



Information gathering and motivated decision making in health and disease

Bahaaeddin Attaallah

University College



University of Oxford

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Supervised by Prof Masud Husain and Prof Sanjay Manohar

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Abstract

Almost every aspect of our lives involves making decisions. From deciding to get out of bed in the morning to saying "I do" at a long-awaited wedding. Humans, like animals, often try to optimise their decisions to maximise reward and avoid losses. Understanding the mechanisms and neural correlates of such behaviours can provide crucial insights into human cognitive and psychological functioning in health and disease. In this thesis, two common forms of motivated decision making are examined: i) decision making under uncertainty and information gathering, and ii) effort-based decision making (EBDM). Through behavioural experimentation, computational modelling, and neuroimaging analysis, I reveal novel mechanisms and brain networks involved in these forms of behaviour and investigate their clinical implication on affect and motivation. In addition to healthy humans, different groups of patients were investigated, including autoimmune limbic encephalitis (ALE), subjective cognitive impairment (SCI), and Alzheimer's disease (AD). The results across these study groups converged to characterise two potentially dissociable psycho-cognitive-brain axes. The first draws a link between uncertainty processing, affect, and the hippocampus. The second highlights the relationship between apathy (reduced motivation), deficits in EBDM, and key functional brain networks such as default mode and fronto-parietal networks. The findings in this thesis thus highlight an experimental and mechanistic framework for investigating information gathering and EBDM, and provide insights into their clinical implications and associated brain networks.

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List of abbreviations

OCD		Obsessive Compulsive Disorder
PD		Parkinson's Disease
AD		Alzheimer's Disease
MCI		Mild Cognitive Impairment
SCI		Subjective Cognitive Impairment
ALE		Autoimmune Limbic Encephalitis
SVD		Small Vessel Disease
ICD		Impulse Controls Disorder
ADHD		Attention Deficit Hyperactivity Disorder
JTC		Jumping to Conclusions
OFC		Orbitofrontal Cortex
PFC		Prefrontal Cortex
dLPFC		Dorsolateral Prefrontal Cortex
VS		Ventral Striatum
ACC		Anterior Cingulate Cortex
IC		Insular Cortex
EBDM		Effort-Based Decision Making
DA		Dopamine
EE		Expected Error

ISI	Inter-sampling Interval
LMM	Linear Mixed Effects Model
AMI	Apathy Motivation Index
BDI	Beck's Depression Inventory
ACE	Addenbrooke's Cognitive Examination
DS	Digit Span
HADS	Hospital Anxiety Depression Scale
HDDM	Hierarchical Drift Diffusion Model
DMN	Default Mode Network
FPN	Fronto-Parietal Network
LPFC	Lateral Prefrontal Cortex
DAN	Dorsal Attention Netowrk
SMN	Sensorimotor Netowrk

1 | Introduction

1.1 Chapter summary

The study of goal-directed behaviour has seen significant advances over the past decades and has been a central theme in different research fields, including neuroscience, psychology, and economics ([Glimcher and Fehr, 2013](#); [Loewenstein et al., 2007](#); [Rangel et al., 2008](#)). Mechanistic deconstruction of the cognitive and behavioural processes involved has provided crucial insights into our understanding of human motivation and affective regulation in health and disease ([Bishop and Gagne, 2018](#); [Brown and Pluck, 2000](#); [Chong et al., 2016a](#); [Grupe and Nitschke, 2013](#); [Hartley and Phelps, 2012a](#); [Husain and Roiser, 2018](#); [Pulcu and Browning, 2019](#); [Sinha et al., 2013](#)). At the heart of goal-directed behaviour lies value-based decision making, which involves economic cost-benefit evaluations where agents make decisions based on their expected value ([Rangel et al., 2008](#)).

Two key examples of such decision making processes are i) decision making under uncertainty and active information gathering, and ii) effort-based decision making (EBDM). This first chapter provides a summary of previous work and studies investigating these two forms of decision-making. It introduces the conceptual framework for examining active information gathering under uncertainty and associated brain regions, networks, and neurotransmitters. It then provides a comparative overview of EBDM in terms of cognitive components, brain regions, and neuromodulators involved. Finally, based on this review, at the end of this chapter, I discuss the key objectives of this thesis addressing gaps in the literature to advance our understanding of goal-directed behaviour in health and disease. These objectives are i) developing and refining behavioural paradigms and models to investigate the two forms of decision making mentioned above, ii) examination of

the role of the hippocampus in decision making under uncertainty and for effort, and iii) investigating the clinical implications of deficits in these forms of decision making on affective regulation and motivation.

1.2 Decision making under uncertainty and active information gathering

Uncertainty by definition is a state of imperfect knowledge or inadequate information ([Smithson, 1989](#); [Walker et al., 2003](#)). It thus pertains to future states with probabilistic outcomes inferred from current observations and experiences ([Begg et al., 2014](#)). Due to the impossibility of having ‘perfect knowledge’, almost all decisions humans make in their lives are made under various degrees of uncertainty. Whether it is buying a new item in a local grocery store or making a life-changing decision, people try to optimise their decisions depending on the information available. This optimisation process might involve acquiring more information, if deemed beneficial and affordable, to reduce uncertainty around decisions ([Kuhlthau, 1993](#); [Pirolli and Card, 1999](#); [Stigler, 1961](#)). Although the goal of information gathering may often be the same – to maximise decision-dependent rewards and minimise losses – people may differ in many aspects of this behaviour. In this section, I review the literature on active information gathering in health and disease to provide a summary of disease effects, neuroanatomy, and neuromodulation of this behaviour.

1.2.1 Active information gathering: a conceptual framework

Active information gathering (seeking, sampling) applies to situations where agents make purposeful decisions to sequentially obtain pieces of information in order to

resolve uncertainty and reach goals ([Dey and Gottlieb, 2019](#); [Gantz et al., 2016](#); [Gottlieb and Oudeyer, 2018](#); [Nwone and Mutula, 2020](#); [Wilson, 2000](#)). This is crucially distinct from passive information gathering, where agents passively process stimuli without explicitly making decisions to acquire information ([Nwone and Mutula, 2020](#)). In the passive form, agents' decisions are limited to whether they keep accepting the information flow from a certain source, rather than interacting with the environment to decide on what sources to consult and how to obtain information from them, i.e., agents have limited control over the characteristics of the information they are obtaining.

A typical experimental example of passive information gathering in the psychology and neuroscience literature is the random dot motion task ([Britten et al., 1992](#)) where participants attend to random dots moving on a screen to infer the overall direction of the dots (attention here is regarded as a surrogate of information gathering) (but see [Dey and Gottlieb 2019](#)). This, while being a simple and robust way to examine specific constructs related to information seeking, confidence, and uncertainty processing, lacks the element of agency that many ecological situations involving information gathering share. Consider the example of an animal deciding which patch to explore for food. It naturally seeks evidence that helps it find the best food patch, that is, the patch with the highest reward yield and the lowest risk ([Arvidsson and Matthysen, 2016](#); [Stephens, 1987, 2008](#)). Through such a process, agents spend time and energy collecting evidence and observations and might adopt a certain information gathering strategy from observing other animals or from their own previous strategies – for example, some animals might prefer ‘sit and wait’ strategy while others might actively explore the environment ([Arvidsson and Matthysen, 2016](#); [Dall and Johnstone, 2002](#)). Regardless of the strategy and the external flow of evidence, animals in these situations have agency over most aspects of the information gathering process (e.g., where to look, what sources of

information to consult, and when) and decide when evidence is sufficient to make a decision to commit to a patch. Similarly, in humans, such a strategy is prevalent across many aspects of their daily activities, ranging from simple decisions (e.g., what to wear today) to a life-changing course of action such as moving to another country for work.

Crucially, in these scenarios, information is sought for its epistemic value (i.e., its impact on uncertainty) rather than its intrinsic rewarding attributes, e.g., curiosity-driven sampling ([Gottlieb and Oudeyer, 2018](#); [Sharot and Sunstein, 2020](#)). Thus, the subjective value of information will change depending on its impact on uncertainty and its cost, making such a behaviour subject to classical cost-benefit economic evaluations, weighing the cost(s) of acquiring new pieces of evidence against their expected benefits ([Clark et al., 2006a](#); [Jones et al., 2019](#); [Juni et al., 2016](#)). This characterisation helps further distinguish active information gathering prior to committing to a decision from other exploratory behaviours such as foraging for reward or curiosity-driven information seeking, where agents consume information as they explore the environment, i.e., exploitation.

With this economic view in mind, it is possible to deconstruct information gathering into several cognitive or behavioural components. Such an approach not only helps disambiguate concepts and processes linked to this behaviour, but also allows empirical testing and delineation of mechanisms that might be of significant clinical utility. One potential formulation of optimal sampling behaviour is shown in [Figure 1.1](#).

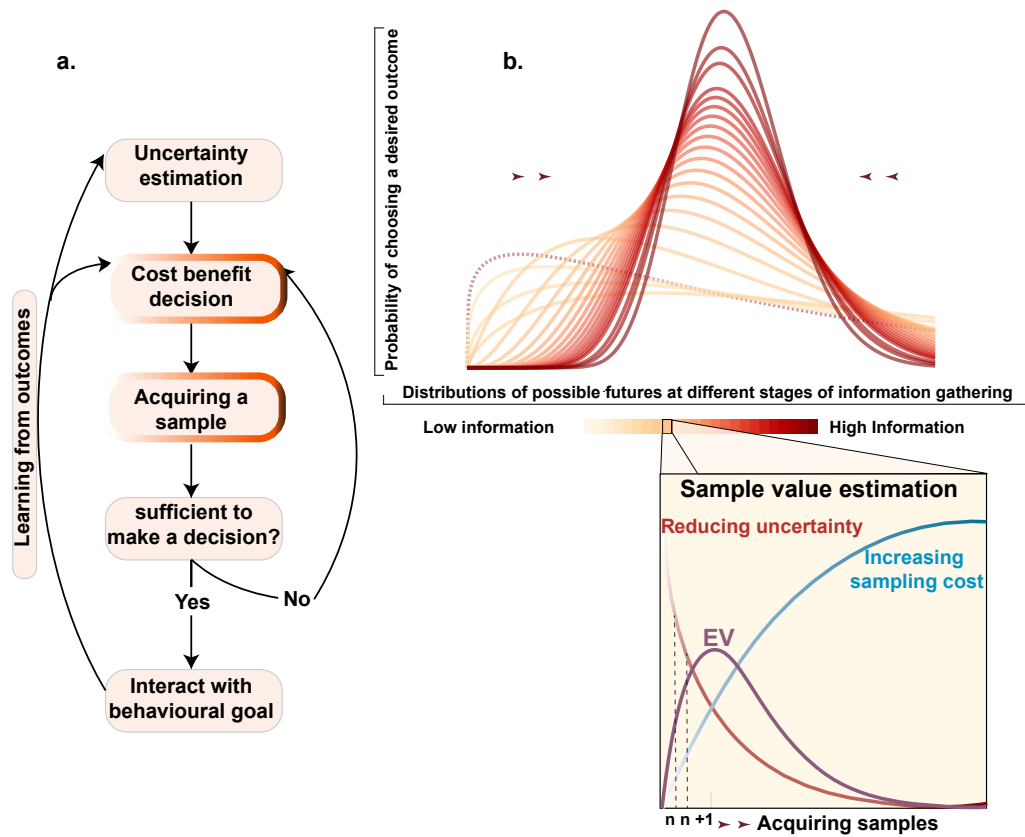


Figure 1.1: Active information gathering framework. **a.** Behavioural components of ideal active information gathering. At each step, upon acquiring information, agents estimate uncertainty in the environment in which they are making a goal-directed decision. To decide whether a sample is worth acquiring, agents engage in a cost-benefit analysis, evaluating the cost of acquiring a new observation against its expected benefit (i.e., how much it will help reduce uncertainty). If the benefit of the sample outweighs its cost, the agent proceeds to acquire that sample. Agents repeat this process with each additional sample until the cost of the sample outweighs its benefit. At this point, they stop sampling and make a final decision that leads to an outcome. They then interact with these outcomes to consume the expected reward, compare them with prior expectations, and learn from these interactions. **b.** The probability of choosing the desired outcome depends on how much information agents have. If agents have no previous information, all options will be equally probable, and decisions will be purely random. However, on many occasions, decision makers have some previous experience (so the initial distribution might be skewed). With successive sampling, the distribution of possible futures becomes narrower (i.e., uncertainty becomes smaller). The transition from one distribution to the next depends on sampling efficiency (i.e., the rate at which acquired samples reduce uncertainty) and sampling cost. As uncertainty decreases and cost accumulates, this imposes an optimal stopping point where the expected value (EV) of the decision is maximum. The insert shows the evolution of EV with time, given the cost and benefit of the sample at each step of sampling (e.g., moving from sample n to sample $n+1$).

The first step when considering decisions and information gathering under uncertainty is to assess the uncertainty agents are faced with. This involves having subjective estimates of uncertainty mapped onto the information content of the environment (Daunizeau et al., 2010; Grupe and Nitschke, 2013; Pulcu and Browning, 2019). Consider the example of someone trying to buy a new item on an online store. Buyers assess the different options available on the website prior to committing to an item. If agents have no prior information about these options, their uncertainty about which item to buy will be the highest. The value they assign to each of these available options based on the current state of information will not differ and therefore, if a decision was to be made at this stage, the different options will have equal probability of being selected by the decision maker. However, in many scenarios, agents have prior experiences that would allow them to have lower subjective estimates of uncertainty depending on how rich these prior experiences are.

A crucial aspect related to assessing uncertainty content involves how accurately agents read the environment and how they assign costs to these estimates (Daunizeau et al., 2010; Grupe and Nitschke, 2013; Pulcu and Browning, 2019). Subsequent decisions and processes might be altered on the basis of these factors. For example, inability to accurately read uncertainty in the environment might lead participants to have inflated subjective estimates in situations of relatively low uncertainty, resulting in them collecting more information than needed. Similarly, having low subjective estimates of uncertainty might result in hasty decisions without sufficient information. These uncertainty estimation deficits have previously been linked to biases observed in disorders of affect and motivation (see the next sections) (Grupe and Nitschke, 2013; Pulcu and Browning, 2017).

Alternatively, people might accurately estimate uncertainty but assign different costs to it. Some people may consider a certain level of uncertainty intolerable

and require more information to make decisions ([Boswell et al., 2013](#); [Bredemeier and Berenbaum, 2008](#); [Freeston et al., 1994](#); [Garety et al., 1991](#); [Ladouceur et al., 1997](#)). Others might assign lower weight to the same level and make decisions without additional observations. Similarly, when weighed against reward and other costs, some people might disregard uncertainty for reward or underweigh it relative to some costs. Others might do the opposite. These components provide the basis for cost-benefit evaluation driving behaviour and governing whether agents commit to a decision (e.g., buy a specific item) or gather more information to help them reach their goal (e.g., check other websites, read item specification) ([Rangel et al., 2008](#)).

Crucially, these calculations are applied to the information (samples, observations) agents intend to obtain to reduce uncertainty, i.e., they evaluate the expected benefit of the sample against its cost ([Clark et al., 2006a](#); [Jones et al., 2019](#); [Juni et al., 2016](#)). A decision to acquire a new piece of evidence is made when the expected reduction of uncertainty from this observation (expected benefit) outweighs its cost. This process of uncertainty estimation, cost assignment, and cost-benefit evaluation is repeated with each new sample acquired (Figure 1.1 b.). According to this perspective, agents dynamically update their uncertainty estimates with this evidence to be re-incorporated in their cost-benefit evaluation assessing the utility of obtaining more samples.

An optimal agent will decide to stop sampling and commit to a decision once the sampling cost is no longer justified by the expected benefit of acquiring more samples, i.e., its expected value reaches maximum) ([Clark et al., 2006a](#); [Jones et al., 2019](#); [Juni et al., 2016](#)). Such an optimal solution to the problem is imposed by two competing economic variables that evolve over time: i) the sampling cost, which is added with each sample acquired, and ii) the impact of the samples on uncertainty, which decreases with sampling as agents' knowledge improve ([Phillips](#)

et al., 1966). Depending on the situation, sampling cost might take different forms including money, time, effort, cognitive resources, etc. Similarly, the trajectory that the accumulation of this cost follows, as well as uncertainty, might also differ depending on the task at hand. Figure 1.1 b. shows an example of how such computations evolve dynamically over time with successive sampling.

Following the information gathering phase, agents commit to a final decision, e.g., choose an item to buy. This will result in them interacting with the goal including a hedonic phase of consuming the reward that was pursued (consummatory phase of behaviour). Naturally, this involves comparing expectations with outcomes, generating prediction errors and driving learning process (Den Ouden et al., 2012; Glimcher, 2011; Schultz, 2016, 2017). Note that learning and prediction errors occur also during the sampling phase, which might result in agents adjusting their sampling strategies. This is a crucial element of *active* sampling, as agents have agency over the samples they obtain.

To summarise, active information gathering is a complex behavioural process that involves several cognitive components that drive sampling decisions. These components involve estimating uncertainty, performing cost-benefit valuations, interacting with goals, and learning from outcomes.

1.2.2 Behavioural paradigms used to investigate information gathering

Several previous behavioural tasks have been used to investigate information gathering in humans. The beads (urn) task is one of the earliest examples of these (Figure 1.2 a.) (Phillips et al., 1966). Many versions of the task have been developed over the years in order to examine different cognitive mechanisms involved in probabilistic decision making and information sampling (Dudley et al., 2016;

Garety et al., 1991, 2005; Moritz et al., 2007; Speechley et al., 2010; Sternheim et al., 2011; Voon et al., 2016; Westermann et al., 2012). In this paradigm, participants draw samples (beads) from a jar that has different proportions of beads of two colours (e.g., 40/60 or 20/80). Participants are required to decide the predominant colour of the jar from the samples they drew. The main behavioural marker derived from the task is the number of draws prior to decisions, which when compared to an optimal solution or a control group's performance, allow behavioural properties about the study group of interest to be inferred. For example, under-sampling characterises reflection impulsivity and jumping to conclusions bias in certain groups of patients (Balzan et al., 2012; Colbert and Peters, 2002; Huq et al., 1988; Messer, 1976; Ross et al., 2015).

Despite providing important insight into human information gathering and probabilistic decision making, the paradigm has several limitations, depending on the version used. These include memory demands, task comprehension issues, and limited agency over the process of sampling. Different versions of the task have been developed to address these issues and expand the scope of the cognitive processes examined in the paradigm. These modifications included changes to the task environment and stimuli (e.g., fish task in Speechley et al. 2010) and manipulating variables that help create economic conditions to provide a fine-grained understanding of the decision process involved (Banca et al., 2015; Esslinger et al., 2013; Fine et al., 2007; Furl and Averbeck, 2011; Jacoby et al., 2014; Lincoln et al., 2010; Menon et al., 2008; Moritz et al., 2017; Ross et al., 2015; Westermann et al., 2012; Woodward et al., 2009). For example, some versions include a cost assigned to acquiring new samples, manipulate the reward that can be won for accuracy or uncertainty that participants face, or a combination of all of these variables together (Banca et al., 2015; Esslinger et al., 2013; Furl and Averbeck, 2011; Ross et al., 2015; Woodward et al., 2009). The exact manipulation depends

on the research question of interest and the hypothesis being tested.

Other paradigms were developed following the same principle as the beads task (i.e., drawing samples from a distribution to reduce uncertainty). For example, the information sampling task (IST) can be regarded as a special version of the beads task that gained popularity over the past two decades, especially in studies conducted in patient groups ([Averbeck et al., 2013](#); [Clark et al., 2006a,b,c](#)). This requires less demand on visual processing and working memory. Participants are presented with a number of boxes that they can uncover to reveal one of two colours (Figure 1.2 b.). Overall there are 25 boxes on the screen that participants can sample before deciding which colour is the predominant one. Based on the number of boxes sampled, accuracy probability can be calculated at the time of the final decision, indicating the level of information (uncertainty) at which participants are willing to make decisions. Again, the task imposes costs of acquiring samples, creating a trade-off between sampling cost and benefit – a critical process when making decisions.

One limitation that these two tasks share is the limited range of uncertainty manipulated. Decisions are often categorical, with two or a few solutions to the problem, limiting the ecological validity of the task and constraining economic analyses of sampling behaviour. Addressing these issues, [Juni et al. \(2016\)](#) designed a paradigm where uncertainty represents a distribution of possible solutions that is updated and quantified with additional observations (Figure 1.2 c.). In this task, participants are instructed to localise a hidden object on the screen. Clues about the location of this target can be requested at a cost and are derived from a Gaussian distribution with a mean at the target centre. With this design, the researchers were able to compute an optimal solution that depends on subjective utility function, estimating the utility of sampling as information gathering progresses (Figure 1.2 d.).

Although these paradigms provided crucial insights into the economics of information gathering in health and disease, they still have at least one key limitation: the degree of agency on information gathering. As discussed previously, the acquisition of observations or samples from the environment often involves many agent-related factors that are of critical importance to the process. Agents differ not only in the amount of information they collect but also in *how* this information is collected. Some people might opt to collect information faster than others, reflecting urgency to resolve uncertainty or less consideration of reward costs of information. Similarly, some might sample their environment with different degrees of efficiency, depending on how they utilise their cognitive resources or simply on their understanding of the problem the task imposes. Capturing these differences would provide new behavioural markers with crucial insights into human goal-directed behaviour and the brain mechanisms involved. Testing this empirically requires experimental features that are missing from existing paradigms: (1) some candidate samples should be more informative than others; and (2) it should be nontrivial to find them. I address this limitation in Chapter 2 of this thesis, where I introduce a novel behavioural task that examines active information gathering and decision making under uncertainty.

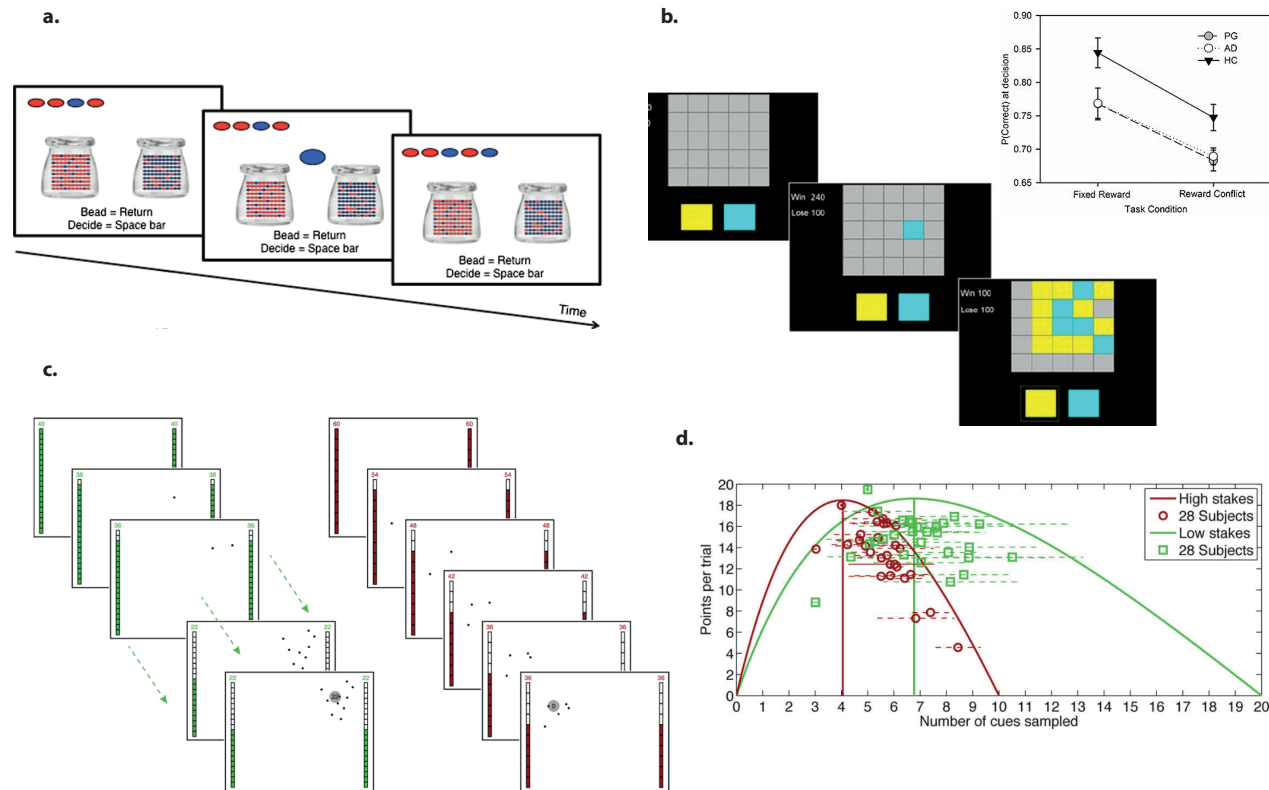


Figure 1.2: **Previous behavioural paradigms investigating information gathering.** **a. Beads task.** In this task participants draw samples (beads) from one of two jars with different colour distributions (predominantly red or blue). Participants are required to infer from which jar the samples are being drawn (illustration from [Voon et al. 2016](#)). **b. Information sampling tasks (IST)** ([Clark et al., 2006a](#)). The task is similar in principle to the beads task. Participants open boxes to determine the predominant colour of the boxes on the screen (blue or yellow). There are two task conditions depending on whether new observations come at cost (reward conflict) or not (fixed reward). $P(\text{Correct})$ can be calculated and used as a behavioural index of reflection impulsivity. For example, one study found that addiction (problem gamblers – PG) and binge drinking (AD) are associated with lower $P(\text{Correct})$ reflecting higher impulsivity ([Lawrence et al., 2009](#)). **c.** Task used in [Juni et al. \(2016\)](#) with a continuous uncertainty space and explicit sampling cost. Participants are asked to find the location of a hidden target by requesting samples derived from a distribution centred at the target. **d.** Calculation of the optimal number of samples based on the information gain function determining the utility of samples based on their number and cost. Participants over-sampled when cost was high.

1.2.3 Information gathering in different groups

1.2.3.1 Healthy humans

Over the past decades, many studies have investigated how healthy participants process and gather information ([Battaglia and Schrater, 2007](#); [Busemeyer and Rapoport, 1988](#); [Faisal and Wolpert, 2009](#); [Ferguson, 1989](#); [Hau et al., 2008](#); [Hertwig et al., 2004](#); [Jones et al., 2019](#); [Juni et al., 2016](#); [Tversky and Edwards, 1966](#)). A central question that such studies aimed to answer was whether humans over- or under-sample, aiming to economically characterise rational human behaviour based on cost-benefit analyses. Over-sampling implies that an agent is gathering information more than expected from an economic cost-benefit optimisation perspective, i.e., acquiring information when the cost of this additional piece of evidence is higher than its expected benefit.

Previous studies have shown that healthy humans can exhibit both forms of behaviour (over- or under-sampling), depending on the task environment. For example, early work by [Tversky and Edwards \(1966\)](#) showed that human participants acquire far more information than needed when compared to an optimal observer. In their paradigm, participants were required to observe and accumulate binary information clues about a light condition (on/off) in order to infer the underlying probabilities of these events. At each decision stage, they were asked whether to keep sampling or to bet on what the next light status will be. Over-sampling behaviour observed in these studies has been referred to as ‘conservatism effect’ in other similar reports ([Phillips et al., 1966](#)), where the effect of new evidence on one’s prior beliefs was not as significant as expected using Bays’ theorem.

However, other investigations have reported contrasting evidence, suggesting that humans also exhibit under-sampling behaviour when making decisions under un-

certainty ([Hau et al., 2008](#); [Hertwig et al., 2004](#)). For example, in a card sampling task, where participants are asked to sample from different decks of cards in order to decide which one offers the most profitable outcomes, healthy participants significantly under-sampled prior to making their decision to choose ([Hertwig et al., 2004](#)).

One crucial distinction that might account for such contrasting reports is the task condition in which participants gather information. For example, in experiments where explicit costs are assigned to the information being gathered (e.g., in beads, ITS and dart tasks), the expressed behaviour is often suggestive of over-sampling, especially when costs are high ([Jones et al., 2019](#); [Juni et al., 2016](#)). Contrary to this, when costs are very low or absent, humans may under-sample in comparison to an optimal decision maker ([Juni et al., 2016](#)). Another key consideration is that when humans deal with these decision problems, despite the fact that there are experimentally defined costs-benefit trade-offs, they have a subjective representation of these costs and benefits, which could alter these trade-offs based on hidden costs (e.g., fatigue, boredom) ([Lorist et al., 2000](#); [Mullette-Gillman et al., 2015](#)) and implicit benefit assignment (e.g., hedonic value of information) ([Kelly and Sharot, 2021](#); [Sharot and Sunstein, 2020](#)).

Thus, it is essential to carefully examine the conditions under which sampling is taking place when attempting to characterise healthy performance. Additionally, and as discussed in previous sections, it should be noted that in all these previous studies, participants' agency was limited (i.e., not involving active decisions regarding where and how to obtain clues), imposing further limitations to the ecologic validity and interpretation of these reports.

1.2.3.2 Delusional spectrum

The earliest reported work on the clinical implications of information gathering deficits was carried out in patients with delusional disorders, mainly schizophrenia. In their seminal study, [Huq et al. \(1988\)](#) compared the performance of a group of patients suffering from schizophrenia with the performance of healthy participants using the Beads task. Patients with schizophrenia were found to sample significantly less than controls before making their decisions. This finding in the psychology literature has been referred to as ‘jumping to conclusions (JTC)’ bias, describing a bias to making decisions without sufficient evidence.

Such an effect has also been shown in non-schizophrenia patients who suffer from delusions ([McLean et al., 2016](#)), as well as in healthy people who are considered to be prone to delusions ([Balzan et al., 2012](#); [Colbert and Peters, 2002](#); [Ross et al., 2015](#)). However, evidence from longitudinal studies examining if JTC is associated with increased risk of delusional dysfunction in healthy people is still limited.

Several accounts may explain JTC bias in delusional disorders. The first is concerned with how people epistemically process information and beliefs. One study, for example, suggested that limited belief flexibility might be mediating the correlation between under-sampling and delusions ([Garety et al., 2005](#)). This is consistent with reports showing that these participants demonstrate biases against evidence that disapproves their prior assumptions (bias against discriminatory evidence) ([Moritz and Woodward, 2006](#); [Woodward et al., 2007a,b](#)). However, other findings from the same research group showed that the three constructs (belief flexibility, under-sampling and delusions) are independent of each other ([So et al., 2012](#)).

The second account is of an economic nature, taking into account cost-benefit analyses of information gathering ([Ermakova et al., 2019](#)). Under-sampling in this

case might be related to devaluation of the expected benefit of the sample on one's beliefs, and thus patients exhibit less willingness to acquire these samples. However, studies using a version of the task where participants were required to make decisions based on probability of winning showed that individuals with delusional disorders have lower thresholds to make a decision rather than impaired economic computations contributing to evidence accumulation (Moritz et al., 2007). In other words, under-sampling in schizophrenia might reflect higher tolerance to uncertainty, rather than impaired active data gathering (Bentall and Swarbrick, 2003; Broome et al., 2007). This effect is abolished when the uncertainty surrounding decisions becomes higher, requiring more data to resolve it (Moritz et al., 2007).

Other researchers have suggested a third, simpler interpretation of JTC bias in schizophrenia, arguing that the findings might reflect miscomprehension of the task or executive dysfunction, rather than mechanistically valid deficits in information gathering (Lunt et al., 2012). Although such an argument has been refuted by the results of several investigations (Ermakova et al., 2019; Fine et al., 2007), it points to a mechanistic insight pertaining to how people read uncertainty in the environment and translate it into subjective estimates (i.e., a metacognitive deficit). This, to my knowledge, has not been extensively investigated and tested, and thus could be a possible future avenue for research.

1.2.3.3 Impulsivity

Many studies investigated information gathering and decision making under uncertainty in impulsivity (Averbeck et al., 2013; Delazer et al., 2012; Djamshidian et al., 2012; Kagan et al., 1964; Lees et al., 2013; Lunt et al., 2012; de Rezende Costa et al., 2016; Snorrason et al., 2011; Voon et al., 2017). In these reports, hasty decision making with little supportive evidence (i.e., under-sampling) is often referred to as 'reflection impulsivity' (Messer, 1976), which is synonymous to

JTC in schizophrenia literature. Early investigations measured this deficit using matching familiar figures test (MFFT) ([Kagan, 1966](#); [Kagan et al., 1964](#)), where participants (usually children) are presented with a figure and then are required to match it from a set of similar figures that differ in one or several attributes. Assessment in such a task and its different versions is usually based on response time and accuracy, with reflection impulsivity usually indicated by faster decisions and higher error rates. This is distinguished from motor impulsivity which pertains to inability to stop an ongoing process, for example, when performing stop signal or Go-No-Go tasks ([Logan et al., 2016](#)), and from waiting impulsivity which is the inability to delay an action, e.g., delay discounting ([Dalley et al., 2011](#); [Voon et al., 2014](#)).

Reflection impulsivity is a dominant cognitive manifestation in many neurological and psychiatric disorders including Parkinson's disease (PD) ([Averbeck et al., 2013](#); [Delazer et al., 2012](#); [Djamshidian et al., 2012](#); [Kehagia et al., 2014](#); [Lees et al., 2013](#); [de Rezende Costa et al., 2016](#)), frontal lobe lesion ([Lunt et al., 2012](#)), addiction ([Banca et al., 2015](#); [Clark et al., 2006a](#); [Irvine et al., 2013](#); [Joos et al., 2013](#); [Mishra et al., 2010](#); [Stevens et al., 2015](#)) and attention deficit hyperactivity disorder (ADHD) ([Stevens et al., 2015](#)). In PD, this deficit was more evident mainly in patients with impulse control disorder (ICD), suggesting a role for excess dopamine in under-sampling as many patients who develop ICD with PD are treated with dopamine agonists or replacement ([Averbeck et al., 2013](#); [Djamshidian et al., 2012](#)). However, studies have also shown that even drug-naïve PD patients exhibit reflection impulsivity ([de Rezende Costa et al., 2016](#)), challenging the notion that dopamine solely explains this feature. By contrast, patients taking l-dopa have also been reported to perform similarly to healthy controls ([de Rezende Costa et al., 2016](#)). These seemingly contradictory findings highlight the complexity of factors that might underlie impulsivity in PD, including bias

towards novel stimuli ([Averbeck et al., 2013](#); [Djamshidian et al., 2011](#)), temporal discounting ([Averbeck et al., 2013](#); [Joutsa et al., 2015](#)), possible association with apathy ([Sinha et al., 2013](#)), and nature of the pathophysiology involving cortico-striatal networks ([Cilia and Van Eimeren, 2011](#); [Van Eimeren et al., 2010](#)).

A few studies performed transdiagnostic analyses of performance in PD and other disorders to highlight similarities and distinguishing features of reflection impulsivity in these conditions ([Averbeck et al., 2013](#); [Djamshidian et al., 2012](#)). For example, one investigation compared PD with and without ICD with illicit drug users and pathological gamblers ([Djamshidian et al., 2012](#)). This showed that PD patients with ICD were closer in their performance to illicit drug users as participants from both groups sampled significantly less than controls in all conditions. On the contrary, patients without ICD were more similar to gamblers (sampling less than controls when uncertainty was high), suggesting a less flexible sampling performance in response to changes in uncertainty in these patient groups. These distinctive features might be related to distinct underlying mechanisms. For example, under-sampling in PD with ICD across different conditions might suggest a generalised reduced sensitivity to uncertainty, while selective impairment in patients without ICD suggests less flexible responses to changes in uncertainty. Computational modelling of behavioural data from these studies suggested that reflection impulsivity in PD with ICD might be related to uncertainty about the ability to map future actions into reward ([Averbeck et al., 2013](#)). This measure was also shared with other related behaviours in PD with ICD such as bias towards novelty and temporal discounting, suggesting that different forms of impulsivity might be sharing a common cognitive mechanism. Whether these features or suggested mechanisms of reflection impulsivity (under-sampling) in PD are shared across different conditions is still under investigation. For example, a wealth of evidence highlighted the relationship between impulsivity and addiction

using self-reported measures ([Frydman et al., 2020](#)) and objective task parameters (i.e., under-sampling on information gathering tasks) ([Banca et al., 2015](#); [Clark et al., 2006a](#); [Irvine et al., 2013](#); [Joos et al., 2013](#); [Mishra et al., 2010](#); [Stevens et al., 2015](#)).

Crucially, reflection impulsivity is prevalent in different types of addiction behaviour, rather than being specific to the substance of addiction or its nature. It has been reported in alcohol dependence ([Joos et al., 2013](#)), binge drinking ([Banca et al., 2016](#)), pathological gambling ([Mishra et al., 2010](#)) and gaming ([Irvine et al., 2013](#)), and substance abuse including cocaine, opioid and amphetamine ([Clark et al., 2006a](#); [Stevens et al., 2015](#)). Under-sampling in these conditions appears to be a stable feature as people who recover from addiction still exhibit impulsivity ([Clark et al., 2006a](#)), indicating that it might be a vulnerability marker to addiction in healthy people ([Verdejo-García et al., 2008](#)). Mechanistically, under-sampling in addiction might be related to hypersensitivity to reward, enhancing valuation of uncertain options that have higher reward component. Several studies have demonstrated this effect in drug users who showed sensitivity to increased reward in shaping preferences and subjective valuation ([Verdejo-Garcia et al., 2018](#)).

Overall, a single unifying mechanism of under-sampling in reflection impulsivity is still not established. While in some conditions it might be related to lower sensitivity to uncertainty compared to reward (e.g., PD), other conditions might be better explained by heightened reward sensitivity, such as addiction. A computational account of how the weights of these two competing processes (reward maximisation and uncertainty minimisation) contribute to sampling behaviour might provide crucial insights into reflection impulsivity and associated conditions.

1.2.3.4 Obsessive compulsive disorder (OCD)

OCD is characterised by intrusive thoughts or urges (obsessions) that may lead to repetitive behaviour (compulsions) aiming to reduce the stress from these obsessions (Stein et al., 2019). Contrary to schizophrenia and delusional disorders, OCD is often associated with over-sampling (Dar, 2004; Fear and Healy, 1997; Foa et al., 2003; Hauser et al., 2017b,c; Pelissier and O’connor, 2002; Stern et al., 2013; Toffolo et al., 2013) (but also see Frydman et al. 2020; Grassi et al. 2015; Jacobsen et al. 2012; Morein-Zamir et al. 2020; Voon et al. 2017). Patients with higher compulsivity scores obtain more information, mainly when information is cheap (Banca et al., 2015; Hauser et al., 2017c). While such a behaviour has been shown to be modulated by reward incentives to improve outcomes, other reports suggested a form of *cognitive rigidity* where over-sampling was resistant to reward manipulations (Chamberlain et al., 2007).

Such a ‘compulsive’ over-sampling behaviour in OCD has been attributed to several mechanisms. For example, a few reports suggested that OCD patients might have a metacognitive deficit affecting subjective uncertainty estimation where they rate themselves as more uncertain than controls for the same uncertainty level (Dar, 2004; Stern et al., 2013). A more recent study, however, pointed to a break between confidence and action in OCD, whereby patients demonstrate comparable confidence updating with new evidence when compared to controls, but fail to use this new knowledge to optimise actions (Vaghi et al., 2017). Such findings have been replicated using a transdiagnostic approach extracting a compulsivity dimension from a large sample of healthy participants who performed the task online (Seow and Gillan, 2020). These observations suggest a ‘stuck in habit’ behaviour in OCD leading to purposeless sampling and disregard of knowledge and its costs (Gillan et al., 2014). An alternative mechanistic

account proposed that over-sampling in OCD might be due to late emergence of costs and related delayed urgency signals manifesting as higher decision thresholds to stop sampling (Hauser et al., 2017b,c).

On the other hand, a few investigations have shown that OCD patients actually under-sample and make hasty decisions, implicating an element of impulsivity in the condition (e.g., impulsive compulsions) (Grassi et al., 2015; Jacobsen et al., 2012; Voon et al., 2017). Such inconsistency regarding whether OCD patients over- or under-sample points to two important considerations when investigating information gathering and goal-directed behaviour in the condition: i) as pointed out by previous reports (Morein-Zamir et al., 2020), the current methods (mainly beads task) used to make inferences about OCD information gathering behaviour needs further development and refinement to be more specific and capture mechanistic components with more validity and ii) due to the high overlap between OCD and other neuropsychiatric disorders (e.g., impulsivity and anxiety), careful phenotyping of the condition or adopting a transdiagnostic approach would be crucial to make reliable advances.

1.2.3.5 Affective disorders: anxiety and depression

Deficits in processing uncertainty have been consistently regarded as one key mechanism in anxiety spectrum disorders (Bishop and Gagne, 2018; Boswell et al., 2013; Carleton et al., 2012; Grupe and Nitschke, 2013; Gu et al., 2020; Hartley and Phelps, 2012b; Hildebrand-Saints and Weary, 1989; Pulcu and Browning, 2019; Saulnier et al., 2019). These might manifest at different stages of goal-directed behaviour influencing value-based decisions and information gathering. One prominent framework conceptualises anxiety as an anticipatory reaction to uncertainty about future aversive or threatening events (Grupe and Nitschke, 2013). According to this model, anxiety might arise from inflated estimation of uncer-

tainty and its cost, leading to overestimation of negative event probabilities and exaggerated anticipatory responses and attention. This overestimation of uncertainty and subsequent hypervigilant responses might result in a vicious cycle impairing safety learning and dysfunctional association between cues and negative outcomes. As a result, it becomes difficult to have an accurate representation of the environment ([Grupe and Nitschke, 2013](#)).

In line with this anticipatory model of anxiety that focuses on future-oriented emotional states, the behavioural inhibition system (BIS) hypothesis also posits that uncertainty perception or expectation fuels behavioural and physiological responses to perceived threat ([McNaughton, 1982](#)). In this model, anxiety is thought to be a function of a septo-hippocampal system which works as a comparator between expectations and observation and leads to behavioural inhibition that results in avoidance of aversive cues such as uncertainty.

Based on such models, it is expected that anxious people might exhibit two seemingly contrasting information sampling behaviours related to hypersensitivity to uncertainty: i) collect as much information as possible (i.e., over-sample) to reduce uncertainty and avoid it when making decisions, or ii) behavioural inhibition and total avoidance of uncertainty. The drivers of such behavioural responses could include exaggerated uncertainty estimation, higher uncertainty weighting, or lower cost of acquiring samples when collecting information ([Grupe and Nitschke, 2013](#)).

Only a few studies have investigated information gathering in anxiety and related disorders ([Jacoby et al., 2014](#); [Sternheim et al., 2011](#); [Volans, 1976](#)). These reports do not indicate a consistent effect. One investigation, for example, showed that participants with anxiety did not differ from healthy controls, despite patients reporting more distress during task performance and greater intolerance to uncer-

tainty on self-report measures ([Jacoby et al., 2014](#)). While this might reflect intact information gathering in anxiety and perhaps support the delineation of anxiety from other disorders that used to be classified under its spectrum such as OCD ([Thomas Widiger et al., 1994](#)), a more fine-grained investigation of the behaviour in this group is needed to support this claim and explore how uncertainty intolerance manifests when people gather information.

Depression shares many aspects with anxiety with regard to how it influences motivated decision making and uncertainty processing ([Bishop and Gagne, 2018](#)). Both conditions have been shown to be associated with increased intolerance to uncertainty ([Dar et al., 2017](#); [Dugas, 1997](#); [Freeston et al., 1994](#)), impaired learning in probabilistic uncertain environments ([Gagne et al., 2020](#)), and reduced reward valuation ([Ng et al., 2019](#); [Winer and Salem, 2016](#)).

The evidence on how depression influences active information gathering is limited. Previous studies in the social psychology literature showed that depression is associated with enhanced information seeking behaviour in social situations, e.g., when required to ask questions in an interview setting ([Hildebrand-Saints and Weary, 1989](#)). Similarly, severity of depression as indexed by Beck's depression inventory (BDI) score has been linked to extensive sampling in IST ([Crockett et al., 2012](#)). It has been suggested that such over-preparation behaviour might be due to worry arising from a sense of controllability over future events ([Abramson et al., 1978](#); [Barlow, 1991](#)). A wealth of literature has indeed emphasised that perception of, and reaction to, controllability over possible outcomes might be a crucial mechanism in affective disorders, e.g., learned helplessness model of depression ([Liu et al., 2015](#)). Previous reports have also indicated decreased reward valuation in depression, which in turn might affect cost-benefit computations of information sampling, e.g., depressed people might over-sample because of reduced sensitivity to sampling cost and implication on potential reward ([Ng et al.,](#)

2019; Winer and Salem, 2016).

Similar to other neuropsychiatric syndromes, affective disorders can manifest in the context of other clinical conditions, including psychiatric illness and degenerative diseases (Bandelow and Michaelis, 2015; Malhi and Mann, 2018; Penninx et al., 2021). One important example that is worth discussing here is subjective cognitive impairment (SCI) – a condition that is increasingly being recognised in ageing populations (Jessen et al., 2020, 2014; Reid and MacLulich, 2006). It is characterised by subjective cognitive complaints without objective clinical evidence of cognitive impairment. The condition is of critical importance in dementia research as it has been identified as a pre-clinical stage of AD in some individuals (Jessen et al., 2020, 2014; Reid and MacLulich, 2006). However, the majority of individuals with SCI do not progress to develop dementia, making the characterisation of SCI a crucial aspect of cognitive ageing research (McWhirter et al., 2020). An increasing number of reports has indicated that affective dysfunction such as depression and anxiety is a key feature of SCI, and maybe accounting for the clinical manifestations of the condition (Hill et al., 2016; Hohman et al., 2011; Pavisic et al., 2021; Reid and MacLulich, 2006). However, no previous research has mechanistically investigated these manifestations in SCI.

One alternative way of describing the key manifestation of the condition might be to consider it as ‘seeking information to resolve uncertainty about subjectively perceived cognitive decline’. This is different from seeking advice for other clinical symptoms such as pain, headache, or visual disturbances, as patients with these manifestations have no uncertainty about their experience. On the other hand, SCI symptomatology features uncertainty. This might involve multiple layers, e.g., uncertainty about memory performance, perception of this performance, significance of this perception, risks including the possibility of progression to dementia, etc. Such a characterisation, in my opinion, potentially makes SCI

a syndrome of dysfunctional uncertainty processing and information gathering. What makes certain individuals with such manifestations seek medical advice and reassurance, while other people with the same problems might not be bothered by these self-observations? And what role does affective dysfunction, which is prevalent in SCI, play? Understanding how people with SCI navigate and react to uncertainty might be key to answering such questions and improving our understanding of the psycho-cognitive manifestations of the condition. This will also provide insights into the mechanisms of anxiety and depression in general. I address these questions in Chapters 4 and 5 of this thesis.

Overall, it seems that anxiety and depression might be both associated with oversampling as a reflection of uncertainty intolerance. Whether this is due to the same cognitive mechanisms, economic processing, and brain networks across the two syndromes or other related conditions such as SCI requires further investigation and characterisation.

1.2.3.6 Age and neurodegeneration

Age might be a significant factor that affects information gathering behaviour in humans. The ability to sample information efficiently approaches adult performance in children between the ages of 6 and 11 years (Jones et al., 2019). A recent investigation showed that children compared to adolescents assign lower subjective costs to information and therefore opt for more extensive sampling when information is free (Bowler et al., 2021). However, other studies have shown that adolescents might tolerate uncertainty more than younger children and adults, resulting in less sampling before decisions and thus following a U-shaped development trajectory (Van Den Bos and Hertwig, 2017). These findings indicate that the ability to weigh costs and benefits of acquiring information to resolve

uncertainty and make decisions might develop early in life and stabilise through adulthood. How information gathering changes with ageing from early childhood to later stages of life is still not fully established. No previous studies have fully followed this trajectory and performed comparative analysis.

However, studies in elderly people have demonstrated that with ageing, people exhibit impaired uncertainty processing and estimation, impairing decision making and learning under uncertainty (Nassar et al., 2016; Pietschmann et al., 2011). Similar reports indicate that older adults are less averse to uncertainty and ambiguity, committing to more decisions with insufficient information (Sproten et al., 2010, 2018), which might be indicative also of under-sampling. In Alzheimer's disease (AD), the incidence of which increases with age, studies using information sampling tasks have shown that AD patients compared to controls gather significantly less information before committing to a course of action and make riskier decisions (Sinz et al., 2008; Zamarian et al., 2015). It is not clear, though, how such results relate to memory complaints in health and disease. This will require in-depth investigation of information gathering in AD spectrum and causes of memory complaints in ageing, including cognitive impairment (MCI) and subjective cognitive impairment (SCI).

Overall, these previous reports suggest that age-sensitive brain regions and networks might be crucial for uncertainty processing and information sampling but little is understood about these factors.

Condition	Sampling behaviour (vs controls)	Examples of relevant studies
Delusional disorders (e.g., psychosis and schizophrenia)	Under-sampling	<i>Ermakova et al., 2019; Garety et al., 2005; Huq et al., 1998; McLean et al., 2016</i>
Obsessive compulsive disorder (OCD)	Over-sampling	<i>Hauser et al., 2017, 2018</i>
Addiction (alcohol, cocaine, pathologic gaming)	Under-sampling	<i>Clark et al., 2006a; Banca et al., 2016; Irvine et al., 2013; Joss et al., 2013</i>
Impulsivity (mainly PD patients)	Under-sampling	<i>Averback et al., 2013; Costa et al., 2016; Djamshidian et al., 2012; Kehagia et al., 2014;</i>
Anxiety and depression	Over-sampling	<i>Crockett et al., 2012; Hildebrand-Saints and Weary, 1989</i>
Alzheimer's disease (AD)	Under-sampling	<i>Sinz et al., 2008; Zamarian et al., 2015</i>
MTL epilepsy	No difference	<i>Zamarian et al., 2015</i>
Narcolepsy & cataplexy	Under-sampling	<i>Gschliesser et al., 2011</i>
Restless leg syndrome	Under-sampling	<i>Heim et al., 2017</i>
PFC lesion	Under-sampling	<i>Xenitidis et al., 2012</i>

Table 1.1: Information gathering in different conditions. Note that most clinical conditions are associated with under-sampling except affective disorders (anxiety and depression) and OCD. Some studies, however, indicate that OCD might have elements of reflection impulsivity and under-sampling.

1.2.4 Neuromodulation of information gathering

1.2.4.1 Dopamine

The fact that information gathering is affected in several disorders that have been linked to dopamine dysregulation, such as schizophrenia and PD, indicates that dopamine might play a significant role modulating the behaviour. However, several studies that directly investigated this hypothesis have reported conflicting findings about dopamine contribution. For example, dopamine agonists and antagonists have been shown to exert no significant effect on sampling behaviour in health and disease ([Andreou et al., 2015](#); [Hauser et al., 2018](#); [Menon et al., 2008](#); [Voon et al., 2016](#)) (but see [Lees et al. 2013](#)). More recent work, however, demonstrated that dopamine might have a specific role when information possesses a hedonic value, e.g., information about potential gains. L-DOPA, a dopamine agonist, was found to blunt the preference to seek more information about potential rewards (compared to information about losses), which was otherwise seen in a placebo group ([Vellani et al., 2020](#)). Such a finding aligns with a wealth of research implicating dopamine in reward processing and valuation ([Bromberg-Martin et al., 2010](#); [Kurniawan et al., 2011](#); [Rogers, 2011](#)). In light of these emerging reports, fine-grained examination of cost-benefit optimisation in information gathering might further uncover more about the potential role of dopamine in the behaviour.

1.2.4.2 Norepinephrine

On the other hand, norepinephrine (NE), another monoamine neurotransmitter, has been shown to modulate information gathering in several reports. A recent study demonstrated that NE blockade can result in gathering less information before decisions, likely due to increasing urgency signals representing increased

costs with extended sampling ([Hauser et al., 2018](#)). In a similar vein, atomoxetine, an agent that inhibits NE reuptake in the prefrontal cortex, has been shown to improve reflection impulsivity indexed by under-sampling in PD ([Kehagia et al., 2014](#)).

These effects of NE modulation might be due to its recognised role in arousal and attention, promoting task engagement and more careful sampling behaviour ([Sara and Bouret, 2012](#)). Such a role could be specifically related to central phasic NE activity from locus coeruleus, which might link to other brain regions involved in decision making and task optimisation, such as the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) ([Aston-Jones and Cohen, 2005](#); [Yu and Dayan, 2005a](#)). Alternatively, the role of NE in information gathering might be related to its contribution to uncertainty representations and modulation of physiologic responses in reaction to it ([Yu and Dayan, 2005a](#)). This association between NE and uncertainty modulation (especially when unexpected) has been reported in several studies using different techniques, including neuroimaging showing locus coeruleus activation ([Payzan-LeNestour et al., 2013](#)), pharmacological manipulation ([Lawson et al., 2021](#); [Marshall et al., 2016](#)), physiological recording of neural activity of NE systems and papillary dynamics in response to uncertainty ([Dayan and Yu, 2006](#)).

Indirect evidence of the role of NE in information gathering might also be derived from the clinical use of NE blocking agents in the treatment of disorders that show excessive sampling such as OCD and anxiety ([Brudkowska et al., 2018](#)). In a similar vein, NE is thought to play a crucial role in hippocampus-centred behavioural inhibition system (BIS) that is hypothesised to underlie anxiety and aversion behaviour ([McNaughton, 1982](#)). According to this model, NE modulates a neurophysiological gate that relates information about uncertainty and aversive stimuli to and from the hippocampus.

It thus seems that NE is one of the key modulators of information gathering behaviour via its contribution to uncertainty representation and modulation of the cost needed to overcome it.

1.2.4.3 Serotonin

Emerging reports are increasingly highlighting a potential role of serotonin in information gathering. For example, acute depletion of tryptophan (a precursor of serotonin) has been shown to be associated with extended sampling by blunting the aversive effect of information cost during sampling ([Crockett et al., 2012](#)). By contrast, a more recent investigation suggested that citalopram, an agent that increases brain serotonin by selectively inhibiting its reuptake, decreases accuracy probability and lowers utilisation of information before decisions ([Livermore et al., 2021](#)). Such results might be related to the well-known role of serotonin in aversive prediction and behavioural inhibition, as it might enhance avoidance of local immediate aversive signals and thus result in less sampling ([Dayan and Huys, 2009](#)).

In summary, several neurotransmitters might be involved in information gathering with different mechanistic contributions. Dopamine seems to play a role when information carries hedonic value and might contribute to reward processing when considering the economics of information sampling. On the other hand, NE and serotonin are more involved in aversion and uncertainty processing, affecting how people optimise costs vs. benefits of informative clues.

1.2.5 Brain regions involved information gathering

Several brain regions have been implicated in processes that can be directly or indirectly related to active information gathering. These include (i) limbic areas such as the amygdala and hippocampus, which are believed to play a role in statistical learning and uncertainty processing, (ii) the insula, which is involved in uncertainty representation and anticipation, (iii) reward-related networks and regions which are crucial for cost-benefit valuation, and (iv) the parietal cortex which has been implicated in representation of information gain value. In this section, I will discuss how these regions can support information gathering based on their functional attributes described in the literature.

1.2.5.1 Limbic system: hippocampus and amygdala

In addition to its established role in memory and spatial cognition ([Bird and Burgess, 2008](#); [Burgess et al., 2002](#); [Eichenbaum et al., 1999](#); [Hartley et al., 2014](#)), the hippocampus in recent years has been increasingly implicated in decision making and uncertainty processing ([Barron et al., 2013](#); [Biderman et al., 2020](#); [Enkavi et al., 2017](#); [Palombo et al., 2015a,b](#); [Wimmer and Shohamy, 2012](#)). Such functions might help support active information gathering.

Reports from animal studies link the hippocampus to *vicarious trial and error* (VTE) behaviour ([Redish, 2016](#)). Rats at decision points on maze tasks pause and look back and forth before continuing their navigation ([Tolman, 1939, 1948](#)). This is thought to reflect animals' deliberative processing of uncertainty by searching and evaluating potential trajectories of action ([Gilbert and Wilson, 2007](#); [Keller et al., 2020](#); [Payne et al., 1993](#); [Rangel et al., 2008](#)) – a process that shares many mechanistic components with active information gathering discussed in previous sections ([Keller et al., 2020](#); [Redish, 2016](#)). Both behaviours require determi-

nation of future state possibilities and evaluation of outcomes to guide decision making. The critical role of the hippocampus here is related to its established contribution to mental time travel into the past (sampling from memory) and future (prospection and imagination) ([Buckner and Carroll, 2007](#); [Gilbert and Wilson, 2007](#); [Schacter et al., 2007, 2012, 2017](#)). Through this mental navigation process, animals are thought to construct and evaluate potential routes prior to making a choice ([Redish, 2016](#)).

Place cells in rodents' hippocampi have been found to encode future trajectories of planned movements toward goals and rewards ([Freyja Ólafsdóttir et al., 2015](#); [Pfeiffer and Foster, 2013](#)). Furthermore, rats with hippocampal lesions seem to have impaired ability to detect and evaluate reward changes in the environment ([Bett et al., 2015](#)). This goal-directed decision process is believed to depend on an interaction between the temporal lobe and reward processing regions such as striatum and PFC in animals and humans ([Hassabis et al., 2007](#); [Lebreton et al., 2013](#); [Peters and Büchel, 2010](#); [Schacter et al., 2012](#); [Spiers and Gilbert, 2015](#); [Wang et al., 2015](#)).

In human participants, a number of investigations have emphasised the role of the hippocampus in uncertainty processing and valuation. For example, several studies report that hippocampal activation correlates with the degree of sensory entropy (uncertainty) of presented stimuli when making decisions based on these cues ([Harrison et al., 2006](#); [Rigoli et al., 2019](#); [Strange et al., 2005](#); [Tobia et al., 2012](#)). Other investigations emphasised a contribution to uncertainty resolution and valuation by demonstrating a hippocampal role in inferring and constructing the value of novel stimuli from previous experiences that link to these stimuli ([Barron et al., 2013](#); [Wimmer and Büchel, 2016](#); [Wimmer and Shohamy, 2012](#)). This hippocampus-dependent valuation has also been demonstrated in reward-based decisions that require future episodic thinking and deliberation. A recent

report, for example, demonstrated that the BOLD hippocampal signals correlate with deliberation time prior to making decisions ([Bakkour et al., 2019](#)). This result is consistent with other studies that highlight hippocampal involvement in delay discounting, where the value of future rewards might be enhanced with more episodic details ([Kwan et al., 2012](#); [Peters and Büchel, 2010](#)).

Such a utilisation of mental time travel not only helps in inferential value processing, but could also assist in stabilisation of preferences and orientation in value space. For example, one study showed that patients with hippocampal damage demonstrate deficits in transitive inferences resulting in volatile and changeable preferences compared to matched controls ([Enkavi et al., 2017](#)). Such a behaviour has been demonstrated also in hippocampal patients when performing the IOWA gambling task with patients not being able to develop preferences for advantageous cards ([Gupta et al., 2009](#); [Gutbrod et al., 2006](#)). In a similar vein, hippocampal patients performing visual search tasks have been shown to demonstrate less consistent pattern of information gathering, indicating more stochastic performance and inability to develop preferential trajectories to optimise behaviour ([Lucas et al., 2019](#)). Crucially, these observations were independent of memory deficit or general reasoning abilities, indicating a separate mechanism by which the hippocampus might be contributing to information seeking and uncertainty resolution.

