflexible behavior [2,3,4,5], are often present, suggesting that they may jointly contribute to pathological behavior. Poor decision making is a hallmark of these mental disorders as these patients are commonly impaired in the Iowa Gambling Task (IGT). This task measures the capacity to balance risks and gains and to resist immediate gratification in order to receive a larger long-term gain [6]. Interestingly, within a healthy population, a subset of individuals described as impulsive and sensation seekers display poor decision making in this task [7], supporting the notion that a continuum may exist between normality and pathological conditions. Accordingly, neuropsychological characteristics leading to poor decision making in healthy individuals are probably shared by clinical poor decision makers, and could be a potential risk factor for developing related mental disorders [8,9].

We have developed a single-session Rat Gambling Task (RGT) that reproduces the IGT principles [10,11,12]. In this uncertain and conflicting situation, individuals without prior knowledge of the outcomes must gradually learn that the less immediately rewarding options are also less risky and more advantageous in the long term.

Using lesion studies, we have recently shown that good performances in the RGT depend of the functional integrity of several areas of the prefrontal cortex [12]. Like humans, a majority of rats are good decision makers (good DM) and choose the best options, whereas a minority prefers the worst options. These inter-individual differences are stable over time, specific to decision-making processes and reproducible across groups [11]. We previously showed that, like humans, rats that are poor decision makers (poor DM) are risk-prone and more sensitive to reward than good DM [11]. However, although these traits were clearly associated with poor decision making in the RGT, they were not sufficient to dissociate good from poor performers individually, as some good DM were also risk-takers and/or higher reward seekers. Therefore, additional factors, such as inflexibility and impulsivity, could be involved in combination with these traits.

Here, we present an analysis of how inter-individual differences in clinically relevant behavioral traits may contribute to poor and good decision making in the RGT. We show that a combination of

several independent behavioral and cognitive characteristics in one individual, namely risk-proneness, motivation for reward, motor impulsivity and behavioral inflexibility, has a cumulative effect and is highly predictive of performance in the RGT. To quantitatively explore the impact of these traits on learning and decision-making, we developed a computational model of the RGT based on the Temporal Difference (TD) learning algorithm [13,14,15]. The basic TD framework was extended to take into account risk seeking, reward seeking and cognitive inflexibility and to estimate those behavioral traits in individual rats. The model provides a possible explanation of their impact on learning and decision-making performances in the RGT.

Materials and Methods

Ethics Statement

All procedures were conducted in strict accordance with the 2010-63-EU and with approval of the Bordeaux University Animal Care and Use Committee (Permit number: 5012087-A).

Behavior

Subjects. Male Wistar Han rats ($n = 29$; Charles River, France) were 12-13 weeks old at the beginning of the experiment. They were housed in groups of four in a temperature (23°C) and humidity-controlled room (60%) on an inverted 12 hr light/dark cycle (lights on at 20:30). Tests were conducted during the dark phase of the cycle. A week before the beginning of the experiments, animals were handled every day. Rats had free access to food and water except during impulsivity and decision-making tests during which they were moderately food deprived (95% free feeding weight). The configuration of the apparatus and the order of testing were chosen to minimize any possible interference between protocols (see Figure 1 for order and duration of tests). The whole behavioral testing phase lasted 6 months (178 days).

Decision-making. The RGT requires successive choices among four options in an operant cage [10,11]. Two of the four options are associated with a higher immediate gain, but are disadvantageous in the long run due to higher unpredictable penalties (time-outs). The experiments were performed in twelve polyvalent conditioning boxes (Imetronic, Pessac, France; 28×30×34 cm). Boxes were equipped with four nose-poke holes, dimly illuminated within the hole with a white LED. These holes were located on a curved wall on one side of the box, equidistant to a food magazine situated on the opposite wall. Each hole was equipped with an infrared detector connected to an external dispenser delivering food pellets (45 mg, formula P, Sandow scientific, USA). Data collection was automated using a control software (Imetronic, Pessac, France) running on a computer outside the testing room. At least thirty minutes before each session, the rats were placed in the light-attenuated and temperature-controlled (23°C) experimental room.

Training: During the training phase, the rats learned to associate two consecutive nose-pokes in one of the four illuminated holes with the delivery of one or two food pellets in the magazine. First, the rats had to associate a single nose-poke in any of the four illuminated holes with the delivery of one food pellet in the magazine. After a nose poke, only the selected hole remained illuminated, but all were inactivated until the rat collected the food reward. This procedure continued daily until rats obtained 100 pellets within a session (30 min cut-off). Then two consecutive nose-pokes in the same hole were required to obtain food, to ensure that the selection of the hole was a voluntary choice. After reaching the same criterion, rats were submitted to two final 15 min training sessions. In the first session, two pellets were delivered after a choice was made (maximum 30 pellets). This session habituated the rats to the quantity of pellets which could be obtained during the test. A second session followed, delivering only one pellet at a time (maximum 15 pellets). The number of reward deliveries was reduced to avoid reduction of sampling and the development of a preference for a hole. The training phase usually lasted 5-7 days and tests were performed the following day.

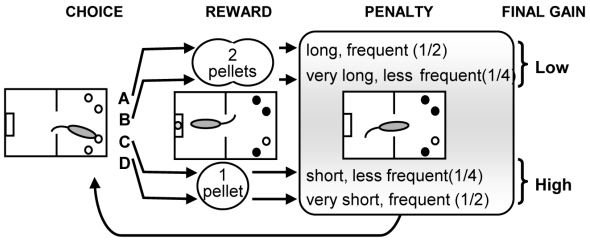

Figure 2. Principle of the Rat Gambling Task. Rats can nose-poke among four different holes (A, B, C and D) in an operant cage, to earn food reward (1-hour test). The selection of one option is immediately rewarded, but can also be followed by a penalty (time-out) of variable duration, according to different probabilities. Two options (C, D) are equally more advantageous than the other two (A, B), which are equally disadvantageous in the long term.
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Test: Rats could freely choose between four nose-poke holes (A-D) during a one-hour test session (or max. 250 pellets obtained). Choices C and D *vs* A and B led to the immediate delivery of one *vs* two pellets, but choices A and B could be followed by longer, unpredictable penalties (222 s and 444 s time-outs) compared to choices C and D (12 s and 6 s). Penalties occurred at a low probability (¼) for choices B and C, and at a high probability (½) for choices A and D (Figure 2). During the penalty, all lights were switched off and nose-poke holes were disabled, but the chosen hole remained illuminated to facilitate association between each choice and its consequences. A brief extinction of this light (1 sec) signaled the end of the time-out. The theoretical maximum gain was the same for advantageous choices C and D, and five times higher than for disadvantageous choices A and B.

Good and poor decision makers were differentiated on the basis of the percentage of advantageous choices (>70% and <30% respectively) during the last 20 minutes of test. The remaining rats

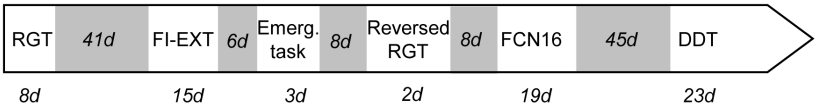

Figure 1. Order and duration of behavioral tasks. The number of days (d) of each behavioral testing phase (below arrow) and inter-test periods (grey zones) are indicated. RGT: Rat Gambling task, FI-EXT: multiple fixed-interval/extinction schedules, Emerg. Task: Light-dark emergence task, FCN16: Fixed consecutive number 16 cue schedule, DDT: Delay discounting task.
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were undecided with intermediate scores (between 30% and 70% advantageous choices) [10,11,12]. The mean latency to collect food pellets after a choice was taken as an indicator of the rats motivation for the food reward [11].

Behavioral flexibility. In a second stage, the contingencies for A-B and C-D were spatially reversed to assess behavioral flexibility [11]. To reduce spatial preferences related to the previous experience in the RGT, animals were first given a new training session (100 pellets or 30 min cut-off) during which only one hole at a time, pseudo-randomly, was illuminated and operating at a time, each nose-poke delivering 1 pellet. The test in reversed condition was done the following day, in the same conditions as the RGT, except that options A-B and options C-D were spatially exchanged.

Performances were calculated as the mean percentage of choices for the preferred contingency during the RGT. Behaviors were differentiated on the basis of the time course of choices and flexibility. The observed behaviors were classified into three categories: flexible behavior, with progressive reversion towards the new location of their favorite options (>60% of choices during last 20 min), undecided behavior (choice between 40% and 60%) and inflexible behavior with perseveration of previously learned choices (<40% of choices).

Impulsive actions: anticipatory hyperactivity and perseveration. The multiple Fixed-Interval/Extinction schedules of reinforcement (***FI-EXT***) was performed during a single session in operant chambers equipped with one lever. The chambers used for this test were different from the ones used in the RGT [16]. Two periods of fixed-interval schedule of reinforcement (FI) alternated with two periods of extinction (EXT) (FI-EXT-FI-EXT). Impulsive responses corresponded to lever presses during frustrating periods where no reward was available.

The apparatus consisted of eight sound-insulated light-tight outer chambers each containing a two lever conditioning box (Imetronic, Pessac). The boxes (32×32×22 cm) were constructed from white plastic panels with a Plexiglas door. They were equipped with a fan providing a background noise. Each box was permanently illuminated by a diffuse 2 lux light source located in the middle of the ceiling (house light). The floor consisted of 5 mm diameter stainless steel bars spaced 1.5 cm apart. Two stainless steel levers protruded horizontally 1 cm from the wall situated at the left of the door, 16 cm apart and 6 cm above the grid floor. A tray was situated centrally on the opposite wall. Food pellets (45 mg, formula P, Sandow scientific, USA) were delivered in the tray by a food dispenser. A program (Imetronic, Pessac) controlled the chambers and collected the data on a computer situated outside the testing room.

Training and test: During FI, the house light was on and the first lever press after a designated time-interval was reinforced by a food pellet. A light above the lever was on when the pellet was available until the rat visited the tray. During EXT (5 min), the house light was off and no pellet was delivered. During each session, the FI and EXT components operated twice in alternation. Rats were first trained with four sessions with a 30s FI-EXT schedule. Then, rats were trained for four sessions on a 1 min FI-EXT schedule followed by three sessions with a 2 min FI-EXT schedule. A maximum of 7 pellets per FI (14 pellets in total) were delivered during the 1 and 2 min FI conditions. Finally, rats were tested for four sessions on a 1 min FI-EXT schedule to assess adaptability to a change for a shorter FI phase. This latter condition has been chosen for analysis.

Data measure: The mean number of lever presses during each FI and each EXT conditions was recorded. As previously described [16], data from the initial FI after the start of the session, as well as that from the first interval following the first EXT were excluded because the behavior during these intervals might deviate from those during the other intervals. The total mean number of lever press, the number of visits to the empty tray as well as the speed in collecting pellets were also measured for FI and EXT.

Impulsive actions: premature responses. The Fixed Consecutive Number of 16 lever press schedule (***FCN16***) measures behavioral inhibition in operant chambers by testing the rat's ability to carry out a long chain of sequential lever presses before obtaining a reward [17]. The schedule required a fixed minimum number of 16 responses on one lever (FCN lever), signaled by a cue light, before a response on the second lever (Reinforcement lever) resulted in the delivery of one food pellet. Impulsivity was reflected by the proportion of prematurely ended chains of presses on the FCN lever. These chains reset the count and were not rewarded. Chains longer that 16 responses were scored as perseveration.

The operant chambers used for FCN16 testing were similar to the ones used for the FI-EXT schedule, except that they had 2 levers situated on the wall opposite to the food magazine. A cue light above the right lever was also added. The reinforcement lever, much less used than the FCN lever, was the one previously used in the FI-EXT schedule.

Training: On the first day, only the reinforcement lever was available and every press resulted in the delivery of a food pellet in the tray. The rats quickly obtained at least 100 pellets within 40 min (criterion). The following days, both levers were available and the light above the FCN lever was turned on and rats were required to press the FCN lever first and then to press the Reinforcement lever to obtain food (FCN1). The cue light was switched off when the rats had completed the number of consecutive presses required on the FCN lever to obtain food. The cue light signaled the completion of the response requirement to avoid confounds related to time estimation [17].

This cue light was turned on again when rats visited the tray. If the chain was shorter than the number required, the rat had to start a new chain. If the chain was longer, it had no consequence, and the pellet was delivered when the rat pressed the reinforced lever. When 100 pellets were obtained within a session (40 min cut-off), the FCN requirement was progressively increased to 2, 3, 5, and then 8 and 12 using a less strict criterion (45-min cut-off and at least 70 pellets) to avoid overtraining. Rats that failed to reach the criterion in FCN5 after 20 training sessions were excluded from this task. Training under FCN12 lasted a minimum of two consecutive 30-min sessions until rats had reached a stable level of performance.

Test: Rats were tested using the same procedural conditions as in training but with a FCN requirement of 16 lever presses (FCN16) during three consecutive sessions (30 min or 100 pellets cut-off). A rewarded chain of lever presses corresponded to 16 or more lever presses executed on the FCN lever before pressing the reinforced lever.

Data measure: Only data from the third session of FCN16 were analyzed because they revealed the largest inter-individual behavioral differences between good and poor decision makers. Impulsivity in this task is reflected by a low percentage of rewarded chains (<70%). Among rewarded chains, some were just as long as necessary (16 presses) and reflect high response efficiency, whereas some others exceeded the number of presses required and reflect low response efficiency. Thus, response efficiency was estimated by the number of FCN lever presses divided by the total number of food pellet consumed. The number of sessions needed to reach the

test phase (learning score) and response rate (total number of each lever responses per min) were also considered. The distribution of the mean number of chain of lever presses according to their length was analyzed.

Impulsive choice: delay discounting. The Delay Discounting Task (***DDT***) measures impulsive choice in an operant chamber by assessing the preference for an immediate small reward (one pellet, when pressing one of the levers) over a larger one delivered after a delay (5 pellets, when pressing the other lever). The delay preceding the delivery of the larger reinforcement was progressively increased between sessions.

The operant chambers were the same as those used for the RGT, except that the curved wall was replaced by a straight one equipped with two levers facing the food magazine on the opposite wall. The house light, two cue-lights above the two levers and one cue light in the tray of the food magazine were available and could be turned on and off depending of the procedure.

Training: During training, a press on the right lever (L1) resulted in the immediate delivery of one food pellet whereas a press on the left lever (L5) readily delivered five pellets. Given that the rats were previously trained in the FCN16 schedule that also used two levers (the previous FCN lever being now the L1 lever), a training period was conducted in order to obtain stable performances with no interference from previous requirements. This training period lasted until the rats made more than 70% L5 selections with less than 15% variation in this score on 2 consecutive sessions (in total, 3 sessions were necessary). Whenever an operant lever press was made, a light above this lever was switched on for 1s. Three seconds after food delivery, the magazine light was turned on for 60s, during which time additional presses were without consequence (time-out). The end of this time-out and the beginning of a new trial was signaled by turning off the food magazine light as well as the house light. The duration of the time-out was adjusted such that the duration of each trial was the same whichever lever was chosen.

Test: During the test phase, a press on L1 immediately delivered one food pellet, and was followed by a 60s time-out, whereas a delay was inserted between L5 pressing and the delivery of the five pellets. During this delay, the light above L5 lever remained on until the pellets were delivered, then a time-out (60s minus the length of the delay) immediately followed food delivery. The delay was fixed for a given daily session and increased progressively over the days by 10s from 0 to 40s according to a criterion of stability: scores over two consecutive sessions should not vary by more than 10%. All sessions ended when 100 pellets had been delivered.

Data measures: Percentage of L5 choice, total mean number of lever presses, and presses during the delay and time-out periods were measured. These parameters were calculated for each delay as the mean of the last two stable sessions.

Risk taking. The light-dark emergence test allows assessment of spontaneous risk taking behavior in rats [11]. Exiting from a dark, safe compartment to a brightly illuminated one is a risky and stressful situation for a rat. This test was performed in a box (40×40×35 cm) with two small equal compartments that limit exploratory behavior. An aperture (12×31 cm) enabled the rats to pass from one compartment to the other. One was completely enclosed by black opaque plastic sides, with a lid of the same material, while the other was white, had no lid, and was illuminated (560 lux). The rat was placed in the illuminated compartment facing the wall opposite the door. Rat was free to explore the two compartments of the apparatus during a single 10 minute session. Rats were tested in the middle of the dark phase between 10:00a.m and 1:00p.m.

Data measures: From rat first entrance in the dark box, the latency to emerge from this compartment to the illuminated one was recorded (600s cut-off). Risk assessments were evaluated by number of body stretching and by head protruding in the light compartment, with at least the hind limb remaining in the safe compartment. Because these two parameters are correlated with the number of visits of the extremity of the open arms of an elevated plus-maze, which is the more risky area of this task (see [11]), we considered them as a measure of risk-taking. Proportions of visits and time spent in the dark compartment (%) were also measured.

Analysis of individual differences. For each test, the proportion of rats with scores above or below the median of the whole population was recorded. These measures were used to compare good and poor DM subgroups and to identify behavioral parameters that could discriminate between the two groups. The scores measured in each of the four individual tasks in which good and poor DM differed were ranked and then summed across the four tasks to produce a global index for each rat.

Statistical analyses of behavioral data. Student's t-tests were used to compare subgroup scores in the RGT (mean ± s.e.m.) with indifference level. Comparisons of scores between good and poor decision making groups were made using the non-parametric Mann-Whitney test (*U*). Correlations between scores were evaluated using the non-parametric Spearman correlation test (Statistica, Statsoft 7.1). Comparisons of proportions of individuals were conducted using the non-parametric Fisher exact test (StatXact 9).

Computational model

Temporal Difference learning model. The environment of the RGT was modelled using a Markov decision process. The four possible choices (actions) in the task lead to different rewarded states *s* (i.e. high reward 'r = 2 food pellets' for choices A & B or a low reward 'r = 1 food pellet' for choices C & D). Each of these states is then followed by a probabilistic transition to the penalty associated with the reward state *s* (penalty transition probabilities are ½, ¼, ¼, ½ for the A, B, C and D states respectively). Penalties correspond to time-outs during which no food can be obtained. In the absence of penalties, rats obtain and consume on average one food pellet in nine seconds ($\delta_{episode} = 9$ s). Therefore, time-outs of duration $\delta_{timeout}(s)$ can be expressed in terms of a gain loss (in units of food pellets) equivalent to an immediate penalty defined as:

$$plty(s) = \frac{\delta_{timeout}(s)}{\delta_{episode}} \quad (1)$$

This results in penalty values of −50, −25, −4/3, −2/3 food pellets for the states A, B, C, and D respectively.

The reward received after taking action *a* in state *s* is described by a state-action pair value Q(s,a), which gradually comes to reflect the 'goodness' of selecting action *a* when in state *s* [22−24]. In this framework, the agent learns the value corresponding to each state-action pair Q(s,a) by updating its expectations of the reward Q(s,a) towards the reward received the last time action *a* was chosen in state *s*. This updating is based on the prediction error between the predicted reward for the state-action pair Q(s,a) and the reward actually received *r*.

$$Q(s_t,a_t) \leftarrow Q(s_t,a_t) + \alpha(r_{t+1} - Q(s_t,a_t)) \quad (2)$$

where α is the learning rate parameter, r_{t+1} is the reward received after choosing action a, $Q(s_t,a_t)$ is the current estimate of the value of choosing action a in state s at time t [23]. This learning process causes Q(s,a) to gradually approach the real value of choosing action a. No temporal discounting parameter was introduced in this model as individual trials were considered to be independent each of them leading to immediate reward consumption as well as possible penalties.

Learning model with behavioral traits. We have extended this basic framework to account for risk seeking, reward seeking, and cognitive inflexibility.

Modeling cognitive inflexibility. The cognitive inflexibility trait is modelled for simplicity by adjusting the learning rate parameter α: α is split into two separate components, an initial learning rate parameter α_0 and an exponential decay with time constant τ_0, which gradually reduces the learning rate across the session:

$$\alpha \leftarrow \alpha_0 \cdot e^{-\frac{t}{\tau_0}} \quad (3)$$

Parameter α_0 is comprised between 0 (no learning) and 1. Parameter τ_0 determines how quickly the agent stops learning and becomes insensitive to the reward prediction error. Each rat is described by particular values of α_0 and τ_0 and is thus characterised by a unique learning rate profile. Individuals with low α_0 and/or low τ_0 describe rats that are inflexible. A further global index of flexibility is given by the integration of α over time. We are aware that recent modelling studies have suggested using a state-splitting mechanism [18,19] to account for the commonly observed rapid recovery of performances during re-instatement of learned contingencies after extinction. However, our experiments did not address the recovery of the initial RGT conditions after the reversal. Therefore, implementing the state-splitting mechanism would have greatly increased the model complexity (i.e. number of free parameters) without improving the fit to the data.

Modeling reward seeking behavior. The reward seeking trait is introduced as a modulation of the magnitude of the actual rewards r_t by a multiplicative weight:

$$r_t \leftarrow \omega \cdot r_t \quad (4)$$

Values of $\omega > 1$ correspond to the agent representing the reward values as higher than they really are. It was shown experimentally that poor decision makers were able to perform optimally, similar to the good decision makers, in a penalty-only version of the RGT. Therefore, sensitivity to penalty was left constant across animals. In the RGT, rewards are equal to either one or two. Therefore, modelling reward seeking as a multiplicative weight on the true reward provides the simplest way to describe the transformation from objective to subjective reward values [20].

Modeling risk seeking. Following previous work [21], the behavioral trait of risk seeking (or risk aversion) is implemented by adding a positive (or negative) component to the reward that is proportional to the risk level of the action. We define the risk level associated with an action a as the standard deviation of penalty values experienced by the agent each time it has taken action a:

$$\sigma_{plty}(s_t,a) = \left(\frac{1}{n-1} \sum_{i=1}^{n} \left(plty(s_i,a) - \overline{plty(s,a)} \right)^2 \right)^{\frac{1}{2}} \quad (5)$$

where n denotes the number of times the action a was taken from the start of the session and $\overline{plty(s,a)}$ is the average of past penalties:

$$\overline{plty(s,a)} = \frac{1}{n} \sum_{i=1}^{n} plty(s_i,a) \quad (6)$$

Therefore, the combination of reward seeking and risk seeking is modelled replacing the reward by:

$$r_t \leftarrow \omega \cdot r_t + \rho \cdot \sigma_{plty}(s_t,a) \quad (7)$$

where ρ controls the strength of the risk seeking trait and is unique to each individual rat. A positive value denotes risk-seeking while a negative value corresponds to risk aversion. We choose to model risk in this form, in contrast to some other methods [22,23,24], as the present form requires only one parameter and allows learning to reach larger asymptotic values in risky situations.

Final learning model. The resulting model is a TD learning algorithm where risk seeking and reward seeking traits affect the value of rewards, while cognitive inflexibility controls the rate of learning. Putting all the traits together, the learning rule is:

$$\begin{aligned} &Q(s_t,a_t) \leftarrow Q(s_t,a_t) + \\ &\alpha_0 \cdot e^{-\frac{t}{\tau_0}} \left[\left(\rho \cdot \sigma_{plty}(s_t,a) + \omega \cdot r_t - plty(s_t,a) \right) - Q(s_t,a_t) \right] \end{aligned} \quad (8)$$

All actions values are initialised to zero prior to learning.

Decision-making. Actions are selected according to a Softmax process, by assigning a probability of selection to each available action $p(s_t,a)$ depending on the value of all available states:

$$p(s_t,a) = \frac{e^{\frac{Q(s_t,a)}{\varepsilon}}}{\sum_i^n e^{\frac{Q(s_t,i)}{\varepsilon}}} \quad (9)$$

where ε is a temperature parameter which controls the amount of exploration. A high level of exploration is imposed to all subjects during the first 10 min of simulation to ensure that all the options are initially sampled (by analogy with the behavioural procedures).

Parameter estimation & model fitting. The performance of this model during the RGT is fitted to the performance profile of each individual rat using Maximum Likelihood, in order to extract a set of parameters that best describes the rat's behavior (i.e. a set of four parameters influencing learning α_0, τ, ω, ρ and one parameter influencing the exploration/exploitation trade-off ε):

$$\hat{\theta}_{mle} = argmax \ell(\theta | x_{10}, \cdots, x_{60}) \quad (10)$$

where $\ell(\theta|x_{10},\cdots,x_{60})$denotes the likelihood of the data under the model, θ are the model parameters, and x_{10} to x_{60} are the experimental performance levels (percentage of advantageous choices) of the rat over successive 10 min blocks. The likelihood is computed by running the RGT model 50 times for a given set of parameters. Using the performance profiles extracted for each model iteration, we calculate the probability distribution of getting an advantageous choice at every 10 minutes time-bin. The maximum likelihood is the set of parameters that gives the highest probability of resulting in the observed rat performance profile at each of the 10 minutes time-bin.

Model comparison. We used the Likelihood Ratio Test and the Bayesian Information Criterion to test whether simpler models including only 1 or 2 behavioral traits could be as predictive of poor decision making as the full model.

Data analysis. The significance of the observed correlation coefficient between the experimental measures and the modeled behavioral traits was tested using Monte Carlo permutations.

Monte Carlo permutation test. This method performs random permutations to mix the paired values (i.e. modelled trait parameter values and the experimental analogue values) and measure the new correlation coefficients for each new permutation. Doing so a large number of times (i.e. 100000 iterations) provides a distribution of correlation coefficients for random permutations of values so as to test the null hypothesis.

Group correlation measure. This correlation measure was used to assess whether the model parameters and experimental measures agreed on the classification of individual rats as having a low or high score for each trait. For each behavioral trait, rats received a score of '-1' (lower than median value for the behavioral trait) or '+1' (higher than median). This was done both for the experimental measures and the estimated parameters. The correlation coefficient between the experimental and theoretical pairs of scores was then computed and the p-value was extracted using the Monte Carlo permutation test.

Individual correlation measure. We also measured whether the estimated model parameters correlated with the experimental measures of reward sensitivity, cognitive inflexibility and risk seeking.

Results

Behavior

Decision-making in the RGT. The RGT measures, across successive trials, the ability to make the most advantageous choices. In this task, the contingencies associated with a higher immediate gain are disadvantageous in the long run due to higher unpredictable penalties. Decision-making could not be properly measured in six rats because they immediately demonstrated a preference without sampling the different options at the beginning of the test. These rats were discarded from the analysis. Three rats did not display preference for any particular option (undecided subgroup). Because of the small size of this group they were also discarded from our analyses. Among the remaining rats ($n = 20$), behavior during the test was not influenced by prior spatial preference: proportions of individuals with analogous choices during training and testing did not significantly differ from chance (Chi-square test, $\chi^2 = .438$; $p = .33$; ns).

As observed previously, typical good and poor decision makers can be distinguished within a normal group of rats. Because this task measures a preference between two kinds of options, two subgroups can be easily distinguished, as shown by the bimodal distribution of RGT scores (see meta analysis on Figure 3). Good DM first choose randomly and then gradually orient most of their choices toward the advantageous options (Figure 4A). By contrast, poor DM sample the different options and rapidly orient their choices toward the disadvantageous options (within 10 minutes). During the last 20 minutes, percentages of choices for advantageous options could be divided into two main subgroups: a majority of good DM ($n = 14$; 61%, with scores above 70%) and a minority of poor DM ($n = 6$; 26%, with scores below 30%) that preferred the disadvantageous options (n.b. scores for the remaining undecided subjects were 38%, 54% and 63%).

Decision-making and reward seeking. Poor DM showed a shorter latency to collect their reward than good DM, as previously observed [11] (Figure 4B). All poor DM scores (100%) were below the median *vs* 36% for good DM (Fisher exact test, $p = .032$; group medians, 1.12 and 1.26 s respectively; $U = 16$, $p = .07$). However, the global activity of the two groups, reflected by the total number of visits to the nose poke holes, did not statistically differ (median scores: 1025 and 857 for good *vs* poor DM respectively; $U = 20$, ns).

Behavioral flexibility. Reversing contingencies in the RGT measures the rats' adaptation when advantageous/disadvantageous outcomes are spatially exchanged. Persistence to choose the same location reveals cognitive inflexibility (flexibility <35%), whereas shifting choices reflects detection of the change and behavioral flexibility. All poor DM *vs* only a third (36%) of good DM were inflexible (Fisher exact test, $p = .014$; Figure 4C). Among the remaining good DM, 36% gradually reoriented their choices toward the new location of advantageous options, and 28% distributed their choices between all options (Figure 4D).