This unique set of properties could implicate the hippocampus not only in the representation of uncertainty and probabilistic future states but also in the active process of acquiring informative clues to resolve uncertainty ([Johnson et al., 2012](#); [Keller et al., 2020](#)). A detailed account of how this might manifest in humans is not yet established, as the hippocampus could contribute to several components of the process. This includes supporting valuation of samples agents intend to acquire when gathering information as well as generation and evaluation of possi-

ble sampling trajectories that lead to the goal. It might be difficult thus to predict whether hippocampus-related deficits affecting these components would trigger increased sampling or the opposite without empirical investigation. Would hippocampal damage decrease one's sensitivity to uncertainty and result in under-sampling? This prediction might be supported by one model arguing that the hippocampus is central for behavioural inhibition against aversive stimuli such as uncertainty ([McNaughton, 1982](#)). Alternatively, would hippocampal damage impair probabilistic reward valuation when acting and deciding under uncertainty, resulting in less flexible sampling when reward conditions change? These and more questions are yet to be answered and require purposeful experimental studies.

In addition, such studies will require highly focal hippocampal lesions in order to draw inferences about the brain-behaviour correlation under investigation. This has been challenging to achieve in many previous studies, as they often involved patients with extensive damage extending beyond the hippocampus, e.g., temporal lobe resection in epilepsy patients ([Enkavi et al., 2017](#); [Gupta et al., 2009](#); [Gutbrod et al., 2006](#); [Lucas et al., 2019](#); [McCormick et al., 2018](#)). However, in the past decade, autoimmune limbic encephalitis (ALE), a neurological condition resulting from auto-antibody pathological activity in the brain, has been increasingly recognised in hippocampal research. This is mainly because, in its chronic phase, it involves highly focal hippocampal atrophy ([Argyropoulos et al., 2019](#); [Finke et al., 2017](#); [Hanert et al., 2019](#); [Irani et al., 2013](#); [Kotsenas et al., 2014](#); [Malter et al., 2014a](#); [Miller et al., 2017](#); [Szots et al., 2014](#)), making it an ideal model of selective hippocampal dysfunction ([Argyropoulos et al., 2019](#); [Miller et al., 2020](#); [Spanò et al., 2020a,b](#)). Moreover, depending on the course of the disease and the timing of treatment initiation from disease onset, patients might vary in the degree of hippocampal atrophy, allowing for examination of variability in behaviour with

different degrees of hippocampal damage due to the same pathological process (Finke et al., 2017; Malter et al., 2014b). Building on these reports, and to address the questions raised above, Chapter 3 in this thesis examines the role of the hippocampus in decision making under uncertainty and active information gathering in patients with ALE.

The role of the amygdala in information gathering stems from its contribution to uncertainty representation and modulation of affective and behavioural responses to it (Morris et al., 2019; Tanovic et al., 2018). Along with the insula, the amygdala is one of the most consistent brain regions to be implicated during tasks and decisions requiring uncertainty processing. The uncertainty anticipation model of anxiety proposes that the amygdala is one of the key regions involved in modulating anticipatory responses to uncertainty (Grupe and Nitschke, 2013). Through its interaction with other brain regions involved in cost and probability estimation of uncertainty such as dorsomedial prefrontal cortex (dmPFC), orbitofrontal cortex (OFC), and the insular cortex (IC), the amygdala is thought to process vigilance and behavioural reactivity in face of uncertainty (Feldmanhall et al., 2019; Grupe and Nitschke, 2013; Kim et al., 2011; Sarinopoulos et al., 2010). Mechanically, such a role is believed to be related to the contribution of the amygdala to associative learning and conditioning, especially for negative and aversive cues (Amorapanth et al., 2000; Holland and Gallagher, 1999; Li et al., 2011; Moscarello and LeDoux, 2013). Previous reports have indeed shown that amygdala activation correlates with expected loss when making decisions (De Martino et al., 2010; Yacubian et al., 2006). Similarly, amygdala BOLD signals were also correlated with subjective reports of intolerance to uncertainty in healthy controls and people with anxiety disorders (Morris et al., 2015; Schienle et al., 2010; Somerville et al., 2013; Tanovic et al., 2018). These findings thus suggest that increased sampling behaviour might be related to amygdalar dysfunction resulting in hyper-

sensitivity to uncertainty and its prospective costs.

1.2.5.2 The insula and other cortical regions

The insular cortex (IC), especially the anterior part, is perhaps the most consistent region to be implicated in decision making under uncertainty and information gathering ([Morriss et al., 2019](#)). Many fMRI studies reported activation of the insula in response to uncertainty under different task conditions. For example, previous investigations have demonstrated that anticipation of unpredictable negative cues was associated with bilateral insular activity. This effect was found to be associated with higher anxiety scores and sense of uncontrollability ([Alvarez et al., 2015](#)). Such results are consistent with the anticipatory model of anxiety, which implicate the anterior insula in the anticipation and estimation of uncertainty and its costs ([Grupe and Nitschke, 2013](#); [Tanovic et al., 2018](#)). More direct investigations of information gathering using the beads task demonstrated that insular BOLD signals were modulated by the expected reward gain on the task ([Furl and Averbeck, 2011](#)) as well as by degree of uncertainty ([Krug et al., 2014](#)).

These functions of the insula might be due to its rich connection with other cortical regions involved in probability and value computation such as parietal and prefrontal cortices ([Craig, 2009](#); [Namkung et al., 2017](#); [Uddin et al., 2017](#)). Most studies investigating neural correlates of information gathering often report co-activation of these brain regions together with the IC ([Banca et al., 2015](#); [Chang et al., 2013](#); [Furl and Averbeck, 2011](#); [Paulus and Stein, 2006](#); [Pavuluri and May, 2015](#); [Shadlen and Newsome, 2001](#)). For example, one study demonstrated that parietal BOLD signals were greater in participants who collected more evidence before making decisions ([Furl and Averbeck, 2011](#)). Furthermore, the number of beads drawn in one study correlated with the volumes of inferior parietal region and dorsolateral prefrontal cortex (dLPFC) ([Banca et al., 2015](#)). Consistent

with these reports, early studies using the dot motion task showed that evidence accumulation in non-human primates correlates with the activity recorded from parietal neurons ([Shadlen and Newsome, 2001](#)). Parietal regions seem to encode information gain related to reduction in uncertainty independently of neuronal reward processing ([Horan et al., 2019](#)). These signals are therefore considered crucial for the computation of subjective value of samples.

In summary, the contribution of the insula to information gathering has been reported in several studies. The mechanism by which this contribution takes place appears to be shared with other cortical regions such as parietal cortex and dLPFC. It may be by supporting probabilistic computation of the expected benefit of information.

1.2.5.3 Valuation system brain regions

A wealth of literature highlighted a crucial role of reward-related regions in different aspects of value-based decision making. These regions are thought to function in coordination with each other forming what has been referred to as ‘valuation/reward system’ ([Haber, 2017](#); [Haber and Knutson, 2009](#)). This includes cortical and subcortical regions such as OFC and ventral striatum (VS). Within this network, these areas share strong connections with regions of the brain involved in uncertainty processing, such as the amygdala and insula ([Grupe and Nitschke, 2013](#); [Haber, 2017](#); [Haber and Knutson, 2009](#); [Kim et al., 2011](#); [Morris et al., 2015, 2019](#); [Uddin et al., 2017](#)). Most of these reward-related brain structures are also implicated in cost representation as suggested by neurophysiological and neuroimaging evidence in animals and humans ([Chen, 2021](#)).

Gathering information is often a costly process that might involve several forms of cost such as time, effort, money, cognitive energy, etc. ([Hauser et al., 2017a](#),

2018; [Juni et al., 2016](#)). These different forms of cost might be preferentially encoded by different regions. OFC, for example, has been linked to temporal cost encoding. Animals and humans with OFC lesion demonstrated stronger temporal discounting with preference for immediate reward ([Bechara et al., 2000](#); [Berlin et al., 2004](#); [Mobini et al., 2002](#); [Rudebeck et al., 2006](#)). The anterior cingulate cortex, on the other hand, has been linked to effort costs in goal-directed decision making ([Croxson et al., 2009](#); [Pessiglione et al., 2018](#)). However, other studies suggest a degree of overlap in cost and value representations, promoting a view that some of these regions are globally involved in the representation of value and cost regardless of the identity of the stimuli ([Carlezon and Thomas, 2009](#); [Gläscher et al., 2009](#); [Monosov, 2017](#); [Ruff and Fehr, 2014](#); [Vassena et al., 2014](#)).

Regardless of the exact neural mechanism, it is likely that the expected cost (and hedonic value) of a sample during information gathering is represented in a similar fashion in these brain regions. Crucially, the function of the valuation network is not limited to these representations. Through their extensive connections with other brain networks including the limbic, paralimbic, and cortical systems, regions of the network such as the prefrontal cortex might integrate and compare value using information supplied from these sources ([Chen, 2021](#); [Rangel et al., 2008](#)). This process is essential for cost-benefit evaluation resulting in a subjective value assignment that eventually drives decision making. One study has indeed shown that differences between information value and cost correlate with activity of prefrontal cortex ([Basten et al., 2010](#)). Interestingly, this signal as it accumulates was found to correlate with parietal cortex activity, which, as discussed previously, might serve to track accumulation of information utility ([Horan et al., 2019](#)).

Thus, regions in the valuation system such as OFC and ACC might serve to support cost-benefit valuation of sampling process by contributing to cost processing

and subjective value computation.

Overall, as shown in Figure 1.3, information sampling to resolve uncertainty is a complex cognitive and behavioural operation that recruits several cortical and subcortical regions at different stages in order to perform cost-benefit optimisation that underlies sampling decisions.

Importantly, these brain regions, along with the cognitive processes related to them, are not exclusively matched to information gathering and decision making under uncertainty. They are implicated in other forms of goal-directed decision making such as *effort-based decision making*, with various degrees of similarities and distinctions regarding the cognitive components and neurotransmitters involved. In the next section, I comparatively discuss effort-based decision making and highlight such potential similarities and differences that help us advance our understanding of goal-directed decision making and its clinical significance.

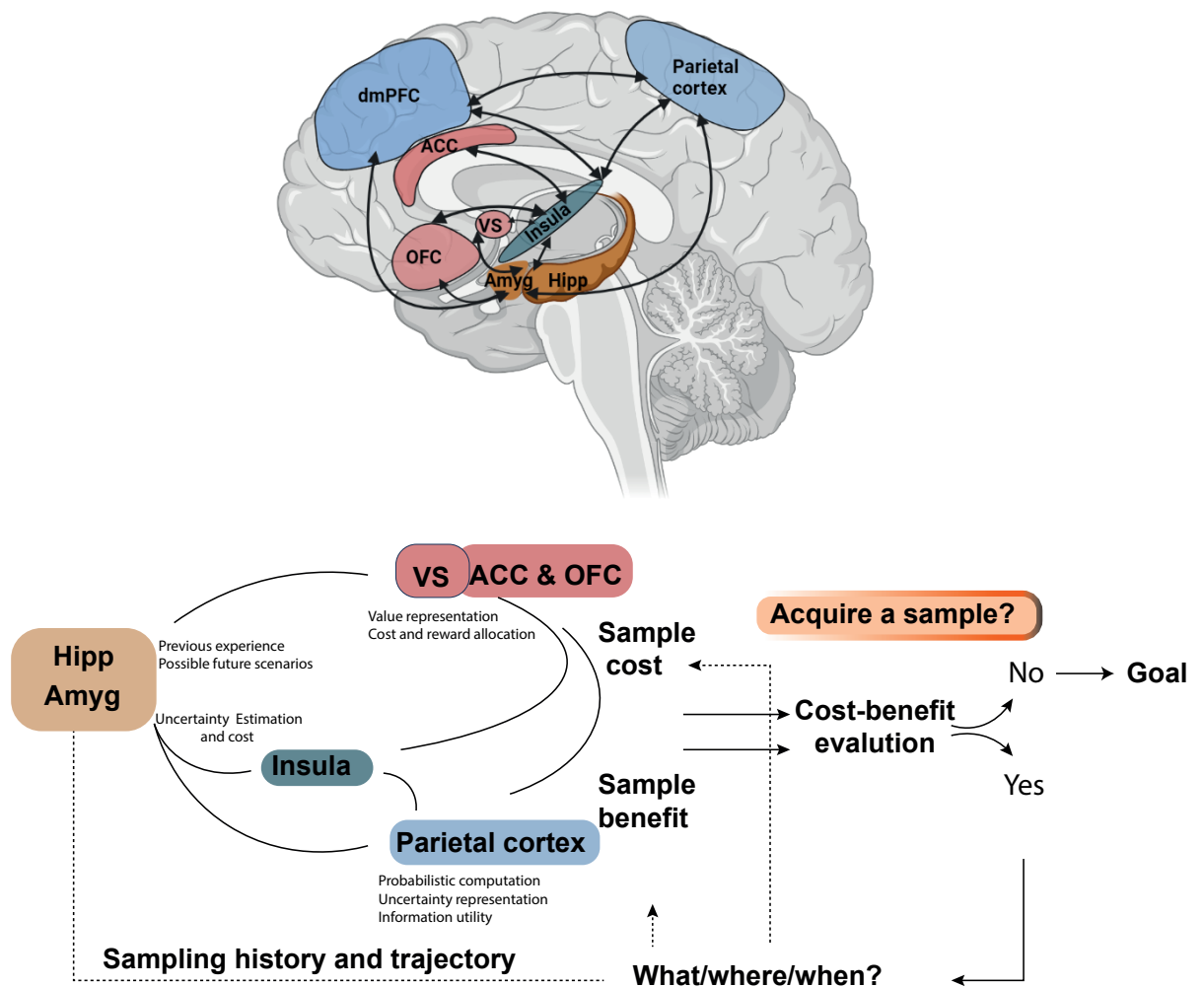


Figure 1.3: Neuroanatomical correlates of information gathering. Active information gathering is a complex behavioural process that engages brain systems and regions involved in valuation, decision making, and learning. This requires neuroeconomic computations taking into consideration the cost and benefit of sampling in order to reach the optimal stopping point that maximises expected value (see Figure 1.1). Determining sample benefit requires estimation of uncertainty in the environment and probabilistic computation of search trajectories. These processes have been linked to limbic brain regions and the insula, which are closely linked to the parietal cortex which have been shown to encode information utility. All these regions share rich connections with reward-related brain regions such as VS, ACC and OFC which are proposed to contribute to sampling cost estimation and overall value computation based on these economic considerations. Hipp: Hippocampus. Amyg: Amygdala. VS: Ventral Striatum. ACC: Anterior Cingulate Cortex. OFC: Orbito-Frontal Cortex.

1.3 Effort-based decision making

Effort-based decision making (EBDM) shares many of the behavioural components involved in information gathering and decision making under uncertainty (Figure 1.1) (Chong et al., 2016b; Husain and Roiser, 2018; Sinha et al., 2013). This is likely due to the economic nature of these decisions, which also imposes cost-benefit analysis and valuation (Le Heron et al., 2019). A total mechanistic separation of the two forms of decision making might not be straightforward because of the overlapping computations underlying these behaviours. For example, overcoming uncertainty and acquiring information might require investment of effort (physical or/and cognitive). Similarly, making effort-based decisions requires people to have information about the effort and reward involved to allow them to evaluate these attributes against each other to guide decisions (Chong et al., 2016b; Husain and Roiser, 2018; Le Heron et al., 2019; Sinha et al., 2013).

A thorough investigation and deconstruction of the behavioural components involved in EBDM has been previously demonstrated in several reports (Chong et al., 2016b; Husain and Roiser, 2018; Le Heron et al., 2019, 2018b; Salamone et al., 2007; Saleh et al., 2021b; Sinha et al., 2013). Figure 1.4 shows a summary of these components, starting with the generation of options that agents evaluate and choose from and ending with the achievement of outcomes and learning from experience. As discussed previously with decision making under uncertainty and information gathering, economic valuations where agents compare reward against costs are key components. EBDM experimental paradigms often test this by imposing trade-offs between different levels of reward and different levels of effort, which could be physical (e.g., squeezing a handle, pressing a button) or cognitive (e.g., performing mental calculations) (Figure 1.4 b.) (Chong et al., 2017, 2016b; Husain and Roiser, 2018; Le Heron et al., 2018b; Pessiglione et al., 2018; Saleh

[et al., 2021a,b](#)).

The obvious and critical distinction between EBDM and decision making under uncertainty is the *nature of the cost* involved, which might implicate distinct brain systems and computations for these distinct costs ([Chen, 2021](#)). Uncertainty imposes a probabilistic consideration of future states with a distribution of expected values reflecting the possible costs that might be encountered ([Begg et al., 2014](#); [Smithson, 1989](#); [Walker et al., 2003](#)). As discussed in the previous sections, these uncertainty-related computations might require functional orchestration between subcortical and cortical brain regions.

On the other hand, in EBDM, the cost, especially physical effort, is more deterministic and might not require significant probabilistic considerations. This suggests that it might not require as much processing by uncertainty-related regions. However, in addition to domain-general value-processing areas involved in reward and cost valuation of motivated decision making, EBDM seems to have specific regions involved in its regulation. For example, a wealth of evidence from animals and humans suggests that ACC might be a key region for effort valuation and integration with reward ([Pessiglione et al., 2018](#)). ACC lesions in rats have been shown to result in effort aversion and disrupted effort-weighted preferences ([Rudebeck et al., 2006](#); [Walton et al., 2003](#)). In humans, several studies demonstrated that ACC BOLD signals correlate positively with effort levels encountered when making decisions, but negatively with reward ([Lopez-Gamundi et al., 2021](#); [Pessiglione et al., 2018](#)). In contrast to ACC effort-related role, OFC seems to influence other aspects of EBDM, including reward valuation and assessment of temporal costs([Chen, 2021](#)). Such findings implicate a double dissociation between ACC and OFC, whereby ACC is related to reward-effort integration and valuation while OFC has a more general role for value and goal encoding ([Chen, 2021](#); [Pessiglione et al., 2018](#); [Rudebeck et al., 2006](#)).

These two regions along with other parts of the valuation system share rich connections with dopaminergic midbrain brain areas ([Haber, 2017](#); [Haber and Knutson, 2009](#); [Lopez-Gamundi et al., 2021](#); [Pessiglione et al., 2018](#); [Russo and Nestler, 2013](#)). Several studies suggest that DA is a key modulator of EBDM ([Kurniawan et al., 2011](#); [Pessiglione et al., 2018](#)). While neuropharmacological evidence in information gathering investigating the role of DA is relatively limited, numerous investigations have highlighted how DA could influence EBDM and motivation. One account from animal and human studies proposes that dopamine is important for invigoration of action and willingness to accept effort costs for reward ([Salamone et al., 2007, 1994](#)). This is known as the ‘wanting’ component of goal-directed behaviour, in contrast to ‘liking’, which pertains to enjoying rewards (consummatory phase) when consumed – a process that seems to be less influenced by dopamine ([Berridge and Robinson, 2016](#)). DA antagonism or lesions affecting DA regions in rats results in effort aversion and reduced vigour with relatively intact hedonic responses ([Kurniawan et al., 2011](#); [Salamone et al., 2007](#)). Studies in humans have also highlighted the role of dopamine in overcoming the effort cost of action and ‘wanting’ behaviour. For example, DA agonists in humans have been shown to energise and increase willingness to accept effortful actions ([Chong et al., 2015](#); [Le Heron et al., 2018b](#)).

EBDM might also be modulated by other neurotransmitters such as NA and serotonin. One investigation, for example, showed that these two neurotransmitters might increase behavioural effort aversion induced by dopamine blockade in rats ([Yohn et al., 2015](#)). Other rodent studies offered a seemingly contradictory finding, showing that NA and serotonin were associated with increased vigour ([Warden et al., 2012](#); [Weber et al., 2009](#)). In humans, pharmacological manipulation of serotonin using escitalopram, an agent that inhibits serotonin reuptake in the brain, was associated with exerting more efforts for rewards, suggesting that it might be

important for overcoming the cost of effort in motivated behaviour ([Meyniel et al., 2016](#)). Similarly, in non-human primates, neurophysiological recording from noradrenergic neurons revealed that their activity is associated with effort production, compared to DA neuronal activity which was more associated with effort expectation and valuation ([Varazzani et al., 2015](#)).

In conclusion, while there are many similarities between decision making under uncertainty and for effort such as comparable economic computations and shared brain regions and neurotransmitters, there are also some key differences related to the distinct nature of the costs involved. Computationally, information gathering and uncertainty processing require probabilistic and inferential functions that might not be as much needed in effort-based decisions, which have a more deterministic nature. This difference in cost estimation might be reflected in the brain regions involved in their processing. Probabilistic estimations might require the recruitment of brain regions that are not often involved in EBDM such as the hippocampus and parietal cortex. EBDM key regions, on the other hand, include ACC and OFC together with dopaminergic systems. Finally, the two behaviours might be modulated by DA, NE, and serotonin. In information gathering, NE and serotonin were more consistently implicated. By contrast, DA seems to be the key modulator of EBDM.

1.3.1 Clinical significance of EBDM

The study of EBDM have provided valuable clinical insights into the cognitive mechanisms underlying human motivation in health and disease ([Chong and Husain, 2016](#); [Chong et al., 2016b](#); [Husain and Roiser, 2018](#); [Pessiglione et al., 2018](#)). While impulsivity has been more consistently investigated in the context of uncertainty processing and temporal discounting (see previous sections), the other end of the motivation spectrum – apathy – has been more related to deficits in EBDM

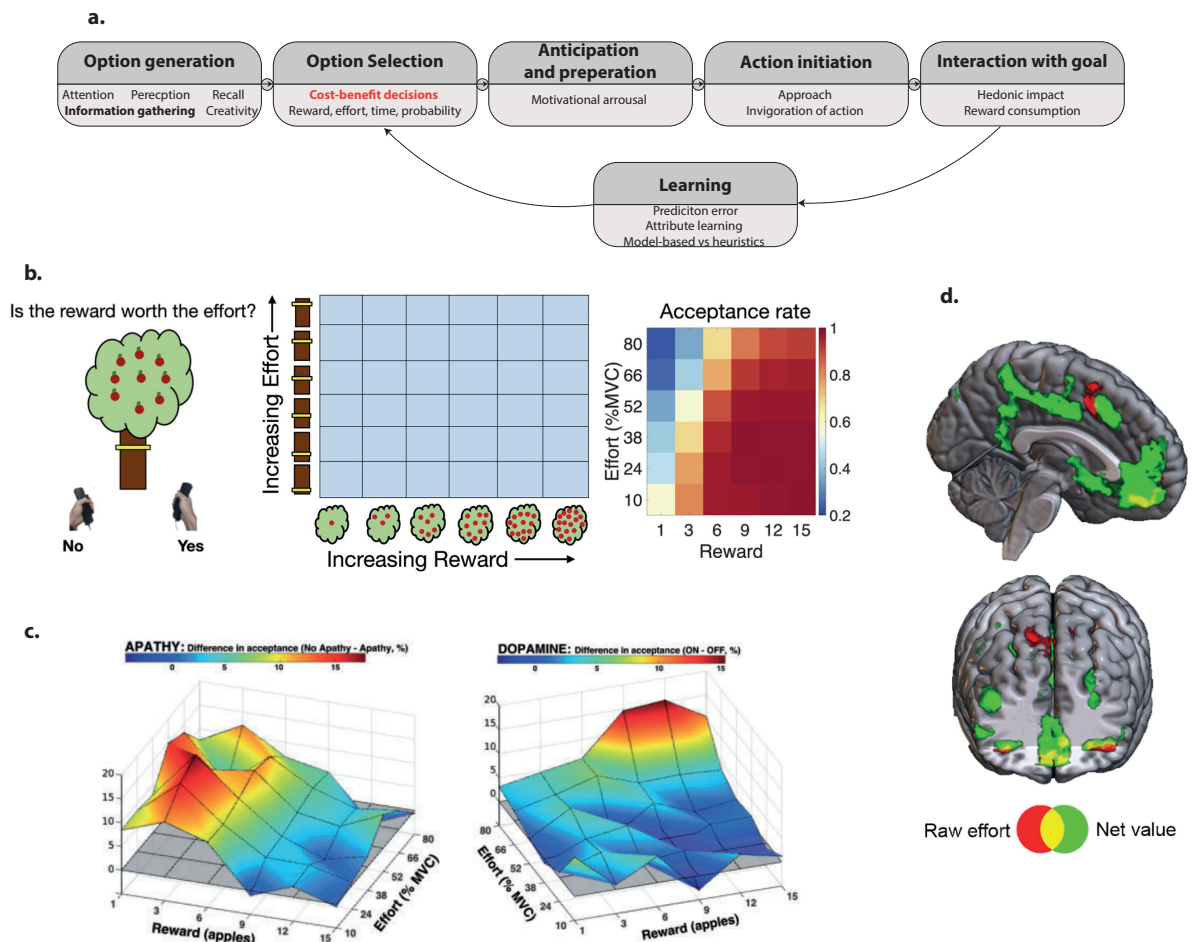


Figure 1.4: Effort-based decision making. **a.** EBDM is a goal-directed decision making process involving several behavioural components. Many of these aspects are shared with other forms of reward-related behaviours such as information gathering (see Figure 1.1). Cost-benefit analysis lies at the heart of these decision processes, providing a basis for empirical testing and neuroeconomic interpretation of behaviour. **b.** This can be tested using behavioural paradigms that require people to make a trade-off between potential reward (e.g., virtual apples with monetary values) and effort (e.g., squeezing an effort handle). By manipulating the levels of these two attributes, a value space can be created to detect differences in valuation. **c.** Such paradigms provide insight into human motivation and neuromodulation of EBDM reflected by changes in reward and effort sensitivity that influence preferences. **d.** Similarly, brain regions involved in EBDM can be identified by correlating their activity with task measures. Studies have shown that effort cost is most strongly associated with ACC, while reward and net value are more strongly correlated with other regions in the valuation network such as OFC. Panels are adapted from (a) (Husain and Roiser, 2018), (b) (Saleh et al., 2021b), (c) (Le Heron et al., 2018c), (d) (Lopez-Gamundi et al., 2021).

([Chong and Husain, 2016](#); [Le Heron et al., 2018b](#); [Saleh et al., 2021b](#)).

Apathy is characterised by decreased goal-directed behaviour. Different degrees of the syndromes have been described in a number of neurological and psychiatric conditions such as Parkinson's disease (PD) ([den Brok et al., 2015](#); [Sinha et al., 2013](#)), small vessel disease (SVD) ([Hollocks et al., 2015](#); [Saleh et al., 2021b](#)), Alzheimer's disease (AD) ([Nobis and Husain, 2018](#)) and schizophrenia ([Bortolon et al., 2018](#)). Dysfunctional EBDM has been a consistent transdiagnostic feature of apathy, demonstrated by hyposensitivity to reward or hypersensitivity to effort ([Chong and Husain, 2016](#); [Husain and Roiser, 2018](#); [Le Heron et al., 2019](#); [Saleh et al., 2021b](#); [Sinha et al., 2013](#)). In PD, for example, apathy has been shown to be associated with reduced incentivisation by reward when making EBDM, and overall lower acceptance of offers ([Le Heron et al., 2018c](#)). This effect has also been demonstrated using physiological markers of reward sensitivity, such as pupillary reaction: apathetic PD patients demonstrate blunted pupillary responses to rewards compared to non-apatetic patients ([Muhammed et al., 2016](#)). Furthermore, the same brain regions and systems involved in EBDM processing have been shown to be related to apathy, including midbrain dopaminergic brain regions, vmFPC, and ACC ([Husain and Roiser, 2018](#)).

Unsurprisingly, reduced dopamine – a key regulators of EBDM – by pharmacological manipulation or lesions of dopamine pathways has been associated with apathetic symptoms in animals and humans ([Chong and Husain, 2016](#); [Salamone and Correa, 2012](#)). Conversely, several reports showed that administration of dopaminergic medications results in improvement of apathy. The vast majority of these studies in humans involve PD, in which neurodegeneration of dopamine regions is the main pathology ([Carnicella et al., 2014](#); [Chong et al., 2015](#); [Czernecki et al., 2008](#); [Le Heron et al., 2018b](#); [Muhammed et al., 2016](#); [Sinha et al., 2013](#)). The therapeutic effect of dopamine on apathy has also been noted in some stroke

survivors ([Adam et al., 2013](#)).

Mechanistically, dopamine has been demonstrated to influence both aspects of EBDM in apathy (reward hyposensitivity and effort hypersensitivity) ([Chong and Husain, 2016](#); [Le Heron et al., 2019](#)). For example, one study in a profoundly apathetic patient (KD) has shown that dopamine supplementation results in a marked reversible improvement in reward sensitivity as indexed by performance on oculomotor tasks measuring saccades towards rewarding stimuli ([Adam et al., 2013](#)). Autonomic pupillary responses in apathetic PD were found to exhibit a similar effect ([Muhammed et al., 2016](#)). Several studies have also demonstrated that DA influences effort discounting in EBDM tasks requiring participants to express willingness to accept effortful actions for reward ([Chong et al., 2015](#); [Le Heron et al., 2018b](#); [Porat et al., 2014](#); [Wardle et al., 2011](#)). In these reports, DA has been shown to increase offer acceptance and boost action invigoration. However, some have noticed a distinct effect of DA from apathy on reward and effort sensitivity in these paradigms, indicating that DA deficiency is not merely a synonym of apathy ([Le Heron et al., 2018b](#)).

In addition to helping uncover possible mechanisms of apathy, EBDM framework highlighted mechanistic differences between the syndrome and related clinical conditions such as depression and autism spectrum. For example, effort hypersensitivity has been more strongly associated with apathy and not depression in several studies ([Chong et al., 2015](#); [Saleh et al., 2021b](#)). In contrast, autistic patients seem to be insensitive to effort regardless of reward on offer ([Damiano et al., 2012](#)).

Overall, EBDM offers an objective, measurable and mechanistic framework that helps in the delineation of motivation syndromes and uncovering underlying brain networks and neuromodulation. This can provide crucial insights into possible

targets for new treatments.

1.4 Chapter conclusions

This chapter provided a summary of previous literature investigating information gathering, uncertainty processing, and effort-based decision making. This was not intended to be an exhaustive discussion of all the available studies and investigations on the subject matter. Instead, the aim was to introduce a conceptual framework for these behaviours along with clinical implications in the context of associated brain correlates and neuromodulation.

Crucially, these forms of goal-directed behaviour can be mechanistically investigated by examining the cognitive components that underlie them. This involves shared components centred around cost-benefit valuation for optimisation of outcomes. The nature of the cost involved in these valuation processes results in key differences between the two forms of behaviour. This is especially evident when considering the active phase prior to commitment to decisions or invigoration of action. These differences might implicate distinct neuroanatomical, neuromodulatory, and clinical considerations, despite overlapping associations.

Several gaps in the existing literature have been identified and highlighted in previous sections. First, while many previous investigations and models of information gathering offered insights into the economics of the behaviour from a cost-benefit optimisation perspective, they often fail to account for agent-related factors that critically influence the process. These previous investigations focused on how much information people gather with little attention to how information is acquired. Accounting for such factors in experimental paradigms and computational modelling can offer a more fine-grained, ecologically valid, and sensitive approach for examining information sampling in humans. This would potentially

advance our clinical characterisation of conditions related to deficits in this behaviour.

Consequently, studies investigating the neural correlates and brain regions involved in *active* information gathering are limited. However, given the extensive literature on similar forms of behaviour (e.g., value-based decision making and uncertainty processing), one could infer the role of important cortical and subcortical brain regions in the process. The hippocampus might be a key region that is under-investigated in this domain. With emerging evidence highlighting its role in valuation and decision making, and previous extensive reports on its prospective and computational functions, it can be a key region in a cortical-subcortical network that orchestrates active sampling and decision making under uncertainty (see Figure 1.3). Empirical evidence testing these assumptions has not yet been established.

This conceptualisation could offer important clinical insights into human affect and motivation in health in disease. In this context, subjective cognitive impairment might be a valuable participants group as the condition has three important features: i) strong association with affective dysfunction, ii) potential hippocampal involvement given its established link to AD, and iii) patients uncertainty and information seeking. Despite the increasing prevalence of SCI in ageing populations, the mechanisms underlying the condition are still poorly understood. Examining the condition from the lens of goal-directed behaviour might aid in its characterisation and advance understanding of its psycho-cognitive manifestations and brain regions involved.

The aim of the next chapters in this thesis will be to address these gaps in the literature through empirically characterising the two types of decision making discussed in this chapter. I will aim to highlight behavioural, neuroimaging and

clinical implications involved. Part of the focus will be on the hippocampus as a key region that might be more mechanistically involved in decisions making under uncertainty.

The remainder of this report is organised as follows:

Chapter 2 — Introduces a novel behavioural paradigm to examine *active* information gathering and decision making under uncertainty. The task was extensively tested and validated in healthy young people over five experiments. Through this, novel behavioural measures of information sampling were derived, and their relationship with affect and motivation in healthy people was explored.

Chapter 3 — Investigates the role of the hippocampus in motivated decision making in patients with autoimmune limbic encephalitis who have focal hippocampal damage. The chapter provides a comparison of this role in decision making under uncertainty vs. effort-based decision making.

Chapter 4 — Assesses information gathering and decision making under uncertainty in subjective cognitive impairment. It provides evidence of hippocampal involvement in these forms of goal-directed behaviour. The results also show that these aspect of decision making might be related to affective dysfunction in this participants group.

Chapter 5 — Examines effort-based decision making in subjective cognitive impairment. It explores deficits in EBDM in the condition and their relationship with motivation and affective dysregulation.

Chapter 6 — Investigates effort-based decision making in Alzheimer's disease. This is in part an extension of the work done in SCI because of the important association between the two conditions. The chapter explores

deficits in EBDM and their relationship with executive function, affect, and motivation in AD.

Chapter 7 — Provides a summary of the main findings of this thesis. These results are then discussed in different sections along with limitations and future directions.

2 | Active information gathering in healthy young people

2.1 Chapter summary

This chapter introduces a novel behavioural paradigm - *Circle Quest* - designed to investigate *active* information gathering and decision making under uncertainty. Following extensive testing in healthy young people, the results revealed that human information sampling is influenced by several factors, including economic constraints and time limitations. A speed efficiency trade-off was found to characterise sampling behaviour, whereby slower sampling was associated with higher efficiency. However, under time pressure, participants were able to break this speed efficiency trade-off. Computational modelling revealed a cognitive effort cost linked to speed and efficiency, and was found to be associated with the development of subjective fatigue during the experiment. Finally, behavioural markers of hyperreactivity to uncertainty, such as faster and more extensive sampling, were found to be associated with higher depression scores and increased subjective reports of uncertainty. Thus, the study provides a rigorous behavioural paradigm and framework to examine active information gathering which has potential clinical insights.¹

¹Some of the data and results in this chapter are published in (Petitet et al., 2021). Details about this are provided in a separate document submitted to the examination committee.

2.2 Introduction

Humans often seek information to limit the pervasive effects of uncertainty on decisions. This involves simple situations such as crossing the road – e.g., observing passing cars and traffic lights – or decisions with potentially drastic outcomes such as deciding whether to pursue a PhD degree. To do this, people need to take into account several factors that help them optimise their information gathering process, obtain information efficiently, and decide when to stop sampling.

From an economic optimisation perspective, information seeking should stop when the cost of obtaining knowledge outweighs its benefits (Clark et al., 2006a; Gottlieb et al., 2013; Hauser et al., 2017a; Jones et al., 2019; Juni et al., 2016). Several behavioural paradigms have been used to investigate this aspect of information gathering in health and disease (see the previous chapter for a summary of these paradigms) (Clark et al., 2006a; Juni et al., 2016; Phillips and Edwards, 1966). While such paradigms provided insights into how much information should be gathered prior to committing to decisions, they often fail to take into consideration agent-related factors that influence how people collect information, such as speed and efficiency of sampling. These factors might significantly alter the economics of the process (Gottlieb and Oudeyer, 2018). For example, a well-chosen piece of information may have the potential to strongly resolve uncertainty, while others may be irrelevant. However, finding the best pieces of information might require additional resources, including time and cognitive energy, adding to a *computational cost* of information gathering, which is not accounted for in previous models of information gathering.

Two factors which theoretically might contribute to this computational cost are worth considering in more detail. First, identifying samples that are more informa-

tive can potentially take longer and therefore carry a **opportunity cost** (Boureau et al., 2015; Kurzban et al., 2013). For example, if someone is deciding where to have dinner tonight, asking a friend for advice may provide more useful information than consulting a guidebook, but at the same time, one might risk not obtaining that information before dinner if the friend is not directly available or does not swiftly answer their phone. Here, the opportunity cost is the useful information that was missed due to the deadline. Numerically, it is therefore a function of the agent's sampling strategy (speed, efficiency), as well as the task's cost-benefit and temporal structure. The second factor is a potential **cognitive effort cost** (Shenhav et al., 2013; Westbrook and Braver, 2015) that arises from mechanisms that enhance the amount of information collected per unit of time, e.g., increasing the rate at which candidate samples are evaluated, inhibiting unhelpful automatic or habitual responses, or allocating more attentional resources to the search for knowledge (Horan et al., 2019). For example, if we decide to phone our friend, we might obtain more information by turning the conversation towards the features of a restaurant that interest us most, and paying close attention to the responses. The cognitive effort expended in honing in on the most valuable information might lead to better decisions, but also incur a cost in terms of neural resources and/or energy consumption.

These additional attributes not only help characterise information gathering in healthy people, but also provide behavioural markers that are potentially sensitive to mental and cognitive disorders related to deficits in uncertainty processing and goal-directed behaviour. As reviewed in the previous chapter, this includes different disorders (e.g., affective dysfunction and impulsivity) for which the underlying cognitive mechanisms are still not established (Averbeck et al., 2013; Bishop and Gagne, 2018; Dar et al., 2017; Delazer et al., 2012; Djamshidian et al., 2011; Dugas, 1997; Freeston et al., 1994; Hildebrand-Saints and Weary,

1989; de Rezende Costa et al., 2016; Voon et al., 2017).

In this chapter, I introduce a novel, more complex behavioural paradigm that accounts for these missing agent-related features in previous studies. In this task, people search spatially for information, by touching areas on the screen, before committing to an answer. Importantly, some sample locations give more information than others. Participants could sample whenever, wherever, and however they wanted.

Over five different experiments that feature different versions of the task, the findings demonstrate that active information before committing to decisions is extremely flexible in humans and adapts to economic and time constraints. A speed-efficiency trade-off was found to characterise information sampling, whereby more informative samples take longer to obtain. Crucially, under sufficient time pressure, agents were able to break this trade-off to collect information both rapidly and efficiently. Computational modelling indicates that such a behavioural flexibility might require additional cognitive effort quantified by a computational cost assigned to speed and efficiency. This effort cost was found to correlate with subjective reports of fatigue during active sampling. On the other hand, behavioural markers of increased responsivity to uncertainty, such as extensive and rapid sampling, correlated with subjective reports of depression, providing mechanistic insights into the relationship between uncertainty processing and affective functioning.

Taken together, these results provide evidence that *active* information gathering paradigms and models that account for agent-related factors and costs provide a better account of human behaviour prior to committing to decisions under uncertainty. This could provide crucial insights into clinical syndromes that might be related to deficits in uncertainty processing such as depression.

2.3 Methods

2.3.1 Participants

Participants were recruited through the Oxford Psychology Research participant recruitment scheme website <https://opr.sona-systems.com/> and through online advertisements. Exclusion criteria included personal history of neurological or psychological illness or current use of psychoactive medications. Sample size was determined based on counterbalancing requirements and previous similar studies (Clark et al., 2006a; Jones et al., 2019; Juni et al., 2016). All participants gave written consent to take part in the study and were offered monetary compensation for their participation. The study was approved by the University of Oxford ethics committee (RAS ID: 248379, Ethics Approval Reference: 18/SC/0448). Different participants took part in five different experiments with no overlap. Forty-eight participants (24 males) took part in the first experiment. Experiments 2–4 included 20 participants each (ten males per experiment) and experiment 5 included 19 participants (nine males). Table 2.1 shows the characteristics of the group including age, gender, years of education, and external measures.

2.3.2 External measures

Participants completed self-report questionnaires of impulsivity (Barratt Impulsiveness scale – BIS-11) (Patton et al., 1995), depression (Beck’s Depression Inventory– BDI-II) (Beck et al., 1961), apathy (Apathy Motivation Index–AMI) (Ang et al., 2017), and uncertainty tolerance (Intolerance of Uncertainty Scale – IUS)(Buhr and Dugas, 2002). They also completed a short timed 10-minute test of fluid intelligence (Raven’s progressive matrices test) (Carpenter et al., 1990).

	Exp. 1	Exp. 2	Exp. 3	Exp. 4	Exp. 5
Age	24.5 (3.8)	24.9 (3.8)	25.7 (5.2)	26.1 (4.0)	23.7 (2.6)
Gender	24F/24M	10F/10M	10F/10M	10F/10M	10F/9M
YOE	18.4 (3.2)	18.3 (4.0)	17.1 (3.2)	17.8 (2.1)	17.4 (1.3)
Raven's matrices	8.7 (2.4)	7.5 (2.6)	8.7 (2.0)	7.5 (1.8)	7.6 (2.9)
BDI total score	7.3 (5.5)	7.1 (5.2)	5.4 (5.0)	7.2 (6.5)	7.6 (7.8)
AMI total score	1.4 (0.5)	1.3 (0.4)	1.3 (0.4)	1.3 (0.3)	1.1 (0.4)
BIS total score	62.3 (9.8)	64.8 (10.7)	58.7 (9.1)	63.0 (13.0)	62.6 (13.6)
IUS total score	60.5 (17.3)	60.8 (21.9)	61.7 (20.0)	59.9 (13.0)	66.4 (24.4)
Active task duration (min)	47.3 (1.3)	51.5 (4.1)	50.0 (2.2)	50.4 (2.3)	42.2 (3.0)
Passive task duration (min)	41.7 (2.0)	-	-	-	-

Table 2.1: **Study demographics.** The table shows group means with standard deviation in parentheses. F: Female; M: Male; YOE: years of education (since kindergarten); BDI: Beck Depression Inventory-II; AMI: Apathy Motivation Index; BIS-11: Barratt Impulsiveness Scale-11; IUS: Intolerance of Uncertainty Scale.

2.3.3 Experimental paradigm – Circle Quest

Two versions (active and passive) of a novel behavioural paradigm investigating active information gathering and decision making under uncertainty were designed. The active version aimed to capture the economic and non-economic dynamics of information gathering. This was tested in five different experiments. The passive version aimed to investigate two questions: i) How do people translate objectively defined levels of uncertainty into subjective estimates? And ii) How do people weigh uncertainty against reward when making decisions with limited agency over information content?

2.3.3.1 Active sampling task

In this paradigm, participants were required to maximise their reward by trying to localise a hidden circle as precisely as possible. They could infer the location of the circle using clues that could be obtained by touching the screen at differ-

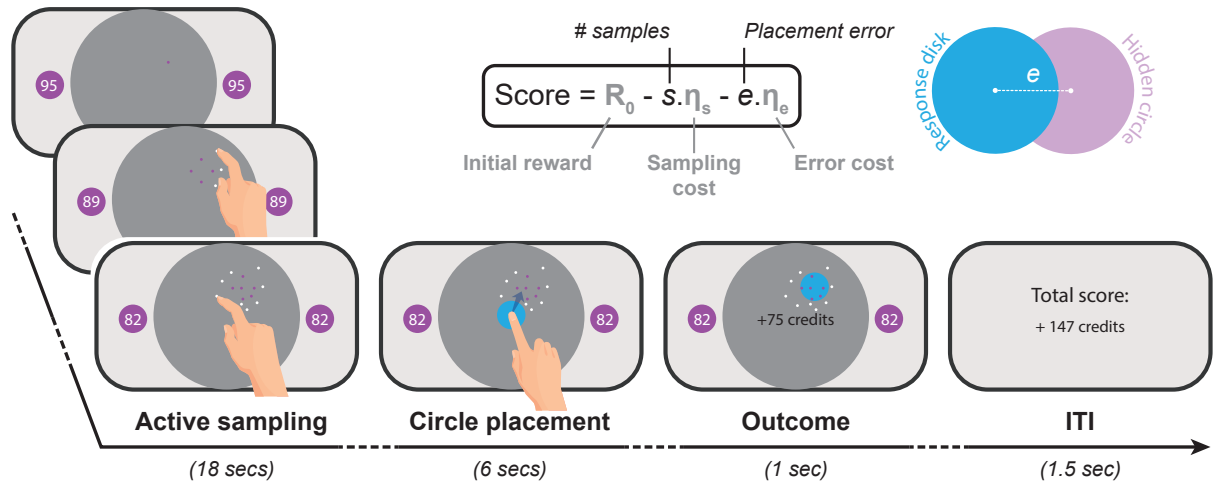


Figure 2.1: **Circle Quest – active sampling task.** Participants were required to find the location of a hidden purple circle as precisely as possible. Clues about the location of the hidden circles could be obtained by touching the screen at different locations. This yielded dots that were coloured either purple or white depending on whether they were situated inside or outside the hidden circle: purple dots were inside and white dots were outside. Two circles of the same size as the hidden circle were always displayed on either side of the screen to limit memory requirements of the task. Within these two circles, an initial credit reserve (R_0) was displayed. At the beginning of each trial, a purple dot was always shown to limit initial random sampling. During the time allocated for each trial (t_{max}), participants could sample without restrictions on speed, location, or number of samples. Each time they touched the screen to add a dot, the number of credits available decreased depending on the cost of sampling (η_s) on that trial. Once t_{max} has passed, a blue disc of the same size as the hidden circle appeared in the centre of the search field. Participants were then required to drag this disc on top of where they thought the hidden circle was located. Following this, the score they obtained on that trial was calculated and presented as feedback at the end of the trial.

ent locations on a designated search field (grey circle in Figure 2.1). Participants could acquire as many samples as they wanted without limitations to when and how these samples were obtained. There were two types of clues: purple dots if the location was situated inside the hidden circle and white dots if the location was outside the circle. The sizes of the hidden circle and dots were fixed on all trials (circle radius: 130 Px, 5.80% of the search space, dot radius: 4 Px). Two circles of the same size as the hidden circle were always displayed on either side of the screen in order to limit memory requirements of the task. Within these two circles, credits (R_0) that participants could potentially win were displayed. After the information-gathering phase, participants could localise the hidden circle using a blue disc that had the same size as the hidden circle.

These aspects of the task were explained to participants using an interactive tutorial with the help of the experimenter. Following this, they performed a training task to further expose them to the task environment and its scoring rules. During training, participants were presented with different configurations of dots (four purple dots and four white dots) from which they could infer the location of the hidden circle with different levels of uncertainty (e.g., when purple dots are spaced out this indicated a lower level of uncertainty than when they were clumped close together). In this training task, participants were instructed to only move the blue disc to where they thought the hidden circle was located. Uncertainty in the task was experimentally quantified as *expected error* (EE) which is equal to the error an optimal agent would obtain if they placed the blue disc at the best possible location. A penalty representing how far the localisation was from the true location of the hidden circle was introduced. This penalty was subtracted from the credits assigned to each trial that participants could potentially win if their localisation was perfect (i.e., placing the blue disc exactly on top of the hidden circle). The penalty incurred for each error pixel (η_e) could be manipulated depending on ex-

perimental conditions. Thus, localisation error penalty was equal to the distance between the blue disc and the centre of the hidden circle multiplied by this error penalty.

2.3.3.2 Different versions of the active task

Five different versions of the active task were tested in healthy young people (Table 2.2). These versions introduced different manipulations with the aim of examining their influence on information gathering behaviour. The variables that were manipulated were

Initial Credit (R_0) – the endowment or reward reserve that participants could win if they managed to find the circle perfectly.

Sampling Cost (η_s) – the cost incurred for each additional sample acquired. The total cost of sampling (η_s multiplied by the number of samples s) is deduced from R_0

Error Cost (η_e) – the number of credits lost per error pixel. The total localisation error penalty (η_e multiplied by the error distance) is deduced from R_0 .

Trial Deadline (t_{max}) – the time available per trial to finish sampling.

Table 2.2 shows the details of how these variables were manipulated and tested.

In the first experiment, R_0 and η_s were both manipulated. Each had two levels: low (R_0 : 100 credits, η_s : -1 credit/sample) and high (R_0 : 125 credits, η_s : -5 credits/sample). Participants also performed a passive counterpart of the task during this experiment. In the remaining experiments, only one variable (R_0 , η_s , η_e or t_{max}) was manipulated while the others were kept fixed. These manipulations resulted in four types of trials (conditions) that were repeated 24 times per partic-

	R_0	η_s	η_e	t_{max}	n trials
Exp. 1b	125	1			24
	100	1			24
	125	5	1.2	18 secs	24
	100	5			24
Exp. 2	50				24
	75	3	1.2	18 secs	24
	100				24
	125				24
Exp. 3		1			24
		3			24
	100	5	1.2	18 secs	24
		7			24
Exp. 4			0.5		24
			1.2		24
	100	3	1.9	18 secs	24
			2.6		24
Exp. 5				6 secs	24
				10 secs	24
	100	3	1.2	14 secs	24
				18 secs	24

Table 2.2: **Different versions of active sampling task.** All experiments included four types of trials (24 repetitions per trial type; 96 trials in total). The table shows the cost-benefit and temporal structure of these trial types. R_0 : initial credit; η_s : sampling cost; η_e : error cost; t_{max} : time allocated to the sampling phase.

ipant, resulting in 96 trials in total. The conditions were counterbalanced between participants.

2.3.3.3 Passive decision task

During the first experiment, participants also performed a passive version of the task (Figure 2.2). This version had two goals: i) investigate inter-individual differences in mapping objective uncertainty as defined by task parameters into subjective estimates and ii) examine decision making under uncertainty to investigate sensitivity to reward and uncertainty.

In this version of the task, participants were required to make passive decisions (accepting/rejecting offers) based on predetermined levels of uncertainty and reward for these offers. At the beginning of each trial, they saw a configuration of dots (four purple dots and four white dots) mapping onto different experimentally defined levels of uncertainty (five levels of EE : 16.3-24.4, 27.1-38.9, 57.5-58.9, 73.33-74.18, 91.9-93.3 pixels). Participants were required to indicate how confident they are about the location of the hidden circle using a rating scale on the side of the scene. Subjective uncertainty score was calculated by z-scoring and sign-flipping these confidence ratings. Following this, the reward on offer appeared in the two circles on the side of the screen (four reward levels R : 40, 70, 100, 125 credits). Participants were required to indicate whether they would like to place the blue disc given the reward and uncertainty of the offers. They did this by pressing "Yes" or "No" appearing on the screen. There were 20 different combinations of offers and each offer was presented five times, thus, participants completed 100 trials in total. Participants were told that after indicating their preferences, 10 of their accepted offers will be randomly selected for them to play, and that these 10 offers would decide their score in the game. Participants were told that these offers will be selected to reflect their overall pattern of responses, so it does not matter how many times they say yes or no.

In summary, participants made two responses on each trial of the passive task the first was to indicate their confidence about the location on the hidden circle when they saw the configuration of dots on the screen. The second was a decision answering the question of whether they would like to place the circle given the available amount of reward and the dots on the circle. Following this they placed the disc for 10 trials and were rewarded based on their performance on these trials.

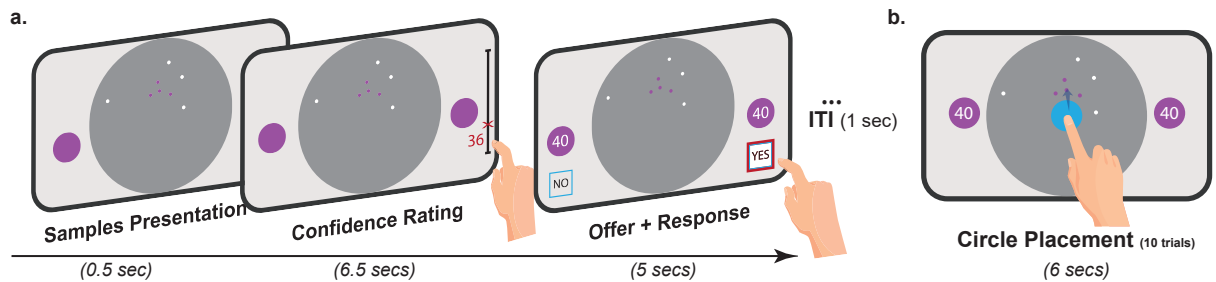


Figure 2.2: **Circle Quest – passive decisions.** **a.** Participants first reported their subjective estimate of uncertainty (i.e., how confident they are about the location of the hidden circle given the information displayed on the screen). After this, the credits on offer appeared (displayed inside the two purple circles on the side). Participants could decide to accept or reject the offer to locate the hidden circle. **b.** At the end of the experiment, participants had to play 10 of the accepted offers placing a blue disc on top of where they thought the hidden circle was located. These trials determined the scores in the task. The score was equal to the reward on offer minus a penalty reflecting their localisation error (i.e., how far the blue disc centre was from the centre of the hidden circle).

2.3.4 Statistical analysis and computational modelling

Analysis and modelling of data were performed in MATLAB (MathWorks version 2019a). Generalised mixed-effects models (logistic or linear) using *glme* function in MATLAB were run to investigate the effect of experimental parameters on behaviour. Robust regression analysis was performed using *fitlme* in MATLAB to investigate correlations with external measures or average individual performance. Details about these models including model specification and results are provided in Appendix.

2.4 Results

2.4.1 Expected error as a measure of uncertainty

Objective uncertainty was quantified as the expected error of localisation (EE). This is equal to the error the ideal agent would obtain on average by placing the blue disc at the best possible location given the information on the screen (Figure 2.3 a.). For each location λ on the screen the probability that this location is the centre of the hidden circle given the observation o at location σ can be calculated using Bayes' rule as follows:

$$p_s(\lambda|o, \sigma) = \frac{p_s(\lambda) \cdot p_s(o, \sigma|\lambda)}{p_s(o, \sigma)} \quad (2.1)$$

$$p_{s+1}(\lambda) = p_s(\lambda|o, \sigma)$$

With successive sampling, this rule is applied sequentially. Therefore, the posterior probability $p_s(\lambda|o, \sigma)$ becomes the prior probability $p_{s+1}(\lambda)$ from one sample to the next.

Given the rules of the task and that there is no uncertainty regarding the radius of the hidden circle, the likelihood of observing a purple dot (o^+) at a location σ is 1 for locations within one radius distance of σ , and zero otherwise. The opposite is true for the likelihood of observing a white dot (o^-). Thus, the likelihood function

can be expressed mathematically as:

$$\begin{cases} p_s(o^+, \sigma|\lambda) = 1 \text{ if } |\lambda - \sigma| \leq r \\ p_s(o^+, \sigma|\lambda) = 0 \text{ if } |\lambda - \sigma| > r \\ p_s(o^-, \sigma|\lambda) = 1 - p_s(o^+, \sigma|\lambda) \end{cases} \quad (2.2)$$

Where r is the radius of the hidden circle which is fixed.

The probability of the observation o at the sampling location σ is the sum over all possible hidden circle centres λ of the probability of the observation given λ , weighted by the probability of λ to be the hidden circle centre:

$$p_s(o, \sigma) = \sum_{\lambda} p_s(o, \sigma|\lambda) \cdot p_s(\lambda) \quad (2.3)$$

Thus, for every possible circle placement, an expected error can be computed as:

$$EE_s(\lambda) = \sum_i p_s(\lambda_i) \cdot |\lambda - \lambda_i| \quad (2.4)$$

When compared to actual performance, expected error mapped well onto the errors participants obtained when placing the blue disc (Figure 2.3 b.).

Given the active nature of the task, participants will vary in how they manage to reduce uncertainty from one sample to the next. This was quantified as information extraction rate α , which is a measure of sampling efficiency. Overall, EE decreased in the task with successive sampling following an exponential decay function and α captures how steep this decline is (Figure 2.3 c. & d.). α was calculated by fitting the following equations:

$$\begin{aligned}
\hat{EE}_{(n,1)} &= \frac{\sum_{i=1}^{60} EE_{(i,1)}}{60} \\
\hat{EE}_{(n,s)} &= (\hat{EE}_{(n,1)} - \hat{EE}_{\infty}) \cdot (1 - \alpha_n)^{s-1} + \hat{EE}_{\infty} \\
0 < \alpha < 1 \quad \& \quad \hat{EE}_{\infty} > 0
\end{aligned} \tag{2.5}$$

Where n is the trial number, s is the sample number and $\hat{EE}_{\infty}$ is the asymptotic EE which reflects the limitations to uncertainty reduction imposed by the task.

2.4.2 Passive performance reflects sensitivity to task measures

The purpose of the passive task was to measure whether participants mapped the expected error measures onto subjective estimates and used them in their decision making process. The results showed that indeed objectively defined uncertainty (EE) was strongly reflected in participants' subjective confidence estimates ($EE \times$ Uncertainty Score: $\beta = 0.80$, 95% CI = [0.76, 0.83], $t_{(8062)} = 49.89$, $p < 0.001$; Table B.1, Figure 2.4 a.). Analysis of choice data also revealed that participants used the attributes of the offers as expected, accepting more when reward on offer increased and less when uncertainty increased (Logistic mixed effects model; Main effect of reward on offer acceptance: $\beta = 1.87$, 95% CI = [1.49, 2.26], $t_{(8060)} = 7.04$, $p < 0.001$; Main effect of EE on offer acceptance: $\beta = -2.53$, 95% CI = [-2.80, -2.27], $t_{(8060)} = -8.57$, $p < 0.001$; Table B.1, Figure 2.4 b.).

The economic considerations characterising decision making in the task were also reflected in the time it took participants to accept/reject offers. Higher conflict between the two attributes (e.g., high reward and high uncertainty) required longer decision times (Effect on decision time; $EE \times$ stake: $\beta = 0.05$, 95% CI = [0.06, 0.03], $t_{8060} = 7.14$, $p < 0.001$; Figure 2.4 b.).