Decision-making and risk seeking. In the light-dark emergence test, poor DM took more risks than good DM. They emerged more rapidly from the dark compartment than good DM (medians, 35 and 416 sec respectively; $U = 13.5$, $p<.02$). A majority of poor DM (83%) *vs* 36% of good DM had a score below the median. Poor DM also made much fewer risk assessments than good DM before the first exit (100% *vs* 29% below the median; Fisher exact test, $p = .0007$; Figure 4E). The median number of risk assessments were 1.5 and 11.2 for poor *vs* good DM respectively ($U = 1.5$, $p<.001$). Poor DM also tended to make

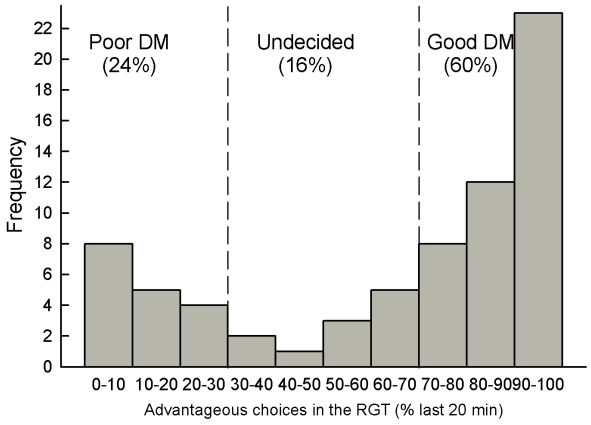

Figure 3. Meta analysis of the RGT data. This analysis is based on 12 distinct experiments (n = 228) using the same protocol. It reveals a bimodal distribution of RGT scores (% of favourable choices during the last 20 min) with a majority of good decision makers (good DM, with scores above 70%), a minority of poor decision makers (poor DM, with scores below 30%) and the remaining, undecided rats with intermediate scores.
doi:10.1371/journal.pone.0082052.g003

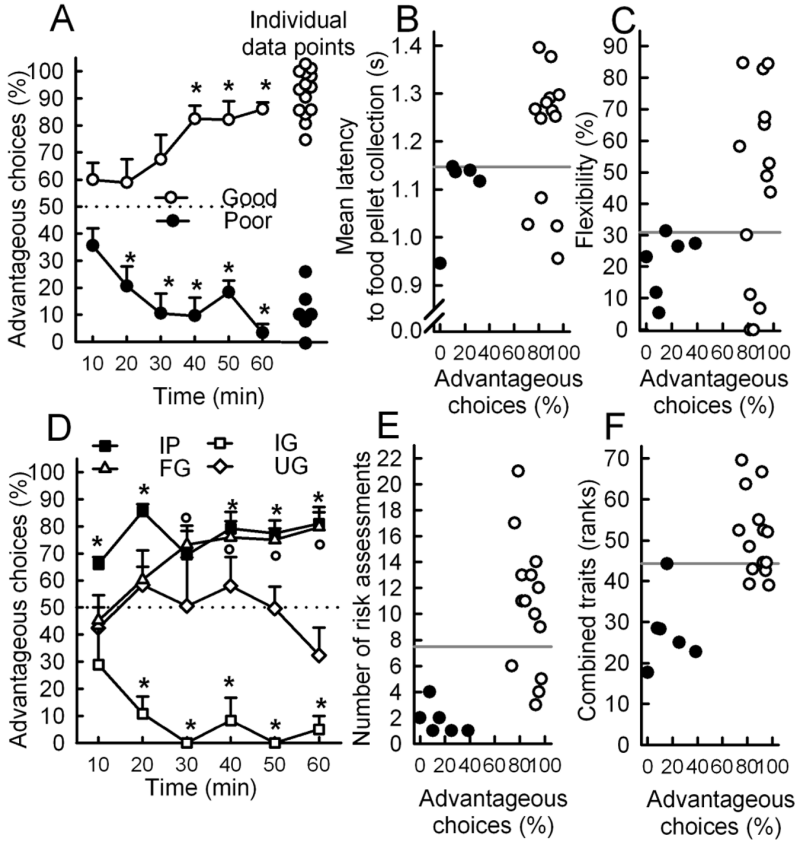

Figure 4. Animal's performance on the Rat Gambling Task (RGT), RGT-reversed version and the light-dark emergence test. Grey lines represent the median used to compute proportions of high and low scores in good and poor decision makers (DM). (A) Time-course of advantageous choices (%) of good and poor DM on the RGT and individual scores during the last 20 min of good ($n = 14$) and poor ($n = 6$) DM. (B) Relationship between individual RGT scores and the mean latency to collect food pellets (one missing value) during the RGT. (C) Relationship between individual RGT scores and flexibility (final scores in the RGT-reversed version). (D) Time-course of advantageous choices of flexible (FG), undecided (UG) and inflexible (IG) good DM and inflexible (IP) poor DM groups on the RGT-reversed version. Comparison with the indifference level, dotted line, *t*-test: * and $^{\circ}$ $p<.05$ at least. (E, F) Relationship between individual RGT scores and (E) the number of risk assessments before the first emergence in the risky compartment, or (F) the individuals' sum of the score ranks for each behavior.
doi:10.1371/journal.pone.0082052.g004

more visits to the bright compartment than good DM ($U = 20.5$, $p<.07$).

Decision-making and impulsivity. Impulsivity is a multifactorial trait encompassing both impulsive actions (inability to delay a response, i.e. premature responses, or to withhold a response, i.e. anticipatory hyperactivity and perseveration) and impulsive choices (inability to wait for a delayed greater benefit) [25].

Impulsive actions: premature responses and compulsive-like behavior. The FCN16 measures response inhibition through the ability to complete a long sequence of lever presses on a first lever (FCN lever) before moving on to another lever (reward lever) that provides a reward [17,26]. Both groups learned the task at the same rate (learning scores, $U = 36$, ns). Poor DM did not exhibit any deficit in inhibitory control (i.e. premature switches to the reward lever). The chain length distribution curve of both good and poor DM showed a peak for the optimal chain length (Figure 5A). Both groups predominantly performed rewarded chains (i.e. of length $>= 16$, Figure 5A-insert). However, poor DM made a higher proportion of long chains of responses (>16), leading to a lower response efficiency (Figure 5B) ($U = 8$, $p<.01$). The occurrence of very long chains of presses was occasional. For instance, the number of chains longer than 22 presses was 1% of the total number of chains for good DM, and 3% for poor DM. However, all poor DM displayed at least one such very long chain during the test *vs* only 6 out of the 14 good DM. Moreover, whilst the number of presses on the FCN lever did not differ between groups ($U = 28$, ns), poor DM were more active on the reinforcement lever ($U = 18$, $p<.05$), making short bursts of presses instead of a single press. These perseverative behaviors, not accompanied by an attempt to collect the reward even when a clear signal announces its availability, are reminiscent of excessive and compulsive behavior. All poor DM had scores on or above the median *vs* 43% for the good DM, which had scores below the median (Fisher exact test $p = .018$) (Figure 5C).

Impulsive actions: anticipatory hyperactivity and perseveration. The FI-EXT task assesses reward anticipation and sensitivity to context during frustrating periods without reinforcement [16,27]. Lever press activity is measured either during a delay before a lever press can deliver the reward (FI) or during an extinction phase (EXT) where no reward can be obtained (light house off). During the 1-min FI and 5-min EXT, 83% of poor DM had a

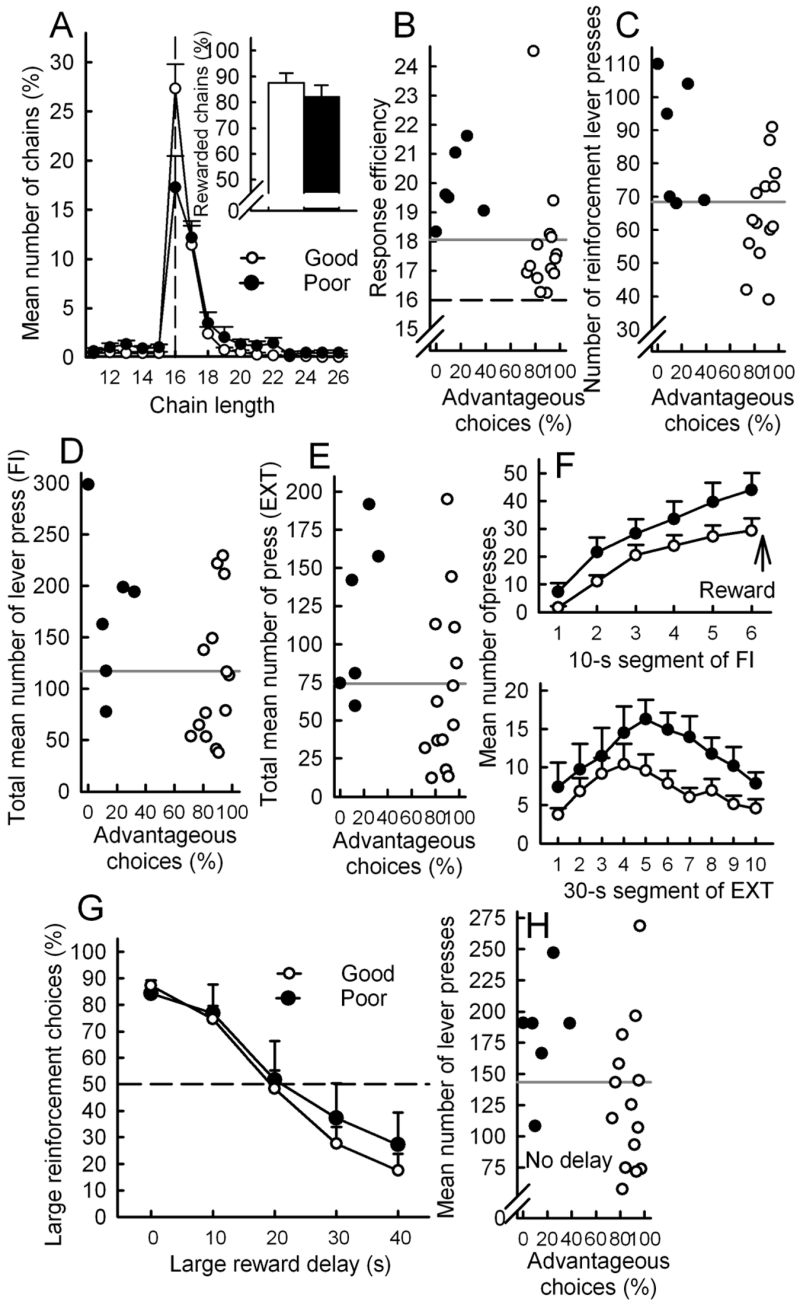

Figure 5. Decision-making and impulsivity. Good and poor decision makers (DM) performances in the (FCN16) Fixed Consecutive Number of 16 lever press schedule (A-C), in the multiple fixed-interval (FI) and extinction (EXT) schedules (D-F) and in the (DDT) delay-discounting task (G-H). Grey lines represent the median used to compute proportions of high and low scores in good and poor DM. (A) Frequency distribution (%) of chain length in the two groups. Optimal chain length (16) is indicated by the vertical dotted line. Inset: Percentage of rewarded chains for good and poor DM (Mean ± SEM). (B,C) Relationship between individual scores in the RGT and (B) response efficiency or (C) the number of reinforcement lever presses. (D,E,F) Relationship between individual scores in the RGT and (D) the mean number of lever presses during the 1-min FI or (E) during the 5-min EXT. (F top panel) Mean number of lever presses of good and poor DM during one 1-min FI component as a function of time. (F lower panel) Mean number of lever presses during the 5-min EXT component as a function time. (G) Percentage of choice for the large, delayed reinforcement as a function of delay in the two groups. (H) Relationship between individual scores in the RGT and the mean number of lever press during DDT training. Dotted line represents chance level.

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motor activity equal to or higher than the median score, *vs* 43% for the good DM (Figure 5D and 5E). Overall, poor DM tended to perform more lever presses than good DM both during FI, (medians, 178 and 98 respectively; $U = 23$, $p = .1$) and during EXT (medians, 111 and 55; $U = 21$, $p = .08$), suggesting both anticipation and perseveration. Both groups exhibited the typical pattern of activity during each interval of the FI, namely a progressive increase in rate as reinforcement availability approached, with poor DM reaching a score 1.5 times higher than good DM. During EXT, poor performers exhibited both a larger and longer episode of increased activity (Figure 5F). The latency to collect rewards did not significantly differ between groups ($U = 31.5$), nor did the number of visits to the empty tray ($U = 35$ and 30, ns). The mean number of lever presses during FI and EXT were positively correlated ($r = .69$, $p<.001$).

Impulsive choice: delay discounting. The DDT assesses the ability to tolerate a delay when a choice between an immediate small reward and a delayed larger reward is given. It indicates for each individual the subjective value of the large reward as a function of the delay and the delay at which both rewards are perceived to be of equal value. Under the no-delay condition, good and poor DM preferentially chose the larger reward (Figure 5G) and poor DM overall performed more lever presses than good DM ($U = 16$, $p<.05$, Figure 5H). When the delay increased, both groups shifted to the immediate reward at the same delay, suggesting that they displayed similar reward discounting and tolerance to delay (Figure 5G).

Correlation between behavioral parameters. As shown in Table 1, no correlation was observed between reward-seeking, risk seeking and behavioral flexibility. A positive correlation was found between impulsive actions and perseverative responses in different experimental contexts. These parameters (except FI activity) were positively correlated with risk taking, and were independent from inhibitory control capacities (FCN schedule) and impulsive choice (DDT). We decided to model all independent traits (risk, reward and flexibility) excluding motor impulsivity since impulsivity/perseveration measures were correlated with risk seeking (see Table 1).

A combination of behavioral traits is highly predictive of poor decision-making. Poor DM consistently displayed above median scores for each of the following behaviors (Table 2), except one poor DM missing motor impulsivity): motor impulsivity/perseveration, risk proneness, reward seeking and behavioral inflexibility. They obtained a lower global index when these behavioral traits were combined (sum of the ranks) compared to good DM (Figure 4F). By contrast, no good DM ever expressed high scores for more than two of these particular behaviors. Thus, in healthy individuals, the combination of these traits more than any particular one was highly predictive of poor decision making in the RGT. The association of cognitive inflexibility and risk taking behavior or motor impulsivity was never observed in good DM and thus may be a particularly relevant combination of risk factors for impaired decision-making.

Computational analysis

The TD model was fitted to each rat's performances in the RGT to estimate the five free parameters describing each rat: two parameters for cognitive inflexibility, one for risk seeking, one for reward seeking and one for the exploration of the environment (see Methods). Partial models with fewer parameters were also tested (see below).