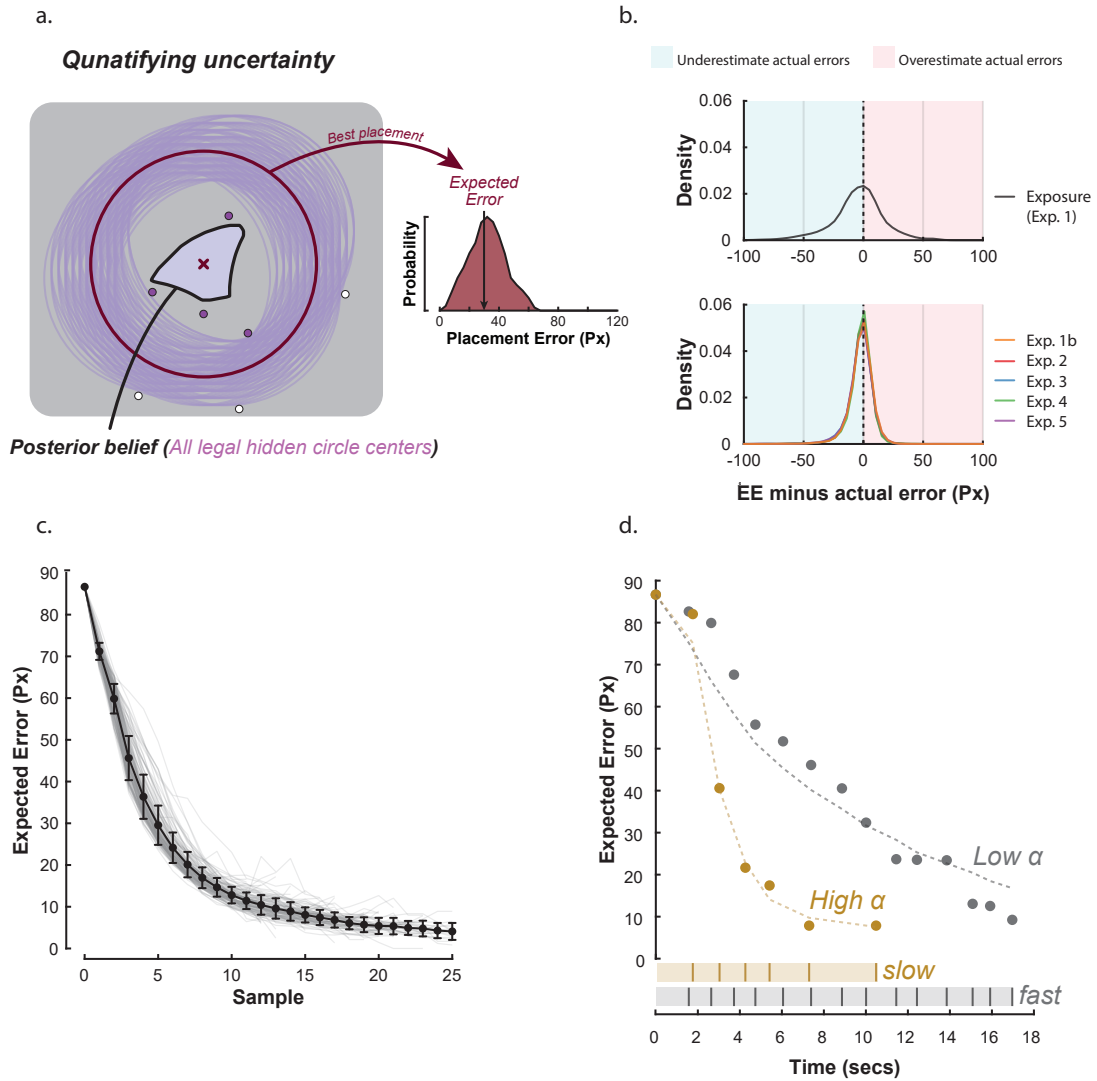


Figure 2.3: **Expected error as a measure of uncertainty** **a.** Uncertainty in the task is quantified as the expected error upon circle localisation (EE). This is equal to the probability-weighted average of all the possible errors that could be resulting when placing the localisation disc at the best possible location. The best possible location is the centroid of the solution space, which is the set of the centres of all the possible circles that could be a solution for the spatial configuration displayed. **b.** The difference between EE and actual errors agent obtain when localising the circle using the blue disc. The upper panel is obtained from the exposure training task performed as part of the first experiment. The lower panel is obtained from all versions of the active sampling task. **c.** Uncertainty (EE) decreases with successive sampling (Exp. 1 –5). **d.** Efficiency is parameterised as information extraction rate α . A higher α means higher efficiency in decreasing EE from one sample to the next.

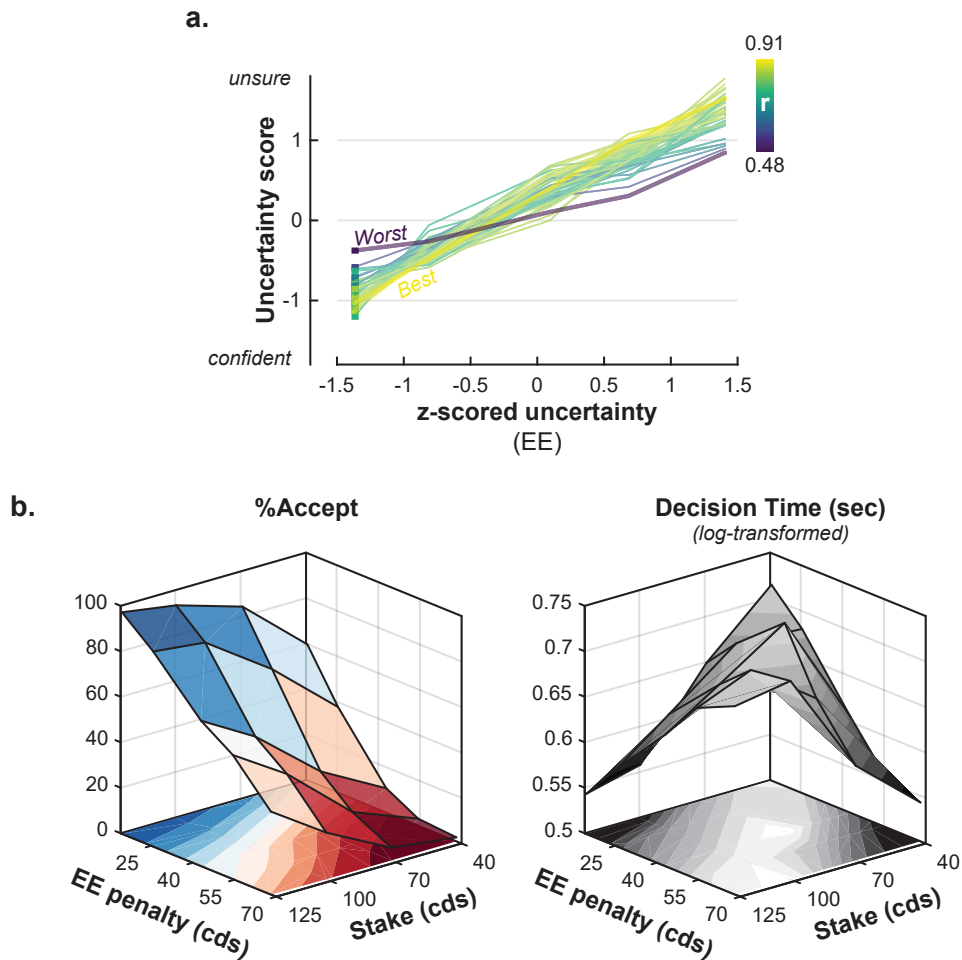


Figure 2.4: **Passive performance reflects sensitivity to task measures.** **a.** Subjective uncertainty mapped well onto experimentally defined uncertainty (expected error – *EE*) (r : slope of the relationship between uncertainty score and *EE*). The two extreme participants are shown as thick yellow (best internal representation of uncertainty) and blue (worst internal representation of uncertainty) lines. **b.** Raw data (mean) showed characteristic signatures of a cost-benefit evaluation: a tendency to accept more when the uncertainty was low and the stake high, slower responses when the two variables were in conflict.

2.4.3 Extent, speed, and efficiency of active sampling are influenced by economic and time constraints

In Exp. 1b, participants adjusted their sampling according to economic constraints of the task: sampling less when samples were expensive (high η_s) and less when sampling was cheap (low η_s) (LMM; effect of η_s on number of samples: $\beta = -0.191$, $t_{4604} = -18.64$, $p < 0.001$; Table B.2, Figure 2.5 a.). Similarly, participants acquired more samples when initial credits were higher (LMM; effect of R_0 on number of samples: $\beta = 0.03$, $t_{4604} = 7.08$, $p < 0.001$; Table B.2, Figure 2.5 a.).

The influence of these economic constraints was also evident on indirect measures of *active* sampling such as speed and efficiency. Sampling speed was indexed using inter-sampling interval (*ISI*), which is the time between each sample and the next. Longer *ISI* indicates slower sampling. Sampling efficiency was indexed using information extraction rate (α), which is a measure of how *EE* drops from one sample to the next. The results showed that participants sampled slower and more efficiently at higher sampling costs compared to low-cost conditions (LMM; effect of η_s on *ISI*: $\beta = 0.12$, $t_{4604} = 13.83$, $p < 0.001$; effect of η_s on α : $\beta = 0.017$, $t_{4606} = 2.54$, $p = 0.01$; Table B.3, Figure 2.5 a.) . These results indicate that agents might be applying more cautious (slower) sampling strategies when sampling is expensive. Across different conditions, such a slower sampling was found to be associated with higher efficiency. That is, information sampling on the task was characterised by a classical speed-efficiency trade-off (LMM; effect of *ISI* on α : $\beta = 0.07$, $t_{4606} = 10.16$, $p < 0.001$; Table B.5, Figure 2.5 b.) .

To further characterise active sampling behaviour and the influence of different economic and task-related factors, additional participants groups were tested on four different versions of the task (Exps. 2–5). Each version aimed to examine

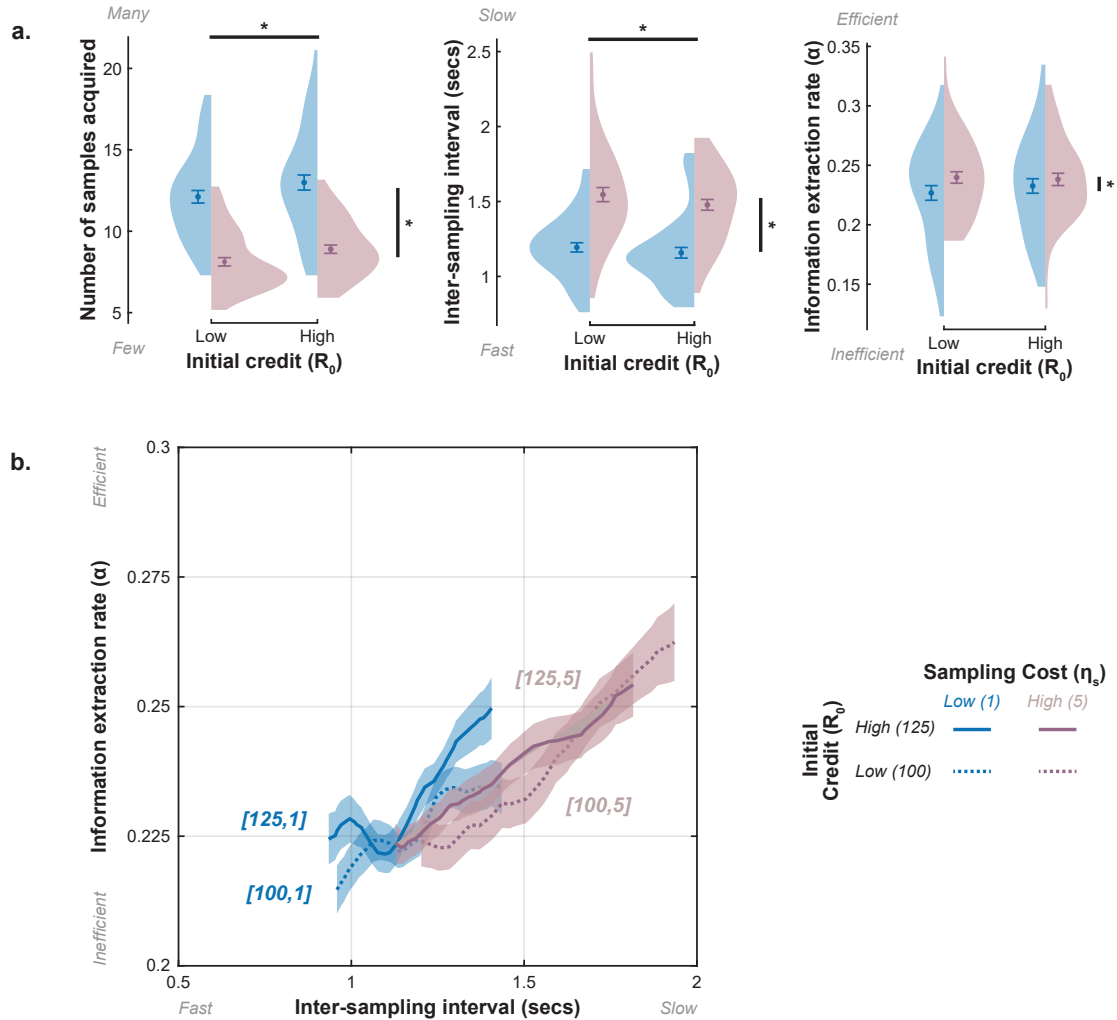


Figure 2.5: Extent, speed and efficiency of active sampling are influenced by economic constraints. **a.** Participants acquired fewer samples at a slower pace (longer *ISI*) when sampling was more expensive (high η_s) and when they started with lower credit. In conditions with high sampling cost, participants were also more efficient as indexed by information extraction rate α . **b.** Active sampling across different economic conditions is characterised by a speed-efficiency trade-off, whereby faster sampling is associated with lower efficiency. Conditional plot was generated by sliding, for each subject and condition separately, 25% quantile bins of *ISI* and computing the mean α for each bin. The error bar shows $\pm$ SEM.

the influence of η_s , R_0 , η_e , and t_{max} independently of the other factors. The first three variables determine the economic structure of the task, while t_{max} influences opportunity cost (i.e., the instantaneous cost of not sampling).

The results from these experiments were consistent with the findings from Exp. 1b. Less stringent economic and time constraints (i.e., higher R_0 , lower η_s , lower η_e , and longer t_{max}) were associated with more extensive sampling (LMM; Main effect of R_0 in Exp. 2: $\beta = 0.039$, $t_{4604} = 7.08$, $p < 0.001$; Main effect of η_s in Exp. 3: $\beta = -0.209$, $t_{1918} = -9.38$, $p < 0.001$; Main effect of η_e in Exp. 4: $\beta = 0.087$, $t_{1918} = 0.01$, $p < 0.001$; Main effect of t_{max} in Exp. 5: $\beta = 0.14$, $t_{1822} = 11.14$, $p < 0.001$; Tables [B.2-B.4](#), Figure [2.6](#)).

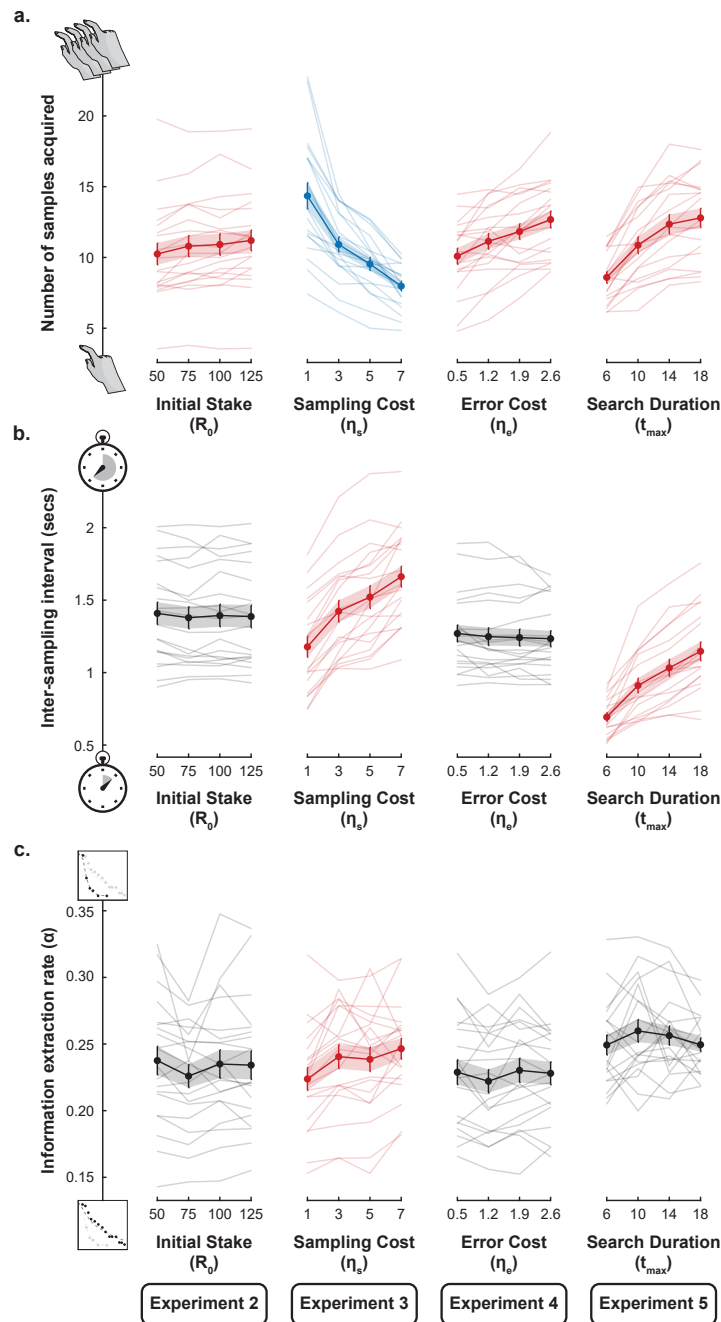


Figure 2.6: **Factors influencing sampling (Exps. 2–4).** **a.** Participants acquired more samples with larger initial credits (Exp. 2), smaller sampling costs (Exp. 3), more penalising error costs (Exp. 4), and longer search times Exp. 5). **b-c.** Slower but more efficient is seen when information was expensive (Exp. 3). By contrast, under tighter time pressure, participants were faster but with no impact on efficiency (Exps. 3 & 5). Error bars indicate $\pm$ SEM. Positive/negative main effect of the experimental variable manipulated is shown in red/blue. Full statistical details are reported in Appendix Tables B.2-B.4.

2.4.4 Breakable speed-efficiency trade-off

As observed in Exp. 1b, the sampling behaviour in all versions of the task was characterised by a speed-efficiency trade-off. Slower sampling was associated with higher efficiency in Exps. 2–5 (Tables B.5; Figure 2.7). Similar to Exp. 1b, participants' sampling was slower and more efficient when acquiring samples costed more (Main effect of η_s on ISI : $\beta = 0.12$, $t_{1918} = 7.41$, $p < 0.001$; Main effect of η_s on α : $\beta = 0.02$, $t_{1918} = 3.97$, $p < 0.001$; Tables B.3 & B.4). Time pressure, on the other hand, was associated with faster sampling (Main effect of t_{max} of ISI in Exp 5: $\beta = 0.18$, $t(1822) = 11.71$, $p < 0.011$; Tables B.3 & B.4). Remarkably, under these time constraints (Exp. 5), participants were able to maintain sampling efficiency and thus exceed the speed efficiency trade-off that characterises sampling behaviour in other conditions (Figure 2.7). Finally, initial reward reserve and error cost had no significant influence on the way participants sampled (all $p > 0.21$; Tables B.4 & B.3).

2.4.5 Computational cost of active sampling

The fact that active information gathering is constrained by a speed-efficiency trade-off that is breakable under time pressure raises the question about other factors that might influence the process. How do people decide on the speed and efficiency of their sampling? And why is it possible to exceed this trade-off under time pressure? These considerations point to additional costs that participants account for when computing the utility of the samples they are acquiring. From an optimal control perspective (Dixon and Christoff, 2012; Manohar et al., 2015; Shenhav et al., 2013), this involves assigning subjective costs to efficiency and speed.

Therefore, the expected utility (EU) of any sample at any given stage is calculated

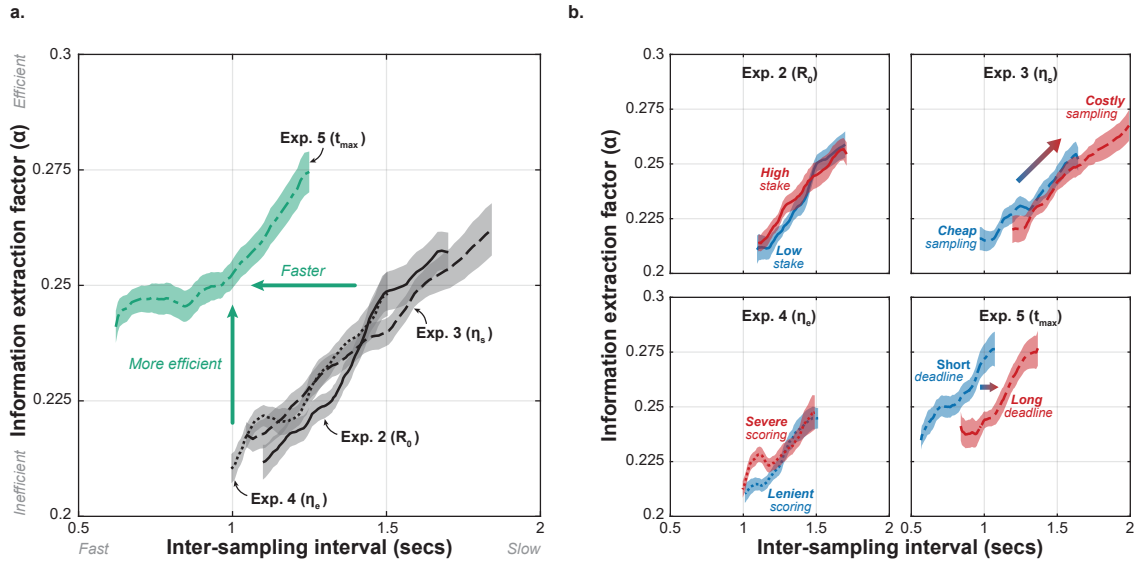


Figure 2.7: Breakable speed-efficiency trade-off of active information gathering. **a.** Overall, in Exps. 2-5 ($n = 79$ participants), longer inter-sampling intervals led to larger information gains at each step, as in Exp. 1b. Participants of Exp. 5 ($n = 19$, green line), however, were able to sample both faster (Contrast Exp. 5 vs. Exps. 2-4 for ln-transformed ISI: $F_{(1,7580)} = 47.65$, $p < 0.001$) and more efficiently (Contrast Exp. 5 vs. Exps. 2-4 for ln-transformed α : $F_{(1,7580)} = 5.26$, $p = 0.022$). **b.** To visualise the effect of economic (Exps. 2-4) and time (Exp. 5) pressure on the speed-efficiency trade-off, the same plot was generated for each experimental condition (highest and lowest two levels grouped together). Individuals lost in speed what they gained in efficiency when sampling costs increased (Exp. 3), but were able to break this trade-off under time pressure (Exp. 5). In both panels, conditional plots were generated by sliding, for each subject and condition separately, 25% quantile bins of ISI and computing the mean α for each bin. The error bar shows $\pm$ SEM. Full statistical details are reported in Appendix Tables B.3-B.4.

as the reward available (remaining credits: $R_0 - \eta_s \cdot s$) minus the expected error penalty ($\eta_e \cdot EE$) minus a cumulative cognitive effort penalty ($\eta_c \cdot s$). The rate at which this cognitive effort penalty grows over successive samples (η_c) was posited to be a function of sampling speed ($1/ISI$) and/or efficiency (α).

This was formalised quantitatively using the following model:

$$EU_s(ISI, \alpha, t_{max}) = EU_{s-1} + p(s|ISI, t_{max}) \cdot [w_e \cdot \eta_e \cdot (1 - \alpha) \cdot (EE_{s-1} - E\hat{E}_\infty) - w_s \cdot \eta_s^{1+\gamma \cdot s} - \eta_c(ISI, \alpha)]$$

Previous EU + Probability of acquiring the sample given the current time

$$\cdot [\text{Expected information benefit} - \text{Sampling cost} - \text{Cognitive effort cost}] \quad (2.6)$$

where w_e and w_s are subjective weights quantifying the contribution of the expected information benefits and sampling cost to the EU , γ is a power term introducing a non-linear transformation of the sampling cost over successive samples, and $\eta_c(ISI, \alpha)$ is a cognitive effort cost function. The information gathering asymptotic limit, $E\hat{E}_\infty$, was estimated for each individual by fitting equation 2.5 beforehand. Thus, the modelling of active information sampling behaviour (ISI, α, s) took into account inter-individual differences in asymptotic information gathering performance.

Various cognitive effort cost functions were evaluated:

$$\begin{aligned}
 \eta_c(ISI, \alpha) &= 0 \quad (\text{No cost}) \\
 \eta_c(ISI, \alpha) &= w_0 + w_{speed} \cdot \frac{1}{ISI} + w_\alpha \cdot \alpha \quad (\text{Linear}) \\
 \eta_c(ISI, \alpha) &= w_0 + w_{speed} \cdot \frac{1}{ISI^2} + w_\alpha \cdot \alpha^2 \quad (\text{Quadratic}) \\
 \eta_c(ISI, \alpha) &= A \cdot e^{w_0 + w_{speed} \cdot \frac{1}{ISI} + w_\alpha \cdot \alpha} \quad (\text{Exponential}) \\
 \eta_c(ISI, \alpha) &= \frac{A}{1 + e^{w_0 - w_{speed} \cdot \frac{1}{ISI} - w_\alpha \cdot \alpha}} \quad (\text{Sigmoid})
 \end{aligned} \tag{2.7}$$

where w_{speed} and w_α are subjective weights – estimated through the fitting procedure – quantifying the contribution of sampling speed and efficiency to the cognitive effort cost. All models included a free intercept w_0 . Logistic and exponential cost functions required the addition of an extra free scaling parameter, A .

The reference model (Model 1) included no cognitive cost. Because it is known that humans exhibit non-linear utility functions when deciding under uncertainty ([Kahneman and Tversky, 2013](#)), a second reference model (Model 2) was introduced to test whether the contribution of sampling cost to EU could increase or decrease non-linearly with successive sampling. This was achieved by assigning a power term γ to sampling cost.

For each of the linear, quadratic, exponential and sigmoid classes, three versions of the model were built: 1) only speed penalised ($w_\alpha = 0$), 2) only efficiency penalised ($w_{speed} = 0$), and 3) both speed and efficiency penalised. These different classes were evaluated in Models 3-14. The sampling cost power term, γ was never used in combination with a linear, quadratic, exponential, or logistic cognitive effort cost function to prevent over-fitting by overly complex models.

The likelihood function was obtained by applying a *softmax* function over the 3-dimensional space of EU (the EU is a function of ISI, α, s) for a given task

environment (combination of $R_0, \eta_s, \eta_e, t_{max}$), as follows:

$$p_s(stop|ISI, \alpha, t_{max}) = \frac{\exp(EU_s(ISI, \alpha, t_{max}))}{\sum_i \sum_a \sum_t^{t_{max}} \exp(EU_s(i, a, t))} \quad (2.8)$$

Model fitting involved finding, for each individual separately, the parameters that minimised the negative log-likelihood of observing the multivariate distribution of number of samples acquired (s , one value per trial), inter-sampling interval (ISI, averaged across samples within a trial to obtain one value per trial) and sampling efficiency (α , one value per trial). Note that sampling speed and efficiency were assumed to be stationary within a trial (i.e., one combination of $[s, ISI, \alpha]$ per trial). Although it is an approximation of actual human behaviour, this assumption was necessary to simplify the framework. Parameter optimisation was carried out in MATLAB (The MathWorks inc., version 2018a) using Bayesian Adaptive Direct Search (BADs ([Acerbi and Ma, 2017](#))), chosen for its high performance with non-smooth cost functions. Model fits were compared using Bayesian Information Criterion (BIC), which quantifies goodness of fit while penalising models for the number of free parameters to avoid over-fitting.

The results showed that models that included computational cost of effort or/and speed (Model 3-14) generally provided better explanatory power compared to reference models without these costs (Figure 2.8 a-b.). The winning model (Model 8) was the one that penalised for speed and efficiency using a quadratic cost function (Model 8 vs 1: $\delta BIC = -22.779$; Figure 2.8 a-b.). This thus confirms that sampling behaviour is influenced by cognitive costs assigned to speed and efficiency, and not limited to explicit economic costs.

To further validate that such parameters meaningfully capture a cognitive effort cost, participants were asked to indicate their fatigue levels on a visual analogue throughout the experiment session in Exp. 1b (Figure 2.1). Analysing this showed

that fatigue increased linearly over successive experimental blocks (LMM; Main effect of block on fatigue ratings: $t_{(1150)} = 4.16, p < 0.001$; Table B.6; Figure 2.8 c.). Crucially, the increase in fatigue levels correlated significantly with the cognitive cost individual incurred for efficiency ($\beta = 0.49, 95\% \text{ CI} = [0.17, 0.80]$, $t_{(43)} = 3.13, p = 0.0032$; Robust multiple linear regression controlling for w_0 , w_{speed} and experiment duration; Table B.7, Figure 2.8 d.). That is, participants who had the highest cognitive cost for efficiency experienced increased subjective fatigue by the end of the experiment. Thus, efficiency cost introduced in the model reflects an effortful process related to an independent subjective fatigue measure reported through the experiment.

2.4.6 Individuals suboptimally give-up reward for information

Participants sampling performance was evaluated with respect to optimal sampling behaviour to determine whether they tended to under- or over-sample (Figure 2.9.).

The score that participants obtained at the end of the active sampling phase was calculated as follows:

$$Score = R_0 - s.\eta_s - e.\eta_e \quad (2.9)$$

Where R_0 is initial credit reserve, s is number of samples acquired, e is localisation error (the distance in pixels between the centre of the hidden circle and the centre of the blue disc), and η_e is spatial error cost.

Using the above equation, it is possible to calculate the expected value of the decision to stop sampling at each sample s simply by replacing the localisation error e with EE .

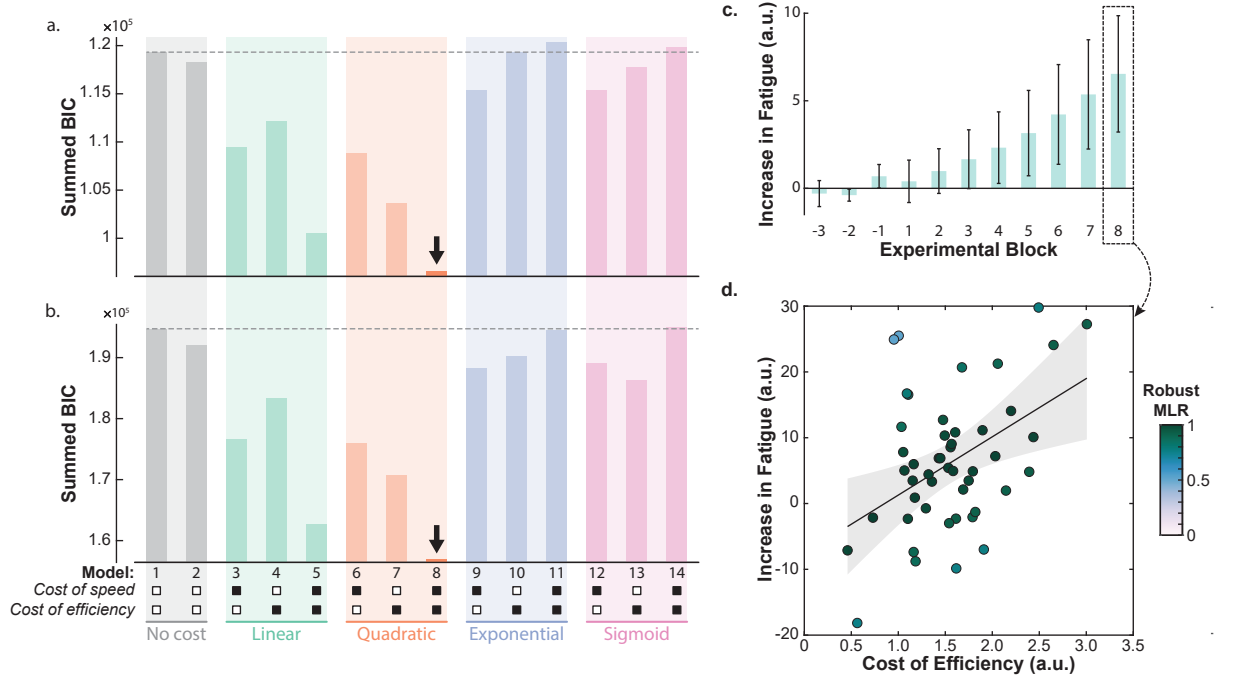


Figure 2.8: Computational cost of active sampling. **a–b.** A model with a quadratic cognitive effort cost best explains active information sampling behaviour in Exp. 1b (**a.**) and Exp. 2-5 (**b.**). Model 1 and 2 included no cognitive effort cost (Model 1: rational specification; Model 2: non-linear utility function; in grey) and were used as a reference. The other 12 models included a cognitive effort cost specified in terms of either speed (Models 3, 6, 9, 12), efficiency (Models 4, 7, 10, 13) or both (Models 5, 8, 11, 14). They differed with respect to the shape of the cognitive effort cost function used (green: linear; orange: quadratic; blue: exponential; pink: sigmoid). **c.** In Exp. 1b, participants rated how tired they felt throughout the session. The average rating during the exposure task (blocks -3 $\bar{A}$ -1) was used as baseline fatigue, which was subtracted from subsequent ratings for normalisation purposes. On average, fatigue increased linearly over successive blocks (Main effect of Block on Fatigue Ratings: $t_{(1150)} = 4.16$, $p < 0.001$). **d.** The cost of efficiency (w_α) was associated with the increase in fatigue observed as a result of the experimental session (standardised $\beta = 0.49$, 95% CI = [0.17, 0.80], $t_{(43)} = 3.13$, $p = 0.0032$; Robust multiple linear regression controlling for w_0 , w_{speed} and Experiment duration). The scatter plot shows the mean normalised fatigue rating in the last experimental block (y-axis) as a function of the cost of efficiency (w_α), controlling for task duration, w_0 , and w_{speed} ; task-duration (w_α and w_{speed} were ln-transformed for normalisation purposes). Colour shows the contribution of individual data points to the robust multiple linear regression (multivariate outliers are down-weighted).

$$EV(s) = R_0 - s.\eta_s - EE(s).\eta_e \quad (2.10)$$

Since participants paid a fixed cost for each additional sample (η_s) from the initial credit reserve (R_0), this put a limit on the number of samples they could obtain before the information benefit of the sample becomes unjustified by its cost (i.e., imposing a sample number at which the expected value EV is maximum). The optimal number of samples s^* is the number of samples at which EV reaches its maximum before it starts declining (i.e., sample benefit becomes lower than its cost). Deviation from the optimal number of samples is simply the difference between the number of samples participants obtain on the trial and s^* ($s - s^*$). Crucially, this formalisation takes into account differences in sampling efficiency within and between participants, as the utility of the samples acquired is not pre-defined and depends on where participants choose to touch the screen (i.e., on sampling efficiency). The optimal number of samples thus provides a more parsimonious account of how sampling behaviour is influenced by economic changes. It provides a useful measure against which to benchmark the willingness to give up rewards in exchange for information. For samples acquired beyond s^* , the cost of acquiring a new sample is objectively greater than its benefit. Conversely, for samples acquired before s^* , the benefit of acquiring a new sample is objectively larger than its cost.

Similar to previous studies that indicate that healthy people tend to collect more information than necessary (Juni et al., 2016; Phillips et al., 1966; Tversky and Edwards, 1966), participants in our experiments demonstrated this behaviour (Figure 2.9). Notably, this was evident in the task environment that required participants to tolerate uncertainty (high η_s , low η_e).

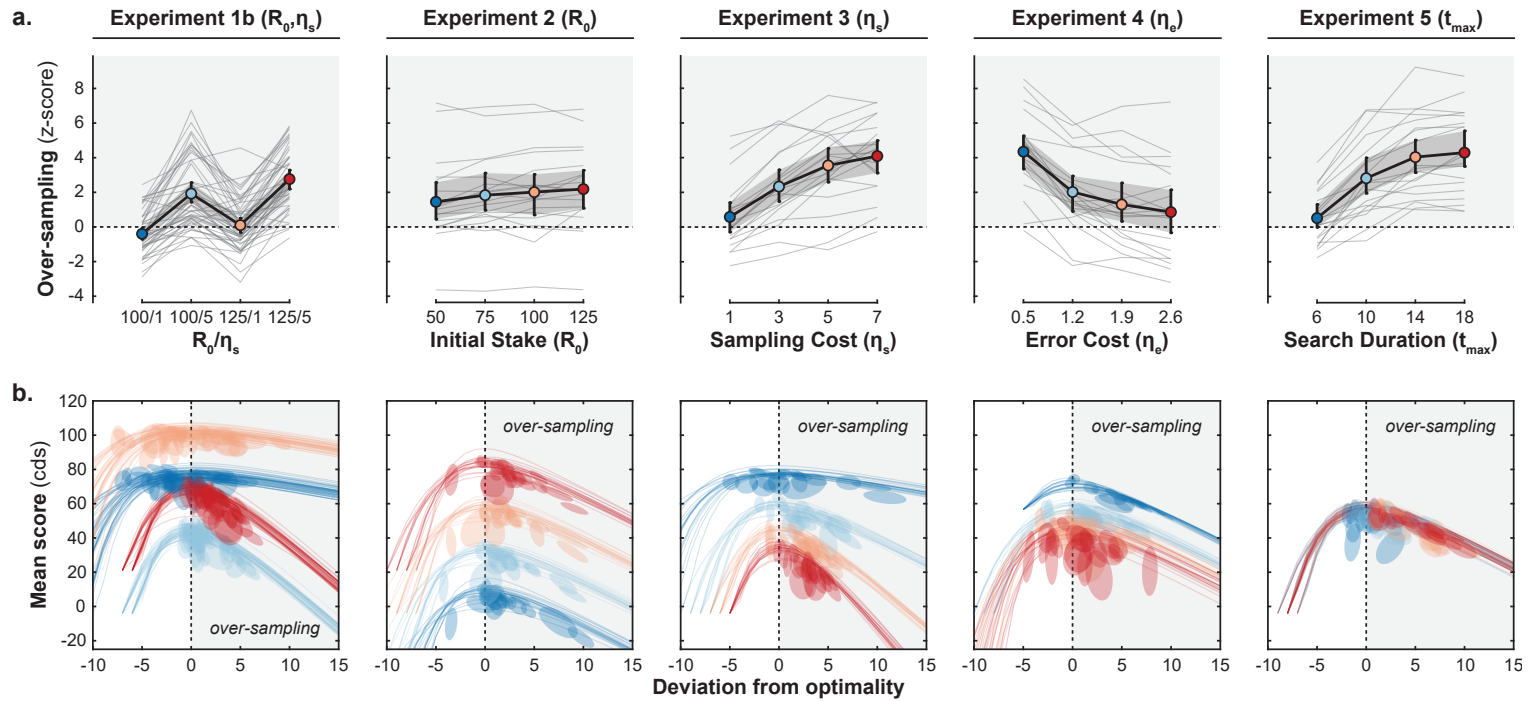


Figure 2.9: **Participants give up more reward for information.** **a.** People tended to over sample in most experimental conditions. This was evident in conditions requiring participants to tolerate uncertainty (high η_s , low η_e). Deviations from the optimal solution were quantified as a z-score: $(ss^*)/SD^*$ where s^* and SD^* are the optimal mean and standard deviation of the number of samples to acquire. Error bar: bootstrapped 95% CI. The light grey lines show slopes for each participant. The colours in the circles indicate the different conditions. These colours are used to differentiate between the same conditions in the lower panel. **b.** By definition, departures from optimal stopping behaviour had negative consequences on reward. Lines show the individual EV timecourses (same as a.), centred on their peaks (optimal number of samples to acquire). EV is calculated as each step of sampling as shown in equation 2.10. Ellipses contain 90% CI of the means for each participant. See also Figures 1.1 & 4.3 for similar illustrations explaining the calculation of sampling EV.

2.4.7 Relationship between active sampling, depression and intolerance to uncertainty

As discussed in Chapter 1, previous reports indicated that sampling behaviour in humans might be influenced by affective syndromes (e.g., depression) and motivation status (e.g., impulsivity) (Averbeck et al., 2013; Crockett et al., 2012; Djamshidian et al., 2011; Hildebrand-Saints and Weary, 1989; Kehagia et al., 2014). To investigate how such constructs relate to human active information sampling in this study, participants completed self-reported measures of depression, apathy, and impulsivity along with a questionnaire reflecting subjective intolerance to uncertainty.

Unsurprisingly, intolerance to uncertainty (IUS score) correlated positively with depression (BDI score) ($r = 0.43$ $p_{uncorr} < 0.01$, $p_{corr} = 0.03$; Figure 2.10 a.) – a relationship that has been previously reported in other investigations (Boswell et al., 2013; Carleton et al., 2012; Dar et al., 2017; Saulnier et al., 2019). No significant correlation between IUS and other questionnaires was found.

However, the task offers an objective and mechanistic account for investigating this relationship by examining behavioural markers of intolerance of uncertainty in active information gathering. Is suboptimal behaviour (over-sampling) observed in high-sampling-cost conditions related to depression and uncertainty intolerance? And how do these self-report measures correlate with indirect measures of sampling such as sampling speed and efficiency under these conditions?

To investigate these questions, robust multiple linear regression analyses were performed for three dependent variables: i) number of samples deviated from optimal ($s - s^*$), reflecting over-sampling and willingness to give reward in exchange for information, ii) inter-sampling interval (ISI), reflecting sampling speed, and iii)

information extraction rate (α), reflecting sampling efficiency. These three models were controlled for age, gender, fluid intelligence, apathy, and impulsivity.

The results showed that higher depression scores were associated with both over-sampling (Effect of BDI-II on $s - s^*$: $\beta = 0.10$, $t(41) = 2.21$, $p = 0.03$; Figure 2.10 b.) and increased sampling speed (Effect of BDI-II on ISI : $\beta = -0.016$, $t(41) = -2.14$, $p = 0.03$). The correlation between over-sampling and depression is also reflected in the average score participants achieved in these conditions, as higher scores of depression were associated with lower credit score (Effect of BDI-II on average score: $\beta = -0.52$, $t(41) = -3.16$, $p < 0.01$). There was no significant effect of any of the questionnaires (including depression) or demographic characteristics on sampling efficiency (all $p > 0.1$), suggesting that depression impairs valuation process rather than problem-solving abilities.

When IUS was included in the models, the relationship between depression and task measures ($s - s^*$ & ISI) became insignificant, suggesting that IUS might be mediating the association between depression and these measures. This hypothesis was tested using Bayesian mediation analysis, which showed that this mediation was not significant for any of the behavioural measures. Alternatively, this might indicate that depression and IUS share a common mechanism that is not mediated by each other.

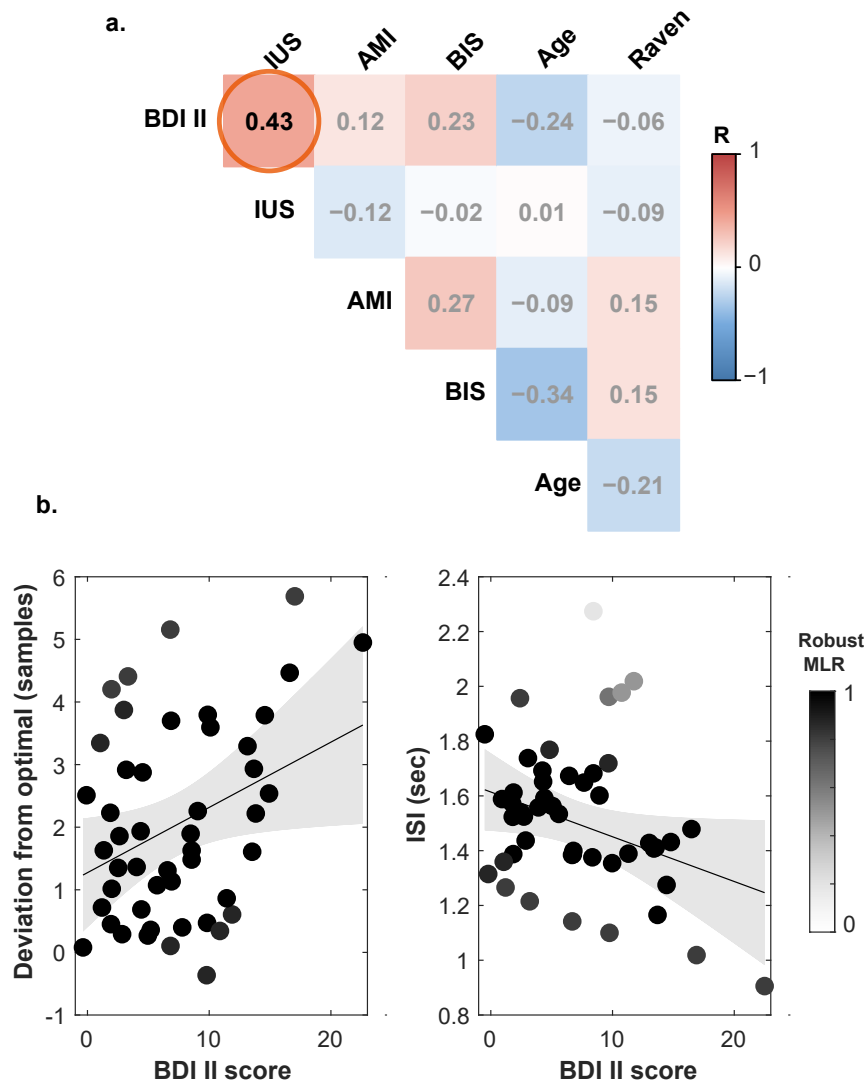


Figure 2.10: **Relationship between active sampling, depression and intolerance to uncertainty** **a.** A correlation plot showing Pearson's pairwise correlation between demographics measures. There is a significant positive correlation between depression (BDI) and intolerance to uncertainty (IUS) (circled box, $r = 0.43$, $p_{uncorr} < 0.01$, $p_{corr} = 0.03$). All other correlations were not significant following correction for multiple comparisons using Benferroni method. **b.** A robust multiple regression controlling for age, gender, apathy, impulsivity and fluid intelligence showed that over-sampling (deviation from optimal) and rapid sampling (shorter *ISI*) both correlated with depression severity. BDI: Beck's Depression Inventory II. IUS: Intolerance to uncertainty. AMI: Apathy motivation index. Raven: Raven's progressive matrices test. *ISI*: Inter-sampling interval.

2.5 Discussion

This chapter introduced *Circle Quest*, a novel behavioural paradigms designed to investigate *active* information gathering and decision making under uncertainty. The development of this task addresses limitations in previous literature focusing on how much information people gather without paying much attention to how information is sampled. By allowing participants to have agency over how, when and where to sample, it was possible to extract behavioural markers (e.g., speed and efficiency) and computational parameters (e.g., w_{speed} , w_{α}) that characterise active information gathering. This helps not only advance our understanding of goal-directed behaviour from an economic and optimisation perspective, but also provides objective behavioural measures related to uncertainty processing with clinical implications.

As discussed in Chapter 1, a key consideration when making decisions to acquire information to resolve uncertainty is whether the agent can afford these samples from an economic perspective (Battaglia and Schrater, 2007; Clark et al., 2006a; Gottlieb et al., 2013; Hauser et al., 2017a; Johnson and Busemeyer, 2010; Jones et al., 2019; Juni et al., 2016; Tversky and Edwards, 1966). The question that is asked at each step of the process is whether the benefit of acquiring samples outweighs its costs. But what costs and benefits do agents consider when engaged in the process? And how do they adjust their behaviour? Similar to previous reports, this study demonstrated that people adjust the extent of sampling according to the economics of the environment (Clark et al., 2006a; Jones et al., 2019; Juni et al., 2016). However, not only the number of acquired samples was sensitive to economic changes, but also the speed and efficiency with which information was collected. These agent-related parameters were found to impose additional computational costs that influence the utility of the samples being collected, and

thus play a crucial role in how people optimise their sampling to achieve the best economic outcomes.

In addition to economic constraints, people adjusted their sampling behaviour in response to time constraints. Under relatively relaxed time constraints, sampling behaviour was characterised by a speed efficiency trade-off, whereby faster sampling was associated with lower information gain. While economic costs did not alter this relationship, participants were able to break this trade-off under time pressure to sample faster without losing efficiency. This behavioural flexibility might be related to cognitive control mechanisms treating speed and efficiency as cognitively costly aspects of information gathering ([Boureau et al., 2015](#); [Shenhav et al., 2013](#)). Incorporating this notion into a standard information sampling model explained human behaviour better than simpler models. Further confirmation of the psychological validity of such a framework was provided by the significant relationship between subjective fatigue reports and the model-derived cost of efficiency. These results resonate with previous research investigating cognitive costs in different behavioural contexts explaining why consumers do not engage in advantageous but potentially cognitively effortful behaviours, for example, reading contracts or comparing products that differ in multiple dimensions ([Payne et al., 1993](#); [Stark and Choplin, 2009](#)).

However, the fact that humans can be pushed to be faster while maintaining their efficiency poses the question why not do this all the time? First, additional cognitive costs might indicate higher brain metabolic costs to achieve high performance behaviour, e.g., higher neural firing rate, optimization of brain network organization or more efficient information processing ([Bullmore and Sporns, 2012](#); [Hasenstaub et al., 2010](#); [Horan et al., 2019](#); [Kitzbichler et al., 2011](#); [Kostal and Kobayashi, 2015](#)). Alternatively, because other cognitive processes also depend on the same shared limited neural resources, prioritisation of one process might

have a negative impact on the others, resulting in an opportunity cost in terms of unprocessed task-unrelated stimuli (Boureau et al., 2015). In this context, sub-optimal sampling performance might leave room (capacity) for parallel processing of other potentially useful information. Finally, although it impinges on search efficiency, there might be indirect benefits to acquiring apparently uninformative, confirmatory samples (Jones and Sugden, 2001). Indeed, they provide timely checks of the reliability of the information source that can only be performed where the agent has perfect knowledge of what the outcome should be (that is, null entropy). Challenging what is already known might confer an ecological advantage in non-deterministic environments where the trustworthiness of past and future observations may drift over time.

Previous reports indicated that sampling behaviour might be related to affective functioning and motivation (Averbeck et al., 2013; Crockett et al., 2012; Djamshidian et al., 2011; Hildebrand-Saints and Weary, 1989; Kehagia et al., 2014). This might be related to deficits in valuation and reward processing, e.g., lower sensitivity to reward or sampling costs in impulsivity (Averbeck et al., 2013), or problems with processing uncertainty as assumed in affective disorders (Bishop and Gagne, 2018; Dar et al., 2017; Dugas, 1997; Freeston et al., 1994; Hildebrand-Saints and Weary, 1989). However, such mechanisms are not clearly delineated for these different disorders, and some syndromes (e.g., apathy) lack similar investigations. The results in this chapter indicate that depression might be a key aspect regulating human information sampling, with increased sensitivity to uncertainty indexed by faster and more extensive sampling being related to higher depression scores. Crucially, motivational deficits (apathy and impulsivity) and intelligence were not related to this effect, indicating a unique correlation between affective dysfunction and deficits in active information sampling and uncertainty processing. This was further supported by a significant correlation between

depression and subjective reports of intolerance to uncertainty.

The paradigm and model used in this study have at least three main limitations. First, the task relies heavily on motor performance, both to sample the search space and to produce a response at the end of every trial. Inter-individual differences in motor abilities may affect performance in ways that are not (or wrongly) captured by the model ([Carland et al., 2019](#); [Cisek and Kalaska, 2010](#); [Morel et al., 2017](#); [Pierrieau et al., 2021](#); [Rangel and Hare, 2010](#); [Scott, 2012](#)). Although this source of variance is likely to be negligible in the population of young healthy adults tested here, it may become a more significant confounding factor in certain age groups or clinical populations.

Second, the definition of uncertainty used throughout this work (expected error) relies on the assumption that people were able to use all of the information that was available on the visual display. However, it can be argued that the level of uncertainty depends not only on the information presented but also on agent's ability to use this information (that is, which solution they select within the solution space). Thus, for the same visual display, an individual who is well able to identify the best solution within the solution space should rightly expect a lower error than an individual who typically picks worse solutions. For simplification purposes, and because the expected error provided a good estimate of actual placement errors, this layer of complexity was omitted in the present work. Similarly, measuring subjective uncertainty based on self-reports in the passive task may not perfectly map to actual internal uncertainty ([Navajas et al., 2017](#); [Peters, 2022](#)). These confidence reports might carry other information such as perceptual uncertainty (e.g., meaning of perceived stimuli on the task), memory (e.g., remembering task instructions or previous estimations) and decisions (e.g., confidence in estimation).

Lastly, the model developed here assumes a constant sampling speed and efficiency within a given trial, and therefore cannot account for within-trial effects (for example, speeding up or slowing down as individuals get closer to the decision deadline). Considering within-trial effects may allow future studies to better characterize dynamic decision processes unfolding during exploration. More specifically, it may enable the segregation of two distinct decisions: (1) whether or not to sample and (2) where to sample.

In conclusion, the paradigm presented in this chapter offers a powerful way of examining active information gathering before decision-making under uncertainty. The results highlight the economic factors that influence this behaviour, including key computational costs attributed to speed and efficiency. This novel approach might provide crucial insights into affective regulation and its relationship to increased reactivity to uncertainty.

3 | Role of the hippocampus in decision making under uncertainty and for effort

3.1 Chapter summary

The role of the hippocampus in decision making is poorly understood. Given its role in prospection and future state value representation, I hypothesised that its contribution to decision making is specific to contexts that involve uncertainty (i.e., requiring evaluation of uncertain values). Nineteen people with autoimmune limbic encephalitis (ALE) – a condition known to focally affect the hippocampus – were tested on how they evaluate reward against uncertainty compared to evaluation of reward against another key attribute – physical effort. Across four experiments requiring participants to make trade-off between reward, uncertainty and effort, ALE patients demonstrated blunted sensitivity to reward and effort whenever uncertainty was considered, despite demonstrating intact uncertainty sensitivity. By contrast, valuation of these two attributes (reward and effort) was intact on uncertainty-free tasks. Further, sensitivity to changes in reward under uncertainty correlated with severity of hippocampal damage. Together, these findings provide evidence for a context-sensitive role of the hippocampus in value-based decision making, apparent specifically under conditions of uncertainty.

3.2 Introduction

Emerging evidence from animal studies suggests that the hippocampus might contribute to reward processing and valuation, with reports indicating several forms of reward representation in the hippocampal formation and its extended networks

(for a review, see [Sosa and Giocomo, 2021](#)). Theories and empirical reports investigating such a possible hippocampal role in humans have, until now, tied it to its well-known functions in memory, associative inference and imagination ([Biderman et al., 2020](#); [Palombo et al., 2015a](#)). Mechanistically, these investigations implicate the hippocampus in several processes including spreading of values between different contexts ([Gerraty et al., 2014](#); [Hassabis et al., 2007](#); [Wimmer and Shohamy, 2012](#)), constructing values from prior experiences ([Barron et al., 2013](#)), updating ([Gupta et al., 2009](#); [Gutbrod et al., 2006](#)) and stabilisation of preferences ([Enkavi et al., 2017](#)).

One evolving concept connecting these unique properties of the hippocampus proposes that it provides context against which reward is evaluated to support value-based decisions and preferences ([Bornstein and Norman, 2017](#); [Elliott Wimmer and Shohamy, 2011](#); [Gershman and Daw, 2017](#)). This process might be mediated by hippocampus-dependent mental time travel both into the past (sampling from memory) and the future (sampling from projected possible futures) to allocate these contexts. For example, ‘preplay’ signals – corresponding to reward delivery in yet-to-be-explored environments – and ‘look ahead’ signals – representing future trajectories leading to goals – have both been recorded in rodent hippocampus ([Freyja Ólafsdóttir et al., 2015](#); [Johnson and Redish, 2007](#); [Pfeiffer and Foster, 2013](#)). Similarly, in humans, fMRI hippocampal activity was observed when people make decisions that involve reward anticipation and future considerations ([Iigaya et al., 2020](#); [Palombo et al., 2019, 2015b](#)).

With this perspective, the hippocampus might be implicated in evaluation of rewards or goals when episodic thinking is critically involved (e.g., to process values of projected possible futures) ([Hunter and Daw, 2021](#)). Such scenarios involve probabilistic consideration of future value states (i.e., making decisions under uncertainty) ([Schacter et al., 2015](#); [Tversky and Kahneman, 1974](#)). By contrast, this

conceptualisation of hippocampal role in motivated behaviour suggests that contexts of deterministic nature (e.g., when evaluating reward against known physical effort costs) should be less influenced by hippocampus-related prospective computations. While previous studies demonstrated that the hippocampus might contribute to uncertainty processing and other forms of decisions requiring episodic thinking (e.g., inter-temporal decision making) ([Harrison et al., 2006](#); [Rigoli et al., 2019](#); [Strange et al., 2005](#); [Tobia et al., 2012](#)), hippocampal contribution to goal-directed decision making under uncertainty is still not fully established.

To test this possible uncertainty-sensitive role of the hippocampus and examine its contribution to motivated decision making, 19 people with autoimmune limbic encephalitis (ALE) – a rare condition known to affect the hippocampus – were recruited. Patients in the chronic phase of ALE characteristically have highly focal hippocampal atrophy ([Argyropoulos et al., 2019](#); [Finke et al., 2017](#); [Hanert et al., 2019](#); [Irani et al., 2013](#); [Kotsenas et al., 2014](#); [Malter et al., 2014a](#); [Miller et al., 2017](#); [Szots et al., 2014](#)), making them an ideal model of selective hippocampal dysfunction that is well suited to making inferences based on structure-function correlations ([Argyropoulos et al., 2019](#); [Miller et al., 2020](#); [Spanò et al., 2020a,b](#)). This is especially feasible in such an experimental group as the extent of hippocampal damage varies between ALE patients depending on the course of the illness and the interval between disease onset and treatment initiation ([Finke et al., 2017](#); [Malter et al., 2014b](#)).

Participants (patients and healthy matched controls) were tested in four experiments examining how people make decisions considering reward, uncertainty and/or physical effort attributes. In the first two experiments, a shorter modified version of *Circle Quest* paradigm validated in Chapter 2 was used: active and passive tasks (Exps. 1 & 2). The active version of the task examines how people give up reward to obtain information and reduce uncertainty before committing to

decisions. The passive version allows limited agency over uncertainty to examine how people make passive decisions on whether to accept or reject offers based on predetermined levels of reward and uncertainty. In Exp. 3, effort-based decision making was examined using a modified version of an extensively validated behavioural paradigm used in previous studies in healthy people and individuals with neurological disorders (Le Heron et al., 2018b; Saleh et al., 2021b). This paradigm has a similar design to the passive version of *Circle Quest* and examines how people make passive decision weighing rewards against physical effort. In Exp. 4, a third version of *Circle Quest* was used to investigate how people make passive decisions considering three attributes (reward, uncertainty and physical effort). In other words, participants were required to make decisions weighing the reward on offer given both physical effort cost *and* uncertainty in the environment.

The results from these studies converged to indicate that in ALE patients, despite intact sensitivity to uncertainty, the presence of uncertainty blunts sensitivity to other attributes (reward and effort cost). In the active version of the *Circle Quest* task (Exp. 1), patients, were less sensitive to cost of sampling when gathering information to support decisions under uncertain conditions, resulting in faster, extensive and wasteful sampling when cost of sampling and reward on offer increased. In the passive version of *Circle Quest* (Exp. 2), ALE patients were significantly less sensitive to changes in reward, and this effect correlated with lower sensitivity to cost observed in active sampling (Exp. 1). When assessed on the effort-based decision making task (Exp. 3), no significant difference was found between patients and controls when they made EBDM decisions *without uncertainty*, indicating intact valuation of reward and effort under conditions that do not feature uncertainty. By contrast, on the third version of *Circle Quest* (Exp. 4), patients were less sensitive to changes in effort and reward compared to controls, while their sensitivity to uncertainty was intact. Intact sensitivity to uncertainty

was observed across all versions of Circle Quest paradigm (Exp. 1, 2 & 4).