Decision-making in the RGT. The model was able to reproduce the distinct performance profiles observed during the RGT session for poor and good DM (Figure 6A). This suggests that differences in risk-proneness, reward seeking behavior and cognitive inflexibility can collectively account for the variability of performance profiles observed experimentally. Moreover, based on the performance of the rats during the RGT, the model could successfully predict the performance profile of all poor DM and of half of the good DM during reversal conditions (Figure 6D).

Table 1. Correlations within and between different measures of decision making, flexibility, impulsivity and risk-taking behaviours.

				Reward-seek.	Flexibility	Risk-taking		Inhib. cont.	Motor impulsivity/perseverations			
Reward-seeking	RGT	mean latency to collect food	1	-								
Behavioral flexibility	RGT-reversal	flexibility index (%)	2	0.09	-							
Risk-taking	Emergence	Mean latency to emerge	3	0.11	0.22	-						
	Task	number of risk assessments	4	−0.24	0.11	***0.69	-					
Inhibitory control	FCN16	rewarded chains (%)	5	−0.27	0.00	−0.35	0.22	-				
Motor impulsivity/ perseverations	FCN16	reinforcement lever presses	6	0.14	−0.36	**−0.51	*0.45	−0.10	-			
	FI	total lever presses	7	0.22	0.02	−0.28	−0.34	0.09	***0.68	-		
	EXT	total lever presses	8	−0.08	−0.07	**−0.5	−0.52	0.07	**0.53	***0.69	-	
	DDT	total lever presses (training)	9	0.2	−0.18	**−0.61	−0.53	0.22	**0.5	0.40	**0.57	-
Impulsive choices	DDT	20s-delayed choice (%)	10	−0.23	0.12	−0.26	−0.22	**0.5	−0.10	−0.056	−0.19	0.07

The three behavioral processes included in the model, reward and risk seeking, behavioral flexibility, were unrelated. Impulsive actions and perseverative responses in different experimental contexts were positively correlated. These parameters (except FI activity) were positively correlated with risk taking, and were independent from inhibitory control capacities (FCN schedule) and impulsive choice (DDT). Significant correlations are shown in bold. RGT: rat gambling task; FCN16: fixed consecutive number schedule of reinforcement; FI: fixed- interval; EXT: extinction: DDT: delay discounting task. Pearson's correlation test; *, $p<.05$; **, $p<.01$; ***, $p<.001$.

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Table 2. Summary of individual behavioral profiles of poor and good DM.

	Poor decision makers							Good decision makers														
rats	3	8	32	15	28	9	subjects (%)	2	4	24	33	6	31	1	17	19	29	12	30	27	26	subjects (%)
motor impulsivity/persev.	X	X	X	X	X		83	X	X	X			X			X	X			X		43
	X	X	X	X	X			X	X	X			X			X	X					
risk-taking	X	X	X	X		X	83	X		X	X			X		X						14
	X	X	X	X	X	X			X	X	X				X							
reward-seeking	X	X	X	X	X	mis.	100		X		X	X	X		X							36
inflexibility	X	X	X	X	X	X	100	X				X		X				X	X			36
Number of high scores	4	4	4	4	3			2	2	2	2	2	2	1	1	1	1	1	1	0	0	

Motor impulsivity/perseverative responses correspond to high activity scores in both fixed-interval (FI) and extinction (EXT) schedules of reinforcement. Risk taking is indicated by a short latency to emerge and a low number of risk assessment in the dark-light box test, reward seeking by a short latency to collect food in the RGT, and inflexibility by performance in the RGT reversed condition. A cross indicates a high score (with respect to the median) for a given parameter. Last line shows the total number of high scores displayed by each rat. Proportions of subjects demonstrating high score in each group are also given. Mis. : missing value.

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Decision-making and flexibility. Cognitive inflexibility was implemented as a gradual decrease of the learning rate over the course of the experimental session controlled by two parameters α_0, the initial learning rate and τ_0 the decay (see Methods). The initial learning rate parameter α_0, extracted from a fit of the RGT session alone was positively correlated with the experimental measure of flexibility during reversal ($r = .3303$, group correlation MC permutation test $p = .0266$). The model predicted an inflexible learning behavior in all modeled poor DM (poor DMm) (Figure 6C), as observed experimentally (Figure 4C). When both the RGT and reversal conditions were used to estimate all model parameters, all flexibility parameters (α_0, τ_0 and the area under α) correlated positively with the experimental measure of flexibility (e.g. for α $r = -.73$, MC permutation test $p = .0002$, see Figure 6*D*).

Decision-making and reward seeking. Reward seeking behavior was modeled by allowing the perceived magnitude of the rewards to be greater than the actual reward. In the model, consistent with experimental data (Figure 4B), all poor DMm except one showed high reward seeking, whereas less than 29% of modeled good DM (good DMm) showed this trait (Figure 6B). The reward seeking parameter estimated from the model correlated significantly with the corresponding behavioural measure of reward sensitivity ($r = -.4014$, MC permutation test $p = .0479$, see Figure 7E).

Decision-making and risk seeking. Risk seeking was implemented by adding a risk-related reward contribution [28] to the actual rewards (see Methods). In the model, as in the experiments (Figure 4E), poor DMm were characterized by higher levels of risk sensitivity than good DMm (Figure 6E). The risk parameter extracted from the model significantly correlated with the two behavioural measures of risk seeking (i.e. mean latency for the first visit in the light compartment and risk assessments, $r = -.5370$ and $-.5555$; MC permutation test $p = .0043$ and $p = .0051$ respectively, see Figure 7F).

Combination of behavioral traits. Finally, when all the different behavioral traits are taken into account (Figure 6F), poor DMm exhibited a combination of high levels for the modeled behavioral traits as observed in behavioural measures. The global index (sum of the ranks of each behavior) of each modeled rat was highly correlated with the global index derived from experimental measures ($r = .7420$, MC permutation test $p = .0003$, see Figure 7C). Furthermore, similarly to the experimental data (Table 2 and Figure 6H), the model showed that the combination of high cognitive inflexibility, reward and risk seeking is particularly discriminative of poor DMm (Figure 6G), since good DMm almost never expressed more than one of those traits (Table 3).

Influences of combined behavioral traits on Learning. To understand why good and poor DM show different choice preferences, we analysed how well good and poor DMm evaluated advantageous and disadvantageous actions. The Q-values representing the valuation of each choice at the end of the RGT session were extracted for all rats, using the TD-learning model.

Figure 7B illustrates the mean Q-values assigned to the disadvantageous choices (A & B) and advantageous choices (C & D) by poor and good decision makers. Poor DMm vastly overestimated the value of all states rather than just disadvantageous options. The over-estimation was more important for disadvantageous choices in comparison to the advantageous ones. By contrast, good DMm stopped exploring disadvantageous choices early in the RGT session due to their negative value.

In the model, high scores in risk seeking, reward seeking or inflexibility lead to an altered estimation of the true value of all states. High scores in a combination of traits lead to a shift in the valuation of the state-action pairs, where disadvantageous choices appear to be more valuable than advantageous ones.

Comparison with simpler models. Model comparison was also performed in order to address whether simpler models with fewer behavioural traits could have accounted for the experimental data just as well. We tested simpler versions of our model with either only one or two behavioural traits and compared the fit of these models to the experimental data. We used the Likelihood Ratio Test and the Bayesian Information Criterion to assess the fit of the models while penalizing for added complexity. The likelihood ratio test revealed that the full model (including reward sensitivity, risk seeking and cognitive inflexibility) was significantly better ($p<0.0001$) than any other simpler model, suggesting that all behavioral traits are necessary to describe the experimental data. Similar results were obtained using the Bayesian Information Criterion (See Figure 7A).

Discussion

Like the IGT in humans, the RGT probably involves a number of cognitive processes, and separating their relative contribution is a challenge. However, our purpose was not to focus on one specific executive function involved in choice, but rather to identify the whole complex phenotype sustaining poor decision making in

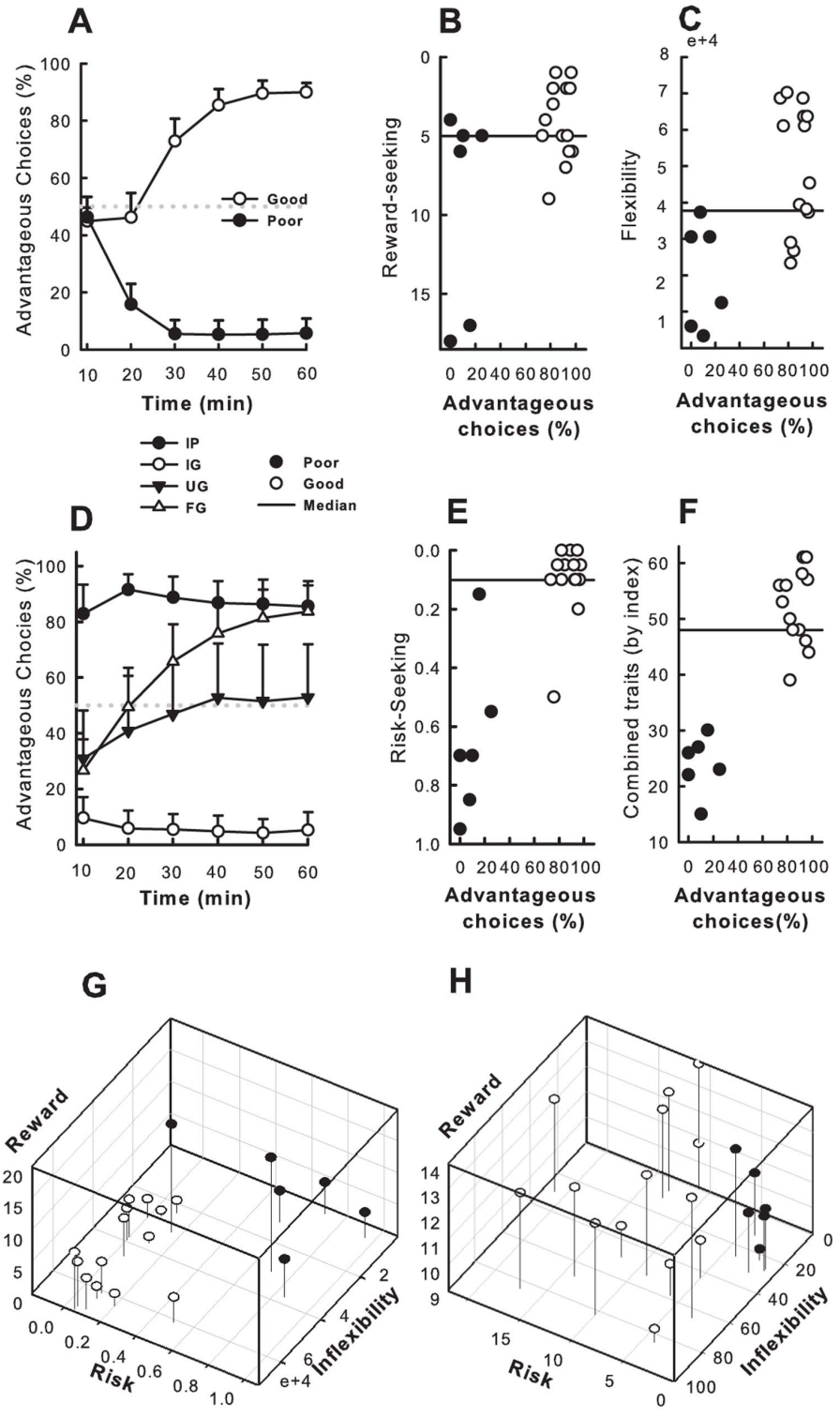

Figure 6. Model's performance on the RGT, reversal conditions and estimates of individual behavioral levels when fitted to the experimental performance profile of each rat. Grey lines represent the median used to compute proportions of high and low scores in good and poor decision makers (DM). (A) Simulated time-course of advantageous choices (%) of good and poor DM on the RGT. (B) Relationship between simulated individual RGT scores and the estimated reward seeking parameters during the RGT + Reversal. (C) Relationship between simulated individual RGT scores and the estimated flexibility parameters affecting the learning rate. (D) Simulated time-course of advantageous choices of

flexible (FG), undecided (UG) and inflexible (IG) good DM and inflexible (IP) poor DM groups on the RGT-reversed version. (E) Relationship between simulated individual RGT scores and the estimated risk seeking parameters. (F) The sum of the simulated score ranks for each modelled behavior. (G) 3-D representation of model parameters for the simulated traits of individual rats. (H) 3-D representation of behavioral measures of the behavioral traits of individual rats.
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conflictual and risky situations, as observed in real life. Indeed, a complex interplay between independent behavioral domains is more likely to reflect the complexity of human phenotype and disorders [29,30,31].

In the present study, we confirm this hypothesis as we establish a clear link between separate behavioral traits in a normal sample of rats and decision-making in the RGT. Although each trait considered separately has a poor predictive value, both the behavioral and the modeling analyses indicate that poor decision making can be accurately predicted when these traits are considered in combination.

While integrating multiple cognitive abilities, the RGT offers the advantage to assess the time-course of the decision making process within a single session. It is particularly suitable for identifying inter-individual differences in decision making, and notably for identifying poor decision-makers because choices are made readily and lead to two opposed decisions: either a preference for advantageous options or a preference for the disadvantageous ones [11]. As shown by the meta-analysis of several experiments in the RGT, these behaviors are reproducible. Importantly, poor decision-making does not result from a slower learning. We have previously shown that repeating the RGT on three consecutive days does not change the rats' preferences (data not shown). Additionally, acquiring information about the value of the options separately before the test does not change the behavior of poor and good decision-makers, nor does it change their relative numbers [11].

We show that poor decision making is expressed by individuals presenting excessive scores for a combination of behavioral and cognitive traits: risk taking, higher reward seeking behavior, motor impulsivity and behavioral inflexibility, expressed simultaneously. This contrasts with good DM which present a wider range of scores and only express up to two of these characteristics (Table 2). The various traits that we examined were largely independent

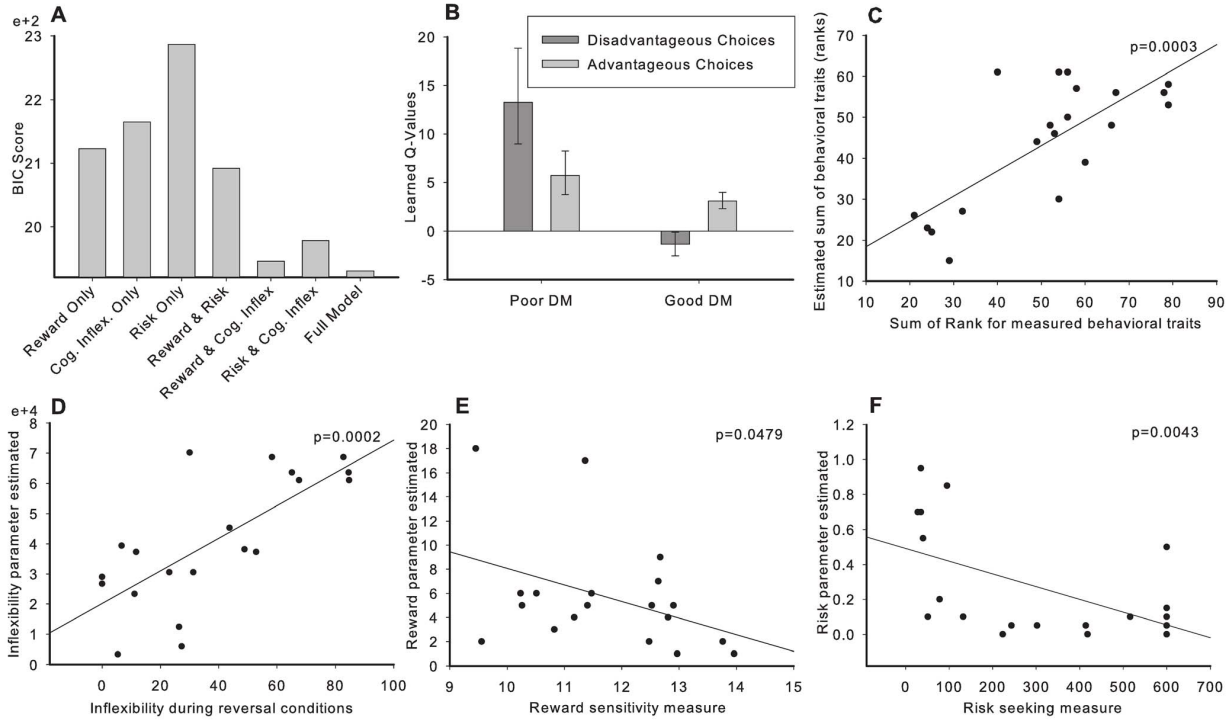

Figure 7. Model comparison and correlations between estimated parameters and behavioral traits. (*A*) Bayesian Information Criterion scores for each model (a low score is better). Models based on two traits fare uniformly better than models based on a single trait. Models with two traits including cognitive inflexibility have better scores than equivalent or simpler models. The model with all three simulated traits provides the best fit to the data even when penalizing for the increased model complexity (number of free parameters). (*B*) Learned Q-Values for advantageous and disadvantageous choices by both Good and Poor DM**.** Bars represent the mean Q-values assigned to the disadvantageous choices (A & B**; dark-grey)** and advantageous choices (C & D**; light-grey**) averaged over all poor or good decision makers at the end of an RGT session. Error bars represent 95% CI around the mean Q-value for all the rats of the population of interest. Poor decision makers vastly over-value disadvantageous choices in comparison to advantageous choices. (*C-F*) Scatter plot illustrating the correlation between: (*C*) The sum of ranks for all the behavioral traits measured experimentally (x-axis) and those estimated by the model (y-axis); (*D*) The measure of cognitive inflexibility (x-axis) and the estimated inflexibility parameter (area under α; y-axis); (*E*) The measured reward sensitivity (x-axis) and the estimated reward sensitivity (y-axis). (*F*) The measured risk seeking (latency to emerge in light compartment; x-axis) and the estimated risk-seeking parameter (y-axis). All estimated parameters correlated significantly with their behavioral counterpart.
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Table 3. Summary of individual modeled behavioral traits of poor and good DM.

	Poor decision makers							Good decision makers														
rats	3	8	32	15	28	9	subjects (%)	2	4	24	33	6	31	1	17	19	29	12	30	27	26	subjects (%)
risk-taking	X	X	X	X	X	X	100			X	X				X	X	X	X		X		50
reward-seeking	X		X	X	X	X	83		X				X	X	X		X		X		X	50
inflexibility	X	X	X	X	X	X	100	X				X				X		X				29
Number of high scores	3	2	3	3	3	3		1	1	1	1	1	1	1	2	2	2	2	1	1	1	

Same representation as in Table 2 for modeled behavioral traits: risk taking, reward seeking and inflexibility parameters.
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from one another. A noteworthy exception was the relationship between motor impulsivity/ perseveration and risk taking (see Table 1).

Poor DM are characterized by risk and reward seeking, which have been found to be associated with trait dominance in rats and humans, and could be necessary for the development and maintenance of social structure [32,33]. Interestingly, risk and reward seeking, in combination with impulsivity, are hallmarks of poor decision making related mental disorders such as ADHD [34], personality disorders, substance abuse [28,35], pathological gambling [36] or mania [37]. Poor DM are also characterized by behavioral inflexibility as well as perseverative and compulsive-like behaviors. Their inflexibility was particularly noticeable in the RGT reversal procedure, which requires redirecting choices on the basis of new response-reward contingencies [38], but also in the FCN schedule with perseverative responses. Indeed, perseverative responses in the FCN have similarly been observed following amphetamine administration (0.8 mg/kg), in a similar procedure [39]. These effects of the psychomotor stimulant are likely to reflect compulsivity, especially at this dose, given that only low doses of amphetamine (0.25 mg/kg) are known to reduce impulsivity in this task [17,26], whereas higher doses (0.5 mg/kg or above) increase impulsive responses. Perseverative behavior, typically observed after acute administration of psychostimulants [39], inflexible and compulsive behavior can be seen in drug addiction [40,41], pathological gambling [2] and in obsessive-compulsive disorder (OCD) [1]. Inappropriate compulsive behaviors [25] may result from attributing excessive incentive value to reward associated stimuli [42,43]. This could explain bursts of activity on the reinforcer level in the FCN schedule, as well as hyperactivity in the FI-EXT schedule. Compulsive behavior could also result from a quicker switch from initial voluntary goal-directed behavior to an habitual, automatic process with loss of control, as observed in drug addiction and OCD [44,45]. Interestingly, poor decision-makers do not have more impulsive tendencies compared to good DM in terms of intolerance to delayed gratification and of inhibitory control. Still, we cannot exclude that more demanding tasks (e.g. the stop-task [46]) could reveal differences in inhibition between both phenotypes. Moreover, the higher sensitivity of poor DM may have influenced the performance in this task. However, a recent meta-analysis also concluded that inhibition and decision-making in the IGT are dissociated [47].

Previous studies have shown that individual behavioral traits can be related to maladaptive behavior in animal models of mental disorders (i.e. novelty-seeking in depression [48]; impulsivity, novelty preference in drug self-administration [49,50,51]). However, the cumulative effect of several symptoms in one individual, as systematically observed in mental disorders [1], has rarely been considered in an animal model [29]. Here, we show that a complex phenotype is highly predictive of poor decision-making, since it only describes poor performers. Each of the traits identified participates to this phenotype that leads to the inability to adapt to the situation because of a distorted representation of the balance between reward and risk, and an inflexible/compulsive behavior precluding readjustment of behavior. This complex phenotype reflects well the relevance of the concept of "domain-interplay" to explore the basis of maladaptive behavior [29,30]. Although we cannot conclude that the different observed phenotypes observed represent innate or acquired differences, it is noteworthy that dominant rats are natural risk takers and display increased motivation for food reward [32,33], two characteristics of poor decision makers in the RGT. This social parameter could be well related to performance in the RGT, a hypothesis that remains to be elucidated.

Recent experiments based on lesion studies have shown that good performances in the RGT depend of the functional integrity of the prefrontal cortex, notably the prelimbic, cingulate and orbitofrontal cortices [12]. Moreover, the brain networks differentially activated during adaptive and maladaptive decision-making reveal striking differences that can be related to the behavioral and cognitive traits identified (manuscript submitted) [52].

Building on the expanding literature indicating that behavioral traits such as risk seeking affect learning and the prediction error signal [20,53], we used a reinforcement learning model of the RGT to investigate the relationship between the traits and the decision making performances. First, we used the model to address whether the behavioral traits could collectively account for the variety of performances observed in the decision-making task (i.e. Can excessive behavioral traits lead to poor and/or undecided decision-making?). Secondly, we used the model to explore the interaction between the behavioral traits on learning and decision-making (i.e. How and why do excessive traits lead to poor decision-making?). The computational model, based on a TD-learning algorithm [54,55,56] was modified to include the behavioral traits of risk seeking, reward sensitivity and behavioral inflexibility.

The model reveals how risk seeking, reward sensitivity and behavioral inflexibility jointly contribute to the learning and the decision-making process. The model of the RGT fits the experimental data very closely (Figure S1), and demonstrates that behavioral traits of high risk seeking, high reward seeking and cognitive inflexibility can be derived from the performance of individuals in the RGT. Importantly, all the parameters used to model the behavioral traits successfully correlated with the experimental measures for each trait, validating the assumptions made during the implementation. This suggests that the mathematical formalization of all the behavioral traits and their independent influence on learning in the RGT were valid. Interestingly, we found that individual traits were insufficient to

lead to poor performances at the task (Table 3). Rather, poor decision-making required specific combinations of at least two of the behavioral traits, namely inflexible learning and risk seeking or inflexible learning and reward seeking. This suggests that single excessive behavioral traits may be compensated for in good decision makers. Yet, such potential compensatory processes may fail when a combination of traits are involved.

Importantly, the computational study is based on the assumption that a failure in decision-making occurs through an altered internal representation of the values in the environment (Figure 7B), as is customary in computational modeling of psychopathology [57,58]. We investigated the difference in valuation of the different choices by poor and good decision makers. Surprisingly, we found that poor DMm vastly over-estimate the value of all choices, but especially those corresponding to disadvantageous options. According to their inflated valuation of disadvantageous choices, poor DM appear to behave optimally according to their inaccurate value-map of the environment, rather than sub-optimally according to the objective outcome of the task. Our findings are in line with recently suggested mechanisms of psychopathology such as addiction [53].

Our model accounts for the role of behavioral traits in learning and decision-making, using a basic TD-learning framework using minimal assumptions. Other formalisms such as win-stay loose-shift, Bayesian models or more elaborate TD models could also be explored [18,19,20,22,23,24]. However, the present model offers a straightforward way to implement the traits of interest and allows a quantitative assessment of the impact of individual differences on the overall decision-making performances. In particular, we show that simple models incorporating fewer discriminative traits have less predictive value than the full model. More biologically targeted versions of this model could be developed [59,60,61] and investigated with regard to the cortical- subcortical interplay specific to good and poor DM [52].

In conclusion, poor decision making in the RGT is predicted by a complex phenotype of cumulated behavioral and cognitive characteristics including risk seeking, reward seeking and inflexibility, combined with motor impulsivity and perseverative/compulsive-like behaviors. This approach, based on the identification of high scores for these behavioral traits expressed spontaneously and in a comparable way as to those observed in the clinic, demonstrates that rat behavior can reliably model dimensions found in humans [8,62]. This work emphasizes the need to use ''integrative'' animal models to mimic the complexity of the clinically relevant phenotype [30]. Our findings are also in line with the recent proposal by Robbins et al. [31] to undertake a more objective description of psychiatric disorders through predisposing traits and neurocognitive endophenotypes, thereby explaining the high level of comorbidities between mental disorders. By integrating multiple behavioral measures, combined with computational modeling, our work provides a promising framework for revealing the neuropsychological determinants of poor decision-making as a potential risk factor for developing related mental disorders [8,9] and for exploring its neurobiological substrates.

Supporting Information

Figure S1 Models' best fit to individual rat performances. Each graph shows the performance of the rat (dashed-line) in terms of % of advantageous choices (y-axis) over time (x-axis). The model mean performance (continuous line) and standard deviation (grey area) is represented on the same graph for each rat.
(TIF)

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Author Contributions

Conceived and designed the experiments: FDH. Performed the experiments: MR VV. Analyzed the data: FDH MR VV PS AM. Contributed reagents/materials/analysis tools: VV PS AM. Wrote the paper: FDH MR VV PS AM.

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Part II

APPENDIX B

Visual statistical learning and Bayesian inference in chronic schizophrenia

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Abstract

Background: Recent models of schizophrenia suggest that positive-symptoms stem from learning deficiencies resulting in distorted internal statistical models of the world (Fletcher & Frith 2009). In line with these assumptions, schizophrenic patients have shown to be impaired in statistical learning and probabilistic inference in decision-making tasks (Averbeck *et al.* 2011).

Aim: We here ask whether schizophrenic patients are also impaired in more implicit/perceptual forms of probabilistic inference, such as visual statistical learning. We used a motion task known to induce rapid implicit learning of the statistics of the stimuli (Chalk *et al.* 2010). In controls, this learning influences perception in two ways: 1) motion stimuli are perceived as being more similar to the most frequently presented stimuli than they really are (estimation biases); 2) in absence of visual stimuli, participants sometimes report perceiving the most frequently presented stimuli (hallucinations). Such behaviour is consistent with the participants acting as Bayesian observers and combining learned perceptual priors with sensory evidence. We investigated whether schizophrenic patients would differ in their acquisition of the perceptual priors and how such priors would impact their perception.

Method: 11 medicated chronic schizophrenic patients (mean illness duration 14.72 ±2.73 years) and 10 controls were recruited and participated in a single task-session lasting 40 min.

Results: Although patients were slower than controls, their estimation and detection performances were similar. In particular, patients showed similar acquisition of perceptual priors, approximating the stimulus statistics. This suggests that patients had no statistical learning deficits in our task. Intriguingly, however, patients made significantly fewer *'hallucinations'* of the most frequently presented directions than controls. The total amount of *'hallucinations'* correlated negatively with symptom severity (PANSS Total & Positive scales).

1. Introduction

An increasingly popular idea in neuroscience is that perception and decision-making can be well described using probabilistic inference (a.k.a. "Bayesian") models (Friston, 2012; 2010; Knill and Pouget, 2004). According to the "Bayesian Brain Hypothesis", the brain learns internal statistical models of the environments ("expectations"), which are used in situations of uncertainty to disambiguate perceptual inputs and guide decisions. For example, statistical and perceptual learning studies have repeatedly shown that the visual system continuously extracts and learns statistical regularities of the environment automatically and without awareness (Series and Seitz, 2013). Expectations have been found to modulate and interact with a variety of sensory modalities such as vision (Chalk et al., 2010; Gekas et al., 2013; Series and Seitz, 2013; Sterzer et al., 2008), audition (Davis and Johnsrude, 2007; Remez et al., 1981), touch (Botvinick and Cohen, 1998), and even complex sensations such as pain (Colloca and Benedetti, 2005; Voudouris et al., 1990) and emotions (Petrovic et al., 2005).