Taken together, the results indicate an uncertainty-sensitive role of the hippocampus in value-based decision making. The findings might represent an important step forward in understanding selective hippocampal contributions to goal-directed and motivated behaviour.

3.3 Methods

3.3.1 Participants

In Exp. 1–3, 19 individuals (age: $\mu = 60.00$, $SD = \pm 11.36$, 13 males) with a previously established diagnosis of ALE were tested along with 19 healthy age- and gender-matched controls (age: $\mu = 61.16$, $SD = \pm 11.71$, 13 males). In Exp. 4, eight ALE patients and 12 controls completed an additional follow-up task. All participants gave written consent to take part in the study and were offered monetary compensation for their time. The study was approved by the University of Oxford ethics committee (RAS ID: 248379, Ethics Approval Reference: 18/SC/0448). Tables 3.1 & 3.2 show the demographics and characteristics of the study groups. Due to a technical error during testing, two blocks (out of five) were missing for one patient in Exp. 2 (code 14 in Table 3.2). Analyses were conducted with and without this patient's data and there was no difference in the results or conclusions. After completing practice sessions, participants had to answer correctly all the questions of task comprehension quizzes in order to be eligible to do the tasks and continue the experiment.

3.3.2 External measures

All participants underwent a cognitive assessment using Addenbrooke's Cognitive Examination III (ACE III) (Hsieh et al., 2013a) and executive function assessment with digit span (DS). In addition, they completed self-report questionnaires of apathy (Apathy Motivation Index, AMI; Ang et al. 2017), depression (Beck Depression Inventory-II, BDI-II; Beck et al. 1996), fatigue (Fatigue Severity Scale, FSS; Krupp et al. 1989), and hedonic experience (Snaith-Hamilton Pleasure Scale, SHAPS; Snaith et al. 1995).

3.3.3 Procedure

The tasks were presented on a 17-inch touchscreen PC using MATLAB (The MathWorks inc., version 2018b) and Psychtoolbox (Brainard, 1997; Kleiner et al., 2007) version 3. Testing was done in a quiet room with an experimenter present at all times. Participants sat within reaching distance of the screen (~ 50 cm) and were instructed to use the index finger of their dominant hand to respond. The task environment was adjusted according to handedness (e.g., uncertainty rating on the side of the dominant hand in the Exps. 2 & 3).

3.3.4 Experimental paradigm – Exps. 1 & 2

A modified, shorter, version of *Circle Quest* task was used (described in detail in chapter 2; Figures 2.1 & 2.2). In Exp. 1, participants performed the active sampling version of the task designed to test active information gathering prior to committing to decisions. In Exp. 2, participants performed the passive choices/decisions version designed to test decision making under fixed, experimentally defined levels of uncertainty and reward. Participants were told that their goal in the two versions of the task was to maximise reward. All participants

performed a training task followed by the active task and then the passive task. The purpose of this order was to ensure that by the time participants performed the passive choices version of the task, they had extensive training and exposure to the task environment and scoring function through their interaction with the task during the active version. The average total duration of the testing session of Exps. 1 & 2 was approximately one hour (Average duration in minutes $\pm$ SD; training: 7.38 ± 2.96 , active sampling: 30.11 ± 5.20 , passive choices: 22.86 ± 1.48).

Training and exposure. As illustrated in Chapter 2, the task was explained to participants using an interactive tutorial in the presence of the experimenter. In this interactive tutorial, participants were simply required to localise a hidden purple circle on the screen. This circle had a fixed size on all trials (radius: 130 Px; area: 5.80% of the search space). Two purple circles of the same size were always present on the right and left sides of the screen as a visual reminder of the circle on quest. This served to limit the memory demands of the task. Clues about the location of the hidden circle could be obtained by touching the screen. If a purple dot appeared where they touched (radius: 4 Px), this indicated that the location was located inside the hidden circle. Alternatively, if a white dot appeared where they touched, the location was situated outside the hidden circle. After completing the search, they were asked to move a blue disc of the same size as the hidden circle on top of where they thought the hidden circle was located, based on the information they gathered. During this tutorial, participants performed five trials with no constraints on the number of samples they could acquire and without any sampling penalty. They were also encouraged to ask the experimenter in case they had any questions.

Following this short introduction to the game, participants performed a training task that included 20 trials. The goal of this task was to: (1) practice localising the hidden circle for various levels of uncertainty, and (2) expose participants to the

scoring function. On each trial of this training task, a configuration of eight dots (four purple and four white) was displayed on the screen, and participants were required to move the blue disc on top of where they thought the hidden circle was located. Different configurations mapped onto different levels of uncertainty. For example, displays with spaced out purple dots represented lower levels of uncertainty than displays in which the purple dots were clustered more closely. The former configuration had a lower number of possible circle placements that were compatible with the dots displayed on the screen (purple dots should be inside the hidden circle), and consequently, the expected localisation error (EE , a quantitative measure of uncertainty) for such a configuration was smaller. EE was calculated as the probability-weighted average of all possible errors a participant could incur by placing the blue disc at the best possible location (centroid of posterior belief) (Figure 2.3 a-b., for more details see Chapter 2). The two circles on the right and left side of the search space contained the reward at stake which participants could obtain if they managed to perfectly localise the hidden circle. After placing the blue disc, the location of the hidden circle was revealed and the score they obtained for this localisation appeared. The score was calculated as the reward at stake minus the localisation error penalty upon placing the blue disc ($\eta_e \cdot e$), where e is the distance between the centre of the blue disc and the centre of the hidden circle in pixels. η_e is the spatial error cost per pixel which was constant and equal to 1.2 credits/pixel.

Active sampling task. In the active version of the task (Figure 2.1), participants could reduce their uncertainty about the location of the hidden circle by actively sampling the search space, i.e., touching the screen to obtain information. Similar to the training tutorial, this provided them with binary information about the location of that sample in relation to the hidden circle. If where they touched was inside the hidden circle, the sample location was indicated by a purple dot. Other-

wise, the sample location was a white dot. At the beginning of every trial, participants had 18 seconds to sample whenever, wherever, and however they wanted. After this, they were required to move the blue disc to where they thought the hidden circle was located in order to collect monetary credits. Participants started each trial with an initial reward reserve, R_0 , from which they lost credits each time they acquired a new sample depending on the cost of sampling, η_s , on that trial. There were two levels of initial reward (R_0 : low = 95 credits and high = 130 credits) and two levels of sampling cost (η_s : low = -1 credit/sample and high = -5 credits/sample) giving rise to four conditions in four blocks that were counterbalanced between participants. Each condition included 15 trials. All calculations (e.g., expected error, score, expected value, optimal solutions, etc.) were the same as in chapter 2.

Passive choices task. Each trial of the passive version of the task had two parts (Figure 2.2). First, participants saw a configuration of dots on the screen (four purple dots and four white dots) that mapped onto an experimentally defined level of uncertainty, EE . Based on this configuration, they were required to indicate how confident they were about the location of the hidden circle. Participants could do this by touching on a rating scale on the side of the screen ranging between zero and 100. A zero on this scale meant that they had no idea where the hidden circle was, and 100 meant that the participant knew exactly where it was. Subjective uncertainty was simply calculated by sign-flipping these confidence estimates.

Next, once participants reported their confidence, the reward on offer appeared. They then were required to make Yes/No decisions based on whether they wished to place the blue disc given the reward on offer and the uncertainty they have just rated. There were four reward levels (R : 40, 65, 90, 115 credits) and five uncertainty levels (EE : 16.3-24.4, 27.1-38.9, 57.5-58.9, 73.33-74.18, 91.9-93.3 pixels). Participants were told that ten of the offers they accepted would be randomly

selected at the end of the experiment, and they would be required to play them (i.e., localise the hidden circle using the blue disc). The credits they collected on these ten trials determined the monetary rewards they won in this version of the task. The score was calculated in the same way as the training task.

3.3.5 Experimental paradigm – Exp. 3

A modified version of a well-validated effort-based decision making task was used (Aridan et al., 2019; Bonnelle et al., 2016, 2015; Chong et al., 2016a; Le Heron et al., 2018c; Saleh et al., 2021b). This task had a similar design as *Circle Quest* passive choices task (Exp. 2), however, instead of uncertainty as the discounting attribute, participants evaluated reward against physical effort (Figure 3.1). Reward in the task was represented as apples on trees and effort levels were indicated by bars on the trunk of the trees. The higher the effort bar, the more effort participants needed to exert in order to obtain the apples. Effort in the task was exerted by squeezing a hand-held dynamometer. Participants were first asked to squeeze the handle as hard as they could in order to measure their maximal voluntary contraction (MVC). Crucially, the effort handle was calibrated based on MVC for each participant. Participants were then familiarised with the different effort levels that they would encounter when making decisions. These effort levels corresponded to 16, 32, 48, 64 and 80% of MVC. Each effort level was experienced twice before moving to the decisions phase of the task where participants had to evaluate the worthiness of reward (apples) against these effort levels. There were five reward levels corresponding to different numbers of apples (1, 4, 7, 10, and 13). Participants could indicate whether they would like to accept or reject the offer on the screen by pressing either the left or right arrow on the keyboard to select either "Yes" or "No", which were displayed on the sides of the screen. The positions of "Yes" and "No" changed randomly between trials. Participants

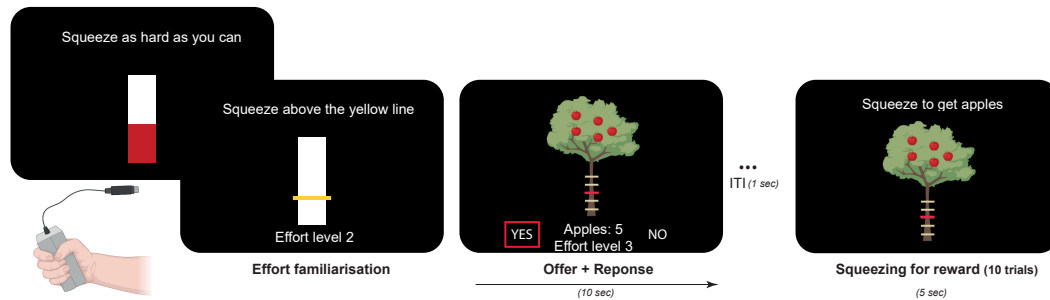


Figure 3.1: **Exp. 3 – Effort-based decision making task.** The task was similar in design to *Circle Quest* passive choices task. First, calibration of the hand-held dynamometer was done based on each participant’s maximum voluntary contraction. Participants were then familiarised with the effort levels they would encounter in the task by asking them to squeeze the handle up to the effort level indicated by the yellow line: the higher the line the more effort they needed to exert. They did this twice for each effort level. Next, participants made decisions indicating whether the reward (apples) on offer is worth the effort assigned to it. They were told that at the end of the experiment, 10 of their decisions would be selected randomly and that they would have to play them in order to obtain the apples.

were told that 10 of their decisions would be randomly selected at the end of the experiment and that they would have to play them (i.e., squeeze the effort handle to obtain reward). Before making their decisions, participants had the opportunity to perform five practice decisions.

3.3.6 Experimental paradigm – Exp. 4

In Exp. 4, a novel version of *Circle Quest* (Exps. 1 & 2) was designed to investigate effort-based decision making under uncertainty. Participants were familiarised with uncertainty, reward and effort cues using the same training as in Exps. 1–3 (Figure 3.2 a-c.). After training, they were required to respond (accept or reject) offers that had three attributes: reward, uncertainty and effort (Figure 3.2 d.). Reward was presented as credits that participants could win if they managed to complete two steps: i) achieve the required level of effort (as in Exp. 3)



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and ii) find the location of the hidden circle without errors (as in Exp. 1 & 2). The blue disc used to localise the hidden circle appeared only when the required level of effort was achieved. If effort level was met, participants then could win credits depending on how far their localisation using the blue disc was from the true location of the hidden purple circle. There were four levels of reward (R : 40, 65, 90, 115 credits; same as in Exp. 2), five levels of effort (16, 32, 48, 64 and 0.8% of MVC; same as in Exp. 3) and two levels of uncertainty (present and absent). Absence of uncertainty was indicated by showing the true location of the hidden circle on the screen when offers were presented. On trials in which uncertainty was present, it corresponded to the mid-range of expected error (EE) used in Exp. 2 (EE : 31.8-73.95 pixels). Additional catch trials (20 in total) were added to increase the range of uncertainty during confidence rating (EE : 13.2 - 93.3) to fully capture subjective estimation of uncertainty as in Exp. 2. Unlike Exp. 2, confidence ratings were blocked and reported during the training phase rather than prior to each decision. This was done to ensure that offers with and without uncertainty were experimentally matched during the decision phase. The decision phase involved 40 different trial types (four reward levels $\times$ five effort levels $\times$ two uncertainty levels), each was repeated five times over ten blocks (200 trials in total). Participants were told that at the end of the decision phase, 20 trials (ten with uncertainty and ten without) will be randomly selected for them to play. Performance on these trials decided the reward that participants eventually won.

3.3.7 Statistical analyses of behavioural data

Statistical analyses and modelling were done in MATLAB R2019a or R version 4.0.2. Generalised mixed effects models and robust regression models were fitted using *fitglm* and *fitlm* functions in MATLAB, respectively. Bayesian mixed effects models was performed using *Stan* computational framework (<http://mc-stan.org/>)

accessed using *brms* in R (Bürkner, 2017). Bayes factors (BF) were calculated using *brms hypothesis* function. For group comparisons, student t-test was used if parametric assumptions were fulfilled and Wilcoxon rank sum test if not. Full description of mixed effects models used and statistical results are reported in Chapter Appendix.

3.3.8 Magnetic Resonance data acquisition

MRI scans were obtained at Acute Vascular Imaging Centre (AVIC) at John Radcliff Hospital (Oxford) using SIEMENS Verio 3T scanner. High-resolution T1-weighted structural MR images (MPRAGE; 208 sagittal slices of 1 mm thickness, voxel size = 1 mm isotropic, TR/TE = 2000/1.94 ms; flip angle = 8°, FOV read = 256, iPAT = 2, prescan-normalise) and T2 weighted fluid-attenuated inversion recovery (FLAIR) images (192 sagittal slices of 1.05 mm thickness, voxel size = 1×1×1.1, TR/TE = 5000/397 ms; FOV read = 256; iPAT = 2, partial Fourier = 7/8, fat saturation, prescan-normalise) were acquired. Four patients and two controls were not MRI compatible or did not consent to be scanned, therefore, imaging data were acquired for 15/19 patients and 17/19 controls.

3.3.9 Magnetic Resonance data analysis

Voxel-Based Morphometry (VBM) was performed to compare gray matter volumes between patients and controls using FSL-VBM (Douaud et al. 2007, , <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM>). An optimised VBM protocol (Good et al., 2001) was performed using FSL version 6.0 (Smith et al., 2004). Non-linear registration was used to register structural brain-extracted and grey matter-segmented images to the MNI 152 standard space. A study-specific grey matter template was then created using the resulting images. To avoid having a biased template, 15 controls were randomly selected to match the 15 patients

who had MRI scans. Non-linear registration was used to register all native grey matter images to the study-specific template and this was modulated using the Jacobian of the warp field. These modulated grey matter images were then smoothed with an isotropic Gaussian kernel with a sigma of 4 mm. Finally, non-parametric testing using *randomise* with 5000 permutations and corrected for multiple comparisons across space was used to detect voxel-wise differences in grey matter volumes between patients and controls.

Whole hippocampal volumes were extracted using T1 and T2 imaging in Freesurfer version 7.1 (<http://surfer.nmr.mgh.harvard.edu/>). The automated standard segmentation protocol was used. Hippocampal volumes were adjusted for intracranial volume (*ICV*) using the following equation (Jack et al., 1998; Voevodskaya, 2014):

$$V_{adj} = V - \beta \times (ICV - \overline{ICV}) \quad (3.1)$$

where V_{adj} and V are the adjusted and observed volumes respectively, β is the slope of the relationship between *ICV* and V in a larger sample of healthy controls with similar demographics ($N = 31$, including the study sample and participants recruited for a different study), and $\overline{ICV}$ is the mean intracranial volume in this control sample. Amygdala volumes were also extracted and used as a control comparison region (Figure 3.9).

Count (M/F) Variable	Controls 19 (13/6)		Patients 19 (13/6)		p-value
	Mean	SD	Mean	SD	
Age	61.16	11.71	60.00	11.36	0.76
ACE-III	97.52	2.03	93.42	5.64	0.005
DS	18.05	3.49	19.79	5.00	0.21
AMI	1.18	0.40	1.25	0.49	0.65
FSS	3.06	1.12	3.36	1.86	0.59
BDI-II	5.9	5.26	10.95	10.15	0.06
SHAPS	18.84	4.56	21.58	4.85	0.08
Lt. Hipp Volume*	3495.06	199.41	3357.71	722.71	0.457
Rt. Hipp Volume*	3662.99	167.06	3288.50	675.58	0.034

Table 3.1: **Demographics.** ACE-III: Addenbrooke’s Cognitive Examination. DS: Digit Span. AMI: Apathy Motivation Index. FSS: Fatigue Severity Scale. BDI-II: Beck Depression Inventory. SHAPS: Snaith-Hamilton Pleasure Scale. Hipp: Adjusted Hippocampal Volumes.* 15 patients and 17 controls.

3.4 Results

3.4.1 Demographics

Demographics and group characteristics are summarised in Tables 3.1 and 3.2. Similar to previous reports, ALE patients had lower cognitive scores on Addenbrooke’s cognitive examination (controls: $\mu = 97.52$, $SD = \pm 2.03$, ALE: $\mu = 93.42$, $SD = \pm 5.64$, $t(36) = 2.99$, $95\%CI = [1.31, 6.89]$, $p < 0.01$). These cognitive differences were seen mainly in two domains of ACE-III: memory (controls: $\mu = 24.79$, $SD = \pm 1.36$, ALE: $\mu = 23.16$, $SD = \pm 2.54$, $z = 2.19$, $p = 0.02$) and fluency (controls: $\mu = 13.32$, $SD = \pm 1.36$, ALE: $\mu = 11.21$, $SD = \pm 2.69$, $z = 2.81$, $p < 0.01$). The other three domain including language, visuospatial abilities and attention were not significantly different between the two groups. There was no significant difference in measures of executive function (DS), apathy (AMI), fatigue (FSS), depression (BDI-II) or hedonic experience (SHAPS).

Code	Age	Gender	Abs	Lt. Hipp.		Rt. Hipp.		Years Since Diagnosis
				Volume	Percentile	Volume	Percentile	
1	53	F	LGI1	3559.64	29	3547.33	21	3.38
2	47	F	LGI1	3157.67	6 ^c	2717.64	<2.5 ^c	3.44
3 ^a	59	F	LGI1	2332.83	<2.5	2255.53	<2.5	3.49
4	63	F	LGI1	2860.65	<2.5	3744.13	43	2.59
5	72	F	LGI1	3170.72	17 ^c	2495.43	<2.5 ^c	7.67
6 ^a	64	M	LGI1	-	-	-	-	4.66
7 ^a	55	M	LGI1	4835.20	97	4125.12	46	2.56
8 ^a	53	M	LGI1	3663.60	19	3754.24	17	2.36
9 ^a	66	M	LGI1	4109.11	72	4341.71	80	1.18
10	65	M	LGI1	3488.01	18	3379.20	9	3.27
11	72	M	LGI1	2973.83	5	2905.04	3	1.82
12 ^a	26	M	LGI1	-	-	-	-	0.96
13	68	M	CASPR2	3050.27	4	3364.09	10	1.03
14	77	M	CASPR2	-	-	-	-	10.52
15	65	M	CASPR2	3455.68	16	3411.77	10	5.29
16	67	M	CASPR2	4118.84	74	3942.82	48	4.30
17 ^a	58	F	LGI1/CASPR2	3670.25	41	3073.41	4	3.26
18 ^a	58	M	LGI1/CASPR2	-	-	-	-	7.16
19	52	M	Seronegative	2370.64	<2.5 ^c	2752.98	<2.5 ^c	1.99

Table 3.2: **Patients characteristics.** Abs: Autoantibodies. Lt. Hipp.: Left Hippocampus. Rt. Hipp.: Right Hippocampus. Percentile is determined by plotting raw hippocampal volumes against normative brain volumes from UK biobank data (Nobis et al., 2019). ^a: Participants tested in Exp. 4. ^c: Describes percentiles outside the age range of the UK biobank normograms. Percentiles according to the closest age value within the UK biobank range were used instead.

3.4.2 Exp. 1 – Active sampling

3.4.2.1 Reduced sensitivity to changes in information cost in ALE patients when gathering information to reduce uncertainty.

Participants in both groups acquired samples to reduce uncertainty. As in healthy young people (Chapter 2), reduction in uncertainty followed an exponential decay as a function of the number of samples acquired, indicating purposeful sampling abiding with task rules (Figure 3.3 a.). Both patients and healthy controls behaved rationally, sampling less when acquiring samples was more expensive (Main effect of η_s on the number of samples acquired: $\beta = -0.11$, $t_{2272} = -6.25$, $p < 0.0001$; Table B.8), and not responding to changes in initial reward reserve (Main effect of R_0 on the number of samples acquired: $\beta = 0.023$, $t_{2272} = 1.29$, $p = 0.20$).

Furthermore, there was a significant interaction between the effect of sampling cost and the effect of initial reward reserve ($\eta_s \times R_0$: $\beta = -0.030$, $t_{2272} = -2.07$, $p = 0.038$; Figure 3.3 b., Table B.8), indicating that higher initial reward reserves blunted the aversive effect of the sampling cost on the number of samples acquired. This interaction effect was significantly greater in patients than controls ($ALE \times \eta_s \times R_0$: $\beta = 0.054$, $t_{2272} = 2.68$, $p < 0.01$). In other words, patients were *less sensitive to changes in sampling cost* when initial reward reserve was high. They acquired more samples when sampling cost was high but initial reward reserve was also high (Group difference in the number of samples acquired in the high R_0 high η_s condition: $z = -2.2484$, $p = 0.024$).

Next, patients' and controls' performance in the active task was evaluated with regard to optimal sampling behaviour to determine whether they tended to under- or over-sample (Figure 3.3 c-d.). Optimal sampling refers to the number of sam-

ples, s^* , that maximises expected return, given the current cost-benefit structure (R_0, η_s, η_e) and search efficiency (i.e., the rate at which participants reduce uncertainty from one sample to the next, parameterised as the information extraction rate, α ; see *Methods* in Chapter 2). In the *Circle Quest* paradigm, uncertainty decreases exponentially over successive samples, and for each participant, sampling efficiency captures how steep this decline was (Figure 3.3 a.).

The optimal number of samples – which takes into consideration such differences in sample utility – thus provides a more parsimonious account of how sampling behaviour is influenced by economic changes. It provides a useful measure against which to benchmark *the willingness to give up rewards in exchange for information*. For samples acquired beyond s^* , the cost of acquiring a new sample is objectively larger than its benefit. Conversely, for samples acquired before s^* , the benefit of acquiring a new sample is objectively larger than its cost (Figure 3.3 c.).

Both ALE patients and healthy controls over-sampled when sampling cost was high (Deviation from optimal; ALE: $\beta = 3.93$, $t_{1138} = 4.32$, $p < 0.0001$; Controls: $\beta = 1.93$, $t_{1138} = 3.485$, $p < 0.001$, see also Table B.10), but patients over-sampled to a greater extent than controls when the initial reward reserve was high in these conditions ($z = 2.267$, $p = 0.023$; Figure 3.3 d.). When sampling cost was low, performance of ALE patients approached optimal behaviour ($\beta = -0.94$, $t_{1138} = -0.76$, $p = 0.44$) while controls under-sampled ($\beta = -1.78$, $t_{1138} = -2.59$, $p < 0.01$). However, there was no significant difference between the two groups ($t(36) = 0.579$, $p = 0.56$).

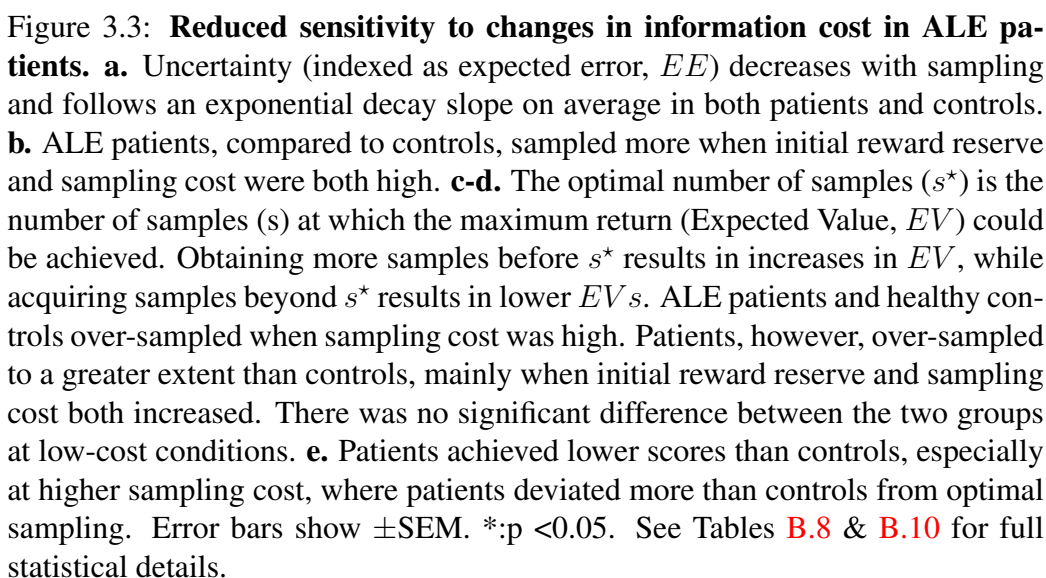
These findings suggest that ALE patients' sampling behaviour demonstrates, at least partially, blunted sensitivity to reward when trading it for information to reduce uncertainty, leading to over-sampling (i.e., giving up more reward than needed in exchange for information). Lower weights were assigned to change in

sampling cost by ALE, and this was maximally exposed when they had more reward to give in the high initial reserve condition (see additional analyses section below for a computational model characterising this effect). This sampling behaviour had consequences in terms of total reward received as patients' scores suffered to a greater extent than controls' when the sampling cost increased ($ALE \times \eta_s : \beta = -3.66, t_{2272} = -2.00, p = 0.046$; Figure 3.3 e., Table B.8). I explore the drivers of this sampling behaviour in Exp. 2 to experimentally ascertain if increased sampling indeed reflects reduced sensitivity to changes in reward rather than increased sensitivity to uncertainty.

3.4.2.2 ALE patients commit to decisions at similar uncertainty levels as controls.

Despite sampling more, ALE patients did not reach lower final uncertainty levels compared to controls (Main effect of disease (ALE) on EE at the end of the sampling phase: $\beta = -0.683, t_{2272} = -0.23, p = 0.82$; Figure 3.4 a.). This did not differ across different conditions (Figure A.1, see Table B.8 for full statistical details). Two explanations can account for this observation.

First, since uncertainty decreases exponentially with successive sampling in the task, samples obtained towards the end of the search (i.e., when the uncertainty is already low) carry little information as the remaining uncertainty to be reduced is small (Figure 3.3 a.). As discussed in the previous section, this imposes an optimal stopping point beyond which benefits of sampling more are negligible compared to the costs incurred. When hippocampal patients sample more than controls, the extra samples acquired tend to occur beyond this optimal stopping point, and thus the impact of these additional samples on reducing uncertainty is limited. In fact, in the experimental condition in which patients over-sampled the most (high R_0 / high η_s), the actual localisation error was not significantly dif-



ferent between ALE patients and controls (Difference in mean localisation error: $z = -0.81$, $p = 0.38$; Figure 3.4c, Table B.8). This indicates that the extra samples acquired did not help patients make better localisation judgments (i.e., they provided no extra instrumental value). Put simply, patients wasted resources on uninformative samples at the end of their search when they over-sampled.

Second, ALE patients tended to over-prioritise sampling speed over efficiency in comparison to healthy controls who adopted a slower but more efficient strategy. As discussed in Chapter 2, sampling behaviour in the active task is constrained by a speed-efficiency trade-off, with people needing more time to compute where the most informative (better quality) samples are to be found. This trade-off was apparent in the positive relationship between inter-sampling interval (*ISI*) and sampling efficiency (α) in both controls (Main effect of *ISI* on α : $\beta = 0.13$, $t_{1138} = 2.96$, $p < 0.01$) and ALE patients (Main effect of *ISI* on α : $\beta = 0.26$, $t_{1138} = 4.82$, $p < 0.0001$; Table B.11, Figure 3.4 d.). In the experimental condition in which ALE patients over-sampled the most (high R_0 / high η_s), patients sampled significantly faster (Difference in mean *ISI*: $z = -2.53$, $p = 0.01$), which might have come at the cost of a lower efficiency (Main effect of disease (ALE) on α in the condition: $\beta = -0.026$, $t_{566} = -1.98$, $p = 0.048$; Difference in mean α : $t(36) = -1.52$, $p = 0.06$, one-tailed; Table B.9). Put simply, in order to obtain more samples, hippocampal patients sampled at a faster rate than controls but made poorer choices regarding the pieces of evidence to collect, which might have contributed to reaching comparable levels of uncertainty despite having collected more individual samples.

Collectively, the results from the active sampling experiment suggest that patients put less emphasis on reward during active information gathering (indexed by lower sensitivity to sampling cost when reward reserve was high and over-sampling), while maintaining sensitivity to uncertainty as they made final deci-

sions at the same level of uncertainty as controls.

3.4.3 Exp. 2 – Passive decision-making under uncertainty

The passive task paradigm offers a reliable mechanistic delineation between response to reward and uncertainty when making value-based decisions. This helps to answer whether over-sampling in ALE patients is indeed related to lower sensitivity to changes in reward, rather than increased sensitivity to uncertainty.

3.4.3.1 ALE patients are less sensitive to changes in reward under uncertainty.

A generalised logistic mixed effects model (L_gMM) with maximal randomness was used to analyse the choice data (Table B.12). As expected, participants (patients and controls) adjusted their decisions rationally according to offer attributes: accepting more offers with higher rewards and lower uncertainty (Main effect of reward on offer acceptance: $\beta = 1.41$, $t_{3748} = 7.16$, $p < 0.001$; Main effect of uncertainty on offer acceptance: $\beta = -2.73$, $t_{3748} = -8.72$, $p < 0.001$; Figure 3.5 a.). Patients and controls did not significantly differ in the time they took to accept ($z = 3.79$, $p = 0.70$) or reject offers ($t(36) = -0.34$, $p = 0.73$). However, they differed with regard to the influence reward exerted on the decision to accept the offer. Compared to controls, ALE patients were overall less influenced by reward on offer (Disease (ALE) $\times$ Reward: $\beta = -0.983$, $t_{3748} = -3.58$, $p < 0.001$). By contrast, their sensitivity to uncertainty was not significantly different from controls' (Disease (ALE) $\times$ EE: $\beta = 0.336$, $t_{3748} = 0.76$, $p = 0.45$). Taken together, this means that patients accepted fewer of the high-value offers (high-reward and low-uncertainty) ($z = -2.14$, $p = 0.03$ & $z = -2.93$, $p < 0.01$, for the two offers of the highest value; Figure 3.5 b-c.).

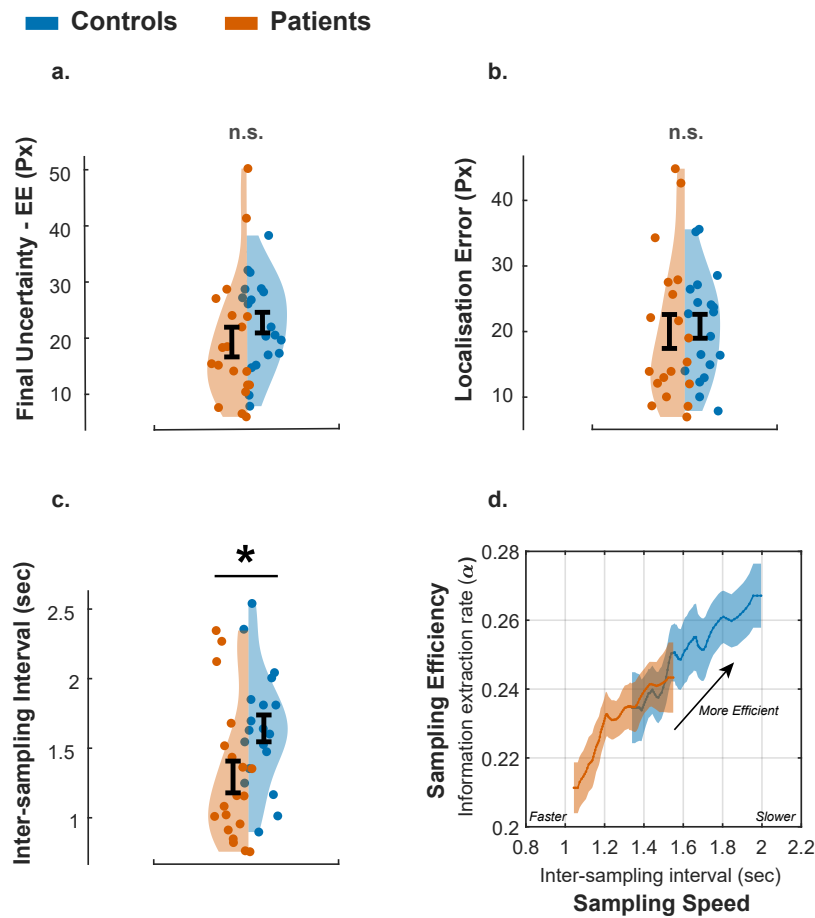


Figure 3.4: **Active sampling – ALE patients commit to decisions at similar uncertainty levels as controls.** **a.** Final uncertainty is the expected error (EE) in pixels (Px) that a participant is likely to obtain at the end of their search. In the experimental condition where hippocampal patients over-sampled more than controls, there was no significant difference between patients and controls in this measure. **b.** Similarly, the actual error that participants obtained upon localising the circle (distance to hidden circle in pixels) was not significantly different between patients and controls. These two results indicate that ALE patients wasted monetary resources on samples with limited utility (i.e., over-sampled). **c.** In the same condition, patients gathered information at a significantly faster rate than controls. **d.** Sampling behaviour in ALE patients and controls was characterised by a speed-efficiency trade-off whereby faster sampling rates (shorter ISI) were associated with lower sampling efficiency (smaller α). The figure shows this trade-off for the same condition in which patients over-sampled more than controls, demonstrating that ALE patients were also both faster and less efficient than controls. Error bars show $\pm$ SEM. * : $p < 0.05$. See Tables B.8, B.5 & B.9 for additional statistical details and Figure A.1 for the rest of the conditions.

Next, I investigated whether sensitivity to changes in reward and uncertainty were associated with differences observed in sampling behaviour in Exp. 1. Sensitivity to reward and uncertainty were extracted from a L_g MM that included the two attributes and their interaction as predictors of offer acceptance (i.e., the same model used above but with no group effect). For each participant, reward and uncertainty sensitivity correspond to model-derived parameter estimates that capture how decisions are influenced by changes in these two offer attributes. A robust regression model showed that reward, but not uncertainty sensitivity, correlated significantly with the sensitivity to sampling cost at high initial reward reserve in the active task, i.e., the effect differentiating patients from controls in Exp. 1 (indexed by difference in number of samples between low and high sampling cost conditions) ($R^2 = 0.23$, $t_{17} = 2.26$ $p = 0.03$; Figure 3.5 d.).

In brief, the findings from Exps. 1 & 2 converge to indicate that ALE patients are less responsive to changes in reward under conditions of uncertainty in active and passive contexts. This is evidenced by partially less flexible sampling in response to changes in sampling cost in the active task, and reduced sensitivity to changes in reward on offer in the passive task.

3.4.4 Exp. 3 – Intact effort-based decision making in ALE patients

In Exp. 3, I asked whether blunted reward sensitivity observed in ALE patients for decisions involving a trade-off with uncertainty was also evident for a different discounting attribute – physical effort. In other words, is this a generalised phenomenon? A novel version of well-validated paradigm measuring effort and reward sensitivity was used to examine effort-based decision making (see *Methods*).

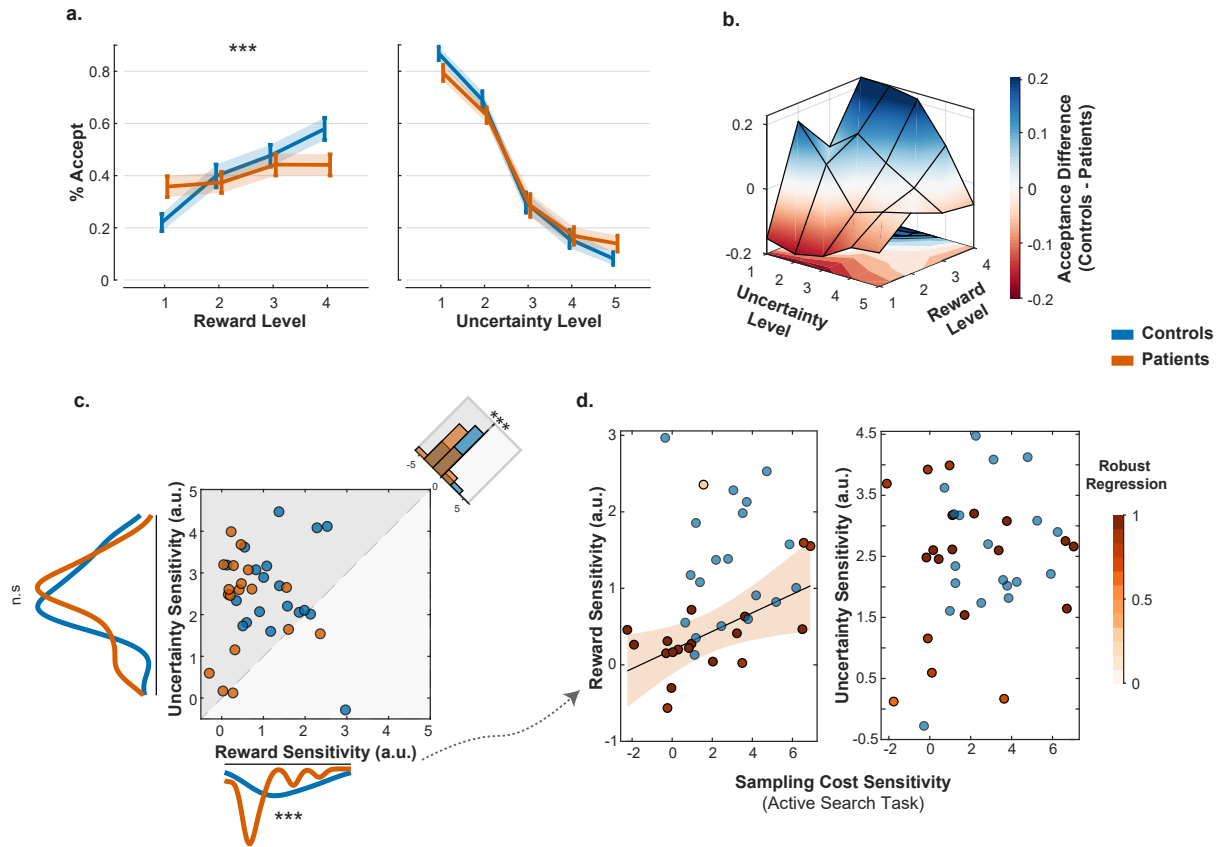


Figure 3.5: Exp. 2 – ALE patients are less sensitive to changes in reward under uncertainty. **a.** Participants adjusted their decisions according to the reward and uncertainty on offer. The influence of reward on offer acceptance was blunted in ALE patients when compared to controls (shallower reward slope). Level 1 indicates lowest reward/uncertainty level on offer. **b.** Controls accepted more of the high-value offers (blue region) when compared to patients. **c.** Investigation of the group effect using mixed effects logistic model (L_g MM) revealed that patients had significantly lower sensitivity to reward than controls but did not significantly differ in their sensitivity to uncertainty. Additionally, it showed that the impact of uncertainty on decision making was more significant than the impact of reward (histogram on the corner). **d.** Lower sensitivity to reward, but not uncertainty, in the passive task is associated with lower sensitivity to sampling cost in the active sampling task (Exp. 1) driving group differences in number of samples collected. Colour bar indicates the contribution of each data point to the model. Blue dots represent controls and are added for visual comparison. Error bars in **a.** show $\pm$ SEM. ***: $p < 0.001$. Shaded area in **d.** show 95% CI. See Table B.12 for full statistical details.

A L_q MM with full randomness was used to analyse the choice data (Table B.13). The results showed that, as expected, participants from both groups accepted more offers (showed more willingness to allocate effort) when reward on offer increased and required effort decreased (Main effect of reward on offer acceptance: $\beta = 2.97$, $t_{4739} = 11.12$, $p < 0.001$, Main effect of physical effort on offer acceptance: $\beta = -2.82$, $t_{4739} = -8.45$, $p < 0.001$). However, neither reward nor effort sensitivity differed significantly between patients and controls (ALE $\times$ Reward and ALE $\times$ Effort both $p > 0.05$). To quantify the evidence in favour of this null result, the same analysis was run using Bayesian mixed modelling. Once again, this analysis did not suggest differences between the two groups in reward (or effort) valuation ($BF = 3.78$ for null effect of ALE $\times$ reward, $BF = 5.28$ for null effect ALE $\times$ effort; Figure A.2, Table B.14). Note that there was also no significant difference in total acceptance of offers (Effect of disease (ALE) on offer acceptance: $\beta = -0.40$, $t_{3748} = -0.88$, $p = 0.45$) as well as in decision times (Accept decisions: $t(36) = 0.87$, $p = 0.38$, Reject decision: $t(36) = 0.99$, $p = 0.32$). These results are consistent with a sparing of reward sensitivity in ALE patients when reward had to be weighed against effort, without uncertainty being considered.

3.4.5 Exp. 4 – Blunted reward and effort sensitivity under uncertainty in ALE patients

One might argue that the comparison between reward sensitivity in Exps. 2 & 3 is not fully matched due to the difference in task cues and environment (e.g., reward as virtual apples vs. reward as credits). While this should not affect the conclusions as we are primarily concerned with how people change their response as function of change in reward rather than the absolute responses to certain reward values, these concerns were addressed using a novel version of *Circle Quest* that

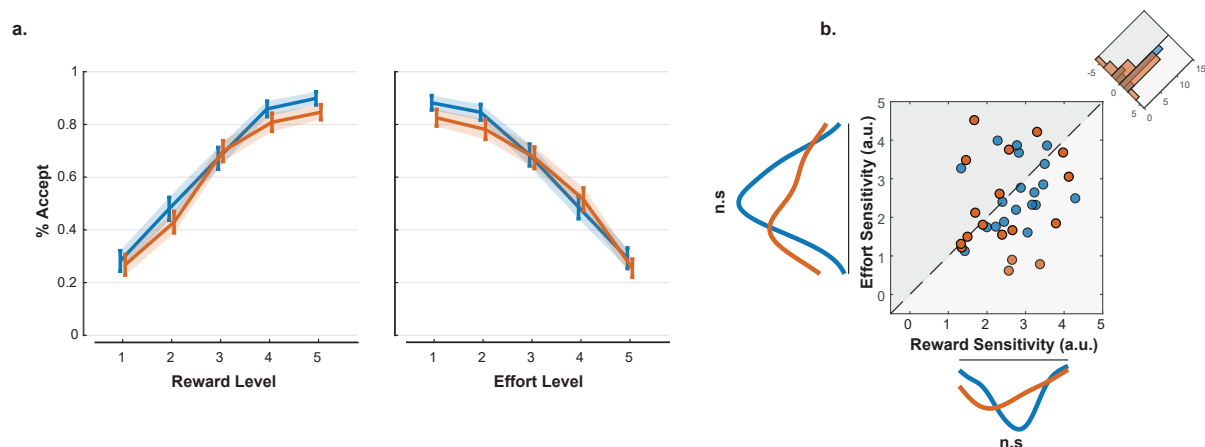


Figure 3.6: **Exp. 3 – Intact reward valuation against effort in ALE patients.**

a. There was no significant difference in offer acceptance between patients and controls. **b.** The estimates of these acceptance slopes indicate how sensitive participants are to reward/effort changes of offers. These sensitivity estimates were extracted from a generalised mixed model with full randomness and plotted for visualisation. Error bars show $\pm$ SEM. See Tables B.13 & B.14 for full statistical details.

was designed to examine *effort-based decision making under uncertainty*. The task had the same reward levels and cues used in Exp. 2 and same effort levels and cues used in Exp. 3. Participants also made the decisions with and without uncertainty. Thus the task overall examined how participants adjusted their decision taking into consideration these three attributes (reward, effort and uncertainty).

Choice data were analysed using the same approach as in Exp. 2 & 3 with generalised mixed models (Table B.16). The results showed that participants from both groups generally made decisions reflecting changes in offer attributes, i.e., accepting more with increasing reward, decreasing effort and absent uncertainty (Main effect of reward on choice: $\beta = +1.73$, $t(4184) = 5.21$, $p < 0.0001$; Main effect of effort: $\beta = -2.45$, $t(4184) = -5.38$, $p < 0.0001$; Main effect of uncertainty: $\beta = -1.9$, $t(4184) = -3.49$, $p < 0.001$). However, ALE patients were significantly less sensitive to changes in reward and effort compared to healthy

controls (ALE $\times$ reward: $\beta = -1.41$, $t(4184) = -2.83$, $p < 0.01$; ALE $\times$ effort: $\beta = +1.24$, $t(4184) = 2.99$, $p < 0.01$; Figure 3.7). On the other hand, patients and controls did not differ in their sensitivity to uncertainty ($p = 0.21$). The two-way interaction between uncertainty and reward was also significant, indicating the presence of uncertainty resulted in blunted sensitivity to changes in rewards (Reward $\times$ uncertainty: $\beta = -0.67$, $t(4184) = -3.61$, $p < 0.001$). This effect was significantly more prominent in ALE patients than matched controls (Reward $\times$ uncertainty $\times$ ALE: $\beta = +0.568$, $t(4184) = 2.09$, $p = 0.036$).

Analyses for Exps. 1–3 were repeated for the eight ALE patients tested in Exp. 4 to make sure that this smaller sample of patients is an adequate representation of the ALE group. The results were similar to the main findings reported for the entire group in Exp. 1–3 (Figure A.3).

These findings are consistent with the results from Exps. 1 & 2 showing intact sensitivity to uncertainty and reduced sensitivity to reward in presence of uncertainty in ALE patients. They also suggest that effort sensitivity can also be blunted in ALE patients under conditions requiring uncertainty consideration. Thus overall, while healthy controls managed to flexibly adjust their decision taking into consideration the three attributes of the offers, ALE patients were generally more concerned with uncertainty component of the offers with less emphasis on other economic attributes such as reward and effort.

3.4.6 Severity of hippocampal atrophy correlates with decreased reward sensitivity under uncertainty

A whole-brain voxel-based morphometry (VBM) analysis was performed. Compared to healthy controls, ALE patients had lower grey matter intensity in three clusters involving limbic, thalamic and temporal regions (Table 3.3). As ex-

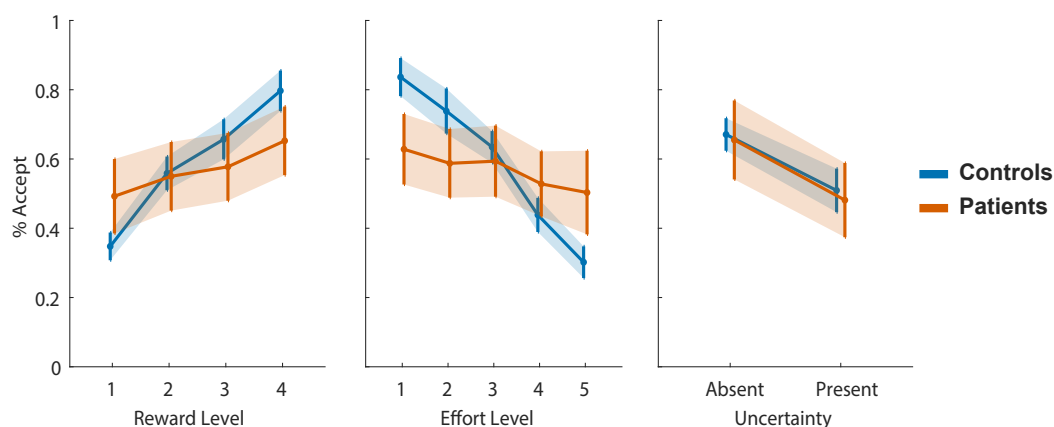


Figure 3.7: Exp. 4 – Blunted reward and effort sensitivity under uncertainty in ALE patients. In Exp. 4, participants were required to accept/reject offers taking into consideration three attributes: reward, physical effort, and uncertainty. The results showed that ALE patients, compared to controls, were less sensitive to changes in reward and effort while having intact sensitivity to uncertainty. Such results are consistent with findings from Exps. 1 & 2, highlighting disrupted reward and cost valuation in ALE patients under uncertainty. Error bars show $\pm$ SEM. *: $p < 0.05$. See Table B.16 for full statistical details.

pected, the largest cluster (limbic region) included mainly the hippocampus and para-hippocampal regions (Figure 3.8 a.). Hippocampal atrophy was also demonstrated by comparing extracted total hippocampal volume using Freesurfer analysis pipeline, showing reduced right whole hippocampal volumes in ALE patients (Table 3.1). Note that a few participants had also severely atrophied left hippocampi (with and without right hippocampal atrophy, see Table 3.2).

Next, robust regression analysis was performed to examine the relationship between hippocampal atrophy and reduced reward sensitivity observed in ALE patients. For this purpose, reward and uncertainty sensitivities from Exp. 2 were used as key behavioural markers characterising performance of hippocampal patients when compared to controls. The results showed that sensitivity to changes in reward was associated with total average hippocampal volumes in patients (Model $R^2 = 0.41$, $t_{13} = 3.05$ $p < 0.01$; Figure 3.8 b.). This correlation remained sig-

Cluster	Main regions involved	Voxels	MAX X (mm)	MAX Y (mm)	MAX Z (mm)
1	Right Limbic (Hippocampus, Para-hippocampus, Amygdala)	199	22	-32	-14
2	Thalamus (Bilateral)	120	2	-14	-2
3	Right Temporal Lobe (STG, MTG, AG)	65	68	-40	6

Table 3.3: **VBM analysis controls vs. patients.** ALE patients had lower grey matter volumes compared to controls in three main clusters (1 –3). The largest difference was seen in the limbic region which includes mainly hippocampal regions (Figure 3.8 a.) STG: Superior Temporal Gyrus. MTG: Middle Temporal Gyrus. AG: Angular Gyrus.

nificant after controlling for age and gender (Model $R^2 = 0.38$, $t_{11} = 2.28$, $p = 0.043$).

Repeating the same analysis for reward sensitivity from Exp. 3 revealed no significant correlation between total hippocampal volume and reward sensitivity against effort ($p = 0.88$). Due to limitation of sample size this analysis was not performed for Exp. 4.

To assess the anatomical specificity of this result, the volume of the amygdala – another limbic brain region that was highlighted in VBM analysis – was also extracted and the same analysis was run on this metric. This showed no significant correlation between amygdala and sensitivity to reward or uncertainty (Figure 3.9).

3.5 Additional analyses

3.5.1 Intact localisation and uncertainty estimation in ALE patients

Two control analyses were performed to examine possible factors that might influence response to uncertainty in the *Circle Quest* task. First, participants might

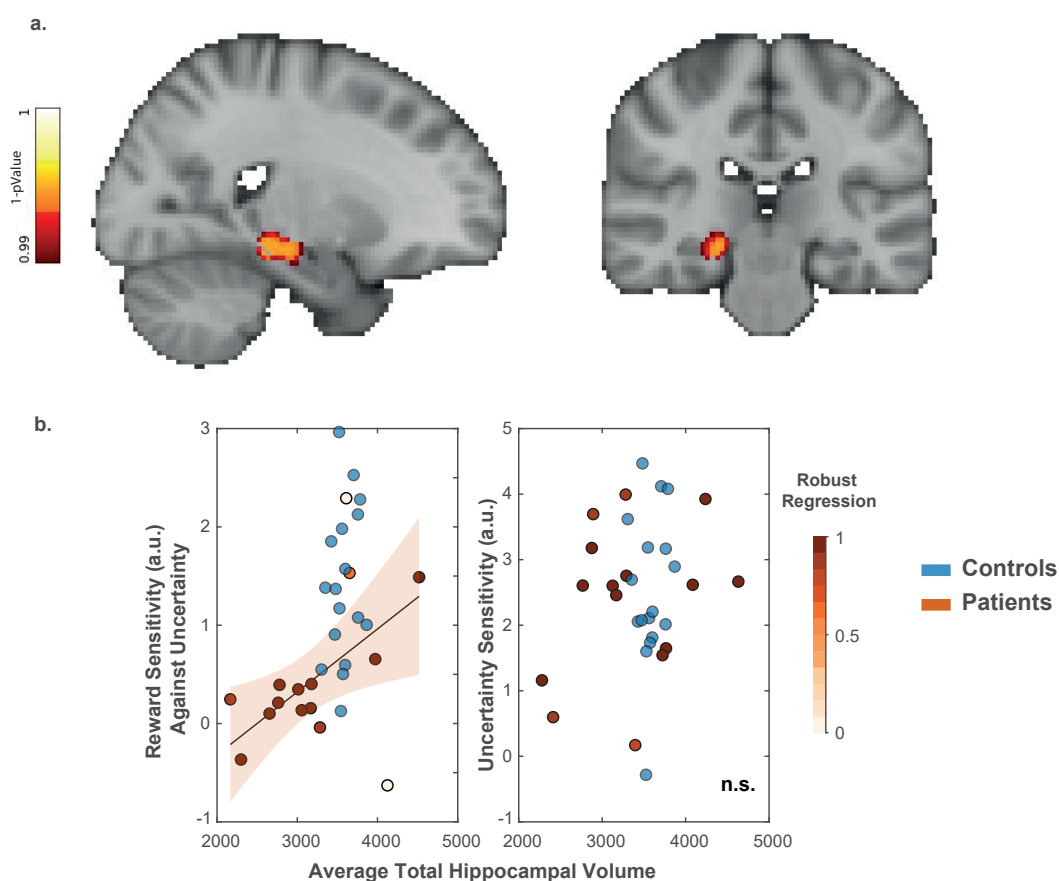


Figure 3.8: **Severity of hippocampal atrophy correlates with decreased reward sensitivity against uncertainty.** **a.** VBM analysis shows that ALE patients have significantly reduced grey matter intensity in right hippocampal region (cluster 1, Table 3.3). **b.** Patients with more severely atrophied hippocampi were less sensitive to reward when traded against uncertainty. By contrast, hippocampal volumes were not significantly correlated with sensitivity to uncertainty which was preserved in ALE patient.

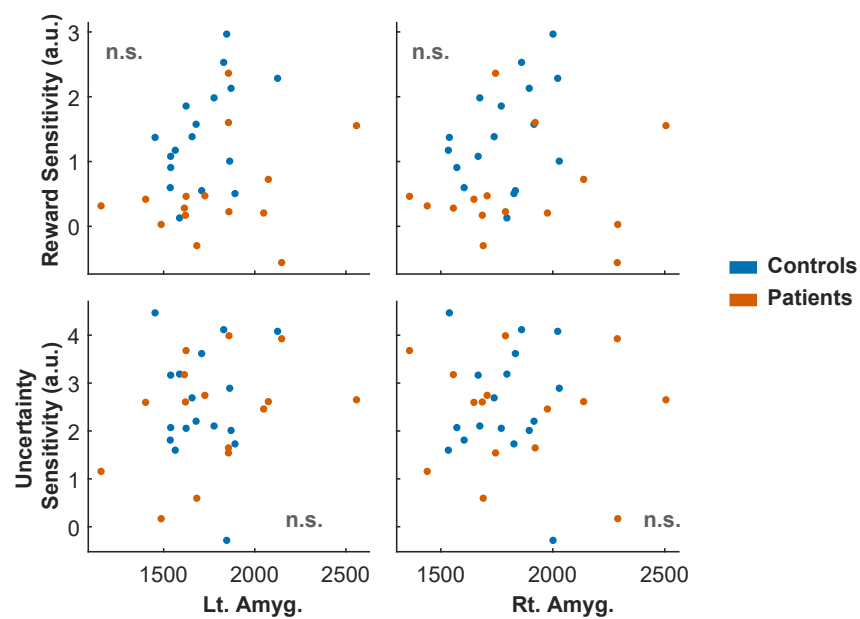


Figure 3.9: **Amygdala as control region.** No significant correlation was detected between amygdala volume and sensitivity to reward or uncertainty. Note also there was no significant difference in total amygdala volumes between patients and controls.

differ in their motor performance and accuracy of placing the blue disc for given uncertainty levels, which might bias their estimation and valuation. To examine this, participants completed a training task where they were required to move the blue disc for fixed levels of uncertainty. Distance to hidden circle was compared between the two groups. There was no significant difference between ALE patients and controls in this metric, indicating similar placement performance on the task (Difference between ALE and controls in Exps. 1 & 2: $z = 1.10$, $p = 0.26$; Exp. 4: $z = 0.10$, $p = 0.91$; Figure 3.5 a.).

Second, different participants might have different estimations of uncertainty for the same visual displays, ultimately affecting their performance on the task as they gather information and make decisions. To examine inter-individual differences in uncertainty, participants provided these estimates as confidence ratings before making decisions in Exp. 2 and during training in Exp. 4 (see *Methods*). A generalised mixed effects model indicated that in both experiments there was no significant difference in subjective uncertainty estimation between patients and controls (Exp. 2; ALE $\times$ EE: $\beta = -0.054$, $t_{3752} = -0.77$, $p = 0.44$; Exp. 4; ALE $\times$ EE: $\beta = -0.022$, $t_{2306} = -0.16$, $p = 0.87$, Figure B.15 b., Table B.15). The results indicate that subjective estimates of uncertainty mapped well onto experimentally defined uncertainty across study participants.

3.5.2 Computational modelling of active search performance

The computational model used in Chapter 2 to analyse performance on the active task was fitted to the active search data from ALE patients and controls. The model calculates the expected utility of a sample (EU_s) accounting for economic and hidden cognitive effort costs to returns five parameter estimates per participant. The first two parameters represent the weights participants assign to sample costs (w_s) and benefits (w_e). Two parameters describe the cognitive cost function

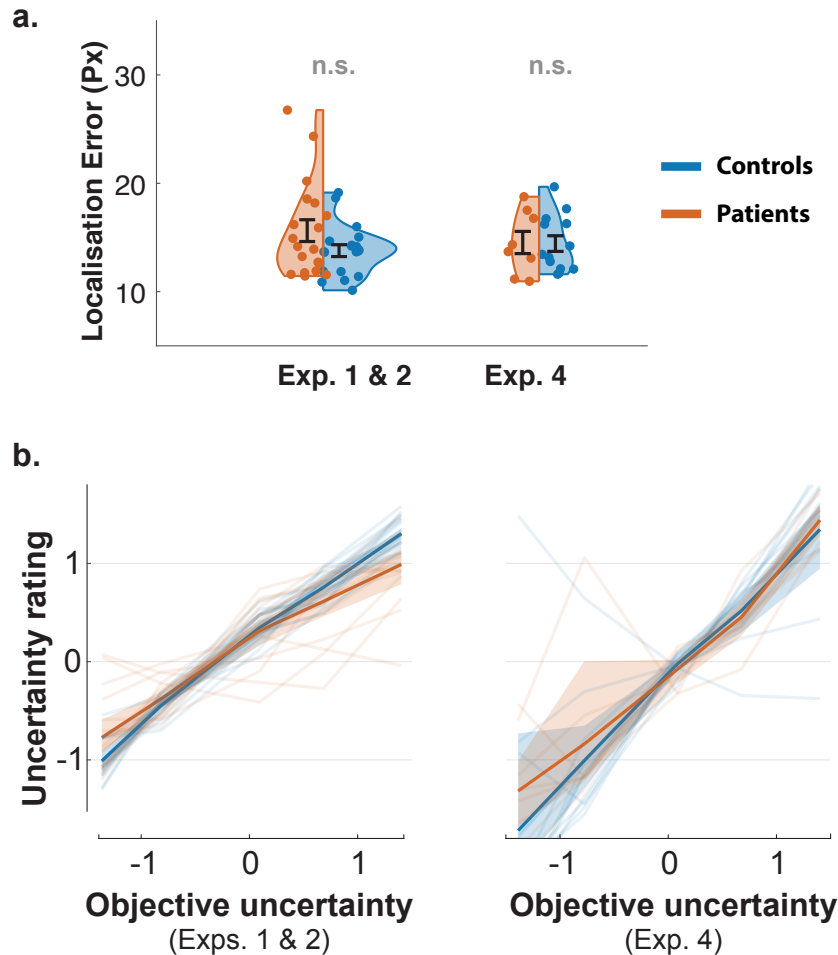


Figure 3.10: **Exp. 1, 2 & 4 – Intact localisation and subjective uncertainty estimation in ALE.** **a.** ALE patients and controls did not differ in their localisation error (distance between the centre of the blue disc and hidden circle) for fixed levels of uncertainty, indicating similar motor and localisation performance. **b.** Subjective uncertainty is z-scored signed-flipped confidence ratings that participants reported before seeing the reward on offer (Exp. 2) or during training (Exp. 4). There was no significant difference between ALE patients and controls in this measure, indicating intact uncertainty estimation. Error bars in **a.** show $\pm$ SEM. Shaded area show 95% CI. See Table B.15 for full statistical details.

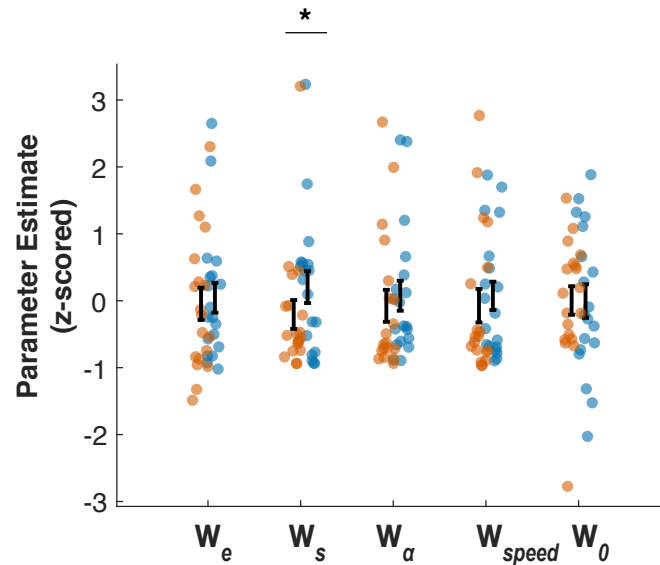


Figure 3.11: **Computational modelling of active information sampling.** Compared to healthy matched controls, ALE patients assigned lower economic costs (w_s) to sample acquisition. All other model parameters including weights assigned to sample benefit (w_e), efficiency w_α , and speed (w_{speed}) were not significantly different between patients and controls. w_0 captures a subjective fixed cost of sampling that is not explicitly specified in the task (e.g., cost of the motor action). This was not significantly different between the two groups. * : $p < 0.05$

in terms of a penalty for sampling speed (w_{speed}) and efficiency (w_α). The fifth parameter represents an intercept per participant describing their baseline valuation of samples (w_0).

After exclusion of potential outliers (1 patient with values $> 3SD$), comparing the two groups showed that ALE patients had lower weights assigned to sampling cost compared to controls ($t(35) = -2.24, p = 0.031$; Figure 3.11). There was no significant difference between the two groups in any of the other parameters. These results thus represent a computational formalisation of the findings from Exp. 1 suggesting that ALE patients have lower sensitivity to the cost of sampling.

3.5.3 No correlation between sampling speed and affective functioning in ALE patients

In the previous chapter, I reported that markers of hyperreactivity to uncertainty such as increased sampling speed and over-sampling were associated with worse affective functioning in healthy young people.

Such an association was not evident in hippocampal patients ($p > 0.9$), despite sampling faster when sampling cost was high. Note also that depression scores (BDI-II) did not significantly differ between the two groups. These findings suggest that faster and more extensive sampling seen in ALE might reflect a different psychological dimension other than affective functioning as seen in healthy people, especially that such findings (sampling speed and over-sampling) in ALE were dependent on the economics of the condition (e.g., sampling cost) rather than presenting a general feature of performance.

3.6 Discussion

The studies presented here assessed acute limbic encephalitis (ALE), which is associated with damage to the hippocampus. In four experiments, patients were assessed on how they evaluate reward, uncertainty, and effort when making value-based decisions. The results converged to indicate that ALE patients had intact uncertainty processing across different contexts such as passive reward valuation and active information gathering prior to decisions. On the other hand, whenever uncertainty was considered, sensitivity to other attributes (reward and physical effort) was blunted, despite the fact that patients demonstrated intact valuation of these attributes in a separate behavioural paradigm that does not feature uncertainty. Reduced sensitivity to changes in reward in the context of uncertainty

correlated with severity of hippocampal atrophy in ALE patients. Thus, the results indicate a specific role of the hippocampus in processing uncertain rewards and costs.

Previous decision-making studies demonstrated a potential role of the hippocampus in different forms of goal-directed behaviour. For example, several reports indicated that the hippocampus might be critical for inter-temporal decision making, especially when participants are required to imagine future outcomes ([Benoit et al., 2011](#); [Lebreton et al., 2013](#); [Peters and Bü, 2011](#)). Other investigations suggested that the hippocampus might be needed for deliberation prior to value-based decisions, but not sensory discrimination ([Bakkour et al., 2018](#)), suggesting that the hippocampus supports valuation by sampling from memories and previous experiences. Similarly, other researchers demonstrated hippocampal involvement in inferring values of novel stimuli from previously encountered cues and stimuli ([Barron et al., 2013](#); [Hassabis et al., 2007](#); [Wimmer and Shohamy, 2012](#)). These functions are thought to be related to the established role of the hippocampus in episodic thinking and prospection ([Buckner and Carroll, 2007](#); [Gilbert and Wilson, 2007](#); [Schacter et al., 2007, 2012, 2017](#)).

A common theme of such decision making scenarios is that they critically involve uncertainty regarding future rewards that agents need to infer to guide their decisions. For example, several previous reports highlighted similarities between delay and probabilistic discounting (i.e., decisions under uncertainty), suggesting that they might be related to a common cognitive process ([Green and Myerson, 1996](#); [Myerson et al., 2003](#); [Prelec and Loewenstein, 1991](#); [Rachlin et al., 1991](#); [Stevenson, 1986](#)). These similarities are of special relevance when considering hippocampal contribution to inter-temporal decision making as its role seems to be specific to temporal discounting that requires simulated future trajectories ([Palombo et al., 2015b](#); [Peters and Büchel, 2010](#); [Ye et al., 2021](#)). Accord-

ing to this perspective, exaggerated delay discounting observed with hippocampal damage in previous studies might reflect intolerance to uncertainty of future reward. Such reports highlighting potential role of the hippocampus in uncertainty processing are supported by functional neuroimaging studies which have demonstrated hippocampal activation which correlates with the degree of uncertainty (entropy) of sensory stimuli when making decisions ([Harrison et al., 2006](#); [Rigoli et al., 2019](#); [Strange et al., 2005](#); [Tobia et al., 2012](#)). These investigations align with the view that regards uncertainty as a threatening stimulus (i.e., carries risk signals) processed by hippocampus-centred behavioural inhibition system (BIS) ([Gray and McNaughton, 2003](#)). The hippocampus, according to this view, is considered to work as a mismatch detection system comparing expectation with perceived stimuli and triggering behavioural avoidance when uncertainty (or other anxiety-inducing stimuli) is faced ([Gray and McNaughton, 2003](#)).

These features of uncertainty as probabilistically discounted risk signal offer a key distinction from other costs such as physical effort, which are more deterministic in nature. The results presented in this chapter provide evidence that the hippocampus is critically involved in valuation processes under the first context (uncertainty) but not the second (physical effort), providing specific insights into the role of the hippocampus in value-based decision making. However, counter-intuitively, hippocampal damage was associated with preservation of uncertainty estimation and valuation, while blunting sensitivity to other decision attributes (e.g., reward and effort) if simultaneously considered with uncertainty.

These findings suggest that hippocampal damage might be related to a specific deficit in integration of relatively intact uncertainty signal with other attributes that contribute to the value space. Note that this does not reflect a general cognitive deficit in decision-making or value computation, as participants demonstrated intact effort-based decision making in Exp. 3. One possible explanation for this

might be that people with hippocampal atrophy possess limited computational resources that prioritise uncertainty processing (and perhaps other risk-related signals) over other value determinants when computing subjective values to guide behaviour and decisions. In fact, the results from the active search experiment could also be interpreted as evidence of uncertainty prioritisation, as ALE patients sampled faster and more extensively than controls to abolish uncertainty before committing to their decisions (Figure 3.4), disregarding changes in sampling cost. The hippocampal role therefore might be to infer decision values by multiplying probability of outcomes (i.e., uncertainty) with other economic attributes such as reward and effort. These signals might then be related to other regions involved in subjective value estimation such ACC and OFC (Bakkour et al., 2019; Chen, 2021; Gluth et al., 2015; Ito et al., 2008; LeGates et al., 2018; Maller et al., 2019; Mizrak et al., 2021; Pessiglione et al., 2018; Rudebeck et al., 2006; Wimmer and Shohamy, 2012).

It is however difficult to determine whether the prioritisation of uncertainty in this process reflects a specific computational property of the hippocampus versus general disruption of cognitive processing that might be observed with other brain lesions. Two factors make this possibility unlikely: i) the correlation between behaviour and severity of hippocampal atrophy, rather than other closely related regions such as the amygdala, which might have been affected by the disease process as well (see Figures 3.3 & 3.9) and ii) the analyses in this chapter were controlled of cognitive dysfunction indexed by ACE-III scores. However, I acknowledge that the ideal way to rule out such an effect is to perform a lesion control study with patients who have extra-hippocampal lesions with intact hippocampi (e.g., vmPFC). In a similar vein, it could be argued that the results might merely reflect a difficulty effect imposed by uncertainty cues in the task which biases participants to focus on uncertainty when evaluating it against other

attributes. If this was the case, one would expect that patients would take longer than controls to make their decisions, which was not the case. More importantly, these effects persisted in the uncertainty-free condition in Exp. 4 where participants were shown the true location of the hidden circle and they did not need to process uncertainty when making effort-based decisions.

These findings resonate with previous reports that highlighted the hippocampus as part of a wider brain valuation network, which includes regions that have established roles in processing reward and costs such as dopaminergic brain regions (e.g., ventral striatum), ventromedial prefrontal cortex and anterior cingulate cortex ([Haber, 2017](#)). The hippocampus shares functional and structural connections with these regions and is thought to provide contextual information that support the valuation process ([Bakkour et al., 2019](#); [Gluth et al., 2015](#); [Ito et al., 2008](#); [LeGates et al., 2018](#); [Maller et al., 2019](#); [Mizrak et al., 2021](#); [Wimmer and Shohamy, 2012](#)). The behavioural results in this chapter indicate that hippocampal processing of uncertainty signals might be a key determinant of how different brain regions evaluate reward and costs when computing subjective values.

The neural mechanism underlying how hippocampal signals support reward-related behaviours is not yet fully established and will require further research. However, previous studies demonstrated that the hippocampus might share future-related signals (e.g., preplay and look-ahead signals) with dopaminergic regions involved in reward evaluation and processing ([Freyja Ólafsdóttir et al., 2015](#); [Johnson and Redish, 2007](#); [Pfeiffer and Foster, 2013](#)). Similarly, several forms of reward representation in the hippocampal formation and its extended networks have been reported, correlating with various reward-related behaviours and cognitive processes such as appetitive responses to rewards ([Jarrard, 1973](#); [Tracy et al., 2001](#)), approach-avoid decisions ([Ito and Lee, 2016](#)), and reward-guided exploration ([Sosa and Giocomo, 2021](#)). While hippocampal-lesioned animals might

show behavioural adjustments in responses to changes in reward in the environment (Flaherty et al., 1998; Kelley and Mittleman, 1999), these findings might differ between contexts and depend on the way reward is manipulated (e.g., whether animals move from high reward environment to low, or the opposite) (Tracy et al., 2001). Consummatory responses of lesioned animals seem to be unaffected despite the changes in behaviour, challenging the notion that the role of the hippocampus in reward processing is of a hedonic nature (Kelley and Mittleman, 1999), and further substantiating its goal-related and context-dependant contribution.

This uncertainty-sensitive hippocampal contribution might serve to support not only passive valuation but also active goal-directed behaviours such as information seeking to resolve uncertainty. While results from a previous investigation have shown that people with hippocampal damage exhibit a less structured and stochastic visual information exploration compared to controls (Lucas et al., 2019), it was unclear how economic factors come into play. In this study, less optimal decision making when uncertainty-related value computations had to occur was evident in hippocampal patients when they actively gathered information and sequentially updated the expected values of their decisions, as well as when they made passive decisions under uncertainty. The source of this disruption was related to less flexible decision adjustments based on reward changes in the environment while maintaining sensitivity to uncertainty. Thus, the results provide insights into how the hippocampus contributes to the economics of information gathering, in addition to its potential exploratory role (Johnson et al., 2012), which in this chapter was not strongly affected in ALE patients as they managed to reduce uncertainty as efficiently as healthy controls.

In this chapter, a positive correlation was observed between total hippocampal volumes and reward sensitivity under uncertainty. Future investigations might

build on this to investigate the drivers of this relationship. For example, such an association might be related to specific hippocampal subfields and sub-circuits. In rats, reward cells have been described in subiculum and CA1 subfields ([Gauthier and Tank, 2018](#)), which might suggest that atrophy or disruption of these regions might have a more specific role in the process. Moreover, distinct hippocampal subfields and regions might have differential functional connectivity profiles with other cortical and sub-cortical regions that might be contributing to motivation and decision making ([Dalton et al., 2019](#); [de Flores et al., 2017](#); [Vos De Wael et al., 2018](#); [Zeidman et al., 2015](#)). Hippocampal damage observed in ALE is likely to be associated with more widespread disturbances of such networks contributing to reward valuation under uncertainty ([Argyropoulos et al., 2019](#); [Heine et al., 2018](#); [Navarro et al., 2016](#); [Qiao et al., 2020](#)). With advanced neuroimaging acquisition and analysis techniques, it would be crucial to try to answer these questions at the subfield level and provide a more comprehensive account of hippocampal contribution to motivation.

In conclusion, the results presented here provide evidence from human participants that suggests that the hippocampus plays a crucial role in decision making. This contribution appears to be specific to contexts that involve uncertainty, influencing how people evaluate other economic attributes such as reward and effort. In the next chapters, I examine these forms of decision making in two hippocampus-related conditions: subjective cognitive impairment (SCI) and Alzheimer's disease in order to characterise their neuropsychiatric profile and underlying brain networks, including hippocampal networks.

4 | Hyperreactivity to uncertainty is key feature in subjective cognitive impairment

4.1 Chapter summary

With an increasingly ageing global population, more people are presenting with concerns about their cognitive function, but not all have an underlying neurodegenerative diagnosis. Subjective cognitive impairment (SCI) is a common condition describing self-reported deficits in cognition without objective evidence of cognitive impairment. Many SCI individuals suffer from depression and anxiety, which have been hypothesised to account for their cognitive complaints. Despite this association between SCI and affective features, the cognitive and brain mechanisms underlying SCI are poorly understood. In this chapter, I use *Circle Quest* paradigm to show that people with SCI are hyperreactive to uncertainty and that this might be a key mechanism accounting for their affective burden. Twenty-seven individuals with SCI performed along with 27 matched controls performed the task. Across different conditions, SCI participants sampled faster and obtained more information than controls to resolve uncertainty. Remarkably, despite their ‘urgent’ sampling behaviour, SCI participants were able to maintain their efficiency. Similar to results in Chapter 2, hyperreactivity to uncertainty indexed by this sampling behaviour correlated with the severity of affective burden including depression and anxiety. Analysis of MRI resting functional connectivity revealed that SCI participants had stronger insular-hippocampal connectivity compared to controls, which also correlated with faster sampling. These results suggest that altered uncertainty processing is a key mechanism underlying the psycho-cognitive manifestations in SCI and implicate a specific hippocampal brain network for this

mechanism.

4.2 Introduction

With an ageing population, an increasing number of people are seeking medical advice for concerns about cognitive decline (Deary et al., 2009; Harada et al., 2013). While in some individuals these complaints might be related to a progressive pathological process such as Alzheimer’s disease (AD), they can also be expressed by people without an underlying neurodegenerative disorder (McWhirter et al., 2020). When objective clinical evidence of significant cognitive impairment is not evident alongside self-reported cognitive complaints, individuals are categorised as having subjective cognitive impairment/decline (SCI/D) (Jessen et al., 2020, 2014; Reid and MacLulich, 2006). Although most follow a relatively benign course, a small proportion develops objective cognitive impairment and subsequently progress to dementia (Arvanitakis et al., 2018; Kryscio et al., 2014; Mendonça et al., 2016). Nevertheless, it remains unclear what drives subjective cognitive complaints in those people who do not have evidence of underlying neurodegeneration. Understanding the mechanisms of cognitive, behavioural, and psychiatric manifestations in SCI is thus crucial to improve clinical outcomes and enhance understanding of presentation of people who present with cognitive concerns.

A wealth of evidence suggests a particularly high prevalence of a range of mental health problems associated with SCI, in particular affective disorders such as anxiety and depression (Hill et al., 2016; Hohman et al., 2011; Pavisic et al., 2021; Reid and MacLulich, 2006). Similarly, people who primarily suffer from these psychiatric disorders often report sub-optimal cognitive performance, further emphasising the intertwined relationship between affective burden and subjective

cognitive experience (Millan et al., 2012). Moreover, treating anxiety and depression may improve subjective cognitive complaints in individuals with SCI (Allott et al., 2020). Despite the association between SCI and affective burden being increasingly recognised, little is understood about the underlying cognitive mechanisms and brain networks involved.

A rich body of theoretical and empirical work suggests that affective dysregulation might be related to uncertainty processing and related behaviours (Bishop and Gagne, 2018; Carleton, 2016; Grupe and Nitschke, 2013; Gu et al., 2020). People who express higher levels of anxiety and depression often report higher levels of intolerance to uncertainty (Boelen et al., 2016; Boswell et al., 2013; Carleton et al., 2012; McEvoy and Mahoney, 2011; Saulnier et al., 2019). Mechanistically, as outlined in Chapter 1, intolerance to uncertainty might be reflected in several cognitive and behavioural processes underpinning goal-directed behaviour when people decide and act under uncertainty (Grupe and Nitschke, 2013). For example, when someone is crossing the road, they make their decision based on how confident they are that the environment is safe (i.e., they have an assessment of how uncertain the environment is for their intended action) (Bach and Dolan, 2012; Gottlieb and Oudeyer, 2018). If uncertainty is high, agents often try to reduce it by gathering information to inform their decision (e.g., checking passing cars and traffic lights and looking for a safer place to cross). People who are more sensitive to uncertainty might have an exaggerated estimation of uncertainty or preparedness when required to face it, eventually affecting their decisions and outcomes (Grupe and Nitschke, 2013). Similarly, uncertainty sensitivity might affect self-evaluation of cognitive abilities (e.g., having lower confidence in recollection) amplifying memory complaints and subsequent emotional reaction (Fitzgerald et al., 2017; Nelson, 1990). Such a framework, which involves estimation, valuation, preparation, and learning under uncertainty allows a detailed investiga-

tion of the psychopathology of affective dysfunction ([Gottlieb and Oudeyer, 2018](#); [Grupe and Nitschke, 2013](#); [Sharot and Sunstein, 2020](#)).

Investigation of the dynamics of how people decide and act under uncertainty might hold an important key to understanding the relationship between SCI and affective dysfunction. This would be challenging to achieve using classical behavioural paradigms, e.g., beads task or variants of it ([Phillips et al., 1966](#)). These paradigms often involve randomly drawing samples from a distribution to make inferences about the distribution (e.g., deciding the predominant colour of beads in a jar). However, when people gather information to reduce uncertainty, they dynamically assess their environment and update their expectations in order to decide whether a new piece of evidence is needed and whether they can tolerate its cost ([Juni et al., 2016](#)). While the economic aspect of this behaviour has been extensively examined in previous studies ([Clark et al., 2006a](#); [Jones et al., 2019](#); [Juni et al., 2016](#)), investigation into *how* information is gathered is limited. Capturing behavioural markers that might not be directly apparent using such tasks (e.g., sampling speed and efficiency) might provide important insights into underpinning mechanisms of affective disorders. This distinction has been formalised as ‘active’ information gathering, characterised by situations in which participants have agency over not only how much information they gather but also how information is collected in face of uncertainty (e.g., what resources to consult and when) ([Gottlieb and Oudeyer, 2018](#)).

In this study, I adopted this approach using the *Circle Quest* paradigm to investigate how people with SCI decide and act (gather information) under uncertainty. A crucial question of this study was whether uncertainty processing is associated with affective burden in SCI, as seen in healthy controls in Chapter 1. Further, to investigate the underlying brain structures and networks that might be implicated in the process, brain resting functional neuroimaging (rs-fMRI) data were

also collected. In an *active form* of the task, participants collected informative clues, which came at a known cost, to reduce their uncertainty before committing to decisions. Crucially, they were allowed to freely gather information whenever and in whichever way they wanted. In a *passive form* of the task, this agency over uncertainty was removed. Participants were allowed only to accept or reject offers that had fixed levels of uncertainty weighed against potential reward. They also reported their subjective estimates of uncertainty to measure their metacognitive assessment of uncertainty and its contribution to active and passive performance.

The results from the behavioural tasks showed that individuals with SCI gather significantly more information than healthy matched controls before they commit to final decisions. They did this regardless of the cost of information and at a faster rate than controls. Despite this faster sampling, SCI participants impressively were capable of maintaining their sampling efficiency (i.e., gathering samples that were as informative as controls). This meant that they exceeded the speed-efficiency trade-off that characterises sampling behaviour of healthy controls. Crucially, in individuals with SCI, sampling speed and over-sampling (indices of heightened reactivity to uncertainty) were associated with affective burden (derived from self-report measures of anxiety and depression).

By contrast, when they had no agency over the reward and uncertainty on offer (passive choice task), SCI participants had intact metacognitive assessment and valuation of uncertainty. This suggests that controllability when dealing with uncertainty might be a crucial aspect in affective dysfunction, as differences between SCI participants and controls were apparent only when they had agency over uncertainty (i.e., during the active information gathering phase preceding decisions).

Functional neuroimaging analysis investigating whole-brain resting connectivity between regions of interest across all known brain networks revealed that individ-

uals with SCI, in comparison to healthy controls, had increased insular hippocampal connectivity. Further, the strength of this connectivity in SCI correlated with reactivity to uncertainty indexed by sampling speed.

Taken together, the results indicate that hyperreactivity to uncertainty might be a key mechanism in SCI, and link this process to the insular cortex and hippocampus.

4.3 Methods

4.3.1 Participants

Twenty seven individuals with SCI (age: $\mu = 59.81$, $SD = 7.70$, 14 females) along with 27 healthy age- and gender-matched controls (age: $\mu = 62.04 \pm SD = 6.28$) were recruited for the study. Sample size was determined based on the previous study testing and validating the behavioural paradigm in healthy young controls (see Chapter 2) as well as comparable studies investigating information gathering in patient groups (Clark et al., 2006a; Hauser et al., 2017d). SCI participants were clinically assessed by trained neurologists (co-authors MH & SM) in the cognitive disorders clinic at John Radcliff Hospital, Oxford. In addition to clinical assessment, the diagnosis of SCI was supported by normal performance on standardised objective cognitive assessment using Addenbrooke's Cognitive Examination (ACE-III) with cutoff $> 87/100$ (Bruno and Vignaga, 2019; Elamin et al., 2016; Hsieh et al., 2013b) as well as normal clinical MRI scan. This definition is consistent with the criteria proposed in previous key reports (Jessen et al., 2020, 2014), suggesting that SCI diagnosis relies on two key components i) subjective report of cognitive decline and ii) normal performance on standardised objective cognitive tests.

All participants gave written consent to take part in the study and were offered monetary compensation for their participation. The study was approved by the University of Oxford ethics committee (RAS ID: 248379, Ethics Approval Reference: 18/SC/0448). Table 4.1 shows demographics of the study groups. All participants completed the behavioural tasks and questionnaires. Neuroimaging data were obtained from 23 SCI participants and 25 healthy controls who were MRI compatible and gave consent to be scanned for research purposes.

4.3.2 Clinical measures

All participants underwent a cognitive assessment using Addenbrooke's Cognitive Examination III (ACE-III) (Hsieh et al., 2013b). They also completed self-report questionnaires of depression and anxiety (Beck Depression Inventory II BDI-II, (Beck et al., 1996) and Hospital Anxiety Depression Scale, HADS (Zigmond and Snaith, 1983)).

4.3.3 Procedure

A 17-inch touchscreen PC was used to present the task, which was coded using MATLAB (The MathWorks inc., version 2018b) and Psychtoolbox version 3 (Brainard, 1997; Kleiner et al., 2007). The distance between participants and the screen was (~ 50 cm) allowing them to reach it comfortably using their dominant hand. Task environment was adjusted according to handedness and participants were instructed to use their index finger for all their responses. An experimenter was present at all times in the testing room to answer any questions they might have.

4.3.4 Experimental paradigm

Participants performed the shorter two versions of *Circle Quest* paradigm used in Exp. 1 & 2 in Chapter 3. In short, participants were asked to maximise their reward by trying to localise a hidden purple circle of a fixed size as precisely as possible. In the active version, they could reduce uncertainty about the location of the hidden circle by touching the screen at different locations to obtain informative clues: if a purple dot appeared where they touched, this meant that the location was situated inside the hidden circle, otherwise, the dots were coloured white. Obtaining these clues came at a cost (η_s) that participants had to pay from an initial credit reserve (R_0) they started each trial with. Participants could sample the search field freely without constraints to the location or the speed at which they touch the screen. At the end of each trial, participants were required to move a blue disc to where they thought the hidden circle was located. A feedback was given after this, indicating credits participants won (or lost) based on how precise their localisation was and the credits they lost to obtain information (i.e., participants had to make a trade-off between obtaining more information and the cost of this information). There were two levels of sampling cost (low and high) and two levels of initial credit reserve (low and high). In the passive version, participants were required to i) provide their subjective estimates of uncertainty as confidence ratings and ii) decide on offers (accept or reject) given their fixed reward and uncertainty attributes. Uncertainty in the task was quantified as expected error (EE) which is the average error that an optimal agent is expected to obtain when placing the blue disc at the best possible location. For more details see *Methods* in Chapters 2 & 3.

4.3.5 Statistical analyses

Statistical analysis was performed either in MATLAB R2019a or R version 4.0.2. Data from active and passive tasks were analysed mainly using generalised mixed effects models with full randomness using *fitglme* function in MATLAB. These were either logistic or linear models depending on the response variable. Full description and statistical details of these models can be found in Appendix Tables. Post-hoc follow-up analyses were conducted using appropriate statistical tests of difference (student t-test or Wilcoxon rank-sum test) depending on whether parametric assumptions were met. Principal component analysis was applied to HADS anxiety and BDI-II questionnaire scores using *pca* function in MATLAB. The first component of this PCA analysis was used as a measure of affective burden. All correlations were performed using Spearman's non-parametric testing within the two groups separately, controlling for possible confounds such as age, gender and cognitive score when required.

4.3.6 Magnetic Resonance data acquisition

Structural and functional magnetic resonance scans were obtained using 3T Siemens Verio scanner at John Radcliffe Hospital, Oxford. Structural images were T1-weighted with 1 mm isotropic voxel resolution (MPRAGE, field of view: $208 \times 256 \times 256$ matrix, TR/TE = 200/1.94 ms, lip angle = 8° , iPAT = 2, prescan-normalise). Resting-state functional MRI (rs-fMRI) measures spontaneous changes in blood oxygenation (BOLD signal) due to intrinsic brain activity. rs-fMRI images had voxel size = $2.4 \times 2.4 \times 2.4$ mm (GE-EPI with multi-band acceleration factor = 8, field of view: $88 \times 88 \times 64$ matrix, TR/TE = 735/39 ms. flip angle = 52° , fat saturation, no iPAT). MR images were obtained from 23/27 SCI participants and 25/27 healthy controls who were MRI compatible or consented to have

MR scans as part of the study.

4.3.7 Magnetic Resonance data processing and analysis

Resting-state connectivity analysis was performed in MATLAB 2019b using CONN toolbox v20.b ([Whitfield-Gabrieli and Nieto-Castanon, 2012](#)) running SPM12. Default processing pipeline was used. This included functional realignment and unwarp, slice-timing and motion correction, segmentation, and normalisation to MNI space. To increase signal-to-noise ratio, spatial smoothing was applied using spatial convolution with Gaussian kernel of 8 mm full width half maximum. Denoising was done using linear regression of potential confounds and temporal band-pass filtering (0.008 - 0.09 Hz). This linear regression controlled for noise components from white matter and cerebrospinal fluid areas (16 parameters each). Head motion was controlled for using 12 noise parameters, which included three translation and three rotation parameters in addition to their first-order derivatives. Confounding effects arising from identified outliers and from linear BOLD signal trends were also controlled for.

Following this, whole-brain ROI-to-ROI was run using 40 atlas-defined ROIs. These ROIs included the default nodes in CONN used to run network functional connectivity analysis as they represent key nodes in brain networks including salience, default mode, sensorimotor, visual, dorsal attention, frontoparietal, language, and cerebellar networks. In addition, limbic brain regions including the hippocampus, para-hippocampus and amygdala were added, as these regions have been consistently implicated in processing uncertainty ([Harrison et al., 2006](#); [Morris et al., 2019](#); [Rigoli et al., 2019](#)). Overall, this analysis examined 780 connections, controlling for age and gender differences. Significance testing was done using Threshold Free Cluster Enhancement (TFCE) with corrected connection significance threshold equal to 0.05.

4.4 Results

4.4.1 Demographics

All participants (healthy controls and individuals with SCI) had ACE-III cognitive scores within normal performance limits ($> 87/100$) (Bruno and Vignaga, 2019; Elamin et al., 2016; Hsieh et al., 2013b). There was no significant difference between SCI participants and controls in cognitive scores (Controls: $\mu = 97.89$, $SD = 1.80$; SCI: $\mu = 95.41$, $SD = 4.21$; $z = 1.91$, $p = 0.06$). Consistent with previous reports (Hill et al., 2016; Hohman et al., 2011; Pavisic et al., 2021; Reid and MacLulich, 2006), SCI participants in the study were significantly more depressed and anxious than healthy controls (Depression: $z = 4.41$, $p < 0.001$, Anxiety: $z = 3.08$, $p < 0.01$; Table 4.1 & Figure 4.8 a.). Since depression and anxiety correlated positively with each other in both groups (Controls Spearman's $R^2 = 0.19$, $p = 0.02$, SCI Spearman's $R^2 = 0.47$, $p < 0.001$; Figure 4.8 b.), a principal component analysis (PCA) was performed to extract a dimension that accounts for the maximum shared variance between the two measures. This dimension could be regarded as a measure of affective burden in participants and accounted for 84% of the variance shared between depression and anxiety. Higher scores of affective burden indicate more severe depression and anxiety. There was no significant correlation between cognitive scores and this affective dimension ($p = 0.07$ & $p = 0.49$, for controls and SCI respectively, controlling for age and gender).

4.4.2 Extensive sampling in SCI

As prescribed by rational behaviour, participants in both groups (SCI and healthy controls) adjusted the extent of their search (s) to the sampling cost (η_s), acquiring

N (M/F)	Controls		SCI		p-value*
	27 (13/14)		27 (13/14)		
	Mean	SD	Mean	SD	
Age	62.04	6.28	59.81	7.70	0.34
ACE-III	97.89	1.80	95.41	4.21	0.06
BDI-II	4.59	4.36	15.44	11.24	< 0.001
HADS Dep.	1.48	1.81	5.26	4.61	< 0.001
HADS Anx.	4.30	3.16	7.04	3.32	< 0.01

Table 4.1: **Demographics.** ACE-III: Addenbrooke’s Cognitive Examination. BDI-II: Beck Depression Inventory. HADS: Hospital Anxiety Depression Scale. * Student-test or Wilcoxon rank-sum test for parametric and non-parametric data, respectively.

fewer samples when this cost increased (Effect of η_s on s : $\beta = -0.11$, $95\%CI = (-0.14, -0.077)$, $t_{3232} = 6.52$, $p < 0.0001$; Figure 4.1 a., Table B.17). While there was no significant main effect of initial credit (R_0), its interaction with sampling cost was significant ($\beta = 0.02$, $95\%CI = (-0.04, -0.004)$, $t_{3232} = 2.41$, $p = 0.016$; Table B.17), which means that the aversive effect of sampling cost on the number of samples obtained was blunted when participants started their search with a larger credit reserve (Figure 4.1 a.).

The influence of these economic features (η_s and R_0) on the number of samples acquired was not significantly different between SCI participants and controls ($SCI \times \eta_s$: $p = 0.13$; $SCI \times R_0$: $p = 0.27$). Nevertheless, overall, individuals with SCI sampled significantly more than controls (Main effect of SCI on s : $\beta = +0.19$, $95\%CI = (0.058, 0.32)$, $t_{3232} = 2.81$, $p < 0.01$; Figure 4.1 a., Table B.17). Gathering more samples led SCI participants to finish their active search at lower levels of uncertainty (EE) than controls on average (Main effect of SCI on the EE reached at the end of the sampling phase: $\beta = 0.26$, $95\%CI = (-0.453, -0.06)$, $t_{3232} = 2.66$, $p < 0.01$; Table B.17), which translated into smaller localisation errors (Main effect of SCI on localisation error: $\beta = -0.18$, $95\%CI = (-0.35, -0.004)$, $t_{3232} = -2.01$, $p = 0.045$).

Next, I asked whether SCI participants' more extended information gathering led to better performance. To answer this question, I calculated, on each trial, the optimal number of samples, s^* , that maximises the expected value of the trial (EV). Both acquiring extra samples beyond this point (i.e., over-sampling) and not sampling enough to reach it (i.e., under-sampling) result in a smaller expected value (Figure 4.3). Thus, this analysis provided some insight into the usefulness of the extensive sampling behaviour SCI participants exhibited compared to controls.

Both healthy controls and individuals with SCI over-sampled relative to the optimal stopping point when the sampling cost was high ($p < 0.001$ for both groups, see Table B.19 for statistical details). Consistent with above, over-sampling in these conditions was significantly more pronounced in SCI participants compared to controls (Group difference in $(s - s^*)$ at high η_s ; Low R_0 : $t(52) = 2.066$, $p = 0.04$, High R_0 : $t(52) = 3.32$, $p < 0.01$). Thus, SCI participants' tendency to gather more information than controls in these conditions led them to acquire samples with a price outweighing their instrumental benefit.

By contrast, when the sampling cost was low, controls under-sampled relative to the optimal solution ($p < 0.001$ for the two conditions with low η_s , see Table B.19). Thus, because they acquired more samples in these conditions too, SCI participants better approached optimal sampling behaviour (Group difference in $(s - s^*)$ at low η_s ; Low R_0 : $t(52) = 3.29$, $p < 0.01$, High R_0 : $t(52) = 3.7$, $p < 0.001$; Figure 4.1 c.).

To summarise, individuals with SCI sampled more than controls across all experimental conditions, regardless of economic constraints. This was sub-optimal when sampling was expensive (i.e., they overpaid for information) but led to more optimal behaviour when sampling was cheap.

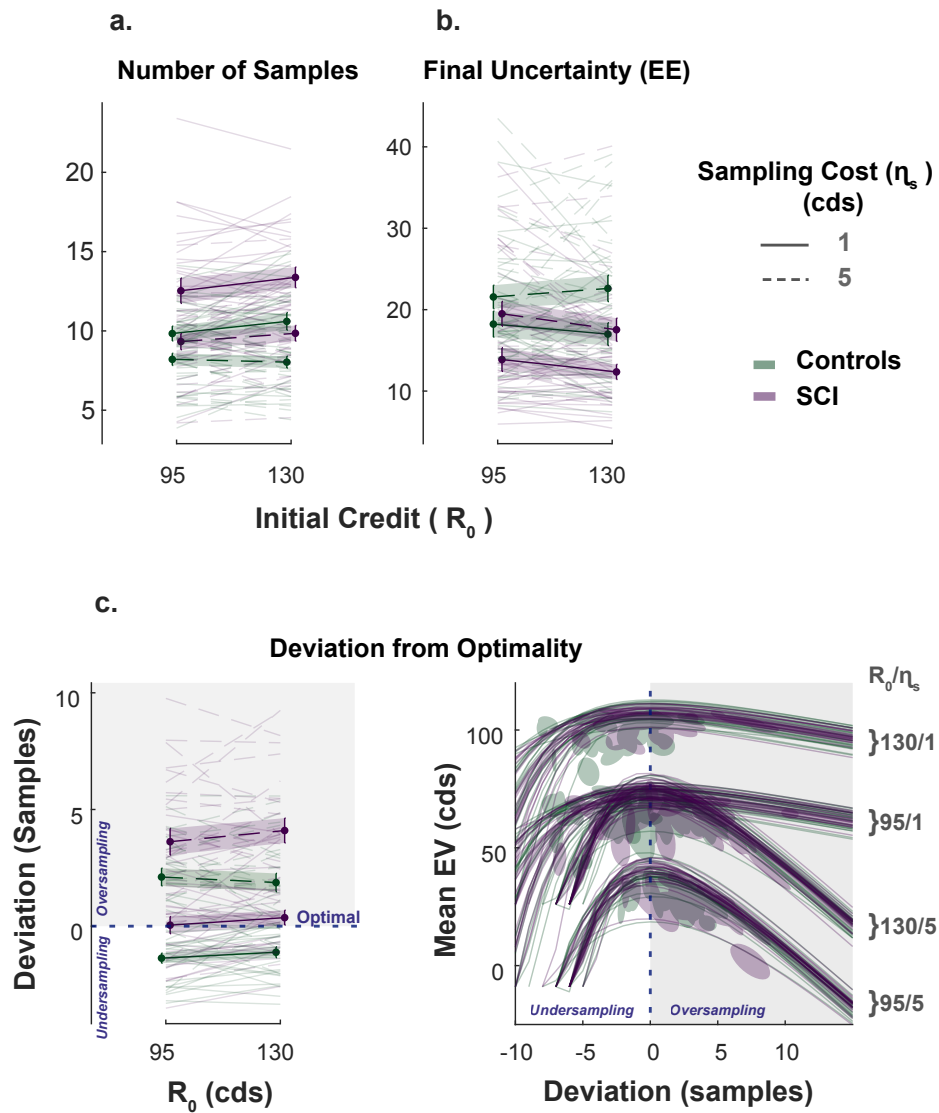


Figure 4.1: **Extensive sampling in SCI.** **a.** Across different conditions, individuals with SCI sampled more than healthy controls. **b.** Consequently, SCI participants reached final uncertainty levels (EE) lower than controls prior to committing to decisions. **c.** Healthy controls and individuals with SCI over-sampled when sampling cost was high. Over-sampling was more significant in SCI than healthy controls. When sampling cost was low, healthy controls under-sampled while SCI participants were optimal. The panel on the bottom right depicts the changes in expected value (EV) as a function of the number of samples deviating from optimal. The optimal number of samples is when EV is maximum. Error bars show $\pm$ SEM. See Tables B.17, B.18 & B.19 for full statistical details.

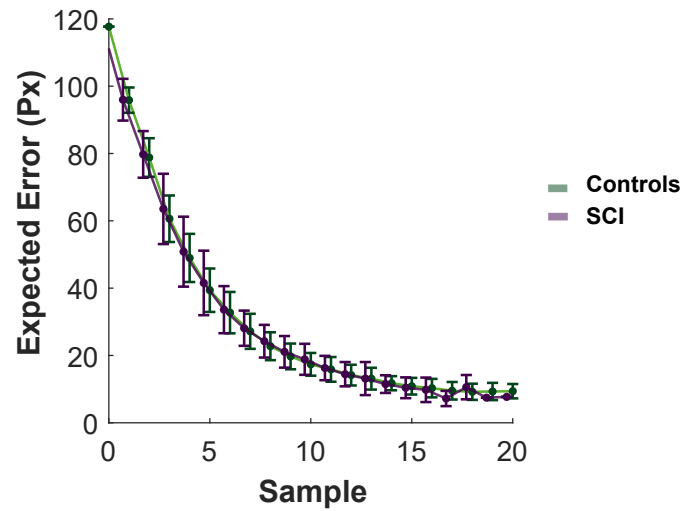


Figure 4.2: **Expected error as a function of sampling.** Reduction in uncertainty (expected error, EE) with successive sampling follows an exponential decay curve. The samples obtained towards the end of the search have limited benefits compared to the samples obtained earlier. Error bars show $\pm$ SEM.

4.4.3 Intact passive decision making in individuals with SCI

The passive version of the paradigm was used to investigate what drove SCI participants' extensive sampling behaviour. More specifically, two hypotheses were tested. First, SCI individuals might have inflated subjective estimates of uncertainty. If this were the case, they might need to reduce uncertainty to a greater extent in order to reach comparable subjective uncertainty levels. Second, SCI participants might have intact estimation of uncertainty but nonetheless assign greater weight to it when balancing it against reward. To test these hypotheses, SCI participants and healthy controls performed the passive version of the task in which they were required to first, report their estimations of experimentally defined levels of uncertainty and second, to accept/reject offers based on whether reward on offer is worth the risk imposed by uncertainty (Figure 4.4 a.).

Generalised mixed effects model was used to investigate the differences in sub-

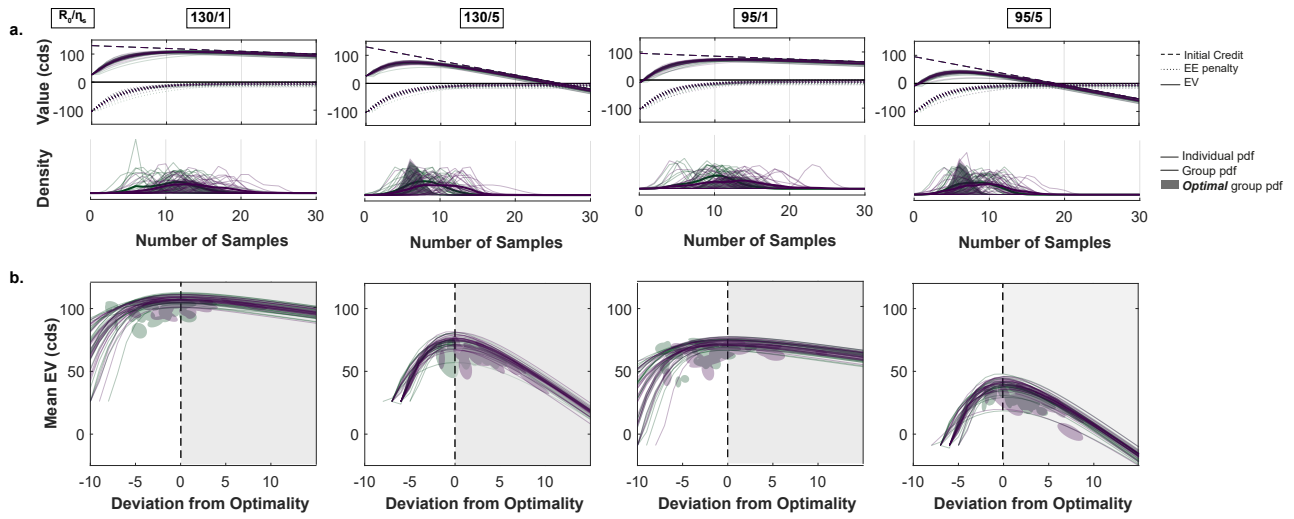


Figure 4.3: **Optimal sampling.** **a.** Expected value (EV) was calculated as ($EV = R_0 - s \cdot \eta_s - EE \cdot \eta_e$). This is the same as equation the scoring formula in task but with the error term replaced with expected error (EE). The timecourse of EV as a function of sampling is shown for every condition (R_0/η_s) and every participant. Optimal model predictions were computed as the *softmax* over EV timecourse per condition and participant (filled distribution). The thin and thick lines represent individual and group distributions from data, respectively. **b.** Deviation from optimal sampling was quantified as $(s - s^*)$ where s is the number of samples collected and s^* is the optimal mean. Lines show EV timecourses centred at maximum which represents optimal stopping point (s^*). Ellipses contain 90%CI of the means per participant.

jective uncertainty between SCI participants and controls. This showed no significant difference in this measure between the two groups (Interaction Group $\times$ EE : $\beta = +0.001$, $95\%CI = (-0.12, 0.11)$, $t_{5396} = -0.03$, $p = 0.98$; Figure 4.4 b., Table B.20), suggesting that the tendency to sample more in the active experiment was unlikely caused by biased subjective estimates of uncertainty (i.e., there is no difference in the perceived informational utility of the samples). Similarly, there was no significant difference between the two groups in offer acceptance or in the effects of uncertainty and reward on offer acceptance (Main effect of SCI on offer acceptance: $\beta = +0.029$, $95\%CI = (-0.75, 0.80)$, $t_{5392} = +0.07$, $p = 0.94$; SCI interaction with reward and uncertainty: $p = 0.70$ & $p = 0.60$, respectively; Figure 4.4 c., Table B.21). This is consistent with the finding that SCI participants' extensive sampling behaviour in the active paradigm was mostly independent from economic constraints (no significant interaction SCI $\times$ R_0 or SCI $\times$ η_s ; Figure 4.1).

Taken together, these results indicate that extensive sampling in SCI is not related to the way individuals estimate or value uncertainty. Instead, it is likely to capture an intrinsic drive to gather information specifically when SCI have agency over the level of uncertainty (i.e., during active sampling) (see computational modelling results below capturing this effect).

4.4.4 Faster and more efficient sampling in SCI

The key advantage of *Circle Quest* paradigm is the possibility to investigate not only how much information people gather but also how quickly and efficiently they do so. To capture these extra dimensions of sampling behaviour, I used two behavioural measures: (1) inter-sampling interval, ISI , which is the average time interval between consecutive screen touches (shorter ISI indicates faster sampling); (2) information extraction rate, α , which provides an estimate of the rate

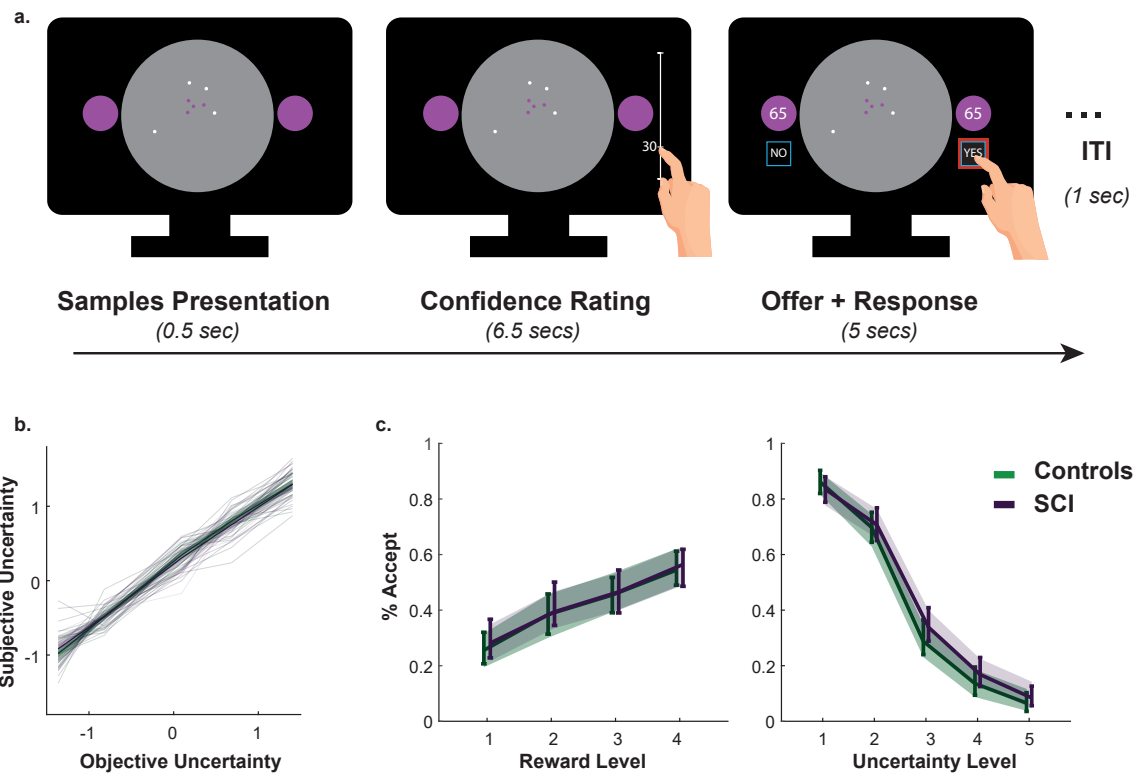


Figure 4.4: Intact metacognitive judgement and passive decision making in SCI. **a.** Subjective estimates of uncertainty (z-scored signed-flipped confidence ratings) mapped well onto experimentally defined uncertainty across study participants. There was no significant difference between SCI participants and controls in estimating uncertainty. **b.** There was no significant difference in offer acceptance between individuals with SCI and controls, indicating similar weights assigned to uncertainty and reward when making decisions. Error bars show 95% CI. See Tables B.20 & B.21 for statistical details.

at which the EE decays over successive samples (higher α values indicate higher sampling efficiency).

In Chapters 2 & 3, I previously reported a speed-efficiency trade-off whereby slower sampling was associated with greater information extraction rate (i.e., greater reduction of uncertainty at each step of the search). This finding was replicated in the present study (Effect of ISI on α ; Controls: $\beta = +0.054$, $95\%CI = (0.032, 0.075)$, $t_{1618} = 4.97$, $p < 0.0001$; SCI: $\beta = +0.052$, $95\%CI = (0.028, 0.076)$, $t_{1618} = 4.97$, $p < 0.0001$; Figure 4.5 c., Table B.22). Investigating group effect using LMM showed that, overall, SCI participants sampled significantly faster than healthy controls (Main effect of group on ISI : $\beta = -0.29$, $95\%CI = (-0.43, -0.16)$, $t_{3232} = -4.24$, $p < 0.0001$; Figure 4.5 a., Table B.22). Remarkably, despite this faster sampling, SCI participants reduced uncertainty as efficiently as controls (Main effect of group on α : $\beta = +0.007$, $95\%CI = (-0.015, 0.03)$, $t_{3232} = 0.61$, $p = 0.54$; Figure 4.5 b., Table B.22). In other words, individuals with SCI exceeded the speed-efficiency trade-off that characterised healthy controls' sampling (Figure 4.5 c.).

Overall, the performance of individuals with SCI indicates *hyperreactivity to uncertainty*, manifested as more extended, faster though equally efficient information sampling compared to controls.

4.4.5 Computational model of sampling speed, efficiency and extent

To further characterise active sampling behaviour, I fitted the computational model validated in Chapter 2, accounting for a putative hidden cognitive cost in addition to the economic costs imposed by the task. Participants are assumed to incur a cognitive cost at each step of their search that is a function of how efficiently and

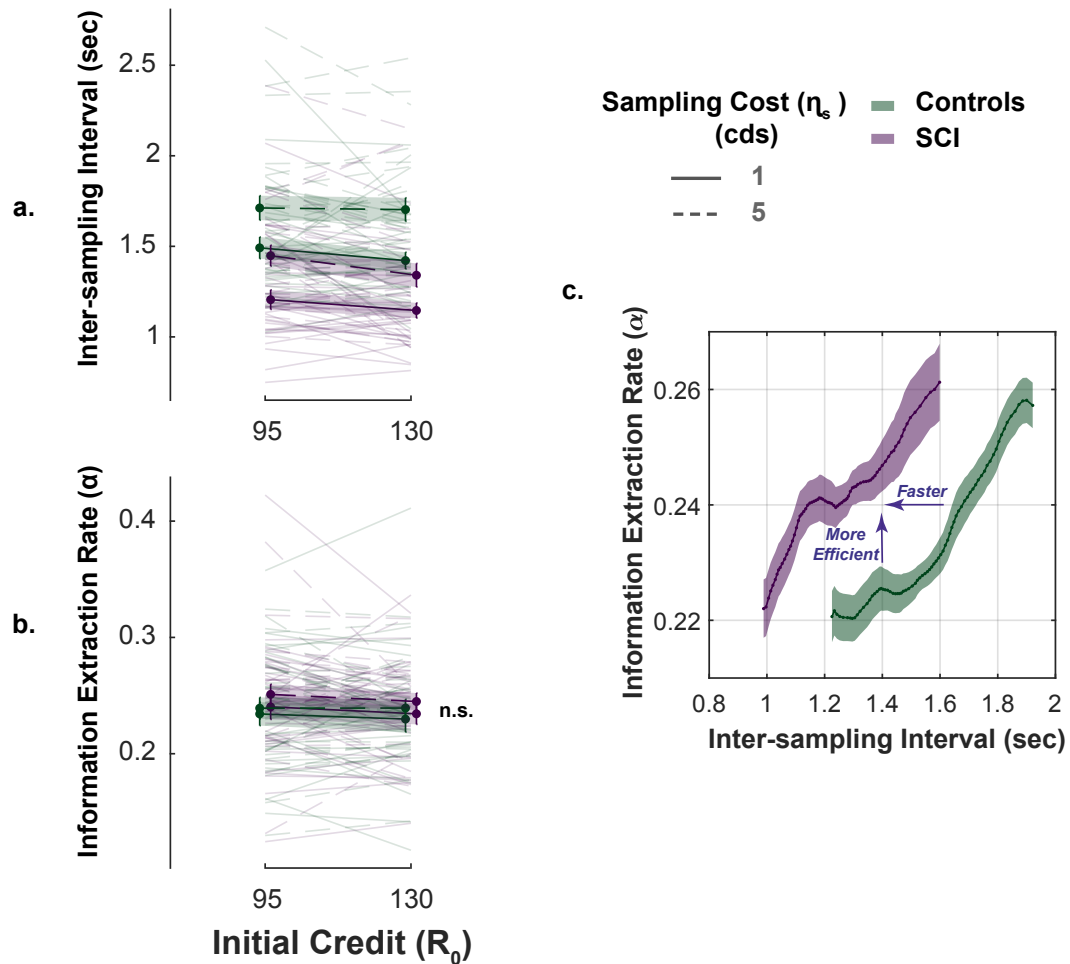


Figure 4.5: **Faster but efficient sampling in SCI.** **a.** Across different conditions of the task, SCI participants sampled faster than the healthy controls. **b.** Sampling efficiency was not different between individuals with SCI and control. **c.** Faster sampling was associated with lower efficiency giving rise to a speed-efficiency trade-off. SCI participants exceeded the speed efficiency trade-off that characterised controls' sampling behaviour as they extracted more information than the control per unit time (sec). Conditional plot was generated by sliding 25% quantile bins of ISI and computing average α for each bin. Error bars show $\pm SEM$. See Table B.22 for full and statistical details.

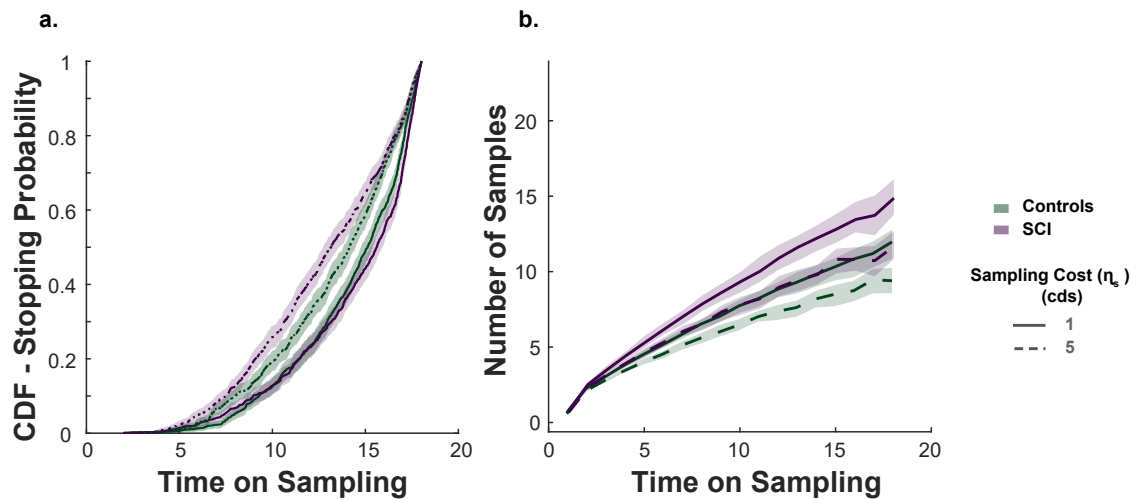


Figure 4.6: **Sampling as a function of time.** **a.** Probability to stop sampling at each time point during the sampling phase. When the sampling cost was high, participants were more likely to finish their sampling earlier. This effect was more evident in individuals with SCI as they had faster sampling rates (see Figures 4.1 & 4.5). **b.** Number of samples as a function of time. This visualisation shows that SCI participants started to acquire more samples than controls early during the sampling phase. This suggests individuals with SCI opted to decrease uncertainty as soon as possible and that their faster sampling was evident throughout the sampling phase. Shaded lines show 95% CI.

quickly they sample. The model calculates the expected utility of a sample (EU_s) given these costs and returns five parameter estimates per participant. The first two parameters represent the weights participants assign to sample costs (w_s) and benefits (w_e). The other three parameters describe the cognitive cost function in terms of a penalty for sampling speed (w_{speed}) and efficiency (w_α), as well as an intercept (w_0).