Weiss *et al.* (Weiss et al., 2002) were the first to use this framework to successful describe perceptual illusions in healthy individuals. In this study, illusions result from the brain's attempts to interpret sensory inputs based on its internal models and expectations. For example, Weiss *et al.* (Weiss et al., 2002) demonstrated that a large number of visual motion illusions could be explained in terms of an *'a priori'* expectation for "slow speeds". Multiple studies have since found that healthy subjects do indeed quickly learn that statistics of their environment and combine these statistics with sensory evidence resulting in behaviour akin to that of an ideal Bayesian observer (Chalk et al., 2010; Gekas et al., 2013; Weiss et al., 2002), for reviews see (Fiser et al., 2010; Knill and Pouget, 2004; Series and Seitz, 2013) This framework is known to result in optimal perception when the inputs match the environment statistics but can result in biases when stimuli deviate from expected inputs (Gregory, 1980). A famous example of this is the "hollow mask illusion" where subjects perceive a face-mask as being convex, while it is in fact concave, presumably due to the very strong *'a priori'* expectation that faces are convex objects (Gregory, 1997; 1968).

Interestingly, schizophrenia is characterised by occurrences of abnormal percepts (hallucinations) and delusions (van Os and Kapur, 2009). Recently, a number of studies suggest that these symptoms could be understood in terms of deficits in probabilistic inference (Adams et al., 2013; Corlett et al., 2009a; Friston, 2005; Frith and Friston, 2012; Jardri and Deneve, 2013), for reviews see (Corlett et al., 2011; Fletcher and Frith, 2009). For example, an increasing number of studies report that schizophrenic patients show a deficit in integrating probabilistic information resulting in faster responses than healthy subjects, an effect called the 'jumping-to-conclusions' bias (Averbeck et al., 2011; Evans et al., 2012; Huq et al., 1988; Speechley et al., 2010). This bias is often measured using the 'beads task' (Huq et al., 1988). Although these findings have not always been replicated (Heerey et al., 2008; McKay et al., 2007), there is a growing body of evidence suggesting that schizophrenic patients are impaired in statistical learning and inference (Garety et al., 2013). Interestingly, while patients with stronger delusional symptoms fare worse at the task than those who do not (Huq et al., 1988; Speechley et al., 2010), healthy subjects displaying delusional ideation also show similar impairments at the task (Freeman et al., 2008) suggesting a link between delusions and probabilistic inference. Following this probabilistic inference framework, if patients with schizophrenia are impaired in statistical learning and inference, their internal model of the world should be erroneous, resulting in abnormal beliefs or delusions. . In this context, it is also argued that hallucinations, as experienced by patients with schizophrenia, could be seen as a severe form of illusions resulting from an incorrect perceptual inference. That is, these hallucinations would arise either from an incorrect mapping between sensory information and expectations, an incorrect acquisition of the expectations, or an imbalance between learnt statistics and sensory information (Corlett et al., 2011; Fletcher and Frith, 2009).

Interestingly, patients with schizophrenia have been found to be less susceptible to a large variety of perceptual illusions such as: the hollow-mask illusion (Dima et al., 2010; 2009; Keane et al., 2013), motion-induced blindness (Tschacher et al., 2006), illusory motion (Crawford et al., 2010), the size-weight illusion (Williams et al., 2010) and the Ebbinghaus illusion (Horton and Silverstein, 2011), reinforcing the idea that patients might suffer from deficits in probabilistic learning or perceptual inference. However, these perceptual studies tend to measure patients' susceptibility to illusions that are driven by pre-existing expectations. Therefore, the authors could not check whether the perceptual priors responsible for the illusion in healthy subjects had also been correctly acquired in patients. As a

result, these studies were unable to discriminate whether the reduced illusory percepts seen in patients stem from weaker expectations, a failure to acquire the perceptual prior altogether, or from an overall reduction in sensory uncertainty.

Following earlier work from Sterzer *et al.* (Sterzer et al., 2008), a recent study found that delusional ideation correlated with the magnitude of expectation-driven illusions in healthy controls (Schmack et al., 2013). That is, in line with previous studies on perceptual illusions in schizophrenia (Crawford et al., 2010; Dima et al., 2010; 2009; Keane et al., 2013; Tschacher et al., 2006; Williams et al., 2010), the authors found that the stronger the delusions of healthy controls, the less likely these were to have their percepts affected by expectations (Schmack et al., 2013). To our knowledge however, no study has looked simultaneously at the implicit acquisition of expectations (i.e. probabilistic learning) and the influence of these priors on perception (i.e. perceptual illusions) in the context of a perceptual task in schizophrenia.

The current study therefore investigates visual statistical learning in patients with schizophrenia. We used a previously developed motion task (Chalk et al., 2010) that is known to induce the rapid acquisition of the statistics of the stimuli. In this task, subjects need to report the direction of motion of a cloud of dots (estimation task) and whether they have perceived the dots or not (detection task; on some trials no stimulus are presented). Unknown to the participants, two directions of motion are more frequently presented than others. In healthy individuals, we found that subjects implicitly and unconsciously learn those stimulus statistics. This learning influences perception such that: 1) motion stimuli are perceived as being more similar to the most frequently presented stimuli than they really are (i.e. estimation biases); 2) participants report perceiving the most frequently presented stimuli in absence of visual stimuli (i.e. illusion/*'hallucinated*' dots). Bayesian modelling can be applied to individual performance to monitor the acquisition of the statistics of the stimuli (perceptual prior).

Using this task, we here aim to address whether patients with schizophrenia can acquire correctly the statistics of the motion stimuli and to assay how these perceptual priors are used in perception.

2. Materials & Methods

2.1. Participants

Twenty-one male subjects (11 Chronic Schizophrenic patients; 10 Healthy Controls) with normal or corrected-to-normal vision were recruited from the outpatient clinic of the Royal Edinburgh Hospital (Participants demographics – Table1). Patients' diagnoses were assigned by experienced clinicians based on standardised interviews (Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders; DSM IV-R). All participants gave informed written consent and did not receive monetary compensation for participation. The study was approved by the Psychiatry and Clinical Psychology subcommittee of the Lothian research ethics committee.

The two groups did not differ in age, pre-morbid IQ or current IQ. All patients were medicated (90% on atypical anti-psychotics, 50% of these were also on mood stabilisers). Patients were well at the time of testing and did not differ from controls on the PANSS positive, general and total symptoms scale (PANSS = Positive and Negative Symptom Scale). Significant differences were found between the two groups on the negative symptom scale and the global assessment of functioning.

Characteristics	Healthy controls (n=10)	Schizophrenic Patients (n=11)	Significance level
Age	36.66 (3.85)	37.63 (3.40)	*n.s.*
Premorbid IQ	114.66 (1.86)	113.90 (2.75)	*n.s.*
Current IQ	118.11 (2.07)	109.09 (4.33)	*n.s.*
PANSS			
Positive Scale	7.77 (0.43)	10.27 (1.26)	*n.s.*
Negative Scale	7.44 (0.24)	11.45 (1.53)	**(p<0.05)
General Scale	21 (2.45)	24.27 (2.71)	*n.s.*
Total	36.33 (2.53)	44.63 (4.78)	*n.s.*
GAF	75.55 (3.96)	58.63 (4.77)	***(p<0.01)
CPZ eq. (mg/day)	—	447.16 (60.30)	*N/A*
Illness duration yr.	—	14.72 (2.73)	*N/A*

Table 1: Participants summary information. *PANSS=Positive and Negative Symptom Scale (lower score is better), GAF = Global Assessment of Functioning (higher score is better), CPZ eq. = Chlorpromazine typical anti-psychotic equivalent dose in mg/day. Values indicate mean and (standard error).*

2.2. Apparatus & Stimuli

Motion stimuli consisted of a field of dots with a density of 2 dots/deg^2, moving coherently (100%) at a speed of 9°/s. Dots were contained within a circular annulus with minimum and maximum diameter of 2.2° and 7° respectively. Using coherent motion direction and speed of 9°/s ensures that motion discrimination *per se* should not differ significantly between patients and control groups (Chen et al., 2005; 2006). Stimuli were generated using the Matlab programming language with the psychophysics Toolbox (Brainard, 1997), displayed on a Dell P790 monitor running at 1024x768 at 100 Hz. The display luminance was calibrated and linearized using a Cambridge Research Systems Colorimeter (ColorCal MKII). The background luminance was set to 5.2 cd/m^2. Participants viewed the display in a dark room at a viewing distance of 100 cm.

2.3. Procedure

Each trial was composed of two tasks arranged as follows (Figure 1a); First, participants were presented with a fixation point (0.5° diameter) for 400 ms. With the fixation point still on-screen, the motion stimulus (field of dots) was displayed along with a red bar extending from this fixation point. During the presentation of the field of dots, participants were required to estimate the direction of motion by aligning the red bar into the perceived direction of motion (*Estimation task*). The angle of this bar was randomized at each trial and participants were instructed to focus their gaze on the fixation point throughout the estimation task. The display then cleared when either the participant clicked the mouse to validate their choice (estimation) or when 3000 ms had elapsed. After the estimation, a 200 ms delay was enforced before the detection screen was presented. The new screen was divided in two equal areas reading 'Dots' and 'No Dots', giving the participants a two-alternative forced choice (2-AFC). Subjects were required to move the cursor to the right or the left to indicate whether they detected dots or not and click to validate their choice (*Detection task*). The cursor then flashed green or red for correct or incorrect responses respectively. No time-outs were enforced during the detection task. Finally, the screen was cleared for 400 ms before a new trial began. Every 20 trials, subjects were presented with feedback on their estimation performance in terms of average estimation error (in degrees).

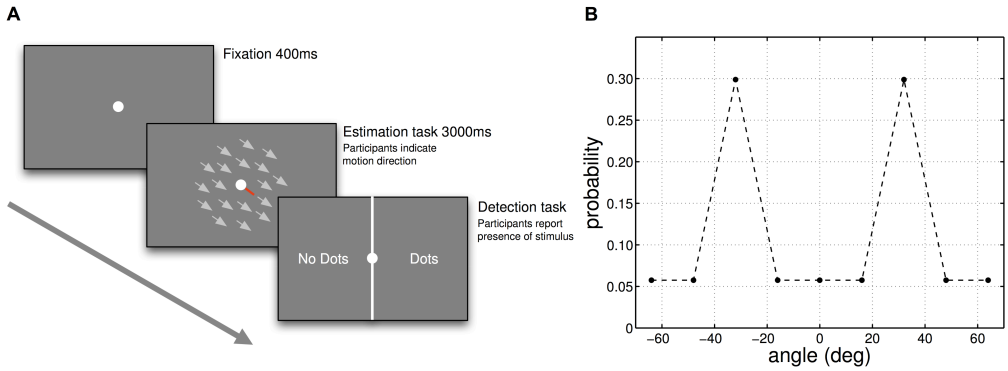

Figure 1: (A) Experimental procedure. Participants were presented with a fixation point followed by the motion stimulus and a response bar (red bar) that they were instructed to align to the perceived motion-direction. The screen was cleared either when participants clicked to validate their estimation or 3000 ms had elapsed. A new screen appeared with a two-alternative forced choice task (2-AFC), requiring participants to indicate whether they perceived the dots during the estimation task. **(B)** Probability distribution of the motion directions. Unknown to participants, the distribution of motion direction was bimodal (i.e. stimuli appeared most often at ±32° around a central direction). The central direction was randomised for each participant.

2.4. Design

Participants each conducted 567 trials (i.e. lasting approximately 40 minutes *vs.* 60 minutes in Chalk *et al.* (Chalk et al., 2010)) with opportunities for breaks every 170 trials (i.e. every 10-15 minutes) to prevent fatigue. Stimuli were presented at four different randomly interleaved contrast levels. The highest contrast level was 1.7 cd/m^2 above the 5.2 cd/m^2 background. There were 167 trials at zero contrast and 67 trials at high contrast. Contrasts of other stimuli were determined using a 4/1 and 2/1 staircase on detection performance (García-Pérez, 1998). Throughout the experiment, there were 90 trials with the 2/1 staircase and 243 trials with the 4/1 staircase. For the two stair-cased contrast levels, on a given trial, the direction of motion could either be 0°, ±16°, ±32°, ±48°, and ±64°, with respect to a central reference angle. This central reference angle was randomised for each participant.
Unbeknownst to participants, we manipulated their expectations about which motion directions were most likely to occur by presenting stimuli moving at ±32° more frequently than others (resulting in a bimodal distribution, Figure 1b). At the highest contrast level, 50% of trials were at ±32° and 50% remaining trials at random directions (i.e. not just the predetermined directions).

2.5. Analysis

Data analysis of the estimation task was performed on confirmed trials only (i.e. trials where participants validated their choice with a click on both *detection* and *estimation* tasks). Since the presented directions were symmetrical around a central reference angle, results were averaged for stimuli moving on either side of the reference angle. The first 130 trials were excluded from the analysis to allow the staircases to converge to stable contrast levels (see Figure 2c-d). Out of the original 21 participants, one had mean absolute estimation error greater than 30° at the highest contrast levels and was therefore discarded from analysis. Responses from high contrast stimuli were used as a performance benchmark to ensure that participants were performing the task. These trials were excluded from the analysis.

In the estimation task, the variance of participants' direction-estimates was large. As in previous work (Chalk et al., 2010; Gekas et al., 2013), we hypothesized that these resulted from random estimations on a proportion of trials, thus increasing substantially the variance of motion-direction estimates. To account for this, we fitted the individual estimation responses to the following distribution:

$$(1-\alpha)\cdot V(\mu,\kappa)+\alpha/2\pi$$

where *'α'* is the proportion of trials where the participant makes random estimates, and *'V(μ,κ)'* is the circular normal (i.e. von-Mises) distribution with mean *'μ'* and width *'1/κ'*, given by:

$$V(\mu,\kappa) = \frac{e^{\kappa \cdot \cos(\theta-\mu)}}{2\pi \cdot I_0(\kappa)}$$

Parameters were chosen by maximising the likelihood of generating the data from the distribution. Participants' estimation means and standard deviation were taken as the circular mean and standard deviation of the von-Mises distribution. This parametric approach allows for more consistent and significantly smaller variances across participants, motion directions, and contrasts, than merely averaging over trials, without compromising the qualitative aspect of the results (Chalk et al., 2010; Gekas et al., 2013). In trials were no stimulus was presented, we reconstructed the probability distributions of participants' responses over motion directions using Kernel Density Estimation (i.e. KDE) across each group. The KDE is a non-parametric method used to estimate the probability density function from discrete measures of a random variable. To do so, a kernel that defines the form of the probability density function (e.g. Gaussian kernel) is placed at each of the observed measurement. Then, all the individual kernels are summed to create the probability density function of the random variable (motion direction). In our case, we used a circular normal kernel since our random variable is circular. As is customary for KDE, the variance of the kernel is estimated from the data using the MSNI method (i.e. minimum of standard deviation and interquartile range improved). This method has proven to be robust against over-smoothing (Silverman, 1986) as well as providing adequate fit to skewed (Wand and Jones, 1994) and multimodal distributions (Bowman and Azzalini, 1997).