The analysis of computational model parameters was in agreement with the analysis of raw behaviour reported in previous sections. SCI participants and controls did not significantly differ in the decision weight they assigned to sampling cost and benefit during active search ($p = 0.80$ & $p = 0.48$, respectively; Figure 4.7). This is an alternative way to parameterise the fact that extensive sampling in SCI was not driven by task-related economic considerations. By contrast, the cognitive cost function of SCI participants differed from those of controls. SCI participants assigned a lower subjective penalty to sampling speed and efficiency (Group difference; w_{speed} : $z = -2.35$, $p = 0.018$, w_α : $z = 2.12$, $p = 0.03$; Figure 4.7). This explains why they performed the task along a different speed-efficiency trade-off from controls. While I previously demonstrated that cognitive cost of efficiency correlates with subjective task-related fatigue reports in healthy young healthy people (Figure 2.8), this correlation was not significant in SCI. This might be due shorter duration of the task used in SCI. Alternatively, it might indicate that cognitive effort cost of efficiency and speed in SCI are not reflective of task-related performance and reflect a more stable trait such as general affective functioning. The intercept term w_0 – which captures a constant subjective cost associated with sampling actions (e.g., motor cost) – did not differ between SCI participants and controls ($p = 0.80$).

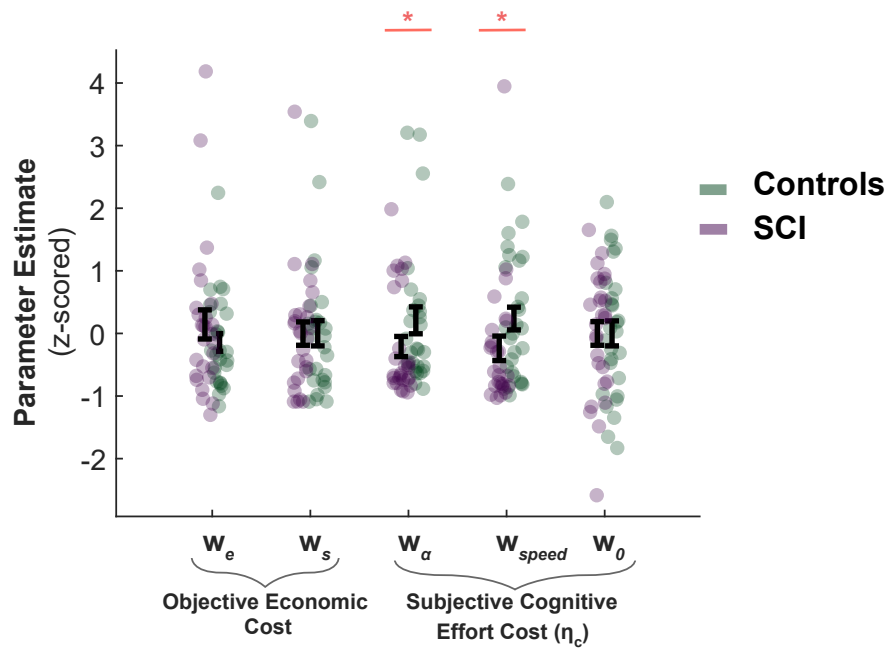


Figure 4.7: **SCI participants assign lower costs to speed and efficiency..** There was no significant difference in the weights SCI participants assigned to sampling benefit (w_e) or cost (w_s), suggesting the differences in active sampling between the two groups were unlikely due to economic constraints of the task. On the other hand, individuals with SCI had lower weights assigned to efficiency (w_α) and speed (w_{speed}), indicating a lower cognitive cost to engage in faster and more efficient sampling. w_0 captures a subjective fixed cost of sampling that is not explicitly specified in the task (e.g., cost of the motor action). This was not significantly different between the two groups. * : $p < 0.05$

4.4.6 Affective burden is associated with more extensive and faster active sampling

Next, I investigated whether markers of hyperreactivity to uncertainty in SCI (faster and extensive sampling) were associated with affective burden. Non-parametric Spearman's partial correlations controlled for age and cognitive score showed that affective burden across SCI participants was significantly associated with sampling speed as well as with deviation from optimal sampling, such that both faster and extensive sampling were associated with higher affective burden (Correlation between affective burden and *ISI*: $R^2 = 0.17$, $p = 0.039$; correlation between affective burden and $s - s^*$: $R^2 = 0.17$, $p = 0.041$; Figure 4.8 c.). A similar pattern was also observed in the control group for over-sampling behaviour ($R^2 = 0.17$, $p = 0.035$) but not for *ISI* ($p = 0.78$).

To assess the individual contribution of anxiety and depression to these findings in SCI, the same analysis was performed separately for each affective component. This showed that BDI-II score (depression) correlated with faster sampling ($R^2 = 0.17$, $p = 0.039$) but not over-sampling ($p = 0.15$) in SCI. The HADS score (anxiety) on the other hand correlated with over-sampling ($R^2 = 0.17$, $p = 0.038$) but not speed ($p = 0.16$). However, these effects became insignificant ($p = 0.12$ for both) when the two affective components partialled out each other (partial correlations), suggesting that while there might be distinctive effects of depression and anxiety, these effects are better explained by the general affective burden imposed by these two dimensions given their association.

Finally, the correlation between affective burden and passive task performance was investigated using LMMs. The results showed that affective burden had no significant effect (main or interaction) on subjective uncertainty or acceptance probability (Main effect of affective burden on subjective uncertainty: $\beta =$

-0.003 , $t_{5394} = -0.27$, $p = 0.79$; Main effect of affective burden on offer acceptance: $\beta = -0.151$, $t_{5390} = -1.96$, $p = 0.05$; See Tables B.20 and B.21 for full statistical details including interactions).

These results thus indicate that hyperreactivity to uncertainty (indexed by faster and extensive sampling) is associated with affective dysregulation in SCI, mainly when agency is involved.

4.4.7 Increased insular-hippocampal connectivity in SCI is associated with faster sampling

Resting-state functional MRI data were collected in 23 SCI participants and 25 controls. I first investigated differences in functional connectivity between SCI participants and controls using a whole-brain network functional connectivity analysis. This entailed investigating the connections between 40 atlas-defined regions of interest (ROIs) that represent the key nodes in brain networks including salience, default mode, sensorimotor, visual, dorsal attention, frontoparietal, language, and cerebellar networks as well as limbic brain regions including the hippocampus, para-hippocampus and amygdala (see *Methods*).

Compared to healthy controls, individuals with SCI showed significantly greater functional connectivity between the insular cortex and hippocampal/para-hippocampal regions (Insular-hippocampal: $TFCF = 64.82$, $p_{FWE} < 0.01$, Insular-para-hippocampal: $TFCF = 70.02$, $p_{FWE} < 0.01$; Figure 4.9 a., Table 4.2). There was no other significant difference in resting functional connectivity between any of the other ROIs included in the analysis. Thus, functional connectivity disruptions in SCI participants appeared to be limited and specific to the insular-hippocampal network highlighted in Figure 4.9 a.

Finally, I asked whether such functional signatures of SCI bore any relationship

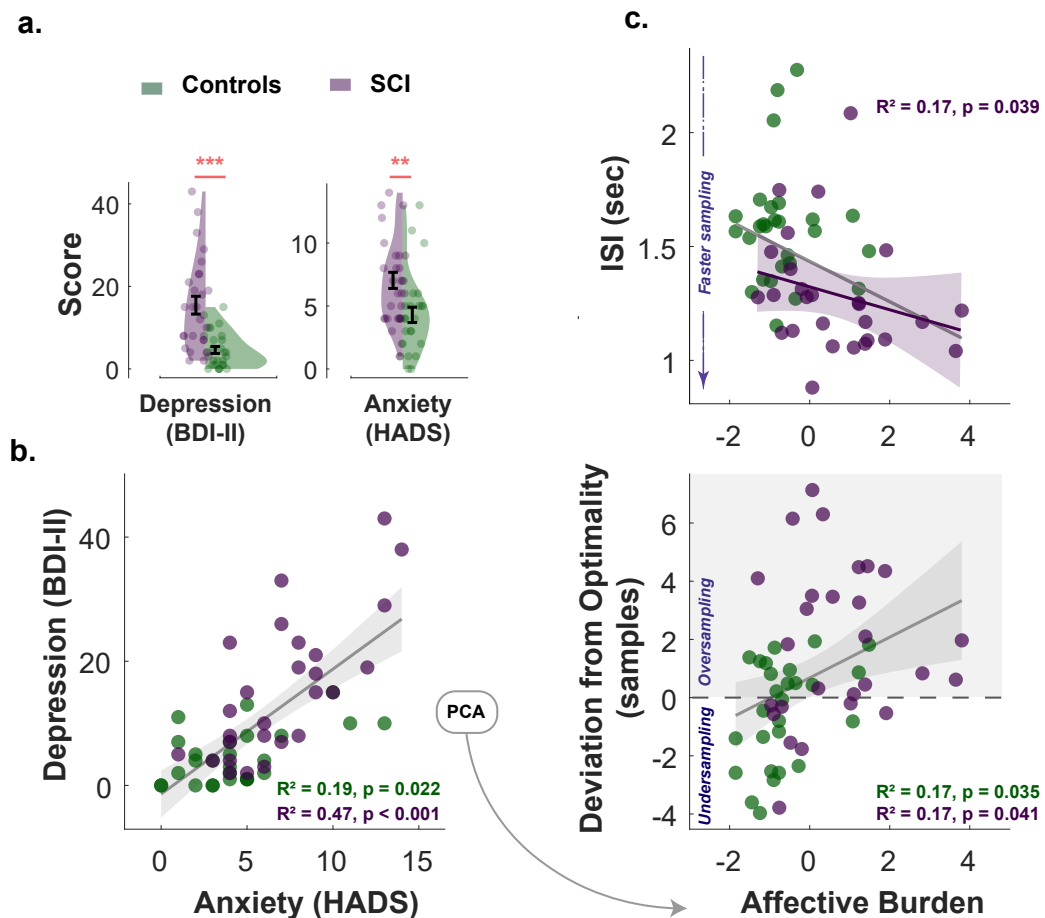


Figure 4.8: Affective burden correlates with faster and extensive sampling.. a. Individuals with SCI were significantly more depressed and anxious than healthy matched control. **b.** Anxiety scores and depression scores significantly correlated with each other across study participants of both groups. An affective burden score corresponding to severity of depression and anxiety was extracted using principal component analysis (PCA). This dimension accounted for 84% of the variance between anxiety and depression. **c.** Affective burden was associated with increased reactivity to uncertainty indexed by speed and extent of sampling. More severe affective burden (i.e., higher severity of anxiety and depression) were associated with faster (shorter *ISI*) and more extensive sampling (i.e., over-sampling). BDI II: Beck's Depression Inventory. HADS: Hospital Anxiety and Depression Scale (only anxiety score was included). *ISI*: Inter-sampling Interval in seconds. ** : $p < 0.01$, *** : $p < 0.001$. Error bars show $\pm$ SEM. Grey and purple lines show regression across all participants and within SCI group, respectively. Shaded area in correlation plots show 95% CI.

Analysis Unit	Statistic	p-unc	p-FDR	p-FWE
Cluster 1	TFCE = 70.02	0.000025	0.001730	0.002000
Connection pPaHC l - IC r	T(44) = 4.63	0.000032	0.017440	
Connection pPaHC l - IC l	T(44) = 4.45	0.000058	0.017440	
Connection pPaHC r - IC l	T(44) = 3.09	0.003464	0.150095	
Cluster 2	TFCE = 64.82	0.000029	0.001730	0.003000
Connection Hipp r - IC l	T(44) = 4.40	0.000067	0.017440	
Connection Hipp l - IC r	T(44) = 4.07	0.000195	0.038090	
Connection Hipp l - IC l	T(44) = 3.74	0.000534	0.083315	

Table 4.2: **ROI to ROI resting functional connectivity.** PaHC: para-hippocampus. Hipp: hippocampus. IC: insular cortex. unc: uncorrected. FWE: family-wise error. FDR: false discovery rate.

to the behavioural markers of hyperreactivity to uncertainty identified above (*ISI* & $s - s^*$). This analysis used non-parametric partial correlations controlling for age, gender, and cognitive score. The strength of connectivity from ROI-ROI analysis between bilateral insular cortex and hippocampus (right and left) was extracted for this purpose. Multiple correlation testing was corrected with Bonferroni's method. Across SCI participants, stronger bilateral insular connectivity with the right hippocampus significantly correlated with faster sampling rate ($R^2 = 0.44$, $p_{corr} < 0.01$; Figure 4.9 b.). This suggests a role for this network over-activity in the urgent information sampling behaviour exhibited by SCI participants. There was no significant association with deviation from optimal sampling ($p = 0.19$), suggesting that sampling speed might be a more sensitive marker of uncertainty reactivity, despite that these two measures were significantly correlated in the group ($R^2 = 0.28$, $p < 0.01$). Similarly, insular-hippocampal connectivity was not significantly correlated with affective burden across SCI participants ($p = 0.37$).

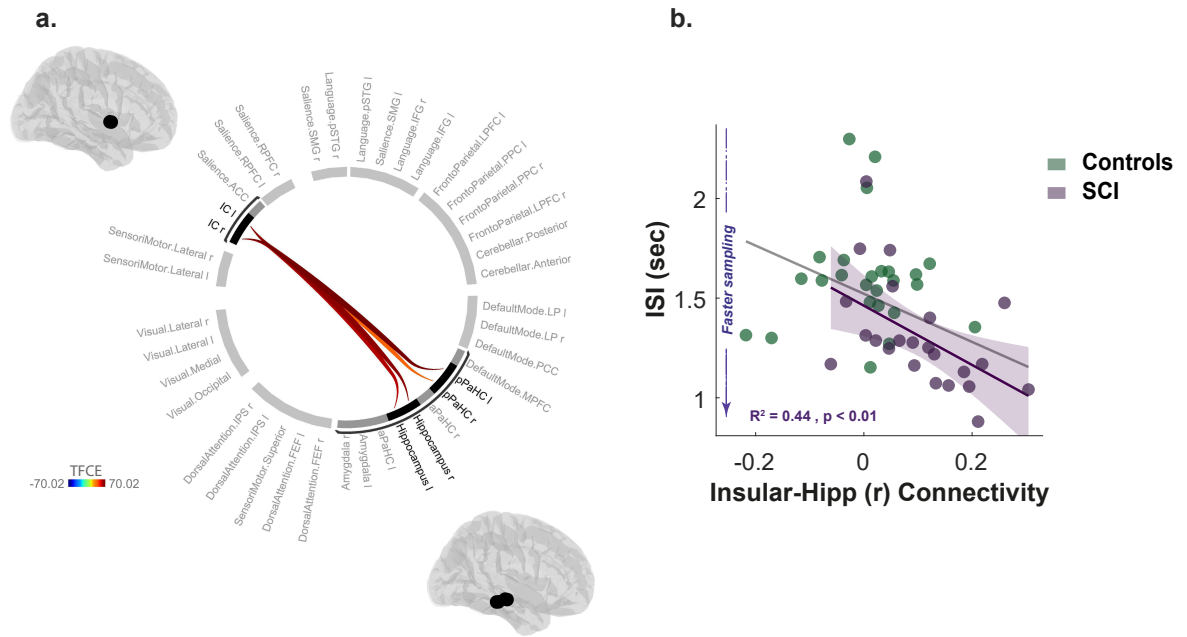


Figure 4.9: Increased insular hippocampal connectivity in individuals with SCI compared to healthy controls. **a.** Whole-brain ROI-to-ROI functional connectivity analysis with 40 ROIs from different brain networks and regions. SCI participants have increased functional connectivity between insular cortex (IC) and hippocampal/para-hippocampal (PaHC) regions. TFCE: Threshold Free Cluster Enhancement. See Table 4.2 for further statistical details. **b.** Increased insular-hippocampal connectivity correlated with faster sampling (shorter *ISI*) in SCI, suggesting that hyperreactivity to uncertainty is related to this specific network. Grey and purple shaded line show regression across all participants and within SCI group, respectively. Shaded area show 95% CI.

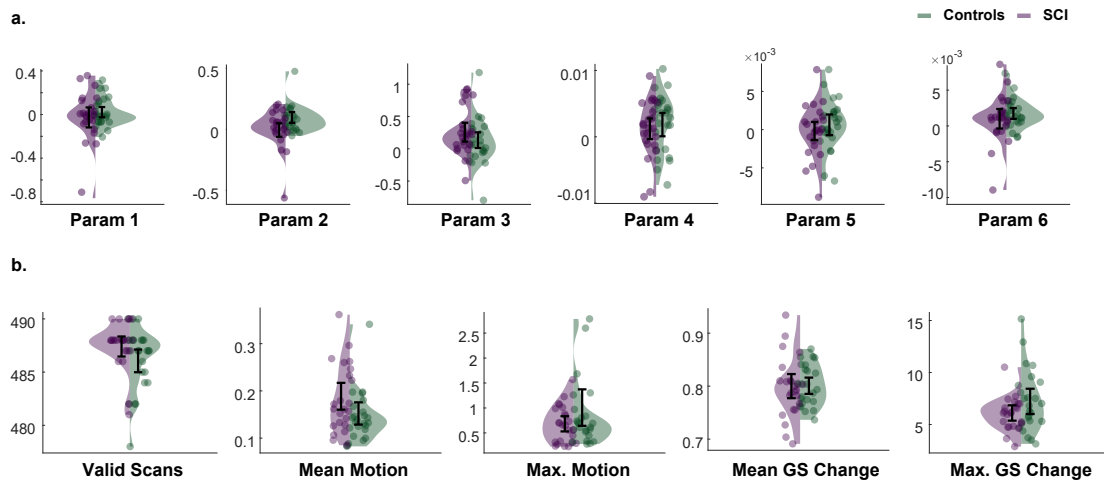


Figure 4.10: Motion parameters and other quality control measures. **a.** Six motion parameters were used during realignment procedure for rs-fMRI processing. These correspond to six timeseries containing three translational and three rotational parameters over time for each subject. None of these parameters was significantly different between SCI and control group (all $p_{corr} > 0.61$). **b.** Five quality control estimates were used during preprocessing of neuroimaging data (Whitfield-Gabrieli and Nieto-Castanon, 2012). These included number of valid scans after scrubbing procedure, mean and maximum motion (extracted from the six parameters above), mean and maximum global signal change. None of these parameters was significantly different between the two groups (all $p_{corr} > 0.16$). Based on mean motion and mean global signal changes, four potential outliers (three SCI participants and one control with values above or below $Q3 + 1.5IQR$) were identified. A second version of neuroimaging analysis was performed with these participants excluded (Table B.25). There were no changes to the results or conclusions made in the paper. These findings suggest that rs-fMRI differences between SCI participants and controls are unlikely due to motion artifacts. Mean and max motion was calculated based on Power et al. (2012). Error bars show $\pm 95\%$ CI.

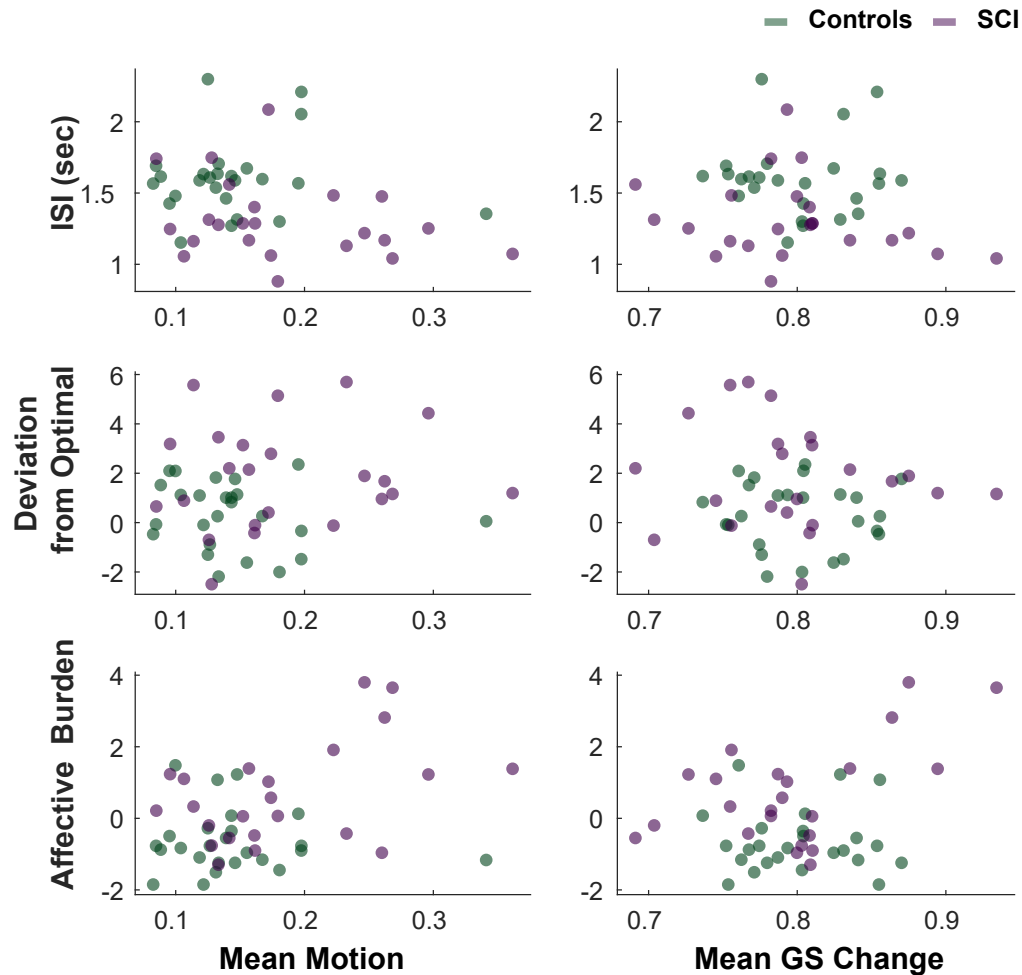


Figure 4.11: **Quality control parameters do not correlate with task measures and affective burden.** Across study participants, no correlation was found between mean motion (or global signal change) and hyperreactivity to uncertainty (*ISI* or Deviation from optimal) or affective burden (all $p_{corr} = 1$). Specifically, no correlation between *ISI* (the measure that correlates with insular-hippocampal connectivity) and these quality control measures (mean motion and mean GS change) across SCI participants ($p = 0.13$ & $p = 0.49$, respectively). These findings suggest that correlation between *ISI* and insular-hippocampal connectivity is unlikely due to motion artifacts. Correlation were controlled for age and gender. Error bars show $\pm 95\%$ CI.

4.5 Discussion

A rich body of literature indicates a strong association between SCI and affective dysregulation such as anxiety and depression (Hill et al., 2016; Hohman et al., 2011; Pavisic et al., 2021; Reid and MacLulich, 2006). However, the mechanisms underlying such a burden are not fully established. In this study, I hypothesised that affective dysfunction in SCI might be related to deficits in processing uncertainty. Using a purpose-designed behavioural paradigm, I investigated how people decide and act under uncertainty in active and passive contexts. In the active form, participants could gather information at a cost to reduce uncertainty before committing to decisions. In the passive form, they made decisions responding to offers that had fixed levels of uncertainty and potential reward.

The results showed that when participants had agency (i.e., in the active form), individuals with SCI exhibited behaviour indicative of increased reactivity to uncertainty, manifested as more rapid and extensive sampling compared to age- and gender-matched healthy controls. These behavioural markers of heightened reactivity to uncertainty correlated with the severity of affective burden in SCI participants. Furthermore, resting functional neuroimaging analysis showed that individuals with SCI had increased insular-hippocampal connectivity, which in turn correlated with reactivity to uncertainty indexed by sampling speed. By contrast, estimation and weighing of uncertainty in passive decisions were both intact in SCI participants, suggesting that their hyperreactivity to uncertainty was specifically expressed in an active situation in which uncertainty is controllable. Overall, the results point to a specific deficit in processing uncertainty in individuals with SCI that might be underlying their affective dysregulation and is related to increased insular-hippocampal connectivity in the condition.

These results resonate with previous research indicating that people with depression and anxiety might have altered uncertainty processing ([Bishop and Gagne, 2018](#); [Boswell et al., 2013](#); [Carleton et al., 2012](#); [Grupe and Nitschke, 2013](#); [Gu et al., 2020](#); [Hartley and Phelps, 2012a](#); [Pulcu and Browning, 2019](#); [Saulnier et al., 2019](#)). A recent investigation, for example, showed that a common factor accounting for shared variance between both syndromes was associated with disrupted learning in probabilistic environments reflecting impaired uncertainty processing ([Gagne et al., 2020](#)). Other reports pointed to a possible alteration of uncertainty estimation and reward-related valuation in these syndromes affecting decision making under uncertainty ([Pizzagalli et al., 2008, 2005](#); [Pulcu and Browning, 2019](#)). However, evidence on how affective dysfunction relates to more active forms of behaviour such as information gathering prior to committing decisions is limited.

One early investigation in social psychology showed that individuals suffering from depression tend to acquire more high-utility information than non-depressed individuals in a simulated interview environment where participants played the role of the interviewer and had to select interview questions from a standardised list of questions that differed in their diagnostic utility ([Hildebrand-Saints and Weary, 1989](#)). While this investigation along with other similar reports from the social psychology literature advance the notion that disrupted information gathering might be a key feature in affective disorders, a mechanistic account supporting this claim is still not established ([Aderka et al., 2013](#); [Camp, 1986](#); [Joiner et al., 1999](#); [Locander and Hermann, 1979](#)). For example, previous studies using classical behavioural paradigms of information seeking such as the beads task failed to report consistent effects of anxiety and depression on performance ([Jacoby et al., 2014](#)). Such inconsistencies might be due to the fact that the behavioural paradigms used in these prior studies often neglect an important aspect of infor-

mation gathering – controllability – which has been hypothesised to be a crucial feature of both anxiety and depression ([Abramson et al., 1978](#); [Barlow, 1991](#)). In the present study, this important component was accounted for by using a novel behavioural paradigm allowing participants to gather information with minimal limitations to the speed and efficiency of sampling. This in turn revealed an insightful aspect of information gathering behaviour in individuals with SCI who not only sampled more than controls, but also showed that they do this more rapidly without losing efficiency.

One might argue that rather than suggesting that SCI individuals are hyperreactive to uncertainty in the active task, the findings might alternatively be explained by a lower reactivity to reward – as participants lost more credits to obtain the extra information. However, some observations in the study suggest that this might not be the case. First, the influence of economic constraints (R_0, η_s) on sampling behaviour and speed did not significantly differ between individuals with SCI and controls. If SCI participants were less reactive to reward, then one would expect economic constraints to affect sampling behaviour in SCI participants to a lesser degree than age- and gender-matched controls. Instead, the group effect (i.e., acquiring more samples in individuals with SCI) was equally manifested in all experimental conditions, regardless of the current cost-benefit structure. Second, acquiring more samples indeed allowed SCI participants to achieve lower uncertainty levels prior to decision, suggesting that these additional samples carried instrumental utility and were not merely reflective of wasteful sampling behaviour driven by insensitivity to reward.

Another account of SCI individuals' extensive sampling behaviour might involve subjective costs that are not directly specified in economic terms in the task. Namely, SCI individuals and controls might differ in the subjective cost they assign to sampling speed and efficiency. As demonstrated previously, these addi-

tional agent-related factors contribute to the utility of the samples being acquired and thus influence the extensiveness of sampling (see Chapters 2 & 3). Given that SCI participants sampled faster but as efficiently as controls, these subjective costs appear to be lower in this population. As a result, samples carry higher utility overall, which promotes more extended data gathering. Potentially, there are several other subjective costs that people might be considering when gathering information. For example, SCI participants might have exaggerated cost linked to bad performance or inaccurate placements of the circle. I aimed to limit this specific cost by not displaying the hidden circle as feedback and showing the credits won or lost instead (task).

In addition, since the task depends on touching the screen to obtain clues, the cost of these motor actions might have influenced sampling behaviour (Carland et al., 2019; Cisek and Kalaska, 2010; Morel et al., 2017; Pierrieau et al., 2021; Rangel and Hare, 2010; Scott, 2012). It is possible, for example, that SCI participants might be regarding reaching and touching the screen as less effortful than controls or assigning lower costs for motor precision. While I tried to limit the influence of the motor aspects on performance by strictly controlling the settings (e.g., fixed distance from the screen, using only index finger of dominant hand), the contribution of motor elements to the observed behaviour cannot be entirely determined or excluded and might pose a limitation. Such inter-individual differences could be in part captured by the intercept term in the computational model used to fit active information sampling data (w_0), which was not significantly different between the two groups.

In a similar vein, while the results from the passive task suggest that SCI individuals have intact estimation of uncertainty, this might not necessarily apply to a dynamic situation such as the active task. The distinct contexts of the two tasks (passive viewing vs. active gathering) may impose different computations

involved in uncertainty estimation. For example, SCI individuals and controls might specifically differ in how they judge self-generated configurations of uncertainty (active task) vs. externally predefined ones (passive task) ([Acosta, 1982](#); [Gaschler et al., 2014](#); [Kemper and Gaschler, 2017](#); [Kemper et al., 2012](#)). People might also differ in the reference points (temporal or spatial) they compare updated environments with as more information is added ([Koop and Johnson, 2012](#); [O'Donoghue and Sprenger, 2018](#); [Sher and McKenzie, 2006](#); [Tversky and Kahneman, 1986](#)). It is also possible that these computations might be cognitively effortful, influencing how frequently or/and efficiently people re-estimate and update uncertainty during their search ([Bhui et al., 2021](#); [Lieder and Griffiths, 2020](#)). All these factors might have contributed with different degrees to the pattern of the results observed in the study and might be a limitation to active information sampling investigations in general.

It should also be noted that the measure of subjective uncertainty based on self-reports in the passive may map imperfectly onto actual internal uncertainty ([Nava-jas et al., 2017](#); [Peters, 2022](#)). Self-reports of confidence might be contaminated by other factors such as perceptual uncertainty (e.g., meaning of perceived stimuli on the task), memory (e.g., remembering task instructions or previous estimations) and decisions (e.g., confidence in estimation). The contribution of these metacognitive dimensions could be explored in future studies, especially given that SCI – by definition – is characterised by inconsistency between self-report estimates and objective measures ([Jessen et al., 2020](#)). Similarly, SCI might involve different cognitive domains (e.g., memory, attention, language, etc.) with different levels of severity ([Diaz-Galvan et al., 2021](#); [Jessen et al., 2020](#); [Miebach et al., 2019](#); [Si et al., 2020](#); [Smart et al., 2014](#)). How such differences relate to uncertainty processing and affective burden will require a fine-grained approach aimed specifically at characterising SCI cognitive complaints in-depth to disentangle the

dimensions involved.

Various brain regions have previously been implicated in anxiety and depression and their mechanistic characterisation as deficits in uncertainty processing including amygdala ([Grupe and Nitschke, 2013](#); [Morriss et al., 2019](#)), hippocampus ([Gray and McNaughton, 2003](#); [Harrison et al., 2006](#); [Rigoli et al., 2019](#); [Strange et al., 2005](#); [Tobia et al., 2012](#)), and insular cortex ([Grupe and Nitschke, 2013](#); [Morriss et al., 2019](#); [Tanovic et al., 2018](#)). Consistent with these reports, I found that individuals with SCI displayed heightened connectivity between these regions (insular-limbic).

Conceptually, the insula stands out in the context of SCI not only because of its consistent implications in various forms of uncertainty processing and affective syndromes in health and disease ([Morriss et al., 2019](#); [Namkung et al., 2017](#); [Paulus and Stein, 2006](#); [Singer et al., 2009](#); [Tanovic et al., 2018](#)), but also because of its potential role in subjective awareness and interoception ([Craig, 2009](#)). The insular cortex receives input from different brain regions carrying interoceptive information about various bodily sensations, such as temperature, heartbeat, bowel distension and more ([Namkung et al., 2017](#); [Uddin et al., 2017](#)). Subjective experience of these stimuli has been shown to correlate with insular activity on functional neuroimaging using MRI or positron emission tomography ([Craig et al., 2000](#); [Critchley et al., 2004](#)). More recent accounts of insular function extend this contribution of subjective awareness to involve emotional states and higher subjective awareness ([Chang et al., 2013](#); [Craig, 2009](#); [Namkung et al., 2017](#)). It is thus not surprising to find insular involvement in a condition that is primarily defined by altered subjective experience.

A few studies have demonstrated altered insular task-related activity in SCI linked to impaired memory performance and future-guided decision making, however,

without pointing to how these findings are related to affective burden or subjectivity (Cai et al., 2020; Hu et al., 2017). By contrast, damage to the insula might impair subjectivity and self-awareness as seen in patients with anosognosia for hemiplegia and other forms of insular injury (Fotopoulou et al., 2010; Karnath et al., 2005; Spinazzola et al., 2008), as well as resulting in dysfunctional emotional awareness (e.g., as seen in fronto-temporal dementia), under-reactivity, lack of self-monitoring and passivity (F et al., 1999; Kleiner et al., 2007; VE et al., 2006). Such findings are opposite to what is observed in individuals with SCI who often report heightened levels of subjective affective dysfunction and were found in this study to be behaviourally more reactive.

This insula-centred formalisation of affective dysfunction, uncertainty processing, and subjectivity might be further supported by taking into consideration hippocampal contribution. One prominent view of hippocampal involvement in goal-directed behaviour suggests that it constitutes a crucial part of a behavioural inhibition system (BIS) that is concerned with processing aversive cues such as uncertainty (Gray and McNaughton, 2003). According to this view, the hippocampus acts as a comparator between one's expectations and the environment, resulting in behavioural aversion to threatening and negative stimuli. It has therefore been suggested that hyperactivity of the BIS might be an important neurobiological basis of anxiety and affective dysregulation (Gray and McNaughton, 2003). When anticipating decisions and actions under uncertainty, the hippocampus might be encoding possible future states and their associated risks (Addis et al., 2011; Martin et al., 2011; Schacter et al., 2008, 2017; Weiler et al., 2010). However, when such situations are avoidable (as in the active task), aversion might be expressed as a propensity to quickly collect information to avoid facing uncertainty in the future.

Hippocampal signals encoding future trajectories and prior experiences from these

contexts might be shared with the insula, which in turn process emotional responses resulting in a feeling of anxiety and depression ([Chang et al., 2013](#); [Craig, 2009](#); [Paulus and Stein, 2006](#)). Additionally, because of the hippocampus' well-established mnemonic function, insular-hippocampal processing of uncertainty might also affect one's awareness of memory performance, giving rise to subjective cognitive complaints characterising SCI. Testing such a hypothesis will require future research with a detailed examination of the nature of subjective complaints, their severity, and association with uncertainty and expression of concerns.

These neuroimaging findings are consistent with previous fMRI studies (task-related and resting) in SCI showing altered connectivity between temporal brain regions (e.g., hippocampus and para-hippocampus) and several other areas and networks including default mode and salience networks ([Cai et al., 2020](#); [Dillen et al., 2017](#); [Hafkemeijer et al., 2013](#); [Hu et al., 2017](#); [Rodda et al., 2009](#); [Verfaillie et al., 2018](#); [Viviano and Damoiseaux, 2020](#)). These investigations have reported both increased and decreased activation in these networks without converging spatial specificity or clear relationship with behaviour. While the hippocampus seems to be a key region commonly involved in SCI by many fMRI studies, a consistent pattern of its activity in the condition is still lacking ([Dillen et al., 2017](#); [Hafkemeijer et al., 2013](#); [Rodda et al., 2009](#); [Verfaillie et al., 2018](#)). This might be due to issues related to sample size, methods used and importantly, phenotyping of SCI group included in such studies.

A recent account of these fMRI studies has tried to reconcile these apparent inconsistencies by promoting the idea that SCI might be related to general inefficiency in signal processing across whole-brain networks ([Viviano and Damoiseaux, 2020](#)). The findings of the present investigation, however, point to a specific hippocampus-related network that might be involved in uncertainty process-

ing and affective regulation. This could have future theoretical implications in SCI as converging reports support the role of regions of this network (limbic region and insula) in uncertainty processing and affective functioning (Gray and McNaughton, 2003; Grupe and Nitschke, 2013; Harrison et al., 2006; Morriss et al., 2019; Rigoli et al., 2019; Strange et al., 2005; Tanovic et al., 2018; Tobia et al., 2012). Further validation of these neuroimaging results might be needed using other techniques (e.g., task-related MRI, lesion studies) as well as replication efforts, ideally with larger samples. This is especially important here as the evidence presented in the chapter is not causal and the highlighted relationship between rs-fMRI measures and uncertainty processing might be related to a third factor that has yet to be investigated or discovered.

One major future direction is to investigate how the mechanisms and brain networks uncovered in this study relate to AD spectrum and prospective risk of developing dementia. For example, while not needed to make a clinical diagnosis of SCI (Jessen et al., 2014), AD-related biological indicators (e.g., CSF biomarkers and amyloid and tau PET imaging) might provide valuable information on how processing uncertainty and information gathering relates to AD pathology in preclinical population with SCI. This could be further supported by evidence from longitudinal follow-up of individuals with SCI to establish risk factors and outcomes. Another line of research might benefit from adopting a transdiagnostic approach to examine whether and how cognitive mechanisms of information seeking and related affective dysfunction are shared (or distinguished) in different stages of AD and other forms of neurodegeneration. Similarly, examining patients who suffer from anxiety and depression without expression of cognitive complaints would help further delineate the association between affective burden and uncertainty-related behaviours.

In conclusion, the results in this chapter provide evidence that hyperreactivity to

uncertainty might be a key manifestation of SCI and is related to heightened functional connectivity between the insula and the hippocampus. These manifestations might be underlie affective burden in the condition.

In the next chapter, I extend this work and use effort-based decision making paradigm to investigate affective and motivational dysfunction in SCI to provide further characterisation of the psycho-cognitive profile of the condition.

5 | Effort-based decision making in subjective cognitive impairment

5.1 Chapter summary

In this chapter, I investigated effort-based decision making (EBDM) in SCI to further characterise the psycho-cognitive manifestations of the condition. I show that deficits in EBDM, mainly decreased sensitivity to effort, are associated with apathy, but not depression in individuals with SCI. This was opposite to the effect observed in healthy matched controls in whom apathy was associated with increased effort sensitivity. Apathy and decreased sensitivity to physical effort in SCI correlated with inter-network connectivity between regions from default mode and fronto-parietal networks. The results thus highlight a key mechanism underlying apathy in SCI and its associated networks, which is dissociable from depression and affective dysfunction that were linked in the previous chapter to uncertainty processing, *cognitive* effort valuation, and hippocampal-insular network.

5.2 Introduction

Apathy (i.e., reduced motivation) is a prominent feature in several neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, and small vessel disease ([Bortolon et al., 2018](#); [Chong and Husain, 2016](#); [Husain and Roiser, 2018](#); [Nobis and Husain, 2018](#); [Sinha et al., 2013](#)). It can result in significant burden to patients and caregivers and has been regarded as a marker of disease progression in some disorders ([Dauphinot et al., 2015](#); [Hongisto et al., 2018](#); [Leroi et al., 2012](#); [Riedijk et al., 2006](#); [Spalletta et al., 2015](#); [Van Dalen et al., 2018](#)).

In subjective cognitive impairment (SCI), apathy is often discussed in the context of affective burden (e.g., depression and anxiety), which constitutes a key feature of SCI (Hill et al., 2016). Despite several reports highlighting the clinical significance of apathy in neurodegenerative disorders (Fahed and Steffens, 2021; Husain and Roiser, 2018; Le Heron et al., 2018a; Nobis and Husain, 2018; Sinha et al., 2013) and its distinction from affective dysfunction (Morgan and Ward, 1980; Starkstein et al., 2005; Varanese et al., 2011), a mechanistic delineation of apathy in SCI is still lacking.

While depression in SCI might be related to deficits in processing uncertainty as suggested in Chapter 4, several distinctive features separate depression from apathy as the two syndromes might be related to distinct cognitive components (Bishop and Gagne, 2018; Husain and Roiser, 2018). Apathy, for example, has been extensively linked to deficits in effort-based decision making, e.g., decreased incentivisation by reward or/and increased sensitivity to effort (Chong and Husain, 2016; Chong et al., 2015; Husain and Roiser, 2018; Le Heron et al., 2018b; Saleh et al., 2021b; Sinha et al., 2013). Depression and affective dysregulation, on the other hand, have been linked in some of their aspects to intolerance to uncertainty and disrupted reaction to it (Bishop and Gagne, 2018; Boswell et al., 2013; Carleton et al., 2012; Grupe and Nitschke, 2013; Gu et al., 2020; Hartley and Phelps, 2012a; Pulcu and Browning, 2019; Saulnier et al., 2019). Investigation of such differences in SCI not only helps to refine the cognitive profiling of SCI and uncover its underlying brain networks, but also contributes to the mechanistic characterisation of disorders of affect (e.g., depression) and motivation (apathy). As such conditions cross the boundaries of diseases and manifest across a range neurocognitive disorders, such mechanistic accounts may provide behavioural markers that help advance clinical diagnostics and management in psychiatry and cognitive neurology transdiagnostically (Husain, 2017).

The study of effort-based decision making (EBDM) has provided crucial insights into human motivation in health and disease ([Chong and Husain, 2016](#); [Chong et al., 2016b](#); [Husain and Roiser, 2018](#); [Le Heron et al., 2018a](#); [Pessiglione et al., 2018](#); [Saleh et al., 2021b](#)). EBDM paradigms aided by computational modelling approaches have highlighted key cognitive mechanisms that might underlie apathy in several neurological conditions, e.g., decreased incentivisation by reward in PD patients ([Le Heron et al., 2018c](#)). Such mechanisms offer objective and quantifiable behavioural parameters that could aid the neurochemical and neuroanatomical characterisation of apathy – e.g., previous EBDM studies emphasised the role of dopamine and involvement of several brain regions such as anterior cingulate cortex, prefrontal cortex and ventral striatum in apathy ([Fahed and Steffens, 2021](#); [Husain and Roiser, 2018](#)).

Along similar lines, using EBDM framework in SCI may provide crucial insights into motivational and affective deficits in the condition. In this study, I used this framework to investigate the mechanisms of apathy in SCI. Forty-one SCI individuals and 41 healthy matched controls performed the EBDM paradigm used in Chapter 3 requiring them to simply accept or reject offers based on their reward and effort attributes. The results showed that individuals with SCI were significantly more apathetic and depressed than controls. Using drift diffusion modelling to analyse choice and decision time data revealed that apathy in SCI was associated with lower sensitivity to changes in effort when preparing decisions. Resting-state functional connectivity analysis revealed that this effect, along with apathy, in SCI was associated with increased inter-network connectivity between default mode and fronto-parietal networks. Importantly, these effects were not observed with depression, suggesting a different mechanism underlying apathy.

The findings thus indicate that apathy in SCI is associated with deficits in effort-based decision making and link it to specific dysfunctional brain connectivity pat-

terns.

5.3 Methods

5.3.1 Participants

The study included 41 participants with SCI (Age: $\mu = 58.17$, $SD = 7.82$, 22 males) and 41 age- and gender-matched healthy controls (Age: $\mu = 58.22$, $SD = 8$, 19 males). Sample size was determined based on comparable previous work in healthy participants and patients ([Chong et al., 2016b](#); [Le Heron et al., 2018b](#); [Saleh et al., 2021b](#)). SCI individuals were clinically assessed and diagnosed in the cognitive neurology clinic at John Radcliffe Hospital, Oxford. The assessment was performed by trained cognitive neurologists (S.M. & M.H.). All SCI participants included in the study had ACE-III cognitive ≥ 84 (82 cut-off was used at initial recruitment, [Bruno and Vignaga 2019](#); [Elamin et al. 2016](#); [Hsieh et al. 2013b](#)) and normal clinical MRI brain scans. All participants gave written consent to take part in the study and were offered monetary compensation for their participation. The study was approved by the University of Oxford ethics committee (RAS ID: 248379, Ethics Approval Reference: 18/SC/0448). [Table 5.1](#) shows demographics of the study groups. All participants completed the behavioural task and questionnaires. Neuroimaging data were obtained from 30 SCI participants and 30 healthy controls who were MRI-compatible and gave consent to be scanned for research purposes.

5.3.2 Clinical measures and procedure

Participants from both groups completed self-report questionnaires of apathy (apathy motivation index, AMI) and depression (Beck Depression Inventory, BDI-

II). BDI-II data were missing for two controls. The task was presented on a 17-inch PC using MATLAB (The MathWorks inc., version 2018b) and Psychtoolbox (Brainard, 1997; Kleiner et al., 2007) version 3. For effort recording, Biobak system (MP160) attached to effort handle (dynamometer) was used. This was calibrated each session for each participant. Testing was carried out in a quiet room with an experimenter present at all times.

5.3.3 Experimental paradigm

The task paradigm used for this study is the same EBDM (apples) task used in Chapter 3 to investigate how people weigh reward against physical effort (Figures 5.1 a. & 3.1). Briefly, participants were presented with different offers that had different combinations of reward (five levels) and physical effort (five levels). For each offer, they had to make Yes/No decisions depending on whether they thought the reward (apples) on offer is worth the effort needed to obtain it. There were 25 different offer combinations, repeated five times in five experimental blocks, i.e., 125 trials in total. At the end of the experiment, participants had to play ten decisions randomly selected from their previous choices to obtain apples which were eventually converted into monetary rewards (one apple = £0.1).

5.3.4 Statistical analyses

Statistical analyses and modelling were performed in MATLAB and Jupyter notebook running Python v.3. Mixed-effects and multiple regression models were fitted using *fitglme* and *fitlm* functions in MATLAB, respectively. Post hoc follow-up analyses were performed using appropriate statistical tests of difference (student t-test or Wilcoxon rank-sum test) depending on whether parametric assumptions were met.

5.3.5 Hierarchical drift diffusion modelling of effort-based decision

Recent approaches analysing similar datasets demonstrated that adopting drift diffusion modelling framework can offer key mechanistic insights into latent psychological processes underlying cost-benefit valuation in EBDM (Saleh et al., 2021b). The model assumes an internal accumulation of evidence towards one of the two responses available (accept or reject). These two responses correspond to upper (accept) and lower (reject) boundaries where evidence accumulation terminates when either of them is reached. The rate of evidence accumulation (v), was assumed to have a linear relationship with reward (r) and squared effort (e) as follows:

$$v_{r,e} = v_0 + v_r - v_e - v_{r \times e} \quad (5.1)$$

Seven parameters were obtained for each participant after fitting the model to the data (responses and reaction time) using a hierarchical Bayesian estimation procedure. Three parameters captured the influence of reward (v_r), effort (v_e), and their interaction ($v_{r \times e}$) on drift rate. The other four parameters were basic drift rate (v_0), decision threshold (a), bias (z) and non-decision time (t). Given the design of the task, a , z and t were kept constant across conditions.

The data were fitted to the model using a well-validated HDDM toolbox (http://ski.clps.brown.edu/hddm_docs/; version 0.6.0; Python 3).

5.3.6 Magnetic Resonance data acquisition

Structural and functional magnetic resonance scans were obtained using 3T Siemens Verio scanner at John Radcliffe Hospital, Oxford. Structural images were 1-mm isotropic T1-weighted (MPRAGE, field of view: $208 \times 256 \times 256$ matrix, TR/TE = 200/1.94 ms, flip angle = 8° , iPAT = 2, prescan-normalise). Resting-state functional MRI (rs-fMRI) measures spontaneous changes in blood oxygenation (BOLD signal) due to intrinsic brain activity. rs-fMRI images a voxel size of $2.4 \times 2.4 \times 2.4$ mm (GE-EPI with multi-band acceleration factor = 8, field of view: $88 \times 88 \times 64$ matrix, TR/TE = 735/39 ms, flip angle = 52° , fat saturation, no iPAT). MR images were obtained from 30 SCI participants and 30 healthy controls who were MRI compatible or consented to have MR scans as part of the study.

5.3.7 Magnetic Resonance data processing and analysis

Resting-state connectivity analysis was performed in MATLAB 2019b using CONN toolbox v20.b ([Whitfield-Gabrieli and Nieto-Castanon, 2012](#)) running SPM12. Default processing pipeline in CONN was used. This included functional realignment and unwarp, slice-timing and motion correction, segmentation, and normalisation to MNI space. To increase signal-to-noise ratio, spatial smoothing was applied using spatial convolution with Gaussian kernel of 8 mm full width half maximum. Denoising was performed with linear regression of potential confounds and with temporal band-pass filtering (0.008 - 0.09 Hz). This linear regression controlled for noise components from white matter and cerebrospinal fluid areas (16 parameters each). Head motion was controlled for in the model using 12 noise parameters, which included three translation and three rotation parameters in addition to their first-order derivatives. Confounding effects arising from identified outliers and from linear BOLD signal trends were also controlled for.

Whole brain network-based ROI-ROI analysis was performed in a similar way to the previous chapter. The analysis included 32 atlas-defined ROIs representing key nodes of the main known cortical functional networks, including salience, default mode, sensorimotor, visual, dorsal attention, fronto-parietal and language networks, in addition to the hippocampal regions (added for comparison with Chapter 4). Overall, the analysis examined 496 connections, controlling for at least age and gender differences. Significance testing was performed using Threshold Free Cluster Enhancement (TFCE) with corrected connection significance threshold equal to 0.05.

5.4 Results

5.4.1 Demographics

Table 5.1 shows demographic characteristics of both groups. SCI participants had slightly lower but significantly different total ACE-III scores than healthy controls (Controls: $\mu = 97.44, SD = 2.3$; SCI: $\mu = 95, SD = 3.94$; $z = 3.18, p = < 0.01$). As expected, and consistent with previous reports (Hill et al., 2016; Hohman et al., 2011; Pavisic et al., 2021; Reid and MacLulich, 2006), individuals with SCI were significantly more depressed (BDI-II score; Controls: $\mu = 5.79, SD = 4.69$; SCI: $\mu = 14.88, SD = 9.78$; $z = 4.61, p = < 0.001$) and apathetic (AMI score; Controls: $\mu = 1.14, SD = 0.42$; SCI: $\mu = 1.55, SD = 0.46$; $z = 3.77, p < 0.001$) than controls. Non-parametric partial Spearman's correlations controlling for age and gender showed no significant association between these three clinical measures (cognitive function, depression and apathy) (All tested correlations $p > 0.09$). These results thus suggest a dissociation between apathy and depression in SCI which might be related to distinct underlying mechanisms.

It is important to note that lower ACE-III scores in SCI group compared to controls do not necessarily reflect cognitive impairment as all SCI individuals had scores higher than test cut-off of 82 and only two participants had scores less than 88. These are the two main cut-offs used in diagnosing mild cognitive impairment (Bruno and Vignaga, 2019; Elamin et al., 2016; Hsieh et al., 2013b). Clinically, low ACE-III scores for these two participants were attributed to their affective dysfunction, and clinical follow-up in the memory clinic at John Radcliff Hospital demonstrated no progressive worsening in cognitive functioning over at least one year, thus excluding progressive neurodegenerative pathology at the time of testing.

	Controls		SCI		p-value
N (M/F)	41(19/22)		41(22/19)		0.90
	Mean	SD	Mean	Sd	
Age	58.22	8	58.17	7.82	0.94
ACE-III	97.44	2.3	95	3.94	< 0.01
AMI Total	1.14	0.42	1.55	0.46	< 0.001
BDI-II	5.79	4.69	14.88	9.78	< 0.001

Table 5.1: **Study demographics.** ACE-III: Addenbrooke’s Cognitive Examination version III. AMI: Apathy Motivation Index. BDI-II: Beck Depression Inventory version II. p-value from student t-test or Wilcoxon rank-sum test for parametric and non-parametric data, respectively.

5.4.2 Lower sensitivity to changes in effort in SCI

To analyse participants’ choices, a logistic mixed effects model was performed. Based on numerous previous reports investigating effort-based decision making using a similar paradigm (Le Heron et al., 2018b; Saleh et al., 2021b), quadratic transformation of effort was used in the model. The results showed that participants responded to offers as expected: accepting more when reward increased and effort decreased (Main effect of reward on choice: $\beta = 3.16$, $95\%CI =$

[2.68, 3.64], $t_{10242} = 12.94$, $p < 0.0001$; Main effect of effort on acceptance: $\beta = -2.42$, $95\%CI = [-2.86, -1.98]$, $t_{10242} = -10.71$, $p < 0.0001$; Figure 5.1 b., Table B.26). The interaction between reward and effort was significant, indicating that the aversive effect of efforts is less prominent when countered by increasing rewards (reward $\times$ effort: $\beta = 0.75$, $t_{10242} = 3.55$, $p < 0.001$; Table B.26). There was no group difference in acceptance probability ($p = 0.63$).

Offer attributes also affected how quickly participants responded to offers such that offers with high conflict (e.g., high-reward, high-effort) had slower responses (Figure 5.1 b.). SCI participants were on average slower than controls in making decisions (Log-transformed reaction times; Controls: $\mu = 0.79$, $SD = 0.28$; SCI: $\mu = 0.90$, $SD = 0.24$; $z = 2.48$, $p = 0.01$), especially when they made decisions to accept offers ($t(80) = 2.01$, $p = 0.046$), indicating more cautious decision processing when accepting offers.

Such differences in decision time along with choice data are best accounted for using hierarchical drift diffusion model (HDDM) as it utilises both time and choice data to derive model parameters corresponding to latent psychological processes related to decision making (Wiecki et al., 2013). Similar to the effects noted above, the results from HDDM showed that reward, effort and their interaction influenced drift rate such that stronger drift rates were observed with higher reward and effort levels (probability for v_r & $v_e > 99\%$). Comparing the two groups, the influence of effort and its interaction with reward were significantly weaker in SCI participants compared to healthy controls (99.81% & 98.33% probability, respectively). All other parameters (v_r , v_0 , a , z , t) were not significantly different between the two groups ($< 95\%$ probability).

The findings thus suggest that individuals with SCI are less sensitive to changes in physical effort when deciding whether the reward on offer is worth pursuing.

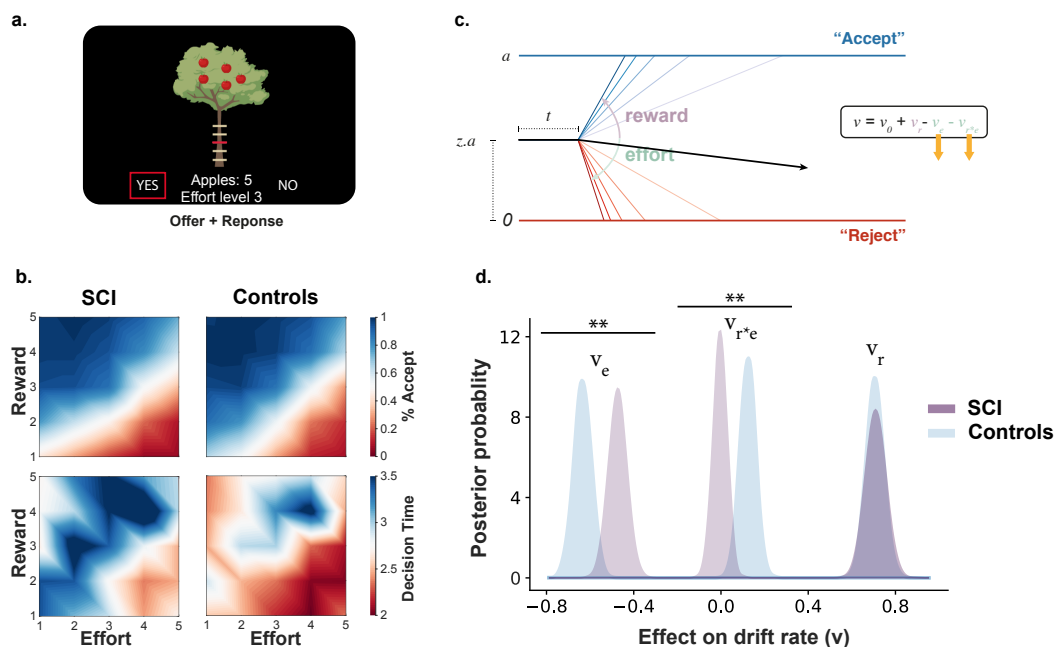


Figure 5.1: **Effort-based decision making in SCI.** **a.** Participants performed EBDM task used in chapter 3 where they decided whether reward (apples) on offer is worth the effort level assigned to it. **b.** Participants from both groups (SCI and controls) responded to offers depending on offer attributes, accepting more when reward increased and effort decreased. Similarly, the time participants took to respond to offers was also reflective of offer attributes, with offers that pose higher conflict between the two dimensions (reward and effort) taking longer. While SCI participants did not differ significantly in acceptance probability of offers, they were generally slower to decide, especially for offers they tended to accept. **c.** To parameterise these effects and provide a parsimonious analysis of decision and reaction time data, a hierarchical drift diffusion model (HDDM) was fitted. The model assumes that decisions arise from a noisy evidence accumulation process leading to a decision boundary (a) at a drift rate (v) that varied linearly with reward (r) and effort (e) on offer, with initial bias (z) and non-decision time (t). **d.** HDDM revealed that SCI participants' drift rates were less sensitive to changes in effort compared to healthy controls. A similar effect was also observed for the interaction of reward and effort. See Figure 5.2 for visualisation of drift rate changes with offer attributes in SCI.

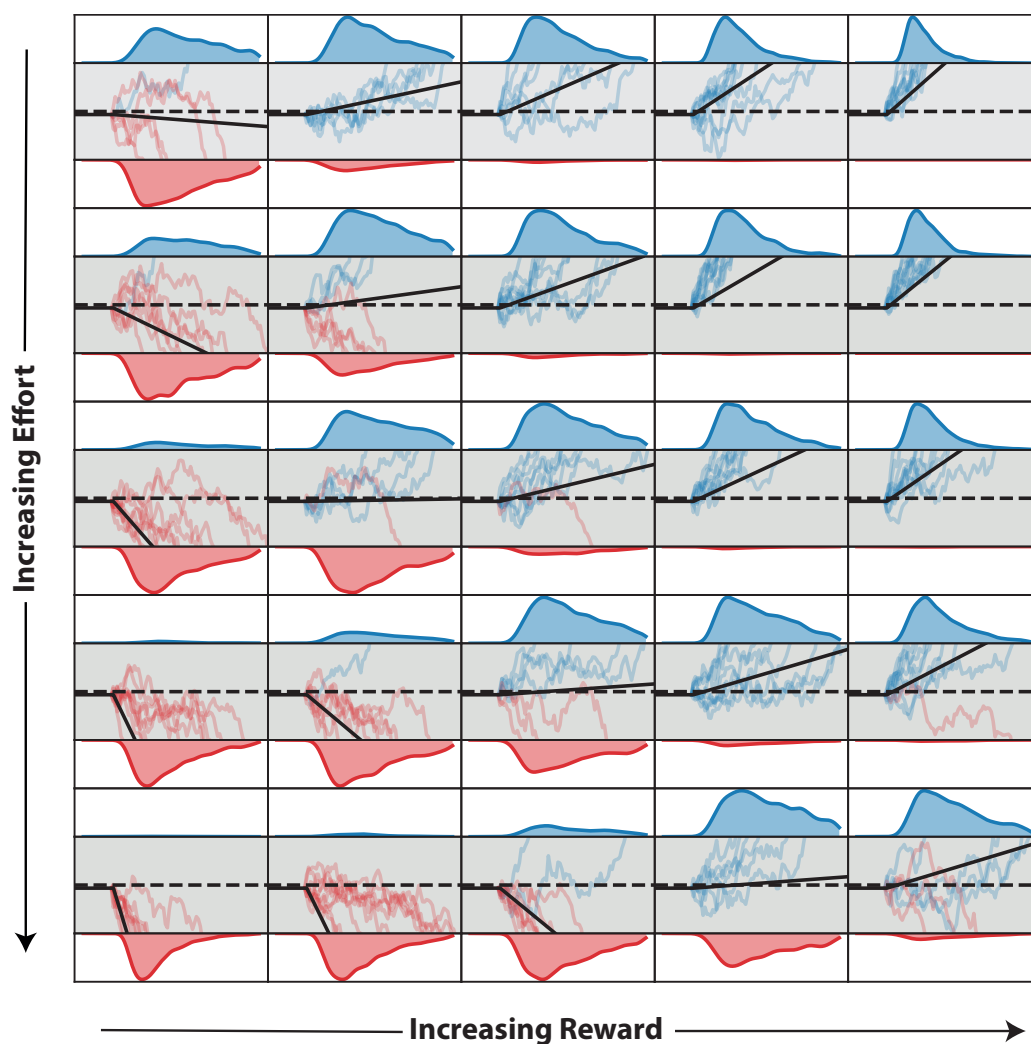


Figure 5.2: **Changes of HDDM parameters with offer attributes.** A demonstration of how HDDM parameters, mainly drift rate (v), change with changes in reward and effort on offer in SCI participants. Note stronger drift rates (solid black line) towards acceptance (upper boundary) with increasing rewards moving from left to right. Similarly, drift rate moves strongly towards rejection (lower boundary) with increasing effort moving from top to bottom. This effect of effort on drift rate was weaker in SCI participants compared to healthy controls.

5.4.3 Behavioural apathy in SCI is associated with lower effort sensitivity in SCI

To investigate the relationship between apathy and EBDM in SCI, a mixed effects logistic model analysing choice data was performed across SCI participants, controlling for age, cognitive score and depression. The results showed a significant effect of the interaction between apathy and effort (AMI $\times$ effort: $\beta = +0.50$, 95%CI = [0.05, 0.95], t_{5113} , $p = 0.02$; Figure 5.3 a-b., Table B.27), indicating that increased apathy is associated with decreased sensitivity to effort changes of the offers.

To further highlight these effects using HDDM framework, robust multiple linear regression models controlling for age, cognitive score and depression were performed with HDDM parameters as predicted variables. The results showed that apathy in SCI was associated with weaker effects of effort on drift change (i.e., lower sensitivity to effort changes) (Robust MLR; effect of AMI: $\beta = +0.23$, $t = 2.86$, $p < 0.01$; Figure 5.3 c.). This effect was evident for the behavioural component of AMI score ($\beta = +0.13$, $t = 2.44$, $p = 0.01$), rather than the social and emotional components ($p = 0.083$ & 0.23 , respectively). Notably, there was no significant effect of depression ($p = 0.46$).

When the same analyses were performed in the control group, apathy had the opposite effect on effort sensitivity, with higher apathy scores being associated with heightened effect of effort on drift rate ($\beta = -0.21$, $t = -2.53$, $p = 0.1$; Figure 5.3 c.). Again, this effect was related to behavioural component of apathy score ($\beta = -0.16$, $t = -2.99$, $p < 0.1$) and not social or emotional subscales ($p = 0.12$ & 0.50 , respectively). Note that this distinct effect of behavioural apathy in the two groups is also evident in the logistic mixed effects model as the three-way interaction between effort, apathy and group effects on offer acceptance

($\beta = 0.6$, $t_{9980} = 2.01$, $95\%CI = [0.01, 1.36]$, $p = 0.04$). Apathy in the control group was also associated with increased effect of reward on drift rate ($\beta = 0.20$, $t = 2.4$, $p = 0.02$). This effect on reward, however, was related to social subscore ($\beta = 0.11$, $t = 2.06$, $p = 0.04$) rather than behavioural ($p = 0.40$) or emotional ($p = 0.20$) dimensions of AMI. Depression, on the other hand, was associated with decreased effect of effort on drift rate (i.e., opposite to the effect of apathy) ($\beta = 0.09$, $t = 2.6$, $p = 0.01$).

Apathy in both groups had no significant effect on all other parameters from HDDM, including the interaction between reward and effort.

The results thus suggest that behavioural apathy in SCI might be related to a distinct pattern of effort-based decision making whereby decreased sensitivity to effort, rather than increased as seen in controls, is a prominent feature.

5.4.4 Apathy and reduced effort sensitivity are associated with increased inter-network connectivity

Next, I investigated the brain networks in SCI that might be related to apathy and effort sensitivity in both groups. First, I examined the difference in functional connectivity between the two groups, controlling for age and gender. The results showed that SCI compared to controls had decreased functional connectivity between salience network and default mode network ($TFCF = 40.27$, $p_{unc} < 0.001$, $p_{FWE} = 0.025$). Connectivity in this network was not significantly associated with apathy or effort sensitivity in the two groups, indicating that the disease effect is different from apathy effect. Therefore, the whole brain analysis was repeated in the two groups to identify the brain networks related to apathy and effort sensitivity, while controlling for age, gender, cognitive function, and depression scores. The results showed that apathy and reduced effort sensitiv-

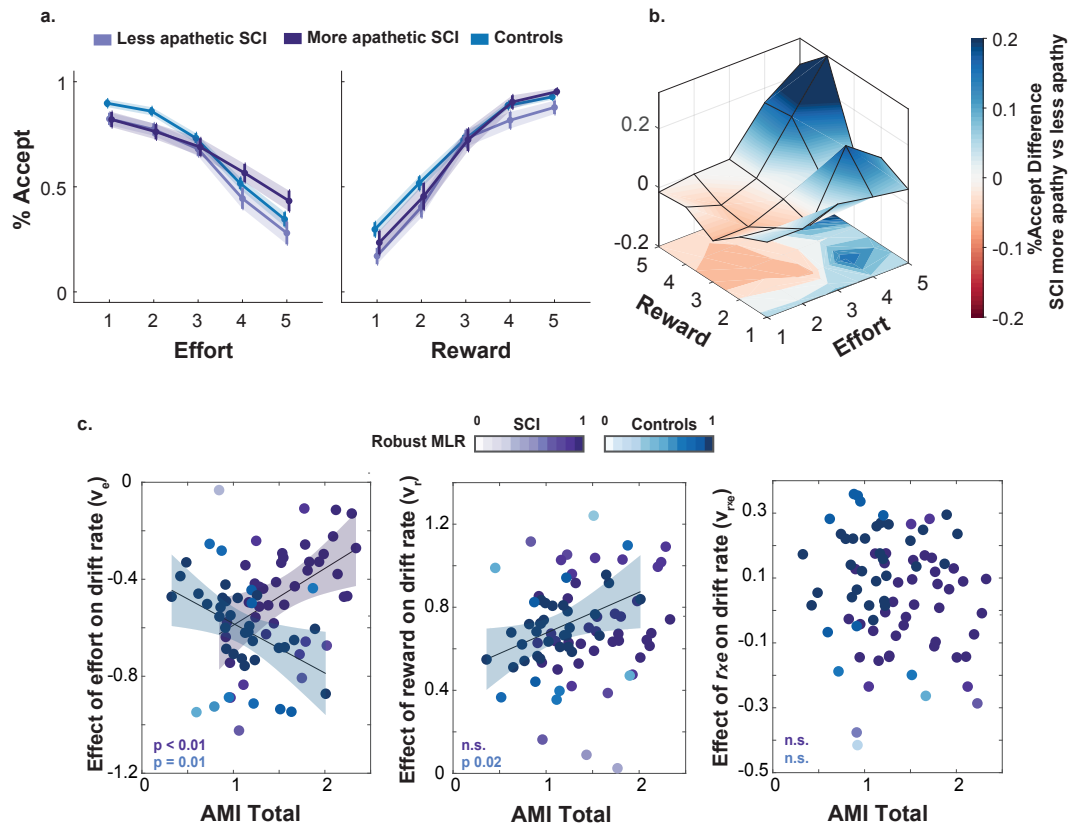


Figure 5.3: Apathy in SCI is associated with lower sensitivity to effort. **a.** A median split of AMI scores showing the difference between SCI participants with higher and lower apathy scores. Apathetic SCI individuals have lower sensitivity to changes in effort ($N = 22$, dark purple) compared to less apathetic SCI participants ($N = 19$, light purple). Controls ($N = 41$) plotted for comparison. **b.** For visualisation, a heat map showing the difference in decision space between SCI individuals with higher and lower AMI score. Apathetic SCI participants accepted *more* of the high-effort decisions. **c.** Higher apathy scores in SCI were associated with weaker effect of effort on drift rate and were not significantly correlated with effect of reward on drift (note that the y-axis for v_e has negative values). In comparison, apathy in healthy controls had the opposite effect on drift rate and was significantly correlated with the effect of reward, with more apathetic individuals being more sensitive to both reward and effort. Apathy in both groups was not significantly correlated with the effect of the interaction (reward $\times$ effort) on drift rate. These correlations were controlled for depression, age, gender, and cognitive score in robust regression model. Colour bar shows the contribution of each data point to the model, with outliers being down-weighted.

ity in SCI were associated with increased connectivity between fronto-parietal network regions (lateral prefrontal cortex and posterior parietal cortex) and default mode network regions (medial prefrontal cortex and lateral parietal cortex) ($TFC E = 35.32$, $p_{unc} < 0.01$, $p_{FWE} = 0.039$; Figure 5.4, see Table B.28 for cluster information and statistics). These associations were not significant within the control group, indicating that a separate brain network might underlie apathy in the two groups.

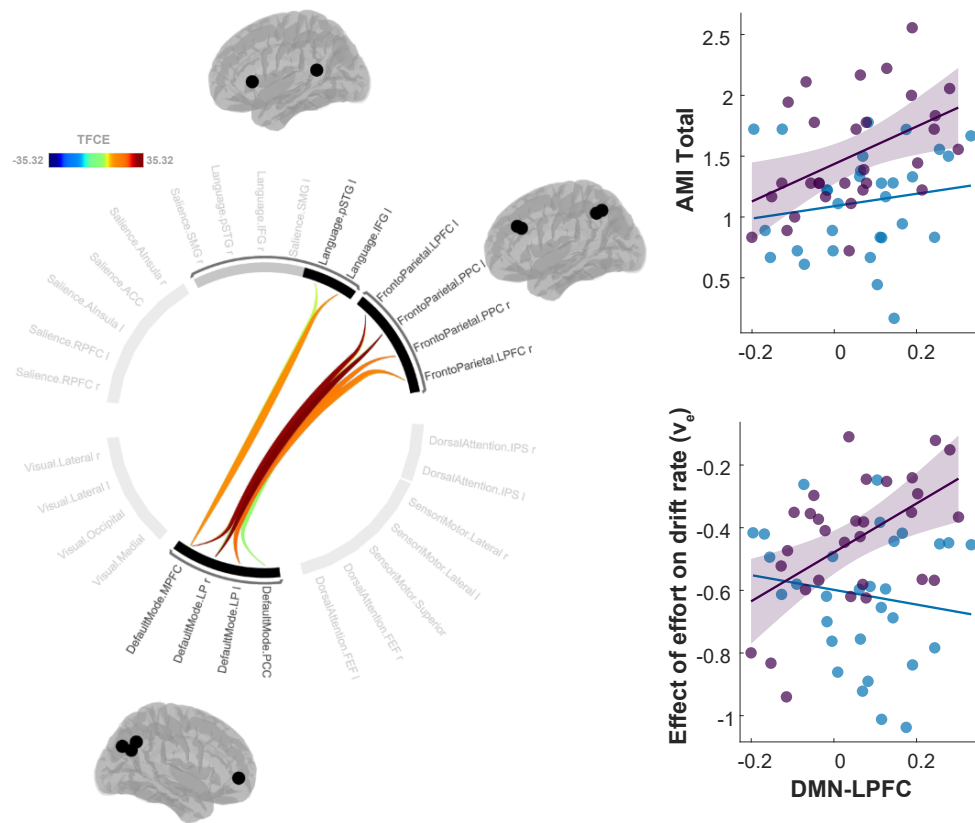


Figure 5.4: Apathy and reduced effort sensitivity are associated with increased inter-network connectivity. Analysing functional connectivity across different brain networks showed that apathy and weaker effect of effort on drift rate (v_e) were associated with stronger connectivity between default mode network regions and fronto-parietal network. Analyses were controlled for age, gender, cognitive score, and depression. These associations were not significant within the control group. AMI: Apathy motivation index. DMN: Default mode network. LPFC: Lateral prefrontal cortex (key node within front-parietal network).

5.5 Discussion

Numerous previous reports have linked deficits in effort-based decision making to apathy in different neurodegenerative disorders ([Chong and Husain, 2016](#); [Chong et al., 2015](#); [Husain and Roiser, 2018](#); [Le Heron et al., 2018b](#); [Saleh et al., 2021b](#); [Sinha et al., 2013](#)). However, studies in SCI have overlooked the syndrome, with limited mechanistic characterisation or delineation from affective dysfunction – a key feature of SCI ([Hill et al., 2016](#); [Hohman et al., 2011](#); [Paviscic et al., 2021](#); [Reid and MacLulich, 2006](#)). In this chapter, effort-based decision making paradigm was used to investigate how individuals with SCI weigh rewards against physical effort in order to extract behavioural metrics that mechanistically characterise apathy in SCI. Analysing the data using drift diffusion modelling showed that SCI participants, compared to healthy matched controls, were less sensitive to effort changes when making effort-based decisions. This specific effect correlated with the severity of apathy, but not depression, in SCI (i.e., SCI individuals with higher apathy scores were less likely to take changes in effort into consideration when making decisions). Notably, apathy in the control group had the opposite effect, with increased sensitivity to effort being associated with higher apathy scores. Resting functional neuroimaging analysis revealed that decreased effort sensitivity and increased apathy in SCI were associated with increased inter-network connectivity between DMN and FPN. Such results highlight a key mechanism that might give rise to apathy in SCI and dissociate it from affective dysfunction.

Apathy has been traditionally linked to at least two key mechanisms: increased aversiveness of effort or/and decreased incentivisation by rewards ([Chong and Husain, 2016](#); [Husain and Roiser, 2018](#); [Saleh et al., 2021a](#); [Sinha et al., 2013](#)). Agents can thus be considered apathetic if they regard the reward on offer as not worth the effort due to one or both reasons. While many empirical reports

have supported this characterisation of apathy (Le Heron et al., 2020, 2018b; Muhammed et al., 2016; Saleh et al., 2021b), the results in this chapter highlight contradictory findings regarding the effect of apathy in controls (associated with increased effort sensitivity) and SCI (associated with decreased effort sensitivity). In this context, it should be noted that the term ‘*sensitivity*’ in this study describes how steep the slope of offer acceptance or drift rate is as a function of changes in effort (or reward), rather than describing absolute effects. In other words, it describes to what extent participants take changes in effort (or reward) level into consideration when they compute subjective values and assign preferences. Consequently, an agent might be deemed less sensitive to effort if their preferences are not strongly affected by alterations in effort levels even if they reject more of the low-effort offers (i.e., even if their preferences show increased avoidance of low effort levels). This was similar to the effect of apathy in SCI participants as they were less sensitive to changes in effort, resulting in lower acceptance of low-effort offers and greater acceptance of high-effort offers (see Figure 5.3 b.).

Two additional explanations might account for the distinct pattern observed in the two groups. First, SCI participants were significantly more apathetic than controls. This means that the correlation between EBDM parameters and apathy was explored at different ranges in the two groups. Such a pattern might indicate a hidden ‘U-shaped’ correlation across the full ranges of apathy and effort sensitivity that might be apparent when the two groups are considered together (see Figure 5.3 c.). Second, SCI participants were also more depressed with lower cognitive scores. While these differences were controlled for in the analyses and had no significant correlation with apathy, this does not completely exclude the possibility that apathy as a psychological construct might be different between the two groups, resulting in different mechanistic attributes. These behavioural results emphasise the complexity of apathy and highlight the importance of trans-diagnostic

investigations to identify common and distinct features of the syndrome in health and across different diseases.

The results presented here align with the findings reported in Chapter 4. Previously, I reported that individuals with SCI sample faster and more efficiently than healthy controls, indicating that they assign lower *cognitive* effort costs to speed and efficiency during information search. This was demonstrated using a computational model accounting for these additional properties (Figure 4.7). On the other hand, the findings in the chapter revealed that SCI individuals were also less sensitive to *physical* effort and that this correlates with apathy, rather than affective functioning which was indirectly linked to cognitive effort cost in the previous chapter. This might indicate that reduced effort sensitivity (both physical and cognitive) might be a global mechanism in SCI accounting for behavioural performance and multiple aspects of their cognitive and psychological functioning.

The findings also highlight the power of drift diffusion modelling in identifying latent psychological processes related to decision making. Investigating group differences using regression models that examined one aspect of the behaviour (choices) did not show differences between SCI and controls. However, examination of another element of behaviour (decision time) provided an indirect measure of cost-benefit evaluation process as SCI participants were generally slower than healthy controls, especially when accepting offers. Using HDDM, it was possible to combine these separate behavioural markers (choice and decision time) in one model to extract biologically plausible metrics that parsimoniously characterise behaviour. This helped to detect important group differences in decision making as well as inter-individual variations with apathy.

Such metrics have also assisted in differentiating apathy from depression in the

two groups, further emphasising the distinction between the two syndromes. This is of critical importance in SCI for at least two reasons. First, previous reports in SCI rarely point to the distinction of apathy from affective dysfunction ([Hill et al., 2016](#); [Hohman et al., 2011](#); [Pavasic et al., 2021](#); [Reid and MacLulich, 2006](#)). Providing a mechanistic delineation as suggested here might advance future research in the condition to better characterise its relationship with neuropsychiatric dysfunction. Second, because SCI is a recognised risk factor for dementia ([Jessen et al., 2020, 2014](#); [Reid and MacLulich, 2006](#)), mechanistically characterising apathy – the most common neuropsychiatric manifestation in AD – may improve our understanding of dementia and neurodegeneration, and help improve risk assessment in SCI ([Fahed and Steffens, 2021](#); [Nobis and Husain, 2018](#)). An important follow-up study will be to use a similar approach to that used in this chapter to investigate apathy in AD patients. This is described in the next chapter of this thesis.

Finally, here I demonstrated that apathy and blunted sensitivity to effort in SCI were associated with increased inter-network connectivity between two main brain resting functional networks: fronto-parietal (aka central executive) and default mode networks. These findings have some resonance with previous neuroimaging investigations, which reported that apathy is associated with altered functional connectivity of these two networks in SCI-related conditions including mild cognitive impairment and Alzheimer’s disease ([Joo et al., 2016](#); [Munro et al., 2015](#); [Tumati et al., 2020](#)). A few previous reports in SCI have also indicated that activity within these networks or some of their key nodes is associated with the degree of subjective cognitive decline reported by patients ([Cespón et al., 2018](#); [Contreras et al., 2017](#)). However, the association with apathy and affective functioning, until now, has not been investigated. From an anatomical perspective, these networks include regions (e.g., medial prefrontal cortex) that have been consistently

implicated in apathy across different conditions ([Fahed and Steffens, 2021](#); [Husain and Roiser, 2018](#); [Le Heron et al., 2018a](#)) as well as in processing effort cost when making value-based decisions ([Pessiglione et al., 2018](#)). These brain regions are also part of key cortical-subcortical networks (e.g., fronto-striatal) that are involved in regulation of reward-related and goal-directed behaviours ([Haber, 2017](#); [Haber and Knutson, 2009](#)). Thus, the findings in this study suggest that while apathy might be behaviourally different in SCI from other clinical conditions, it relates to known EBDM- and apathy-related networks, however, with a different pattern of dysfunction. In-depth investigations of how brain network connectivity patterns relate to distinct behavioural manifestations in the condition might be a key step forward to characterise apathy and the complex psycho-cognitive profile of SCI.

In conclusion, the study provides evidence indicating that apathy, but not depression, in SCI is associated with reduced sensitivity to effort and links this to increased connectivity between DMN and FPN.

6 | Effort-based decision making in Alzheimer's disease

6.1 Chapter summary

One of the key questions emerging from the previous chapter is whether the cognitive and neuroimaging signatures of effort-based decision making (EBDM) and apathy in subjective cognitive impairment (SCI) are also evident in objective forms of cognitive decline such as Alzheimer's disease (AD). In this chapter, I investigate EBDM in AD and examine its association with self- and caregiver reports of apathy along with measures of cognitive and executive function. The results showed that, compared to healthy matched controls, AD patients were significantly less sensitive to effort when evaluating it against potential reward. This correlated with executive dysfunction, but not with apathy or global cognitive scores. Both effort sensitivity and executive performance correlated significantly with resting functional connectivity between the hippocampus and dorsal attention network, one of the key connections that was disrupted in AD compared to controls. Apathy scores obtained from patients' caregivers correlated with a priori decision bias: apathetic patients were less likely to reject offers compared to less apathetic patients who were biased to reject. Decision bias correlated with strength of functional connectivity between nodes from default mode, fronto-parietal, and visual networks. The results thus provide a characterisation of EBDM in AD, highlighting distinct effects of apathy and executive function along with brain networks that might be involved.

6.2 Introduction

Apathy is perhaps the most significant neuropsychiatric feature in Alzheimer's disease (AD), with up to 88% of AD patients developing the syndrome at some point of their illness ([Fahed and Steffens, 2021](#); [Nobis and Husain, 2018](#); [Zhao et al., 2016](#)). It can manifest in early stages of the disease, making it a valuable potential preclinical marker ([Johansson et al., 2020](#); [Starkstein et al., 2006](#); [Van Dalen et al., 2018](#)). It has also been linked to increased morbidity, stress, and caregiver burden, adding more pressure to medical and social care of patients with AD ([Chen et al., 2017](#); [Dauphinot et al., 2015](#); [Hongisto et al., 2018](#); [Riedijk et al., 2006](#); [Spalletta et al., 2015](#)).

Despite its significance, apathy in AD is still poorly understood, with only a few previous behavioural investigations. One study attributed the syndrome to decision making deficits by demonstrating an association between apathy scores and less profitable decisions on the Iowa Gambling Task (IGT) across the study sample that included AD, mild cognitive impairment (MCI), and healthy controls ([Bayard et al., 2014](#)). However, there was no differentiation in the analysis between the different groups, limiting the interpretation of the results and their specificity to apathy in AD. Another investigation argued that apathy in AD is a form of a dysexecutive syndrome, supported by evidence showing that apathetic AD patients perform worse than controls on measures of executive function such as fluency and motor response inhibition ([Grossi et al., 2013](#)). The mechanisms underlying this association, however, were not examined. A more recent study reported elements of social attentional bias in apathetic AD patients (e.g., less fixation on social cues compared to neutral ones), addressing the social dimension of the syndrome but still not addressing goal-directed behavioural deficits which are the core manifestation of apathy ([Chau et al., 2016](#)). These rare few attempts with

their diverse methods and conclusions, along with their limitations, highlight a gap in current mechanistic knowledge about apathy in AD.

While many previous investigations have attributed apathy in several other disorders to deficits in goal-directed behaviour and effort-based decision making (EBDM), this so far has not been examined in AD ([Chong and Husain, 2016](#); [Le Heron et al., 2018b,c](#); [Muhammed et al., 2016](#); [Saleh et al., 2021b](#); [Sinha et al., 2013](#)). For example, in the previous chapter, I have reported that increased effort sensitivity might be a key mechanism accounting for apathy in subjective cognitive impairment (SCI) – a condition that is regarded as a risk factor for AD in some individuals ([Arvanitakis et al., 2018](#); [Kryscio et al., 2014](#); [Mendonça et al., 2016](#)). Is apathy in AD associated with similar deficits in EBDM? How do such deficits, if present, relate to global cognitive decline and executive dysfunction which are highly prominent in AD? And what brain networks or regions are involved?

To answer these questions and address this gap in the literature, I investigated EBDM in 36 AD patients along with 36 healthy matched controls using the EBDM task explained in Chapters 3 and 5. The paradigm investigates willingness to exert effort for potential rewards on offer. Measures of cognitive and executive function, depression, and apathy were collected. Resting-state functional magnetic resonance data were also obtained from MRI-compatible participants to investigate brain regions and networks that are related to EBDM processing and apathy in AD.

Behavioural data analysed using hierarchical drift diffusion modelling (HDDM) framework showed that AD patients were significantly less sensitive to effort changes when making decisions. This effect correlated with their executive dysfunction indexed by reverse Digit Span (DS) scores, and not with global cognitive decline assessed using Addenbrooke's Cognitive Examination (ACE-III) or for-

ward DS. On the other hand, apathy scores obtained from patients' caregivers correlated with initial bias, with less apathetic patients being more biased to reject offers than patients who were considered more apathetic by their caregivers.

Resting functional connectivity analysis showed that AD patients have diminished activity between the hippocampus and key brain networks, including default mode (DMN), dorsal attention (DAN), sensorimotor (SMN) and visual networks. Activity in at least one of these connectivity patterns (hippocampal-DAN) correlated with effort sensitivity and executive function in healthy controls. On the other hand, decision bias, which was related to apathy in AD, was associated with connectivity between fronto-parietal (FPN), DMN and visual networks.

Taken together, the results point to a dissociable effect of apathy and executive function on EBDM and highlight the distinct brain networks that might underlie the EBDM components involved.

6.3 Methods

6.3.1 Participants

The study included 36 patients with a clinical diagnosis of Alzheimer's disease (age: $\mu = 68.67$, $SD = 9.86$, 15 females) and 36 healthy matched controls (age: $\mu = 67$, $SD = 8.24$, 17 females, 19 from the SCI study in Chapter 5). These numbers were finalised after exclusion of eight AD patients who demonstrated severe cognitive impairment limiting their abilities to understand or perform the EBDM task and therefore no behavioural data were obtained from them. Demographics of the study groups are shown in Table 6.1.

All participants consented to take part in the study and were offered monetary compensation in return. The study was approved by the Ethics Committee at

the University of Oxford. Ethics Committee (RAS ID: 248379, Ethics Approval Reference: 18/SC/0448).

6.3.2 Clinical measures and procedure

Participants were cognitively evaluated using Addenbrookes' cognitive examination (ACE-III) and Digit Span (DS) (Hsieh et al., 2013a; Wechsler and Härting, 1987). The DS requires participants to repeat a series of numbers of increasing length. The forward version assesses simple attention by asking participants to repeat the numbers in the order in which they hear them. The backward version is thought of as an index of executive function, as participants recruit working memory resources to mentally manipulate the numbers and repeat in them *reverse* order (Hale et al., 2016). Participants also completed self-report measures of apathy (Apathy Motivation Index, AMI; Ang et al. 2017), Depression (Beck's Depression Inventory, BDI-II; Beck et al. 1996), and fatigue (Fatigue Severity Scale, FSS; Krupp et al. 1989). Reports on AD patients' apathy were also obtained from caregivers when available (AMI caregiver version; Klar et al. 2022).

6.3.3 Experimental paradigm and behavioural analysis

The EBDM task used in Chapters 3 and 5 was used in this study. In brief, the paradigm examines how people respond to offers (accept/reject) based on reward (virtual apples) and effort attributes. There were five reward levels and five effort levels, giving rise to 25 different combinations of offers, each of which was iterated five times (see Figure 3.1 in Chapter 3).

6.3.4 Behavioural analyses

Behavioural data were analysed using the same analysis tools and approaches used in the previous chapter. This included using mixed-effects models fitted using *fitglm* in MATLAB and hierarchical drift modelling using the HDDM toolbox (see *Methods* in Chapter 5).

The rate of evidence accumulation (v), was assumed to have a linear relationship with reward (r) and squared effort (e) as follows:

$$v_{r,e} = v_0 + v_r - v_e - v_{r*e} \quad (6.1)$$

The model returned seven parameters: three parameters captured the influence of reward (v_r), effort (v_e), and their interaction ($v_{r \times e}$) on drift rate. The other four parameters were basic drift rate (v_0), decision threshold (a), initial bias (z) and non-decision time (t). Given the design of the task, a , z and t were kept constant across conditions.

The data were fitted to the model using a well-validated HDDM toolbox (http://ski.clps.brown.edu/hddm_docs/; version 0.6.0; using Jupyter notebook running Python 3). Significance testing was performed by directly comparing posterior probabilities.

Robust regression using *fitlm* function in MATLAB was performed to investigate bivariate correlations between variables of interest while controlling for possible confounds such as age and gender where needed.

6.3.5 Magnetic Resonance data acquisition.

Structural and functional magnetic resonance scans were obtained using 3T Siemens Verio scanner at John Radcliffe Hospital, Oxford. Structural images were 1-mm isotropic T1-weighted (MPRAGE, field of view: $208 \times 256 \times 256$ matrix, TR/TE = 200/1.94 ms, flip angle = 8° , iPAT = 2, prescan-normalise). Resting-state functional MRI (rs-fMRI) measures spontaneous changes in blood oxygenation (BOLD signal) due to intrinsic brain activity. rs-fMRI images a voxel size of $2.4 \times 2.4 \times 2.4$ mm (GE-EPI with multi-band acceleration factor = 8, field of view: $88 \times 88 \times 64$ matrix, TR/TE = 735/39 ms, flip angle = 52° , fat saturation, no iPAT). These acquisition parameters were identical to the UK biobank project MRI acquisition protocol which was also adopted in Chapters 4 and 5 (Alfaro-Almagro et al., 2018).

MR images were obtained from 28 AD patients and 35 healthy controls who were MRI-compatible and consented to be scanned as part of the study.

6.3.6 Magnetic Resonance data analyses

Processing and analysis of resting-state functional MRI (rs-fMRI) steps were the same as in Chapter 4 and 5. These were performed using CONN toolbox v20.b (Whitfield-Gabrieli and Nieto-Castanon, 2012) running SPM12 in MATLAB 2019b.

Whole brain network-based ROI-ROI included 32 atlas-defined ROIs representing key nodes of the main known cortical functional networks including salience, default mode (DMN), sensorimotor (SMN), visual, dorsal attention (DAN), fronto-parietal (FPN) and language networks, in addition to the hippocampal regions. Overall, the analysis examined 496 connections, controlling for at least age and gender differences. Significance testing was performed using threshold-free clus-

ter enhancement (TFCE) with a corrected connection significance threshold equal to 0.05.

6.4 Results

6.4.1 Demographics

Compared to healthy matched controls, AD patients had evidence of significant cognitive impairment, as indicated by lower scores on Addenbrooke's Cognitive Examination III (ACE-III; Controls: $\mu = 97.31$, $SD = 2.68$, AD: $\mu = 79.33$, $SD = 10.82$, $z = 7.06$, $p < 0.001$) and total Digit Span scores (Forward and Backward) (DS; Controls: $\mu = 18.06$, $SD = 2.60$, AD: $\mu = 15.49$, $SD = 4.14$, $t(69) = 3.14$, $p < 0.001$). Both measures of cognitive performance (ACE-III and DS) were significantly correlated in AD ($R^2 = 0.38$, $p < 0.001$). However, examination of the DS domains showed that AD patients had significantly lower DS backward and not DS forward scores, indicating a marked deficit in executive function with relative preservation of simple immediate recall indexed by DS forward (DS backward; controls: $\mu = 7.42$, $SD = 2.34$, AD: $\mu = 5.74$, $SD = 2.41$, $t(69) = 3.62$, $p < 0.001$; Figure 6.1 a.).

AD patients also reported higher levels of depression than controls (BDI-II; Controls: $\mu = 5.33$, $SD = 4.24$, AD: $\mu = 8.26$, $SD = 8.26$, $z = 2.32$, $p = 0.02$). However, self-reports of apathy and general fatigue did not differ between the two groups ($p = 0.16$ & 0.83 , respectively). Because AD might be associated with decreased insight (Horning et al., 2014; Ott et al., 2006), apathy reports were also collected from patients' caregivers ($N = 25$) using a recently validated caregiver version of AMI (Klar et al., 2022). These reports showed that AD patients were rated as being significantly more apathetic than indicated by self-reports (AMI-

CG: $\mu = 1.86$, $SD = 0.76$, AMI: $\mu = 1.35$, $SD = 0.48$, $t(24) = 4.12$, $p < 0.001$; Figure 6.1 b.). The two reports of apathy were also significantly correlated in AD ($R^2 = 0.23$, $p = 0.01$) but they did not correlate with DS backward, indicating that apathy in AD might be independent of executive function (6.1 c.).

	Controls		AD		pValue
N (M/F)	36 (19/17)		36 (21/15)		
	Mean	SD	Mean	Sd	
Age	67.28	8.24	68.67	9.86	0.52
ACE-III	97.31	2.68	79.33	10.82	<0.001
DS ^a	18.06	2.60	15.49	4.14	<0.001
– DS (Forward)	10.64	1.93	9.74	2.13	0.07
– DS (Backward)	7.42	1.34	5.74	2.41	<0.001
AMI Total	1.2	0.39	1.35	0.48	0.16
Fatigue scale	3.02	1.08	3.01	1.47	0.83
BDI-II	5.33	4.24	9.75	8.26	0.02
AMI CG Total ^b	-	-	1.86	0.76	NA

Table 6.1: **Study demographics.** ACE-III: Addenbrooke’s Cognitive Examination III. DS: Digit Span. AMI: Apathy Motivation Index. BDI-II: Beck’s Depression Inventory II. AMI CG: AMI Caregiver version. ^a: missing data from one AD patient. ^b: collected for 25 AD patients.

6.4.2 Lower sensitivity to changes in effort in Alzheimer’s disease

Participants in both groups responded to offers in a way reflecting changes in reward and effort: accepting more when reward increased and effort decreased (Logistic mixed model; Main effect of reward on offer acceptance: $\beta = +3.17$, $95\%CI = [2.67, 3.66]$, $t_{8983} = 1.87$, $p < 0.0001$; Main effect of effort on offer acceptance: $\beta = -2.52$, $95\%CI = [-2.90, -2.14]$, $t_{8983} = -13.02$, $p < 0.0001$; Figure 6.2 a-b., Table B.29). Offer acceptance was significantly less influenced by changes in effort level in AD compared to controls (AD $\times$ Effort: $\beta = +1.42$, $95\%CI = [0.91, 1.94]$, $t_{8983} = 5.44$, $p < 0.0001$; Figure 6.2 a-b., Table B.29), while influ-

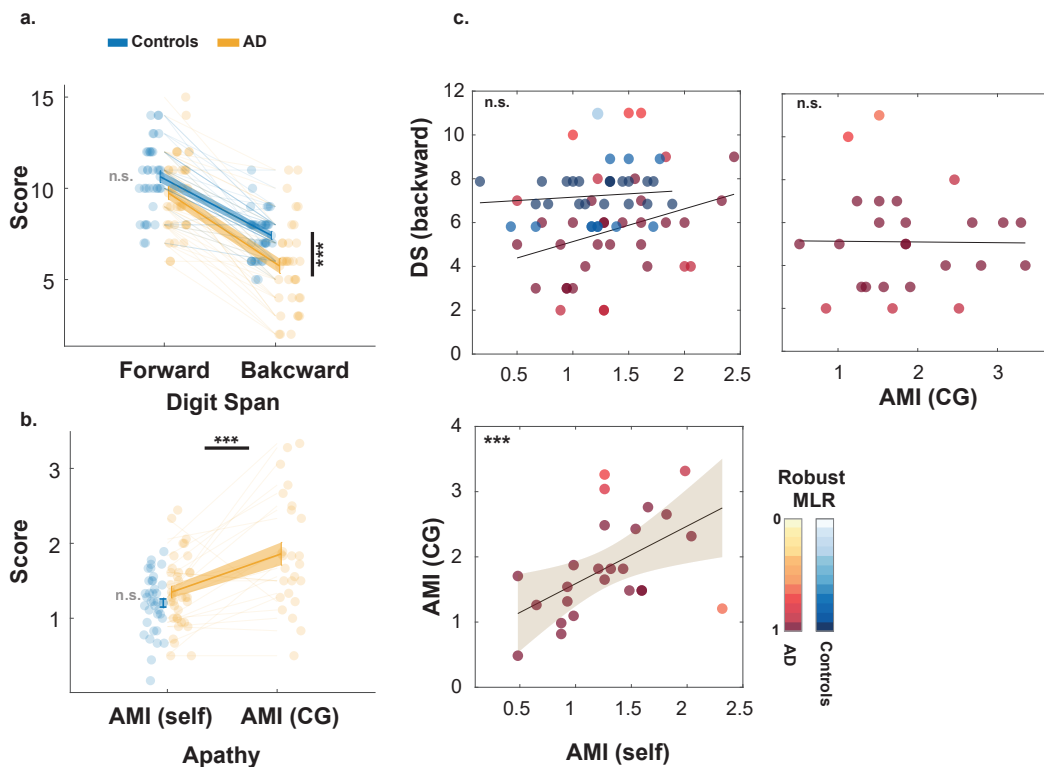


Figure 6.1: **Demographics highlights.** **a.** Digit span (DS) has two components: forward, which is a measure of the simple memory storage function and backward (reverse), which was taken as an index of executive function. AD patients had significantly lower reverse DS scores compared to controls indicating deficits in executive function. No significant difference in forward DS scores. **b.** Self-report measures of apathy indexed by AMI scores were not significantly different between the two groups. AMI scores obtained from patients' caregivers were significantly higher than self-reported scores, which might indicate self-underestimation of apathy in AD. **c.** The two reports of apathy correlated significantly with each other but not with executive function indexed by DS backward. Error bars show $SEM \pm SD$. *** : $p < 0.01$. n.s.: non-significant.

ence of reward changes was not significantly different ($p = 0.09$).

Examination of decision times (DTs) showed that the time participants took to make a decision also was affected by offer attributes as they were generally slower when effort level increased (Main effect of effort on DT: $\beta = 0.04$, $t_{8905} = 5.34$, $95\%CI = [0.02, 0.06]$, $p < 0.0001$; Figure 6.2 c., Table B.30). This effect was exaggerated with increasing reward, posing higher levels of conflict (i.e., high-reward high-effort decision) (Effort $\times$ reward effect on DT: $\beta = 0.05$, $t_{8905} = 7.66$, $95\%CI = [0.03, 0.06]$, $p < 0.0001$; Figure 6.2 c., Table B.30). AD patients were significantly slower than controls regardless of the offer attributes and whether they ended up accepting or rejecting the offer (Main effect of AD on DT: $\beta = 0.28$, $t_{8905} = 4.38$, $95\%CI = [0.15, 0.41]$, $p < 0.001$; Figure 6.2, Table B.30).

Thus, overall, AD patients were slower and less sensitive to changes in effort when making their decisions.

6.4.3 Reduced effort sensitivity in AD is related to executive dysfunction

To better understand choice behaviour and account for differences in acceptance and decision times between individuals and groups, HDDM model was fitted to the choice data in the two study groups (see Methods).

The results further consolidated the findings in the previous section showing that AD patients, compared to healthy controls, were less sensitive to changes in effort (v_e ; Controls: $\mu = -0.59$, $SD = 0.22$, AD $\mu = -0.23$, $SD = 0.21$, $p(\text{Controls} > \text{AD}) > 99.9\%$; Figure 6.3 a.). The influence of reward on drift rate was also weaker in AD than in controls (v_r ; Controls: $\mu = 0.66$, $SD = 0.23$, AD $\mu = 0.53$, $SD = 0.28$, $p(\text{Controls} > \text{AD}) > 95.84\%$), but still significantly

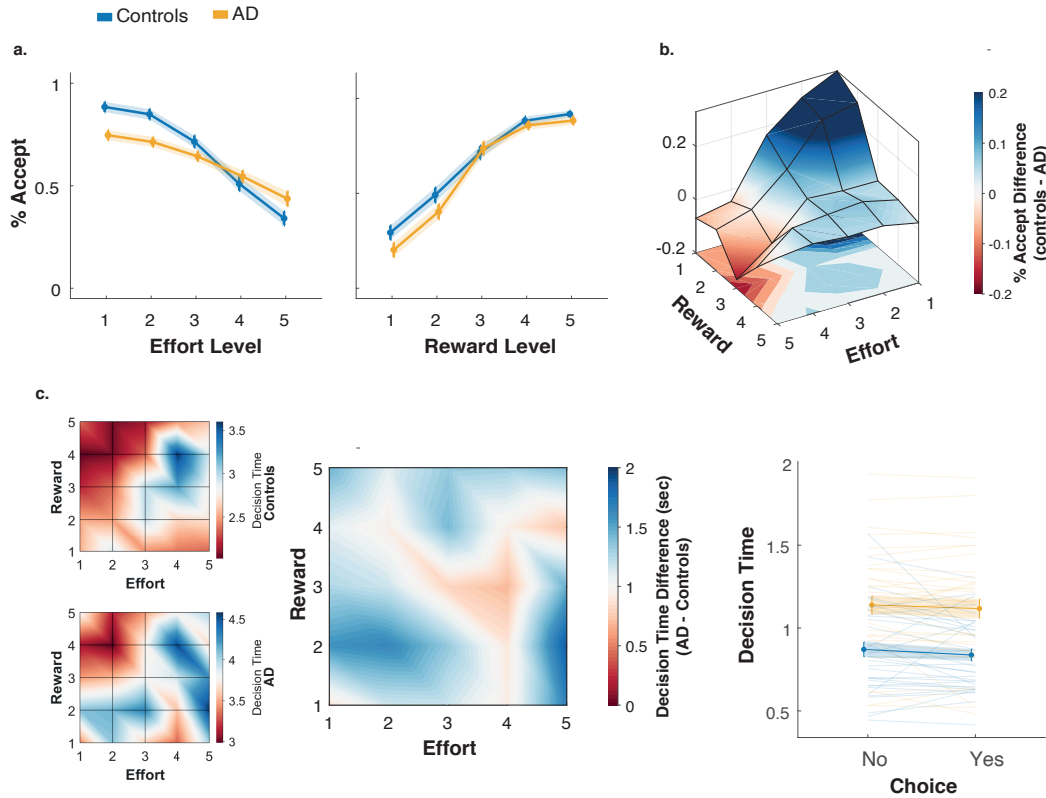


Figure 6.2: Differences in acceptance and decision time between AD and controls. **a.** Participants from both groups responded to offers according to their effort and reward attributes, accepting more when effort decreased and reward increased. AD patients were less sensitive to changes in effort than controls (shallower slope) and had similar sensitivity to changes in reward. **b.** These differences resulted in lower offer acceptance by AD patients, mainly for low-reward low-effort offers (blue region). **c.** AD patients were generally slower than controls in making decisions, this was the case for both accept and reject decisions. The heat maps provide a visualisation of decision time difference between AD and controls based on offer attributes. Error bars show $SEM \pm SD$. See Table B.29 for statistical details.

stronger than the effect of effort (AD: $p(|v_e| > |v_r|) > 99.9\%$). The interaction between the effect of reward and effort on drift ($v_{r \times e}$) was also significantly different between AD patients and controls (Controls: $\mu = 0.08$, $SD = 0.17$, AD: $\mu = -0.02$, $SD = 0.09$, $p(\text{controls} > \text{AD}) = 99.19\%$). Notably, the direction of this interaction was different in the two groups: increasing reward and effort resulted in stronger drift towards acceptance in the control group, but had the opposite effect in AD. However, the magnitude of this effect (i.e., absolute effect) was similar between the two groups ($|v_{r \times e}|$; $p(\text{Controls} > \text{AD}) = 92.43\%$).

Non-decision time was also significantly longer in AD patients compared to controls (t ; Controls: $\mu = 0.96$, $SD = 0.30$, AD: $\mu = 1.26$, $SD = 0.58$, $p(\text{AD} > \text{Controls}) = 99.55\%$; Figure 6.3 b.), consistent in part with the raw results showing prolonged decision time in AD. There was no reliable difference in threshold (a ; $p(\text{AD} > \text{Controls}) = 93.25\%$ probability) or bias ($p(\text{AD} > \text{Controls}) = 89.82\%$) between the two groups (Figure 6.3 b.).

Next, I investigated whether these HDDM-derived EBDM parameters were related to inter-individual differences in apathy, controlling for cognitive and executive function, depression, age and gender. Robust multiple linear regression analyses were performed with DMM parameters as predicted variables and AMI, ACE-III, DS, BDI, age and gender as independent variables, controlling for multiple testing using Bonferroni method.

The results showed that subjective apathy had no significant correlation with any of the parameters from HDDM (all $p > 0.45$). Effort sensitivity instead correlated significantly with patients' executive function as indexed by DS backward score ($\beta = -0.03$, $t = 3.17$, $p_{unc} < 0.01$, $p_{corr} = 0.02$; Figure 6.3 c.). None of the other factors (e.g., global cognitive dysfunction, age, gender or depression) was correlated with v_e .

In the control group, the analysis replicated some of the results in chapter 5 showing that self-reported apathy is associated with increased effect of reward on drift rate ($\beta = 0.17$, $t = 2.16$, $p_{unc} = 0.03$). This might be related to overlapping participants in the two chapters (19 control participants). Executive function in the same model had an opposite effect on reward sensitivity ($\beta = -0.02$, $t = -2.47$, $p_{unc} = 0.01$).

In summary, reduced sensitivity to effort in AD is related to deficits in executive functioning, rather than self-reports of apathy or global cognitive impairment.

6.4.4 Caregiver reports of apathy in AD are associated with less bias in effort based decision making

As patients with AD might lack insight into their own apathy ([Horning et al., 2014](#); [Ott et al., 2006](#)), reports of apathy were collected from patients' caregivers where possible ($N = 25$) using AMI-CG questionnaire. These scores provided a second report of patients' apathy to complement self-reports that might be otherwise compromised by metacognitive deficits (see demographics section).

The same analyses in the previous section were performed with AMI-CG scores instead of AMI. The results showed the caregiver reports of apathy are significantly correlated with the degree of a priori bias z in EBDM ($\beta = 0.011$, $t = 3.18$, $p_{unc} < 0.01$, $p_{corr} = 0.03$; Figure 6.3 c.). Less apathetic patients had a stronger initial bias to reject offers compared to more apathetic patients. The degree of discordance between the two apathy reports (AMI-CG minus AMI) was also significantly associated with decision bias ($\beta = 0.010$, $t = 2.38$, $p = 0.02$), highlighting a potential metacognitive deficit with apathy in AD. None of the other parameters was associated with caregiver reports of apathy.

These results thus point to distinct effects of executive dysfunction and apathy

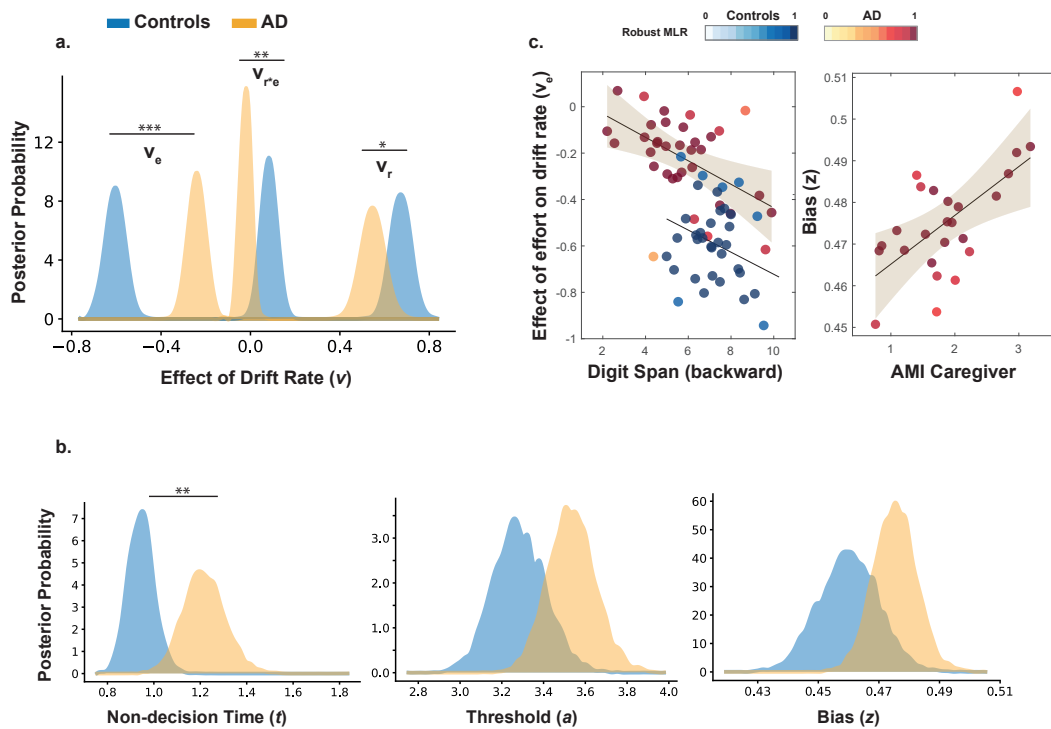


Figure 6.3: Drift diffusion model results. **a.** Hierarchical drift diffusion model showed that drift rate in AD in patients and controls was influenced by both effort and reward. The effect of effort on drift rate was significantly weaker in AD patients. Similarly, but to a lesser extent, the effect of reward was marginally weaker in AD patients. **b.** It was also observed that AD patients required significantly longer times preparing for their decisions (i.e., longer non-decision times). Threshold and bias were not different between the two groups. **c.** robust regression models controlling for age, gender, cognitive function, and depression showed that weaker effects of effort on drift rate were associated with executive dysfunction in AD as indexed by Digit Span backward score. Bias (z), on the other hand, was associated with objective reports of apathy in AD obtained from their caregiver using AMI-CG. *** : $p < 0.001$, ** : $p < 0.01$, * : $p < 0.05$

in AD on EBDM. Executive problems seem to drive group difference (decreased effort sensitivity) between AD and controls. However, apathy, as reported by caregivers, correlates with a priori bias when making decisions, with patients who were reported to be more apathetic being less biased to reject offers.

6.4.5 Functional connectivity disturbance in AD and EBDM

Whole-brain resting-state functional connectivity analysis was performed to investigate i) differences between AD patients and controls, and ii) brain networks related to EBDM in the two groups.

Compared to healthy matched controls, AD patients had decreased functional connectivity in one cluster featuring hippocampal connectivity with different regions in various brain networks including DAN, DMN, SMN and visual networks ($TFC E = 43.47$, $p_{FWE} = 0.01$; Figure 6.5 a., Table 6.2).

I next investigated whether such connectivity patterns are related to effort sensitivity (v_e). Multiple correlations controlling for age and gender and corrected for multiple comparisons were performed between v_e and key connections in the cluster covering hippocampal connectivity with the networks involved. That is, hippocampal-DAN, -DMN, -SMN, and -visual. Stronger hippocampal connectivity with the intraparietal sulcus (IPS) node in DAN was associated with increased sensitivity to effort changes in the control group but not in the AD group (Controls: $\beta = -1.09$, $t(31) = -2.56$, $p_{unc} < 0.01$, $p_{corr} = 0.04$, AD: $p = 0.31$; Figure 6.5 b.). The same network was also significantly correlated with executive function in controls ($\beta = 15.38$, $t(31) = 2.76$, $p < 0.001$). These differences in network connectivity did not correlate with decision bias (z) or AMI caregiver scores.

To establish the networks that might be related to decision bias and thus could be

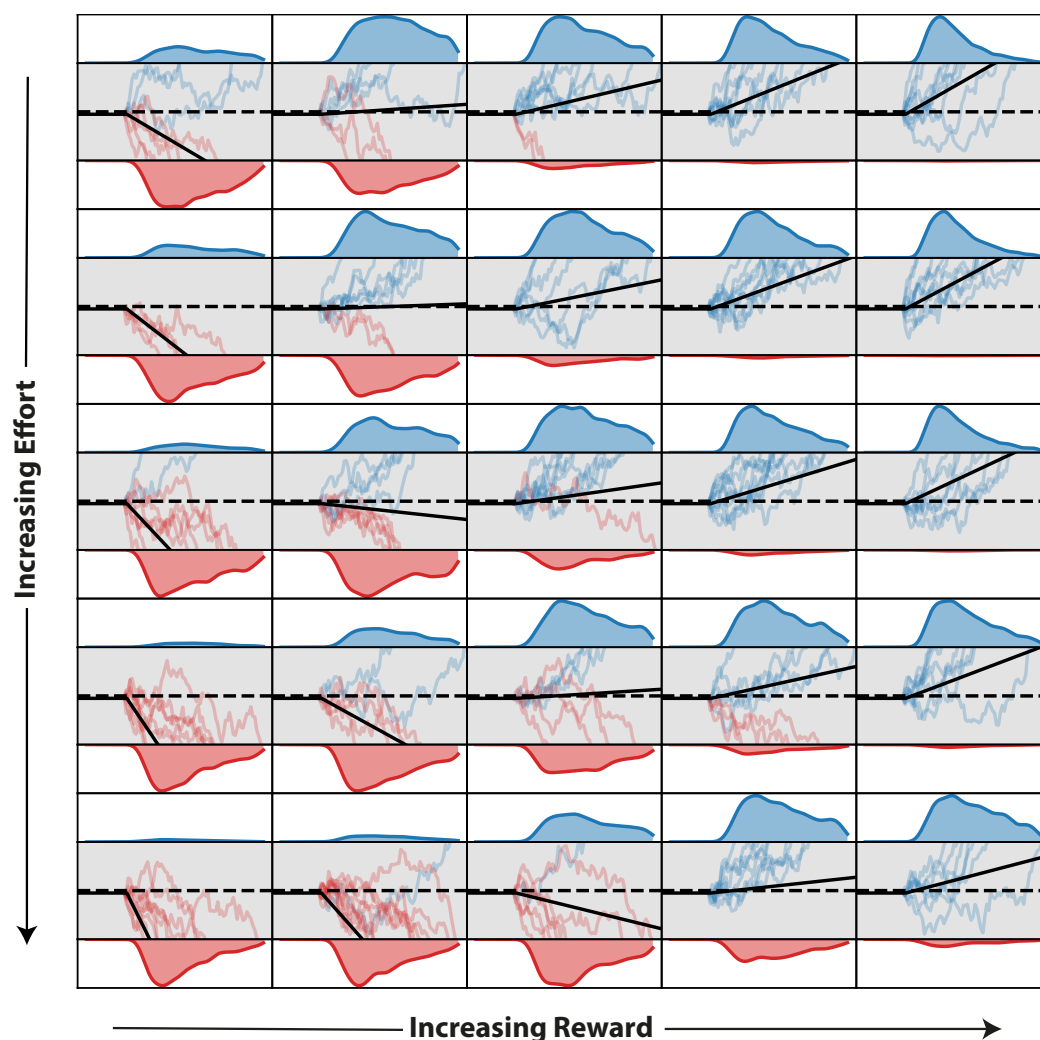
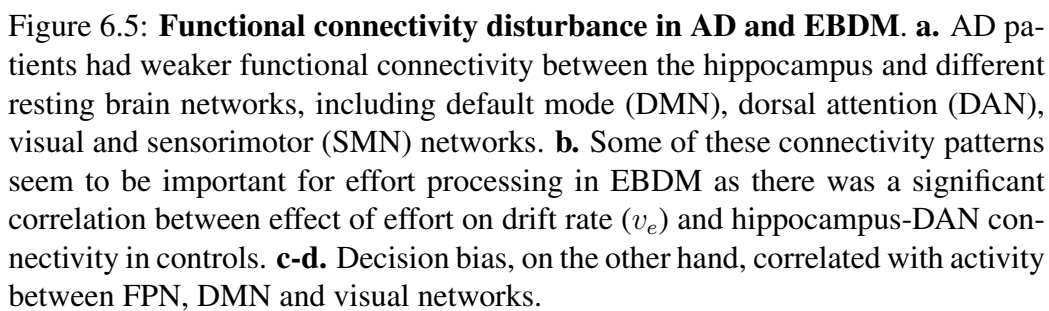


Figure 6.4: **Changes in HDDM parameters as a function of changes in offer attributes.** A demonstration of how HDDM parameters, mainly drift rate v , change with changes in reward and effort in AD patients. Note increasingly stronger drift rates (solid black line) towards acceptance (upper boundary) with increasing rewards moving from left to right. Similarly, drift rate moves strongly towards rejection (lower boundary) with increasing effort moving from top to bottom. This effect of effort on drift rate was weaker in AD patients.

associated with apathy in AD, functional connectivity correlation with bias across participants was examined while controlling for age, gender and effort sensitivity differences (note that bias was not statistically different between the two groups making it feasible to perform transdiagnostic regression). This showed that decision bias is related to FPN and DMN connectivity with visual network (FP-Visual: $TFCE = 30.42$, $p_{FWE} = 0.029$; DMN-visual: $TFCE = 32.14$, $p_{FWE} = 0.047$; Figure 6.5 c-d., Table 6.3). Examining this relationship using robust regression analysis in the two groups separately showed that it is evident mainly in the control group ($\beta = 0.11$, $t(31) = 2.70$, $p < 0.001$; Figure 6.5 d.) and not the patient group. Note that DMN and FP networks have been also previously implicated in apathy in SCI individuals (see Chapter 5).

The results in this section thus highlight two main connectivity patterns involved in effort and bias processing in healthy controls. The disruption of these networks, as evident in Figure 6.5 a., might be therefore related to reduced effort sensitivity in AD compared to controls and reduced a priori bias in apathetic patients.



Analysis Unit	Statistic	p-unc	p-FDR	p-FWE
Cluster 1/1	TFCE = 43.37	0.000182	0.011437	0.013
Hippocampus (l)-DefaultMode.MPFC	T(59) = 3.85	0.000294	0.065924	
DorsalAttention.IPS (R)-Hippocampus (l)	T(59) = 3.68	0.00051	0.065924	
Hippocampus (r)-DefaultMode.MPFC	T(59) = 3.66	0.000537	0.065924	
DorsalAttention.IPS (L)-Hippocampus (l)	T(59) = 3.39	0.001243	0.091705	
Visual.Lateral (R)-Hippocampus (l)	T(59) = 3.31	0.001601	0.099815	
DorsalAttention.FEF (R)-Hippocampus (l)	T(59) = 3.25	0.001907	0.103286	
DorsalAttention.FEF (L)-Hippocampus (r)	T(59) = 3.23	0.002025	0.103286	
SensoriMotor.Superior-Hippocampus (r)	T(59) = 3.19	0.002247	0.105041	
SensoriMotor.Superior-Hippocampus (l)	T(59) = 2.49	0.015469	0.309925	
DorsalAttention.FEF-Hippocampus (l)	T(59) = 2.46	0.016944	0.327781	
DorsalAttention.FEF-Hippocampus (r)	T(59) = 2.15	0.035877	0.498424	
Visual.Lateral (L)-Hippocampus (l)	T(59) = 1.89	0.064327	0.61165	
Visual.Lateral (L)-Hippocampus (r)	T(59) = 1.84	0.070487	0.648249	
Visual.Lateral (R)-Hippocampus (r)	T(59) = 1.82	0.074453	0.661996	
DorsalAttention.IPS (R)-DefaultMode.MPFC	T(59) = 1.43	0.157676	0.860023	
Visual.Medial-Hippocampus (r)	T(59) = 1.00	0.319844	0.897158	

Table 6.2: **Functional connectivity differences between AD Patients and healthy controls.** Compared to healthy controls, AD patients had reduced functional connectivity in one cluster featuring multiple connections between the hippocampus and other brain regions in various brain networks. MPFC: Medial Prefrontal Cortex. IPS: Intra-Parietal Sulcus. FEF: Frontal Eye Field. L: Left. R: Right.