3. Results

3.1. Detection performances and contrast levels

Participants' detection performance was monitored to adapt the stimulus contrast to each participant's just noticeable difference (JND – contrast sensitivity). Using 2/1 and 4/1 staircases, we ensured that the individual detection performances would converge to 70.4% and 84.1% respectively (Levitt, 1971).
Contrast staircases converged to stable luminance levels after about 130 trials for both groups (figure 2b,c); Controls converged to a stable luminance level of 0.48 cd/m^2 (±0.06) after 130 trials, while patients converged to 0.68 cd/m^2 (±0.07) after 51 trials. These results confirm previous findings (Skottun and Skoyles, 2007) suggesting that schizophrenic patients display significantly poorer contrast-sensitivity in comparison to controls *(t(18)=3.42, p<0.01)*.

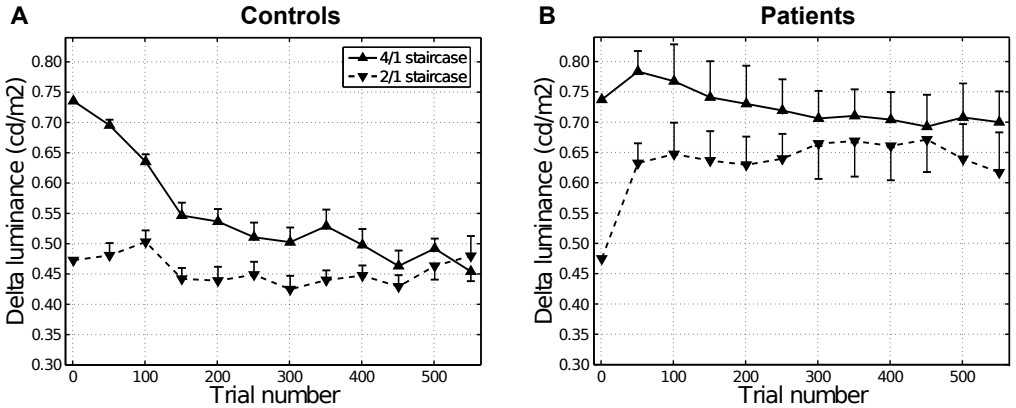

Figure 2: Comparison of contrast discrimination between the two groups. **(A)** Controls' averaged stimulus contrast, relative to background contrast for the 4/1 (plain line) and 2/1 (dashed line) staircased contrast levels. **(B)** Patients' averaged stimulus contrast, relative to background contrast for the 4/1 (plain line) and 2/1 (dashed line) stair-cased contrast levels. For all figures, results are averaged across all participants. Error bars denote standard error.

3.2. Statistical learning

First, we investigated whether participants acquired the statistics of the stimulus. To do so, we looked at patterns suggestive of statistical learning in each group, namely attractive biases towards the most

frequent directions, decreased reaction times and improved detection performance for the most frequent directions (Chalk et al., 2010).

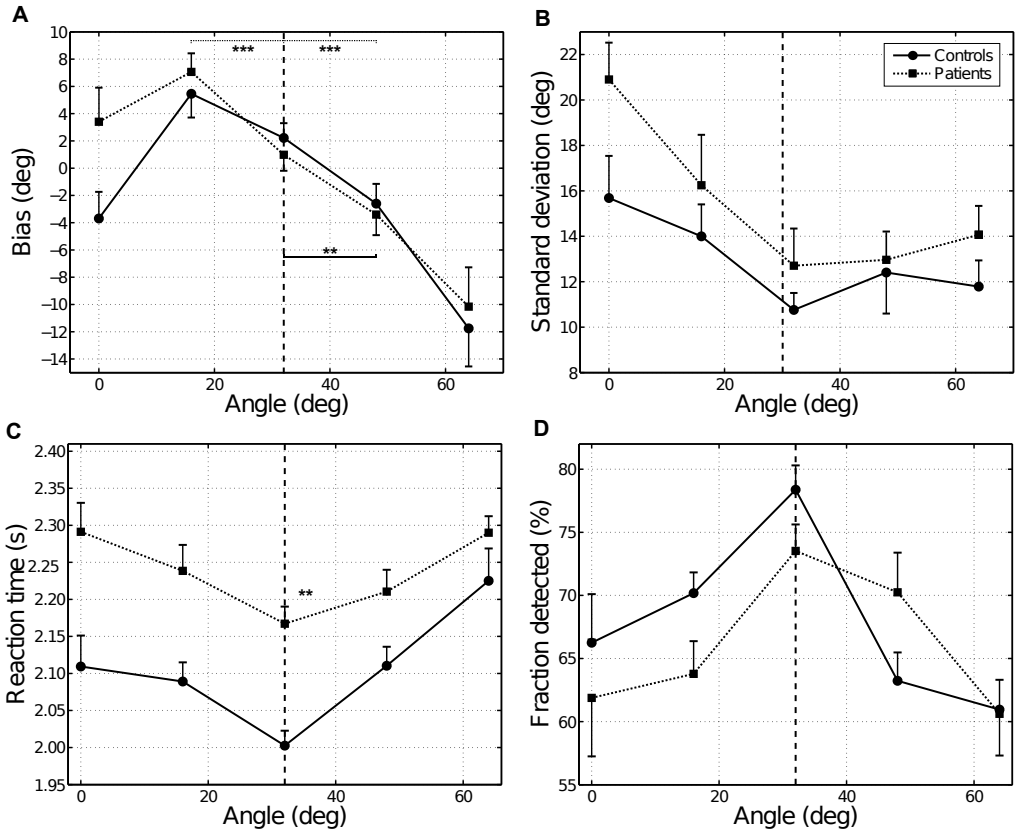

Figure 3: Effect of expectations on estimation biases, detection performance and reaction times between Controls (plain line) and Patients (dotted line). **(A)** Participants' mean bias in the perceived of motion-direction as a function of the true motion direction presented. **(B)** Standard deviation of participants' estimated motion-directions as a function of the presented of motion-direction. Results were averaged over all participants in each group; error bars represent within-subject standard error. The vertical dashed lines correspond to the most frequently presented motion-direction (i.e. ±32°). **(C)** Reaction times during the estimation task as a function of motion direction. **(D)** Proportion of motion directions that were detected by the participants as a function of the presented motion direction. ** & *** denotes $p<0.05$ and $p<0.01$ respectively.

Estimation performance

To investigate whether the participants' perceived motion-directions were biased, we measured the difference between the true motion-direction and the motion direction reported by the participants. Figure 3a displays the average estimation bias plotted against the true motion-direction for each population (i.e. plain lines for controls, dotted lines for patients). Estimates at ±16° and ±48° were respectively positively and negatively biased towards stimuli moving at ±32°, while estimates at ±32° (i.e. on the vertical dashed line) were unbiased. This indicates that for both groups, estimations were biased towards ±32°, the most frequent directions. These results replicate findings by Chalk *et al.* (Chalk et al., 2010) and Gekas *et al.* (Gekas et al., 2013) in control subjects. Overall, there was a significant effect of motion-direction on the estimation bias for controls *($F(1,4)=6.12$, $p<0.001$; One-way ANOVA)* and patients *($F(1,4)=8.27$, $p<0.001$; One-way ANOVA)*. The estimation bias at ±16° and ±48° was significantly different from the bias at ±32° for patients *($p<0.001$ and $p<0.001$ respectively, paired t-test)* and at ±48° *vs.* ±32° for controls *($p<0.05$, paired t-test)*. Together, these results confirm that participants perceived the most frequently presented motion-direction correctly but tended to perceive other motion directions as being more similar to the most frequent directions than they really were.

We also investigated whether the standard deviation of estimated motion-directions changed as a function of the presented motion-direction. In accordance with previous work (Chalk et al., 2010;

Gekas et al., 2013), we found that the mean standard deviation was smaller at ±32° than at other directions (figure 3b). Although there was no significant effect of motion-direction on the estimation standard deviation for both controls *(ns., Kruskal-Wallis H test)* and patients *(ns., Kruskal-Wallis H test)*, the standard deviation at ±32° was significantly lower than the median standard deviation at the other motion-directions *(Controls: p=0.033, Patients: p=0.046, one-tailed MC permutation test – difference of medians)*. These results indicate that participants' estimations were more accurate for the most frequently presented directions than for other directions, consistent with the idea that participants had learned to optimise their performance for these most frequent directions.

Detection Performance

Next we examined whether participants' expectations influenced their performances at the 2-AFC detection task. To do so, we measured the fraction of trials where participants' reaction times were less than the stimulus presentation time (i.e. <3s during the estimation) and where they correctly responded "dots" during the detection task (figure 3d). We observed a common pattern across participants, whereby stimuli were more often detected at the most frequently presented directions than at other directions. Controls were more likely to detect stimuli moving in the most frequently presented motion directions 78.1%±1.5 versus 65.3%±1.4 detected for all other directions *($p<0.001$, two-tailed paired t-test)*. Similarly, patients were significantly more likely to detect stimuli moving at ±32° (73.2%±1.8) in comparison to all other motion-directions (64.2%±3.2; *$p<0.01$, two-tailed paired t-test*). Overall, there was a significant effect of motion-direction on the fraction detected, both for controls *($F(1,4)=11.36$, $p<0.001$, one-way ANOVA)* and patients *($F(1,4)=4.72$, $p<0.005$, one-way ANOVA)*. Patients and controls did not differ at detecting motion-direction at the mostly presented direction (±32°; *ns., two-tailed independent samples t-test*). These results indicate that, in terms of detection responses (hit rates), similar benefits of statistical learning were present in both patient and control groups.

Another measure that reflects how easily participants detected stimuli is their response reaction time during the estimation task. To do so, we measured the elapsed time between the stimulus presentation and the estimation response of the participant (i.e. mouse click). A general pattern was observed across participants, whereby the mean reaction time at the most presented direction was shorter than at all other directions (figure 3c). For trials where controls correctly detected a stimulus, their reaction time was significantly reduced for the most frequently presented motion-direction relative to other motion directions (201±4.2 ms at ±32° versus 214±5.2 ms over all other motion-directions; *$p<0.005$, two-tailed signed-rank test*). Similarly, patients were generally faster at detecting and responding to stimuli presented at the most frequented motion directions (217±7.4 ms at ±32° *vs.* 225±6.5 ms over all other motion-directions; *$p=0.019$, two-tailed signed-rank test*). There was no significant effect of motion direction on participants' reaction *time (*Controls: *ns.;* Patients: *ns., Kruskal-Wallis H test)*. However, although patients were generally faster for the most presented motion direction in comparison to other directions, they were significantly slower than controls at the estimation of motion direction *($p=0.014$; two-tailed rank sum test)*. Slow reaction time is a hallmark of schizophrenia that has been documented thoroughly in the literature in simple reaction-time tasks using visual and/or auditory stimuli (Nuechterlein, 1977).

3.3. Perceived motion in absence of visual stimuli ('hallucinations')

Finally, we investigated whether the acquired statistics about the motion stimulus affected the participants' perception on trials where no stimulus was presented but where participants reported both a motion-direction and seeing a stimulus. We refer to this effect as "hallucinations". The "hallucinations" in our perceptual task are of course different in terms of content and complexity to the visual hallucinations observed in psychosis (Collerton et al., 2005). However, studying these has the potential to shed light on perhaps similar perceptual mechanisms at play between illusions and hallucinations. On average participants "hallucinated" the stimulus on 17.9±4.77 trials for controls and 14.60±5.87 trials for patients, corresponding to 13.8±4% and 11.3±4% of trials where no stimulus were presented (*ns.; two-tailed MC permutation test – difference of medians*). Interestingly, for this subset of trials, participants' estimation responses varied significantly with motion-direction, with a clear peak at the most frequently presented motion-directions (±32°; *Controls: p=0.002 – Patients: p=0.019, two-*

tailed signed-rank test). This suggests that participants did not make random "hallucinations" of the stimulus but rather hallucinated preferentially the most presented motion directions.

To quantify the probability ratio that participants made estimates that were closer to the most frequently presented motion directions relative to other directions, we multiplied the probability that participants estimated within 8° of these motion-directions by the total number of 16° bins:

$$P_{rel} = p\left(\theta_{estimate} = \pm 32\left(\pm 8\right)^{\circ}\right) \cdot N_{bins}$$

This probability would be equal to 1 if participants were equally likely to estimate within 8° of ±32° as they are to estimate within the other 16° bins. We found that the median value of *'P_{rel}'* was significantly greater than 1 for both groups, indicating that participants were strongly biased to report motion in the most frequently presented directions when no stimulus was presented (i.e. hallucinated significantly more stimuli at the most presented directions; figure 4a-b).

The fact that participants report perceiving dots that are not present, more often at the most frequently presented motion directions provides strong evidence to suggest that the statistics of the task have been acquired. Hallucinations of the most presented directions (i.e. hallucinations at ±32°±8°) appear significantly more often than at random directions after only 250 trials in controls (*p=0.029, two-tailed signed-rank test*) and 400 trials in patients (*p=0.019, two-tailed signed-rank test*). It is interesting to note however that while healthy controls and patients did not differ in the amount of *'random'*-hallucinations (i.e. over all directions; *p>0.05; MC permutations test, difference of medians*), patients made significantly fewer hallucinations of the most presented direction than controls *(p=0.0174, two-tailed MC permutation test – difference of medians)*. In fact, 66% of patients made 3 or less hallucinations of the most frequently presented directions, of which 50% made no hallucinations at all. By comparison, all controls hallucinated stimuli at the most presented directions (i.e. 90% of controls hallucinated between 3 to 14 times at ±32°±8°).

To ensure that the stimulus hallucinations at 32°±8° were not the result of a strategy, we analysed the subset of trials were participants made an estimation but did not report seeing a stimulus. In fact, on a large proportion of trials the presented motion stimuli were moving in one of two directions. It is therefore possible that participants could have developed a strategy to move subconsciously the estimation bar towards one of these directions irrespective of their response in the detection-task. If this were the case, we would also expect the 'no-stimulus' estimation distributions to be biased towards the most frequently presented directions for trials were participants did not detect a stimulus. This response-bias could be ruled out since participants were not significantly more likely to move the estimation bar closer to the frequent directions on trials where they did not report seeing a stimulus (i.e. all except 1; Figure 4a-d see "PDF estimated only" line). These results largely replicate those of Chalk *et al.* (Chalk et al., 2010) and Gekas *et al.* (Gekas et al., 2013).

Finally, we found that the participants' hallucinations at 32°±8° correlated significantly with the neuropsychological assessment of the GAF (r_2*=0.532, p=0.0131, MC permutation test*) and the PANSS total *(r_2=-0.498 p=0.035, MC permutation test)* and PANSS positive symptoms scores *(r_2=-0.586 p=0.0077, MC permutation test)*. These findings suggest that the more hallucinations participants make, the less severe the symptoms were (as measured by the PANSS and the GAF). Similar results were found in healthy controls using bi-stable perceptual illusion tasks and measuring delusional ideation in these healthy participants (Schmack et al., 2013). We found no relationship between the daily-dosage of anti-psychotics (Chlorpromazine equivalent; (Andreasen et al., 2010)) and the total amount of hallucinations at 32°±8° (*ns.; MC permutation test).*

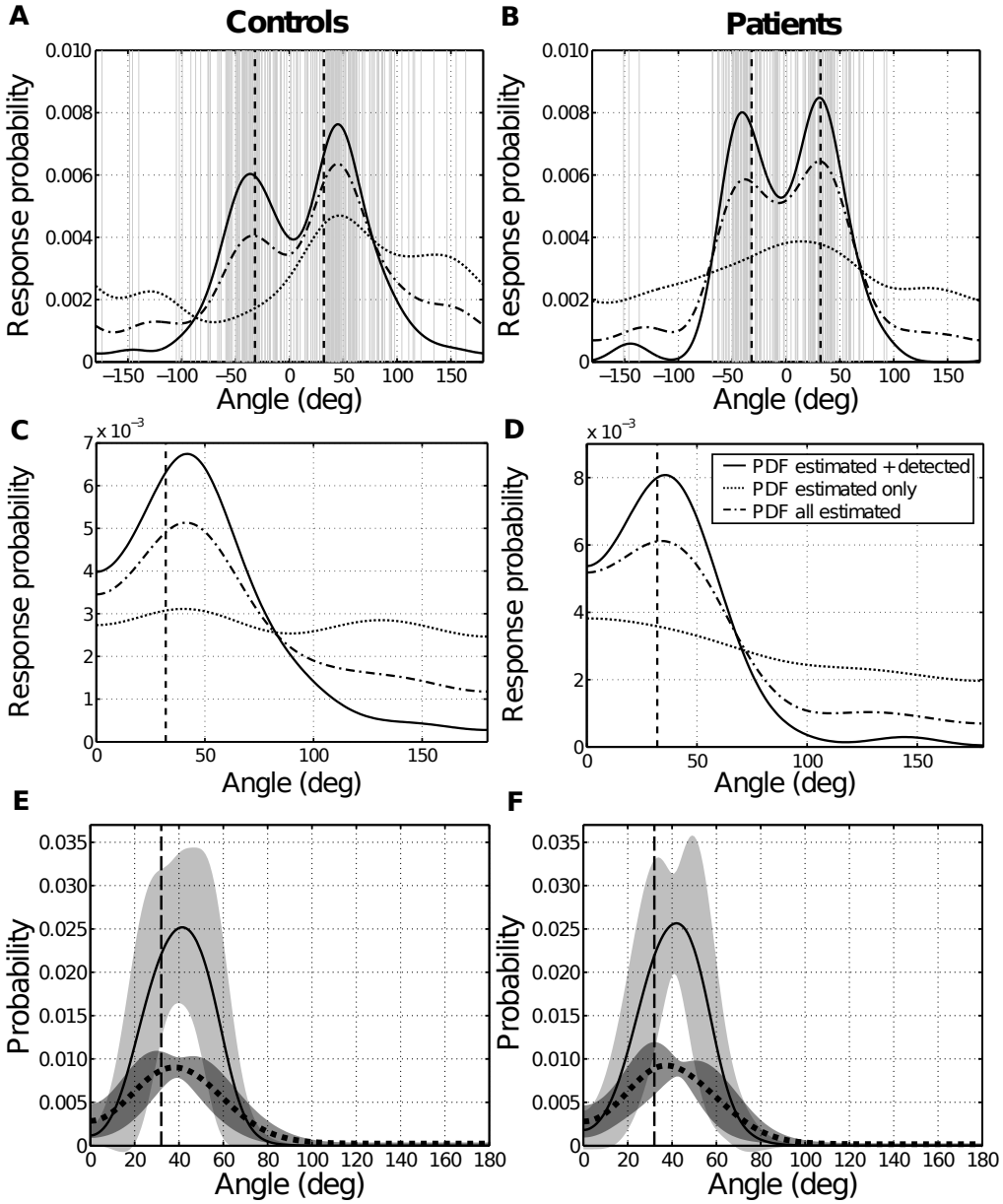

Figure 4: Estimation responses in the absence of stimulus for each group (Controls - A, C, E; Patients B, D, F). **(A, B)** The vertical grey lines correspond to all the estimated motion directions when no stimulus was present (i.e. hallucination) pooled across the whole group (A-controls, B-patients). The black line represents the fitted probability distributions of response for trials where participants report a seeing a stimulus. The dotted line represents the fitted probability distribution for trials where participants reported a motion direction during the estimation but did not confirm seeing a stimulus during the detection task. The dot-and-dash horizontal line depicts the fitted probability distribution for all trials where motion direction was reported. **(C-D)** Data from either side of the central motion are

averaged together. The dotted vertical line in black signals the position of the mode of the prior (i.e. ±32°). **(E-F)** Participants *learned* prior distribution of presented motion directions as predicted by the Bayesian model '`Bayes_dual`' (plain line and light-gray area). The probability distribution of perceptual hallucinations when simulating the task with the Bayesian model '`Bayes_dual`' (dotted bold line and dark-grey area)

4. Discussion

In summary, our results replicate previous findings of Chalk et al. (Chalk et al., 2010) both in the patient and control groups. The performance of both groups show that participants implicitly learn the statistics of the motion stimuli and that those expectations modify their perception. All participants display an attractive estimation bias towards the frequently presented directions and reduced estimation variability for these directions. They also show faster reaction times and higher detection rates for the most frequently presented directions. Finally, they tend to *'hallucinate'* the expected directions in absence of stimuli.
Patients were not qualitatively, nor quantitatively different from controls in these measures used to assess learning of the task statistics. However, we found that patients and controls differed in two ways. First, patients with schizophrenia displayed significantly poorer contrast discrimination thresholds than controls and slower reactions times. Second, we found that patients reported significantly less '*hallucinations*' of the most frequently presented motion directions than controls. The amount of hallucinations of the most frequently presented directions correlated significantly with the GAF, PANSS Total and Positive scores, suggesting that the more participants hallucinate at the task, the better they usually fare in neuropsychological tests..

4.1. Bayesian interpretation of *'hallucinated'* dots

An emerging model of schizophrenia suggests that the disorder would stem from deficits in Bayesian inference. For example, it has been proposed that the recurrent complex visual hallucinations (RCVH; (Collerton et al., 2005)) seen in psychotic could be explained in terms of deficits in the Bayesian integration of perceptual priors and likelihoods (Adams et al., 2013; Corlett et al., 2009b; Fletcher and Frith, 2009).

Our paradigm is well suited to assess whether patients show deficits in probabilistic inference, either due to deficits in acquisition of the sensory priors, deficits in how these priors are used, or due to less uncertainty in the encoding of sensory information. Indeed, we found that participants performance at our task can be well described by a Bayesian model where participants learn an approximation of the stimulus statistics in the form of a perceptual prior and combine it with sensory information. Both the perceptual biases and *'hallucinations'* in absence of stimulus can be understood as the signature of this prior. Moreover, our paradigm allowed for the first time to directly measure this prior in individuals suffering from schizophrenia. Our results suggest that the acquired priors are similar in controls and medicated patients with schizophrenia (figure 4c-d).

However, while patients seem to have learnt the statistics of motion-direction just as well as controls, patients reported fewer *'hallucinations'* of the most frequently presented directions. These results concur with previously reported findings suggesting that chronic schizophrenic patients are less sensitive to expectation-driven illusions (e.g. the Hollow-mask illusion) than controls (Crawford et al., 2010; Dima et al., 2009; Keane et al., 2013; Tschacher et al., 2006). Finally, we find that the strength of positive symptoms correlated negatively with the participants' sensitivity to hallucinations of the motion stimulus (i.e. the stronger the symptoms the fewer the hallucinations). Similar findings have been reported in studies of the hollow-mask illusion in schizophrenic patients (Keane et al., 2013).

It is intriguing however that the influence of the prior is similar to that of controls for the estimation task but different for the detection task in absence of stimulus. To reconcile these results, we considered different hypotheses:

First, it is possible that chronic patients might consistently use a model of the task that is simpler than the Bayesian model. We explored this possibility by assessing whether simpler phenomenological models (for a description see (Chalk et al., 2010)) could better account for the

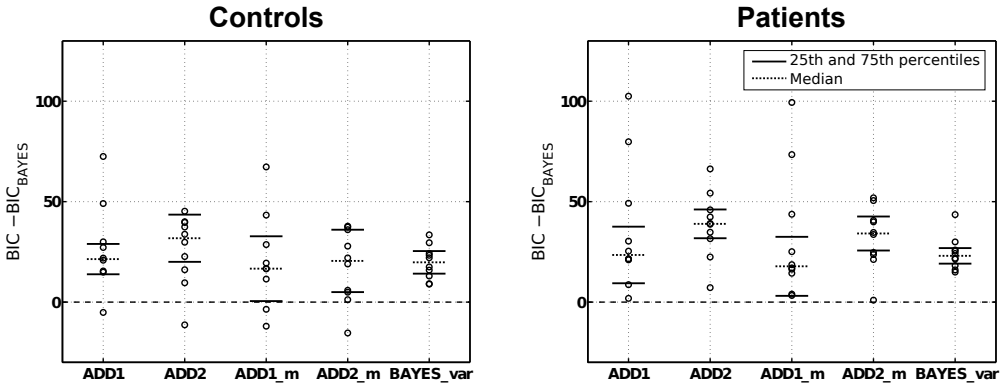

Figure 5: Model comparison using the Bayesian Information Criterion (BIC). The BIC score is evaluated for each model and subtracted by the BIC score evaluated for the simple 'Bayes' model for each participant. Values greater than zero indicate that then simple 'Bayes' model was better at describing the behaviour of the participant.

performance of patients that have fewer expectations-driven hallucinations. To do this, we used a systematic model comparison approach named the Bayesian Information Criterion (BIC) that enables to compare models using a quantitative measure based on the fit to the data and the model complexity. We found that patients were better described by the Bayesian model than by any other model (Figure 5), suggesting that fewer hallucinations in our task are not due to the use of a different strategy by patients.

Second possibility, chronic patients might overestimate the accuracy of their sensory integration (the likelihood), as described in (Adams et al., 2013; Jardri and Deneve, 2013). This would result in perception driven mostly by sensory information when no stimuli are present, therefore seeing no stimulus when nothing is presented. However, this model should result in weaker perceptual biases in patients compared to controls. This was not the case in our study.

Finally, chronic patients might have developed a heightened perception threshold requiring higher amount of evidence (i.e. stronger posterior) in order to perceive a stimulus or make a decision about the presence of a stimulus. In fact, patients require a higher stimulus contrast and to integrate information over longer periods of time before responding (slower reaction times during the estimation task). We hypothesize that it is a possible adaptation strategy used by patients over time to overcome responding to stimuli that are not truly present (i.e. recurrent complex hallucinations). That is, because patients have formerly been exposed to hallucinations, they might now demand heightened evidence to consciously report perceiving stimuli that might not truly be present. This hypothesis deserves more investigation but at this stage it seems compatible with our results.

This hypothesis could be further explored using psychophysical tasks where the prior is explicitly given to the participants (Speechley et al., 2010).

5. Conclusions

In line with studies finding no deficit in implicit learning in schizophrenia (Danion et al., 2001; Kéri et al., 2000; Marvel et al., 2005), for review see (Gold et al., 2009), we find that patients' performances suggest that they correctly acquired the statistics of the stimuli in out task. First, in contrast with studies that assay explicit statistical learning and inference in context with cognitive symptoms (i.e. in learning and decision-making, usually believed to involve frontal cortical regions), here we measured implicit statistical learning of visual stimuli that could be embodied in visual processing areas rather than frontal cortices (Kok et al., 2013). As a review of cognition in schizophrenia recently highlighted (Gold et al., 2009), while patients are generally impaired in explicit learning, they appear relatively spared in implicit learning tasks that do not require integrating information after each trial. Secondly, our patient sample was relatively well at the time of testing and might not be representative of patients experiencing full-blown psychosis (i.e. chronic medicated schizophrenics; mean illness duration 14.72±2.73 years). Our patient sample displayed no significant differences with the control group in terms of positive-symptom scales and current IQ.

Finally, both patients and controls preferentially hallucinated stimuli at the most frequently presented directions when no stimulus were present, strongly suggesting that they correctly acquired the statistics of the task. Moreover, in line with recent studies (Keane et al., 2013), patients appeared to be less sensitive to expectation-driven perceptual *'hallucinations'* than controls, suggesting that they may have a normal top-down *vs.* bottom-up signalling but a heightened perceptual threshold, requiring higher amounts of evidence in order to perceive a stimulus. In agreement with Keane *et al.* (Keane et al., 2013) and Schmack *et al.* (Schmack et al., 2013), we also found that the amount of expectation-driven perceptual *'hallucinations'* were predictive of positive-symptom severity in patients or delusion ideation in healthy controls.

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7. Conflict of interest

SML received financial support from Pfizer (formerly Wyeth) in relation to imaging studies of schizophrenic patients. SML has done consultancy work for Roche pharmaceuticals in connection with a possible treatment for schizophrenia. SML has received honoraria for lectures, chairing meetings, and consultancy work from Janssen in connection with brain imaging and therapeutic initiatives for psychosis. The authors VV, PS and ARS have no conflict of interest.

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