Analysis Unit	Statistic	p-unc	p-FDR	p-FWE
Cluster 1/2	TFCE = 30.42	0.000845	0.055687	0.029
Visual.Lateral (R)-FrontoParietal.LPFC (R)	T(58) = 3.53	0.000407	0.098518	
Visual.Lateral (L)-FrontoParietal.LPFC (R)	T(58) = 3.21	0.001094	0.122717	
Visual.Lateral (R)-networks.FrontoParietal.PPC (L)	T(58) = 2.97,	0.002156	0.152118	
Cluster 2/2	TFCE = 27.14	0.001428	0.055687	0.047
Visual.Lateral (R)-DefaultMode.LP (R)	T(58) = 3.32	0.000779	0.109203	
Visual.Lateral (R)-DefaultMode.PCC	T(58) = 3.01	0.001909	0.152118	

Table 6.3: **Functional connectivity correlation with decision bias (z) across participants.** Bias correlated with increased connectivity between visual-FPN and visual-DMN across study participants. LPFC: Lateral Prefrontal Cortex. PPC: Posterior Parietal Cortex. LP: Lateral Parietal. PCC: Posterior Circulate Cortex.

6.5 Discussion

Despite its significance in AD, apathy is still poorly understood. While previous investigations in other neurodegenerative disorders and related conditions (e.g., PD and SVD) attributed dysfunctional EBDM as a component of the syndrome, such a characterisation in AD is still lacking ([Chong and Husain, 2016](#); [Husain and Roiser, 2018](#); [Le Heron et al., 2018b](#); [Saleh et al., 2021b](#)). In this study, and following the results from the previous chapter showing apathy-related EBDM deficits in SCI (a risk condition for AD in some individuals), I adopted a similar approach to investigate EBDM and apathy in AD.

The same task and analyses were used to examine how people make decisions based on reward and effort attributes of offers. The results showed that EBDM in AD is characterised by lower sensitivity to changes in effort compared to reward, and compared to effort sensitivity in matched controls. This deficit, however, was not associated with self-reported apathy. Instead, reduced effort sensitivity was related to patients' executive dysfunction, highlighting the extent of the disease even on simple decision making processes such as EBDM. On the other hand, decision bias – drift diffusion model parameter that estimates initial tendencies to accept or reject offers – was found to be significantly correlated with reports of apathy obtained from patients' caregivers. Neuroimaging analyses showed that AD patients had reduced hippocampal connectivity with different resting functional brain networks including DMN, DAN, SMN and visual networks. At least one of these networks (hippocampus-DAN) correlated with effort sensitivity in controls, indicating that their disruption in AD might be related to the observed EBDM deficits in the condition (reduced effort sensitivity). These connectivity patterns did not correlate with the degree of bias across participants, which seemed to be associated with different clusters involving visual network connectivity with DMN and

FPN. These results thus provide a characterisation of EBDM processes in AD and their clinical and neuroimaging correlates.

Examining decision making in patients with cognitive dysfunction can be challenging as this can distort the interpretation of results and participants' behaviour. This takes us back to a fundamental question in experimental psychology: "Are we measuring what we think we are measuring?" ([Chiang et al., 2015](#); [Flake and Fried, 2020](#); [Snodgrass et al., 1985](#)). While every effort has been made to make sure that this is the case in this study, e.g., making sure participants understood the task using post-instruction questionnaires, excluding AD patients with doubts regarding their understanding of the paradigm, etc, it remains necessary to consider this question before jumping into conclusions about AD patients' behaviour. This is because we are faced with an equally important question in this condition: "Is it all due to memory impairment?".

Here, I consider two parallel lines of interpretations of the main findings in this study. First, reduced sensitivity to effort in AD might indeed be indicative of lower weights assigned to changes to effort when making value-based decisions. This decision making profile is similar but more severe than the one observed in apathetic SCI individuals in the previous chapter, especially when decision times are considered using HDDM. Such deficits led AD patients to make decisions that were more weighed by their reward attributes, resulting in seemingly irrational and less profitable preferences (e.g., low-reward, high-effort), a finding that has been partially highlighted in one previous behavioural investigation in AD using Iowa gambling task ([Bayard et al., 2014](#)). However, unlike SCI, these deficits in EBDM were not related to apathy in AD.

This opens the door for the second interpretation which considers the possibility that AD patients might be less able to compute subjective values that involve more

than one attribute simultaneously. The fact that effort sensitivity correlates with executive function supports this conclusion. Importantly, this does not seem to be related to global cognitive dysfunction (no correlation with ACE scores), pointing to a more specific dysexecutive component of EBDM value computations in AD. This distinction between global cognitive decline and executive deficits has also been reported in previous studies in different domains such as decision making under risk and ambiguity (for a recent review see [Gaubert and Chainay, 2021](#)). However, if this is indeed the case, then why does it affect the effort component more than reward? Does this reflect a genuine prioritisation of reward information over effort with limited cognitive resources? Or is this related to task-specific factors such as more salient reward cues compared to effort ones? These questions could be answered in follow-up studies aiming to investigate how AD patients attend to, interpret and integrate reward and effort information, e.g., manipulating how effort and reward are presented and delivered.

Another possibility is that AD patients might be forgetting the meaning of the cues while advancing in the task (e.g., what effort levels entail during the experiment) and thus blurring the effect of experimental manipulation ([Ally et al., 2013](#); [Hart et al., 1987](#); [Weintraub et al., 2012](#)). This is unlikely. First, as highlighted earlier, global cognitive function did not correlate with effort sensitivity. Second, we can examine the difference in performance between the first blocks of the task (when information is fresh) and the last ones (when decay might have happened). This analysis did not reveal such a decay-related effect (see Chapter Appendix Figure [A.5](#)). However, it would be worth examining trial-by-trial fluctuations in valuation processes to give a fine-grained delineation of this effect. This is difficult to perform with the ‘yes/no’ task design used in this study and might be more amenable with rating tasks where participants indicate their preferences on a scale rather than absolute acceptance or rejection.

Another challenge with examining the correlation between task measures and apathy scores is to ascertain how reliable self-reports of apathy scores are. Lack of insight is a prominent feature in AD ([Horning et al., 2014](#); [Ott et al., 2006](#)), which might affect their motivation rating. To overcome this, reports of apathy were obtained from patients' caregivers. Despite being significantly correlated with self-reports, caregivers' scores were more sensitive to HDDM parameters, mainly decision bias. Apathy reports from caregivers as well as the degree of discordance between them and self-reports correlated significantly with bias. AD patients who were reported to be more apathetic by their caregivers were less biased in their decisions compared to the less apathetic who were more biased to reject offers (i.e., $z < 0.5$).

These findings highlight a potential mechanism of apathy in AD that involves alterations of internal motivation when evaluating effort against reward, with apathetic patients having less initial bias when making decisions. Such a 'neutral' state when approaching decisions resonates with the classical description of apathy as simply being 'not bothered' ([Baber et al., 2021](#); [Simpson et al., 2015](#); [Stanton et al., 2016](#)). This also accords with recent investigations suggesting that apathy is related to decision inertia, whereby more apathetic people tend to take on more decisions despite effort involved ([Scholl et al., 2022](#)). It would be worth examining whether such a finding is present in other forms of decision making (e.g., risk-based decisions, decision making under uncertainty). The results also draw attention to the importance of holistic assessment of the neuropsychological profile in AD patients, consulting different sources to obtain reliable and objective reports of their functioning, motivation, and affect.

In concordance with previous investigations of resting functional connectivity in AD, rs-fMRI analysis in this study revealed diminished functional activity in AD across multiple brain networks ([Badhwar et al., 2017](#); [Filippi et al., 2019](#); [Vemuri](#)

et al., 2012). This involved reduced connectivity between the hippocampus and other nodes in different networks including DMN, DAN, SMN and visual network. These deficits are most likely related to underlying structural abnormalities in AD, e.g., hippocampal and cerebral atrophy (see Supplementary Information for results of structural analysis highlighting this; Figure A.4) (Deture and Dickson, 2019; Pini et al., 2016; Serrano-Pozo et al., 2011). Some of the nodes in these networks such as mFPC and sensorimotor regions have been highlighted in previous studies for their key role in processing effort in motivated decision making (Lopez-Gamundi et al., 2021). Similarly, executive function in health and disease is thought to be associated with similar connectivity patterns across these networks, mainly DMN and DAN (Fjell et al., 2017; Reineberg et al., 2018). It is thus unsurprising that AD patients, who have disruption in these networks, demonstrate deficits in effort processing and executive functioning compared to healthy controls in whom activity of these networks correlated with these functions.

Involvement of the hippocampus here invites rethinking of the results in the context of the findings from Chapter 3 and 4, where the hippocampus was found to play a role in processing value in context of uncertainty. While the paradigm used in this chapter involves minimal uncertainty, it remains a possibility that some of the results could reflect a form of dysfunctional uncertainty processing in AD that is not directly measurable in the task, e.g., internal uncertainty states about cues, environment, performance, decisions, etc. In a similar vein, hippocampal involvement in effort and uncertainty processing, though involving different networks, further substantiates some of the conclusions made earlier in this thesis arguing for a hidden cognitive effort cost involved during active information gathering to resolve uncertainty.

Decision bias, which correlated with objective apathy in AD, seems to be associ-

ated with distinct network connectivity patterns, involving DMN, FPN and visual networks. Both DMN and FPN have been highlighted in the previous chapter as key networks that might be related to apathy in SCI. Despite not being directly evident in this study sample and based on previous investigations, it is likely that connectivity between these networks is increased in AD patients, mostly as compensation of disrupted hippocampal networks (Badhwar et al., 2017; Filippi et al., 2019; Vemuri et al., 2012). This means shifting bias from rejection to neutrality and then towards more acceptance with stronger activity in these connections. Taking this into account, it is remarkable how apathy-related EBDM deficits cut through metacognitive considerations in the two conditions and involve the same networks. Apathy, which might be a highly subjective phenomenon in SCI vs. being more objectively tracked in AD, might have the same neural signatures across conditions but with different underlying cognitive mechanisms. Such a claim will require future research focusing on metacognitive aspects of apathy in SCI, AD and other conditions that feature deficits in insight and apathy such as schizophrenia (Baier, 2010; Bortolon et al., 2018; Joseph et al., 2015; Kiang et al., 2003; Mintz et al., 2003). Alternatively, these brain-behaviour correlations might be related to a third factor that was not investigated in this chapter, highlighting the need for causal investigations to establish the neural correlates of apathy in both conditions (SCI and AD).

In summary, the findings in this chapter provide one of the first attempts to investigate EBDM and motivation in AD. They highlight distinct effects of executive dysfunction and apathy on EBDM in AD and reveal some of the brain networks that might be involved.

7 | General discussion

In this thesis, I introduced a novel framework and behavioural paradigms for investigation of active information gathering in health and disease. This was coupled by a parallel line of investigation for effort-based decision making to provide comparative and richer insights into goal-directed behaviour. Through extensive testing in different groups (healthy people, ALE, SCI, and AD), along with computational modelling and neuroimaging analysis, I was able to characterise and parameterise key behavioural aspects related to these forms of decision making and provide insights into the underlying brain networks and clinical implications associated with information gathering, uncertainty processing, and EBDM. In this chapter, I provide a summary of these findings and then discuss related considerations, implications, and future directions stemming from this work.

7.1 Summary of experimental findings

7.1.1 The economics of active information gathering

In Chapter 2, I introduced ‘*Circle Quest*’, a novel behavioural paradigm designed to examine *active* information gathering and decision making under uncertainty (Figure 2.1). The task was extensively tested and validated in young healthy people to investigate the factors that influence information sampling and uncertainty processing. The results showed that not only the extent of sampling was influenced by economic constraints and time pressure but also participants’ speed and efficiency (Figures 2.5 & 2.6). Active information gathering was found to be governed by a breakable speed-efficiency trade-off (Figure 2.5 & 2.7). Under sufficient time pressure, participants were able to sample at a faster rate but without losing efficiency. To account for this flexibility, the existence of a cognitive con-

trol mechanism was hypothesised, whereby speed and efficiency were treated as costly cognitive processes. Incorporating this notion into a standard information sample model explained human behaviour better than simpler models (Figure 2.8). This was further validated by a significant correlation between model-derived cost of efficiency and subjective fatigue development during the experiment.

Based on economic cost-benefit calculations and taking into consideration participants' efficiency, it was possible to calculate the optimal number of samples that participants should acquire before committing to decisions. Similar to previous reports (e.g., Jones et al., 2019; Juni et al., 2016; Phillips et al., 1966; Tversky and Edwards, 1966), the results in this thesis showed that people tend to over-sample, especially when sampling cost was high (Figure 2.9). This, along with sampling speed, served as markers of increased reactivity to uncertainty which were found to correlate with subjective reports of intolerance to uncertainty and depression (Figure 2.10).

Together, these findings highlight the importance of accounting for agent-related factors when examining information gathering and provide behavioural and computational markers that have potential clinical significance in understanding affective functioning in humans.

7.1.2 A role for the hippocampus in decision making under uncertainty

Chapter 3 examined the role of the hippocampus as a key brain region that might be involved in decision making under uncertainty and information sampling. The paradigm developed in Chapter 2 was used along with novel paradigms designed to investigate and compare its role in effort-based decision making. Four experiments were conducted in a rare group of autoimmune limbic encephalitis (ALE)

patients – a condition known to result in hippocampal atrophy.

The results in this chapter converged to the conclusion that the hippocampus plays a key role in processing uncertain probabilistic values. This manifested in different decision making contexts. When actively gathering information, while having relatively intact exploratory behaviour (e.g., intact efficiency), ALE patients were less sensitive to local sampling costs resulting in over-sampling behaviour (Figures 3.3 & 3.11). Examining decision making using the passive version of *Circle Quest*, where participants make decisions weighing potential reward against fixed levels of uncertainty, showed that ALE patients were significantly less sensitive to changes in reward than matched controls, while sensitivity to uncertainty was preserved (Figure 3.5). This effect (reduced sensitivity to reward) correlated with reduced sampling cost sensitivity observed in active task, as well as with the severity of hippocampal atrophy in patients (Figures 3.5 & 3.8). Therefore, the result demonstrated a consistent effect across the two *Circle Quest* tasks.

In the third and fourth experiments, I aimed to assess whether reduced uncertainty to reward is a global feature of decision making in hippocampal atrophy, i.e., not necessarily related to contextual uncertainty. Patients were therefore tested on a novel version of a well-validated effort-based decision making task requiring them to make trade-offs between potential rewards and physical effort – a more deterministic form of cost compared to uncertainty. The results showed that EBDM was intact in ALE patients, i.e., no significant difference between patients and healthy controls was found (Figure 3.6 & 3.1). To further characterise the differences observed in performance across the three experiments indicating a specific hippocampal role for decision making under uncertainty but not for effort, a fourth behavioural paradigm was designed to examine how people make decisions considering the three key attributes together (reward, uncertainty and effort) (Figure 3.2). This task further validated the uncertainty-sensitive role of the hippocampus.

Similar to the results from the *Circle Quest* paradigm, ALE patients had intact sensitivity to uncertainty. However, both reward and effort sensitivities were blunted along with exaggerated negative effect of uncertainty on incentivisation by reward in ALE group, suggesting impaired economic valuation under uncertainty (Figure 3.7).

Together, these results point to a key role of the hippocampus in economic valuation apparent specifically under conditions of uncertainty.

7.1.3 Hyperreactivity to uncertainty in SCI

In Chapter 4, I examined information gathering and decision making under uncertainty in subjective cognitive impairment (SCI). The rationale for selecting this group of patients was based on three key features characterising the condition: i) potential underlying hippocampal dysfunction in SCI supported by neuroimaging studies and by the close relationship with AD, ii) strong association with negative affect (anxiety and depression) which is strongly linked to deficits in uncertainty processing, and iii) potential characterisation of SCI as a syndrome of disrupted uncertainty processing and information gathering, given the dichotomy between subjective experience and objective assessment. These three aspects make SCI a neat example to examine the hippocampus-affect-uncertainty axis of neuropsychocognitive functioning.

SCI participants and healthy matched controls were assessed using the *Circle Quest* paradigm. The results showed that overall, SCI participants' behaviour was characterised by hyperreactivity to uncertainty. They collected information more extensively and at a significantly faster rate than controls (Figure 4.1). Consistent with previous literature (Hill et al., 2016; Hohman et al., 2011; Pavisic et al., 2021; Reid and MacLulich, 2006), they also reported higher anxiety and

depression scores representing higher affective burden in the group (Figure 4.8). Markers of hyperreactivity to uncertainty (faster and excessive sampling) correlated significantly with the severity of this burden. This is consistent with the results observed in Chapter 2 in healthy young controls (Figure 2.10) where these markers correlated with depression scores in the group.

Whole-brain resting-state functional neuroimaging analysis showed that SCI participants, compared to controls, have increased connectivity between the hippocampus and insular cortex (Figure 4.9 a.). This hyperconnectivity correlated with hyperreactivity to uncertainty indexed by faster sampling in SCI (Figure 4.9 b.).

Overall, the results indicate that increased responsivity to uncertainty is a key feature in SCI and is associated with affective dysfunction. They also further substantiate the role of the hippocampus and its networks in decision making under uncertainty and information gathering.

7.1.4 Apathy and EBDM in SCI

While the findings in Chapter 4 provided insights into the mechanisms of affective functioning in SCI, these effects were not delineated from other related syndromes, mainly apathy, which often co-exists with depression in many disorders including dementia (Weintraub et al., 2012) In Chapter 5, I aimed to fill this gap and further characterise the psycho-cognitive manifestation in SCI using effort-based decision making framework.

SCI participants performed the EBDM task that was used in Chapter 3 where they evaluated potential rewards against different levels of physical effort. I used a drift diffusion modelling approach to extract latent psychological features related to EBDM.

The results showed that SCI participants were less sensitive to changes in effort when preparing their decisions, i.e., weaker effect of effort on drift rate (Figure 5.1). This effect correlated with the severity of self-reported apathy, but not depression (Figure 5.3). By contrast, apathy in the control group had the opposite effect on effort sensitivity: Higher apathy scores were associated with stronger effects of effort on drift rate. Thus suggesting a distinct mechanism of apathy in healthy people and individuals with SCI, with potential delineation from depression.

Examination of resting-state functional connectivity showed that model-derived effort sensitivity and apathy in SCI correlated with inter-network connectivity between DMN and FPN (Figure 5.4). Such findings are consistent with previous reports on the neural correlates of EBDM and apathy (Lopez-Gamundi et al., 2021).

The results in this chapter highlighted potential mechanisms of apathy in SCI, which were independent of affective functioning. In context of the previous chapters, this distinction between mechanisms of apathy and affective functioning in SCI seems to be related to distinct brain networks. While negative affect was associated with deficits in uncertainty processing and hippocampal-insular connectivity, apathy seems to be related to dysfunctional EBDM related to disrupted DMN and FPN networks.

7.1.5 Apathy and EBDM in AD

Because SCI is often discussed as a risk factor for AD (Arvanitakis et al., 2018; Kryscio et al., 2014; Mendonça et al., 2016), it was crucial and logical to extend the work in the previous chapters to examine AD performance. Due to the complexity of the *Circle Quest* paradigm, it was not possible to obtain reliable data from AD patients and thus work on AD in this thesis was limited to EBDM as the

task is simple and was performed by many AD patients without difficulties.

In Chapter 6, AD patients were found to be significantly less sensitive to effort than healthy controls with weaker effect of effort on drift rate (v_e) (Figure 6.2). This was related to their executive dysfunction deficits and not apathy or global cognitive decline ((Figure 6.3). On the other hand, decision bias (z), which was intact in AD patients when compared to controls, was associated with apathy reports obtained from patients' caregiver. The two parameters (v_e & z) seemed to be processed by different networks in healthy people (hippocampal-DAN for v_e and DMN-visual-FPC for z) that were disrupted in AD. Thus, the results highlight distinct behavioural and brain signatures for executive dysfunction and apathy in AD.

Figure 7.1 provides a visual summary of some of the key results discussed in the previous section.

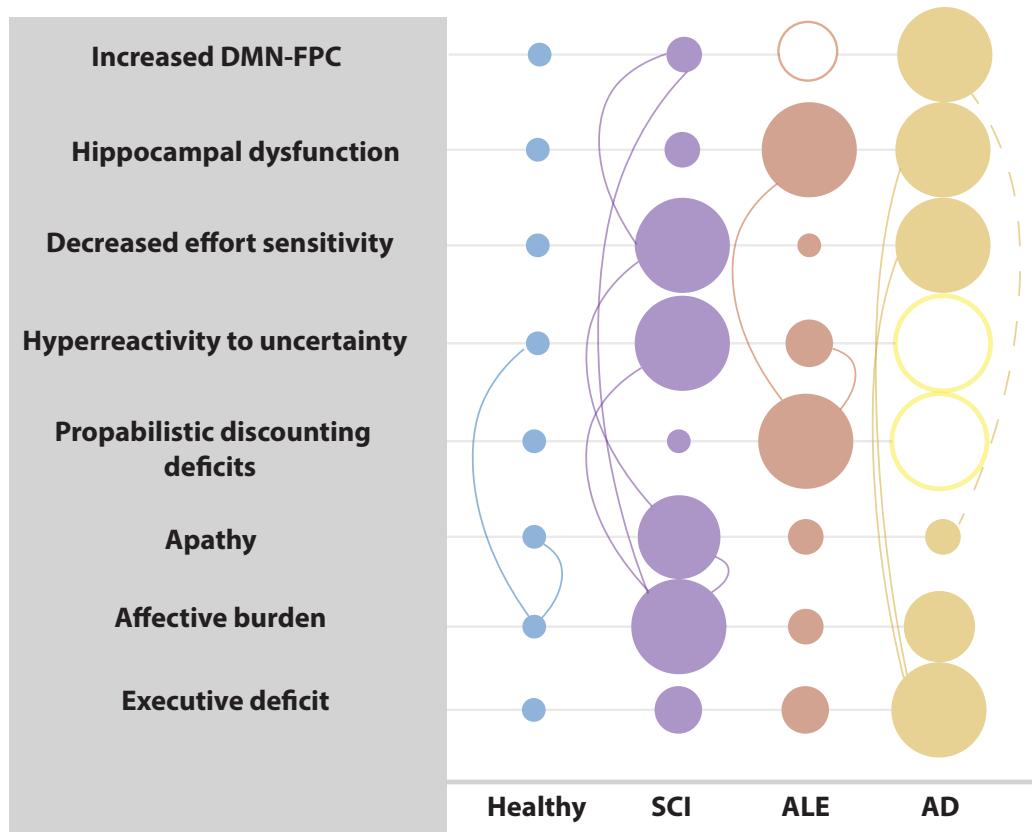


Figure 7.1: **Visual summary of some of the thesis results.** The size of the circles gives a visual approximation of how prominent the effect is compared to other groups. Lines indicate a statistically significant correlation between these effects. Empty circles denote untested effects, and dashed line signifies a relationship that is indirectly inferred.

7.2 Transdiagnostic considerations

While I have highlighted the findings for each of the tasks and study groups separately to answer the specific questions asked in each chapter, it is crucial to consider the results in combination (Figures 7.1 to 7.3). A transdiagnostic and trans-mechanistic account of deficits in goal-directed behaviour can be key to characterising related clinical manifestations and their neural underpinning (Gleichgerricht et al., 2010; Husain and Roiser, 2018; Seow and Gillan, 2020). Two factors make such a consideration feasible in the context of this thesis: i) the same paradigms were used in the different study groups, allowing reliable behavioural comparisons, and ii) participants in these groups could be identified on clinical and hippocampal dysfunction spectra (Figure 7.2), making it possible to link clinical, anatomical, and mechanistic considerations across different disorders.

For example, one can consider the cognitive dysfunction spectrum across these disorders, with healthy controls, ALE, SCI, and AD having different levels (and forms) of cognitive deficits. Examining the performance of the SCI participants, who are comparable to controls in their cognitive abilities but can be considered as pre-AD syndrome, at least in some individuals (Jessen et al., 2020; Reid and MacLulich, 2006), one could generally suggest that it is indicative of reduced sensitivity to effort, both cognitive and physical. This is demonstrated by faster and efficient sampling related to reduced model-derived cognitive effort costs (Figures 4.5 & 4.7), as well as by reduced effect of physical effort changes on EBDM as indicated by HDDM results (Figure 5.1). These two elements, however, differed in their clinical implications and associated brain networks, with the first being more related to general affective burden and specific hippocampal-insular functional network (Figures 4.8 & 4.9) and the second being linked to apathy and more widespread brain networks involvement, including those involved in execu-

tive functioning (Figures 5.3 & 5.4).

As we move further along the spectrum of cognitive dysfunction, we see that AD patients demonstrate more pronounced deficits in EBDM which were related to their executive dysfunction and a range of brain networks that involve the hippocampus (Figure 6.3). Here, ALE patients serve as a crucial comparison group as they also demonstrate cognitive deficits (mainly in the memory domain), but do not show the same pattern of dysfunctional effort processing (Figure 3.1 & 3.7). Instead, their performance on the same tasks was indicative of disrupted probabilistic valuation regardless of effort involved (Figures 3.5 & 3.7), thus suggesting that it is unlikely that physical effort processing and apathy in SCI and AD were hippocampus-dependant. This further supports the notion that apathy in these conditions might be regarded as a dysexecutive syndrome related to wider disruption in resting brain networks. On the other hand, the hippocampus in SCI and ALE was involved in behavioural control and decision making in uncertainty context, which, at least in SCI, has been linked to affective functioning (Figure 4.8).

These overlapping or distinctive mechanistic features across different tasks and groups suggest that across different diseases and in health there might be hidden mechanistic dimensions that map jointly to various clinical syndromes which are otherwise considered separate entities. This invites re-thinking of how we characterise such clinical categories as they often overlap and cross the boundaries between health and disease. Such a characterisation is increasingly becoming more feasible with the availability of large behavioural, clinical, and brain imaging datasets from which one could extract transdiagnostic features that offer a new way of characterising cognitive and mental health disorders. Many recent reports have provided initial evidence that supports this line of work. For example, [Gillan et al. \(2016\)](#), using large-scale assessments of psychiatric symptoms and goal-

directed behaviour, showed that specific deficits in behavioural control are related to a symptom dimension characterising compulsive behaviour and intrusive thinking. This relationship was independent of other aspects of psychopathology which mapped to different symptom dimensions. A similar approach has been used in multiple studies with different behavioural tasks and clinical associations ([Dubois and Hauser, 2022](#); [Rollwage et al., 2020](#); [Seow and Gillan, 2020](#)). The rapid progression toward online studies and digitalisation of health tools that we have seen in the past few years will further enhance these efforts and advance transdiagnostic research, not only in healthy people but also in disease groups.

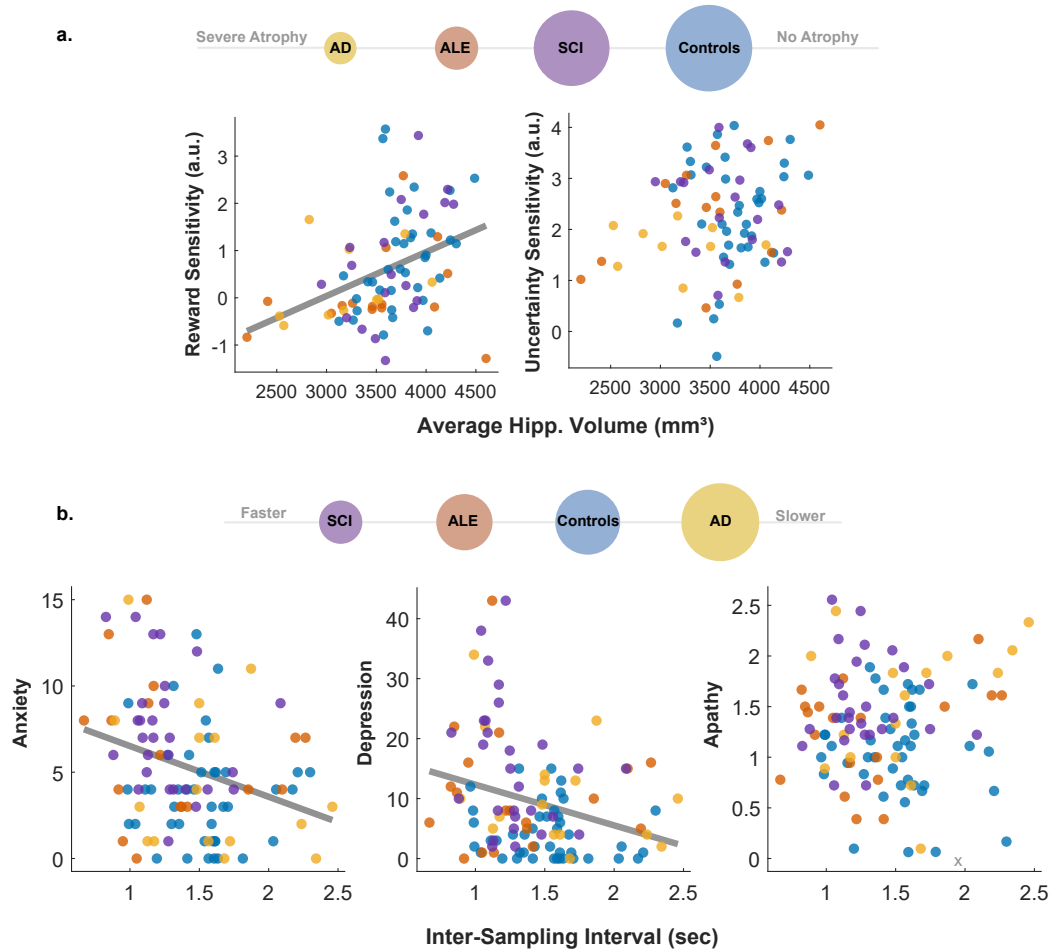


Figure 7.2: Circle Quest transdiagnostics. **a.** Across different study groups, hippocampal atrophy is associated with reduced sensitivity to reward under uncertainty. This relationship was examined specifically in Chapter 3 within ALE patients, and holds when data are pooled from ALE, AD, SCI and control groups. **b.** Similarly, the relationship between faster sampling and affective burden highlighted in SCI participants in Chapter 4 is also evident when data from all study groups are considered. These results highlight behavioural, clinical, and neuroimaging spectra that help further characterise these conditions. *Figure includes preliminary data from AD patients (N=13) not reported separately in this thesis.

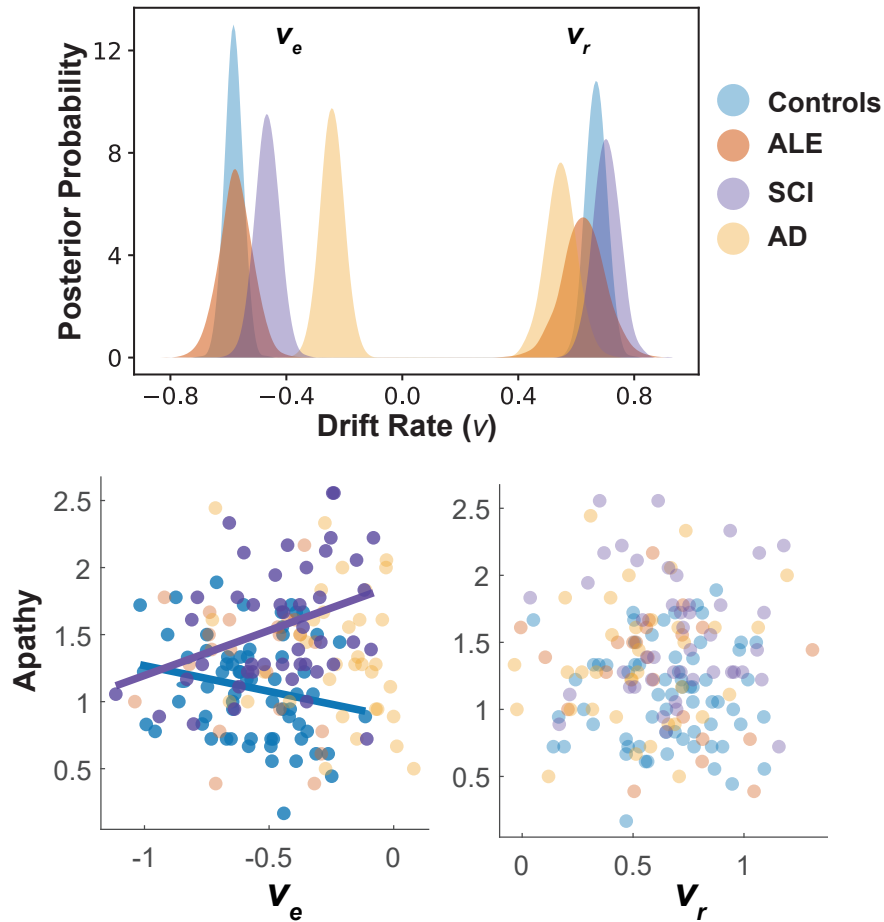


Figure 7.3: **EBDM transdiagnostics.** Different clinical groups are differentiated by effort sensitivity profile. AD patients show the most severe disruption of effort sensitivity. SCI participants are more sensitive to effort than AD patients but less than controls. ALE patients have similar EBDM profile as controls. This spectrum of effort sensitivity is not reflected in the relationship with apathy. SCI and controls had an opposite pattern of correlation, while subjective apathy reports in ALE and AD were not related to effort sensitivity. Such findings highlight the complexity of the clinical syndrome of apathy and indicate that a more fine-grained approach might be needed to characterise it across different health conditions, e.g., incorporation of caregiver reports of apathy as in Chapter 6.

7.3 Uncertainty: related concepts and other perspectives

In this thesis, uncertainty pertained to the state of ‘lack of information’ imposing probabilistic considerations of the future (Duncan, 1972; Miller and Frick, 1949). Acquiring appropriate samples in the context of the experimental paradigms used resulted in improvement of knowledge about these probabilities (i.e., better estimates of the location of the hidden circle). This is often distinguishable from other related concepts such as **ambiguity**, which involves ‘lack of clarity’ even if appropriate information was available (Grenier et al., 2005; Kirschner et al., 2016; Schrader et al., 1993). The primary question relating to ambiguity is about the interpretation of information rather than its availability. Consequently, the two concepts, despite occasionally being used interchangeably, imply different cognitive processes for decision making and problem solving (Grenier et al., 2005; Kirschner et al., 2016; Schrader et al., 1993). Under conditions of uncertainty, agents know, or at least have an idea about what needs to be known to perform the task and solve the problem at hand. Information gathering here is task-directed and serves a pre-determined goal. On the other hand, when ambiguity is involved, the problem solver might find difficulty deciding what information is required as they are unable to determine the scope of the task. To solve ambiguity problems, agents might first need to define an internal model to guide problem solving activity and help demarcate the tasks involved (Schrader et al., 1993).

Experimentally, the distinction between the two operations can be conceptualised as a difference between problems of anticipation and perception. Uncertainty is future-focused, with agents trying to predict outcomes based on available information and *anticipate* probabilistic values (Carleton, 2014; Grenier et al., 2005;

[Grupe and Nitschke, 2013](#)). Ambiguity is concerned with present stimuli and how to interpret them, i.e., it is concerned with what is happening ‘here and now’ rather than what is to come ([Kirschner et al., 2016](#); [Schrader et al., 1993](#)). This distinct temporal formalisation might impose differences in information processing at different stages. For example, goal-directed information gathering might be regarded as a key behavioural step in processing uncertainty, but not as much for ambiguity in which the goal and situation are yet to be clarified. Consequently, intolerance to these aspects might invoke different behavioural responses with distinct clinical implications.

In this thesis, I have focused on uncertainty and demonstrated that reactivity to anticipated uncertainty during the information gathering phase is related to affective functioning. This is in line with previous studies showing altered anticipatory responses to uncertainty, whether behavioural (e.g., worse accuracy and increased reaction time) or physiological (e.g., increased skin conductance), and linking them to affective regulation ([Grupe and Nitschke, 2011](#); [Krain et al., 2006](#); [Sarinopoulos et al., 2010](#)). On the other hand, previous investigations have shown that intolerance to ambiguity is related to biased information processing at time of perception, but without affecting arousal or emotional responses ([Kirschner et al., 2016](#)). The distinction between these two processes and their neural underpinning will require further studies designed to delineate the differences between them and control for overlapping features.

In a similar vein, a distinction could be made between two main types of uncertainty in decision making: **expected** and **unexpected** ([Bland and Schaefer, 2012](#); [Soltani and Izquierdo, 2019](#); [Yu and Dayan, 2005b](#)). The former arises from stochasticity inherent to the environment with stable probabilities based on learned stimulus-response-outcome (S-R-O) relationships. This is the type of uncertainty that characterises the *Circle Quest* paradigm as the probability of finding

the hidden circle could be inferred from clues obtained or presented on the screen. On the other hand, unexpected uncertainty arises from fundamental changes to the learned rules of the task, e.g., if the hidden circles were to be found in a location outside the search field or if clues changed colours. In these examples, the previously learned rules to establish probability estimates about the future (i.e., to infer the location of the circle) will no longer be valid, and participants are thus faced with unexpected changes in the system. This is also distinct from **volatility**, which pertains to variations in the S-R-O relationship over time resulting in different estimates of probabilities, e.g., dynamically changing localisation error penalty in the task without prior warning. In turn, this requires agents to update S-R-O contingencies in order to optimise their behaviour under the new rules ([Bland and Schaefer, 2012](#)).

Detailed examination of these differences in uncertainty operations and how they relate to active information gathering is beyond the scope of this thesis. However, there is a growing body of literature that aims to specifically characterise such differences along their behavioural, clinical, and neural correlates ([Bland and Schaefer, 2012](#); [Morriss et al., 2019](#); [Soltani and Izquierdo, 2019](#)). Accounting for these differences should offer valuable insights that enhance our understanding of goal-directed behaviour in health and disease, and push forward a fine-grained mechanistic characterisation of disorders of decision making. Such efforts add to, and benefit from, investigations in closely related fields such as organisational psychology and policy, where careful delineation of uncertainty and other concepts (ambiguity, volatility, and complexity) is considered critical for strategic planning and resource allocation ([Bennett and Lemoine, 2014](#); [Johansen and Euchner, 2013](#); [Mack et al., 2015](#)).

7.4 The value of information

When information gathering was examined in this thesis, it was regarded as a goal-directed process where information carries *instrumental utility* to help reduce agents' uncertainty and optimise outcomes. While this describes a fundamental aspect of information seeking in humans and animals as discussed in Chapter 1, it should be noted that humans might seek (or avoid) information for other purposes or utilities (for a review see [Sharot and Sunstein, 2020](#)). For example, an individual might seek to know whether their favourite team won their last game or avoid knowing the results of medical screening tests. In these contexts, information is thought to have a *hedonic* value that impacts one's emotions and affect. People seek information that evokes positive emotions (e.g., monitoring investing portfolio when profit is expected) and avoid potentially negative ones (e.g., refusing to receive results of medical tests) ([Gigerenzerk and Garcia-Retamero, 2017](#); [Golman et al., 2017](#); [Karlsson et al., 2009](#); [Persoskie et al., 2013](#)). Such operations have been shown to be associated with activity in brain networks and regions involved in processing reward, value, and prediction errors, supporting the formalisation of this type of information seeking as another form of reward-seeking behaviour ([Blanchard et al., 2015](#); [Bromberg-Martin and Hikosaka, 2009](#); [Charpentier et al., 2018](#); [Gruber et al., 2014](#); [Jessup and O'Doherty, 2014](#); [Kang et al., 2009](#); [Kobayashi and Hsu, 2019](#); [Tricomi and Fiez, 2012](#)).

However, human hedonic information seeking not always follows these rules. For example, people might delay the receipt of good news in order to enjoy the time while anticipating rewarding information ([Caplin and Leahy, 2001](#); [Loewenstein, 1987](#); [Mukherjee et al., 2021](#)). This is known as *anticipatory utility* and has been linked in recent work to hippocampal networks related to the dopaminergic brain system and medial prefrontal cortex ([Iigaya et al., 2020](#)). On the other hand, and

in partial resonance with the results reported in this thesis, people might find uncertainty about potential bad news unsettling and anxiety-provoking, leading them to try to acquire information quickly, even if it is expected to lead to negative outcomes ([Grupe and Nitschke, 2013](#)). Overall, these aspects of behaviour generally follow the same principles of instrumental sampling as agents aim to reach a state of maximum reward (or positive affect) and reduce losses (or negative affect).

It is also worth mentioning that information *actively* collected for instrumental purposes (e.g., as in the *Circle Quest* paradigm) might acquire additional value because of personal effort invested into obtaining these pieces of information, even if this information is hedonically neutral. This corresponds to the model-derived cognitive effort cost incurred during active sampling. It would be insightful if future research empirically compares the valuation of self-acquired information vs. when passively offered. In the *Circle Quest* paradigm, this would be a comparison between the configuration of dots that participants generate prior to decision making vs. passive configurations that carry the same information (i.e., equal expected error). This might provide strong empirical evidence on the existence of additional costs incurred during active sampling. The same principle might also explain the ‘effort paradox’ in certain EBDM situations, where people find more effortful actions more valuable because of the personal effort invested to obtain the goal ([Inzlicht et al., 2018](#)).

Another reason for information seeking in humans is curiosity ([Gottlieb and Oudeyer, 2018](#)). For example, some people might want to know more about the origins of their favourite comic book hero, the life of an ancient philosopher, the principles of evolution, the books of a prominent novelist that they admire, etc. Such information does not directly invoke affect changes or help in solving a particular problem at hand. Instead, they are curiosity-driven and thought to contribute to one’s mental model of the world, i.e., pertaining to a general *cognitive utility* ([Sharot](#)

and Sunstein, 2020). That said, one can reasonably argue that such information also carries delayed instrumental utilities as it might help in solving problems that agents might face in the future or enhance their general abilities to do so. Similarly, learning about things that entice our curiosity might be a rewarding action and induce positive feelings, i.e., carry hedonic utility.

Taking into consideration these different forms of utility and their overlap in certain contexts is crucial for accurate analysis and modelling of information gathering and decision making. In the models used in this thesis, these additional utilities along with other inter-individual differences are most likely related to the intercept parameter. While computationally we could offer further deconstruction of utilities and costs involved in active information seeking, further delineation of these overlapping parameters will require careful behavioural designs aiming to experimentally isolate them and examine their interaction.

7.5 Noise and information

The previous discussions about information gathering assume two key characteristics of observations being collected and processed: they are i) relevant and ii) proportionate. This means that agents not only collect samples, but also filter them depending on task needs. Irrelevant information outside the context of the problem might result in distractions (Ackerman, 1987; Lavie, 2005). Similarly, too much information, even if relevant, might paradoxically increase agent uncertainty and cause decision fatigue (Buchanan et al., 2001; Phillips-Wren and Adya, 2020). In this thesis, I have demonstrated that humans incur additional cognitive costs for sampling efficiently and rapidly to resolve uncertainty. However, I acknowledge that the paradigm was relatively limited in examining how people filter information during sampling as participants did not have different sources

of information to decide between and were not able to acquire too much information because of the binary nature of the clues and economic structure of the task. Many real-life situations require agents to do more extensive filtering while seeking information, adding another layer to *active* information gathering that future experimental efforts should account for and investigate.

In a world where information about almost anything is readily available anytime and anywhere, such operations are becoming increasingly a crucial part of cognitive lives. Humans are facing growing challenges identifying reliable sources of knowledge, filtering out noise and misinformation, and overcoming biases that affect these processes. Deficits in performing these operations have been linked to mental health problems, including anxiety and depression ([Baumeister et al., 2001](#); [Blades, 2021](#)). For example, ‘doom-scrolling’ and ‘doom-surfing’ – phenomena that describe excess information seeking, mainly negative news – are increasingly recognised as maladaptive responses to uncertainty and have been shown to be associated with feelings of anxiety, depression, and stress ([Anand et al., 2022](#); [Blades, 2021](#); [Price et al., 2022](#)). This has partial resemblance with the results observed in individuals with SCI. However, SCI individuals’ information seeking was goal-directed and highly efficient, which is different from unfiltered purposeless and excessive seeking that does no serve (or is distracted from) a specified goal.

7.6 Agency and metacognition

I have demonstrated in this thesis that accounting for agency over the sampling process can reveal insightful aspects about information gathering behaviour and uncertainty valuation and processing. In SCI individuals, for example, it was evident that they deviate from controls’ performance and are hyperreactive to uncer-

tainty when actively gathering information and not during passive decision making. These effects did not seem to be driven by disruption of economic valuation between the two contexts, rather they were more likely related to cognitive control mechanisms as demonstrated by computational modelling of the active sampling behaviour. How can we characterise the effect of agency here? For example, are these differences a demonstration of implicit cognitive processes that could only be revealed by adding agency, or are they related to the effect of awareness of this agency? Does this behaviour manifest differently at different agency levels? If so, how can we measure these alterations?

Behavioural agency could be experimentally challenging to measure as it is often phenomenologically thin ([Moore, 2016](#)). This is because it is often assumed and implicit in behaviour rather than being consciously tracked and reported by agents. In the *Circle Quest* paradigm, agency was inferred implicitly by comparing between active and passive tasks, as well as partially by manipulating trial time (i.e., deadline to finish sampling). We can expand on this to examine agency more directly by introducing different manipulations that limit sampling but still give agents some control over the process. For example, one manipulation that I recently started designing and piloting includes a version of the task where a time pause is forced between each sample and the next. While agents still have control over how much to sample and where to sample, the speed of sampling is limited by these pauses. This new manipulation still allows participants to be as slow as they want but limits their speed at predefined limits. Another similar agency-restricting, but crucially not -omitting, manipulation is to force participants to allocate a predefined number of samples that they are allowed to use. This removes agency over how much to sample but keeps control over speed and efficiency. Similarly, we can also limit efficiency by introducing localisation restrictions to where participants could place the samples. With all these manipulations, a more

explicit measure form of agency can be simply obtained by asking participants to rate their subjective levels of control.

Such measures will help us answer key mechanistic questions with potential clinical significance. For example, does the feeling of lack of control (or its metacognitive attributes) vary with affective functioning as suggested by a number of previous depression and anxiety model (e.g., learned helplessness)? ([Liu et al., 2015](#); [Maier et al., 1976](#); [Miller and Seligman, 1975](#)) Does apathy affect how people operate over different levels of agency? Can apathetic people be enticed to act or engage with increasing agency? All these questions and hypotheses are reasonable directions for future research. Consideration of agency and metacognitive functioning is key to advance our understanding of goal-directed behaviour and decision making in an ecologically valid fashion. This has the potential to help not only improve our understanding of human cognition, but also aid in advancing AI and robotics research aiming to produce autonomous agents with decision making capabilities.

7.7 Treatment implications

The mechanisms highlighted in this thesis provide insights into specific behavioural components and brain networks that could be targets for future treatment in affective disorders, apathy and other related clinical conditions such as SCI. There are at least three types of interventions that could be considered: i) behavioural, ii) pharmacological and iii) neurofeedback.

Detailed examination of the neurotransmitters involved in active information gathering is beyond the scope of this thesis. However, previous research suggested an important role of monoamine neurotransmitters such as serotonin and norepinephrine (NA) (see [Chapter 1](#)) in information gathering with some insights into

specific mechanisms, e.g., modulating effect of NA on the cost and extent of sampling (Crockett et al., 2012; Hauser et al., 2018; Livermore et al., 2021). These previous investigations could provide a starting point for future research that aims to investigate the role of different neurotransmitters in *active* information gathering and determine the clinical implications of their modulation. On-off studies would be key future direction to examine whether some of the mechanisms highlighted in this thesis are amenable to pharmacological manipulation. Many questions will need to be answered, for example, what neurotransmitters modulate uncertainty sensitivity in SCI? How do these neurotransmitters influence hippocampal-insular connectivity? Is there a clinical effect from such manipulations? and so on.

Similarly, once we have a reliable mechanistic characterisation of the clinical implications of deficits in active information gathering, it will be possible to develop and advance behavioural interventions with effective clinical outcomes. With advances in digital biomarkers and cognitive profiling, this could take the form of digital interventions instead of (or in addition to) clinic-based therapies. Such promising solutions might transform how we monitor and manage cognitive and mental health disorders in the future. Aided by real-time data collection and application of machine learning approaches, it might be possible to deliver precision behavioural therapies that are highly personalised and specific. In ADHD, for example, a recent clinical trial provided evidence supporting the effectiveness of software-based digital intervention for the reduction of symptoms severity (Kollins et al., 2020). Similar approaches can be used to address the mechanisms of apathy and affective dysregulation highlighted in this thesis.

Another possible way by which we can provide mechanism-specific interventions for syndromes of goal-directed behaviour is neurofeedback modulation (Dewiputri and Auer, 2013). As some deficits might be related to specific network dysreg-

ulation (e.g., increased insula-hippocampus connectivity in SCI), it might be possible through fMRI-neurofeedback to restore normal pattern of activity in these networks which could influence behaviour and have clinical impacts. Several previous studies supported the validity of fMRI-neurofeedback in modulating brain regions and networks activity with significant behavioural and clinical effect ([Watanabe et al., 2017](#)) – e.g., reduced skin conductance response to fearful stimuli in phobia after modulating vmFPC activity ([Taschereau-Dumouchel et al., 2018](#)).

For all these potential interventions, in addition to establishing the cognitive and neural mechanisms underlying clinical syndromes of interest (e.g., apathy, depression, anxiety, etc.), there are at least two key challenges that need to be addressed in order to achieve clinical breakthroughs. First, the design (or translation) challenge. If we indeed were able to identify specific mechanisms underlying different psychopathologies using behavioural paradigms such as *Circle Quest* and EBDM task, how does this actually translate into real-life behaviour and more naturalistic settings? What does jargon such as ‘hyper-reactivity to uncertainty’ or ‘hyper-sensitivity to effort’ translate to in day-to-day activities? How do we design and introduce behavioural interventions that are beyond the task paradigms and lab-based environment used to capture these effects? The key to overcoming this is to design our behavioural tasks with this problem in mind, with enough complexity to be ecologically translatable but at the same time without losing measurability and specificity. This can be extremely challenging and would require careful piloting, task iterations, and extensive testing to achieve this balance.

The second challenge is clinical validation. There is an enormous number of studies in psychology and cognitive neuroscience claiming to have provided better diagnostics or potential new insights into treatments of many cognitive and mental disorders. However, we rarely see any of these used or considered in traditional

clinical settings, simply because there is limited research on their clinical utility. There is a gap between basic cognitive research and clinical application, which will need to be filled by serious research projects and initiatives to design and implement clinical trials with the goal of providing evidence-based solutions and guidelines.

7.8 Policy implications

Beyond clinical implications and considerations, the findings in this thesis offer valuable insights into our day-to-day lives and thinking patterns. Both individuals and institutions could benefit from understanding and taking into account the processes that contribute to decision making and information gathering. For example, understanding the economics of information gathering would help guide and justify decision makers' investment in information when faced with uncertainty. This could help achieve the best outcomes based on cost-benefit models and calculations, improving budgeting decisions and refining risk policies.

In addition, understanding the cognitive and computational costs involved in decision making processes and their implications on affect and motivation might also help policymakers optimise their human resourcing and performance expectations. For example, knowing that pushing people with deadlines can improve efficiency (as demonstrated by breakable speed-efficiency trade-off in information gathering) might be tempting to enforce stricter time frames for project completion. However, this must be balanced with the additional cognitive cost, fatigue, and affective dysfunction that accompanies such demands. On the other hand, the same phenomenon might be interpreted using what has been known in business and economics literature as Parkinson's law which entails that "Work expands so as to fill the time available for its completion" ([Bryan and Locke, 1967](#); [Gutier-](#)

rez and Kouvelis, 1991; Latham and Locke, 1975; Parkinson, 1957). One student might spend several days preparing for a presentation – deciding what application to use, what slide design they should go for, animation, etc – while another might prepare a similar presentation in a few hours if they are facing a strict deadline. This elastic demand of work on time should be a crucial consideration when thinking of plans, strategies and protocols, especially with increasing bureaucracy that we see in many institutions.

Take, for example, academics working for universities or clinicians working for the NHS in the UK who often find themselves spending considerable amount of time completing tasks that are often irrelevant and unnecessary – e.g., filling forms on regular basis, going through repeated annual training for things unrelated to their work, completing surveys, submitting the same document multiple times to different committees for the same purpose, and so on. These tasks in such organisations might be just a side effect of growing bureaucracy created by growing managerial staff that needs to create (or complicate) tasks to justify their jobs and time allocated for certain projects. A serious reconsideration of these aspects should take place, especially as they seem to be related to a simple bias in goal-directed behaviour whereby people create more work for available time.

7.9 Concluding remarks

In this thesis, I have introduced conceptual and experimental frameworks for investigating active information gathering and effort-based decision making. While I have revealed how parameters from such frameworks can provide insights into human motivation and affect, this only scratches the surface of what is possible. As we transition into an era where every aspect of our behaviour can be tracked and measured, we are likely to see a surge in the complexity and sophistication

of such frameworks. This will have the potential to transform how we categorise, parameterise, and examine cognitive and psychological functions in health and disease. Such a mechanistic characterisation promises to replace the current syndromic description of many clinical disorders, allowing targeted approaches in cognitive medicine and enhancing our understanding of the human brain.

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A | Additional Figures

A.1 Chapter 3

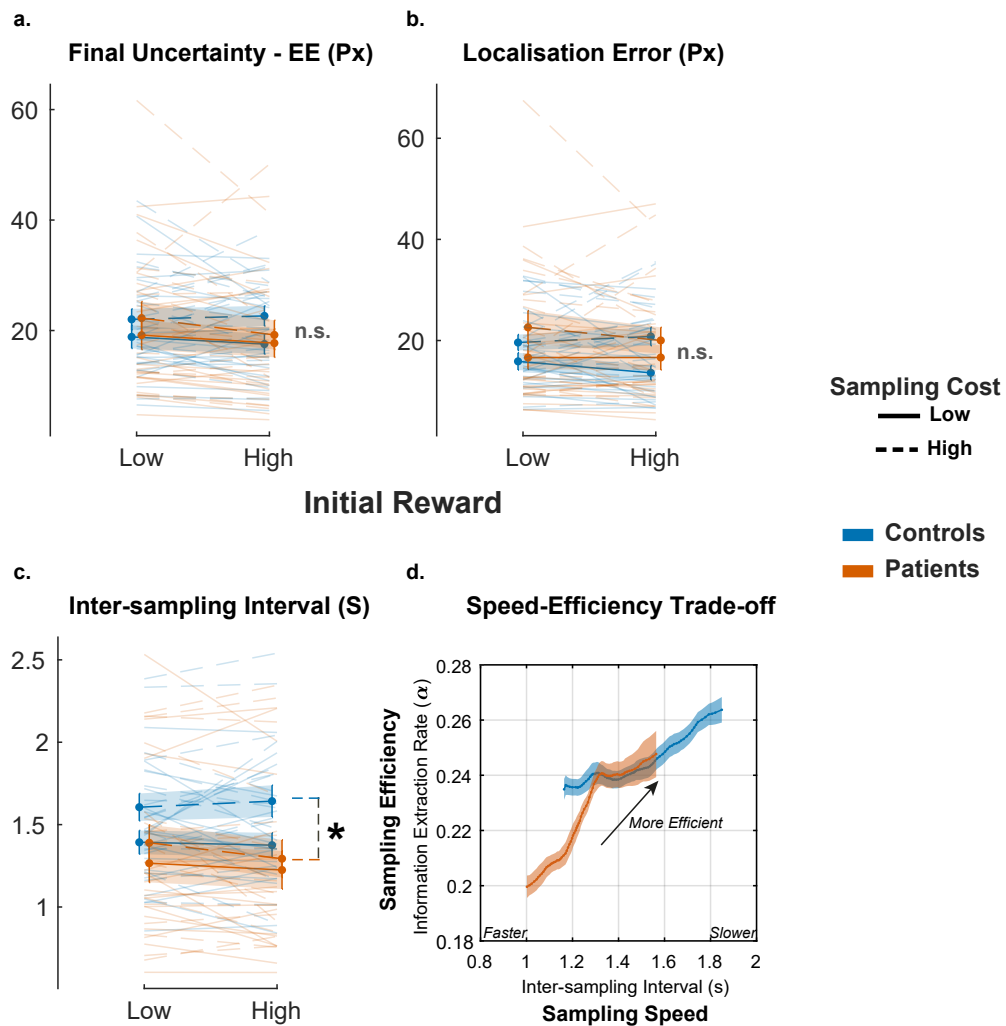


Figure A.1: Active sampling – ALE patients commit to decisions at similar uncertainty levels as controls. **a.** Final uncertainty is the expected error (*EE*) in pixels (Px) that a participant is likely to obtain at the end of their search. There was no significant difference between hippocampal patients and controls in final *EE* across conditions. **b.** Similarly, the actual error that participants obtained upon localising the circle (distance to hidden circle in pixels) was not significantly different between patients and controls. These two results indicate that hippocampal patients wasted monetary resources on samples with limited utility (i.e., over-sampled). **c.** Hippocampal patients gathered information at a significantly faster rate than controls when sampling cost was high. **d.** Sampling behaviour in hippocampal patients and controls was characterised by a speed-efficiency trade-off whereby faster sampling rates were associated with lower efficiency. Error bars show $\pm$ SEM. *: $p < 0.05$. See Tables B.8 & B.5 for additional statistical details.

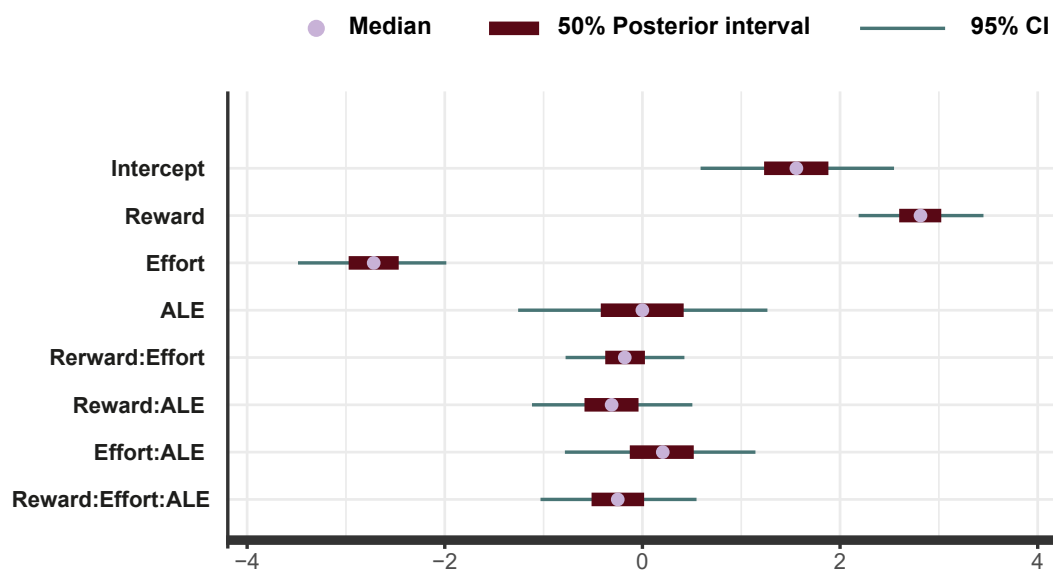


Figure A.2: **Bayesian mixed effects model.** The purple dots show the median of the posterior distributed with 95% credible intervals (thin green line) and 50% posterior interval (thick dark red lines). Model was specified as follows: $\text{choice} \sim 1 + \text{group} * \text{Reward} + \text{group} * \text{Effort} + \text{Reward} * \text{Effort} + \text{group} : \text{Reward} : \text{Effort} + (1 + \text{reward} * \text{Effort} | \text{participant})$.

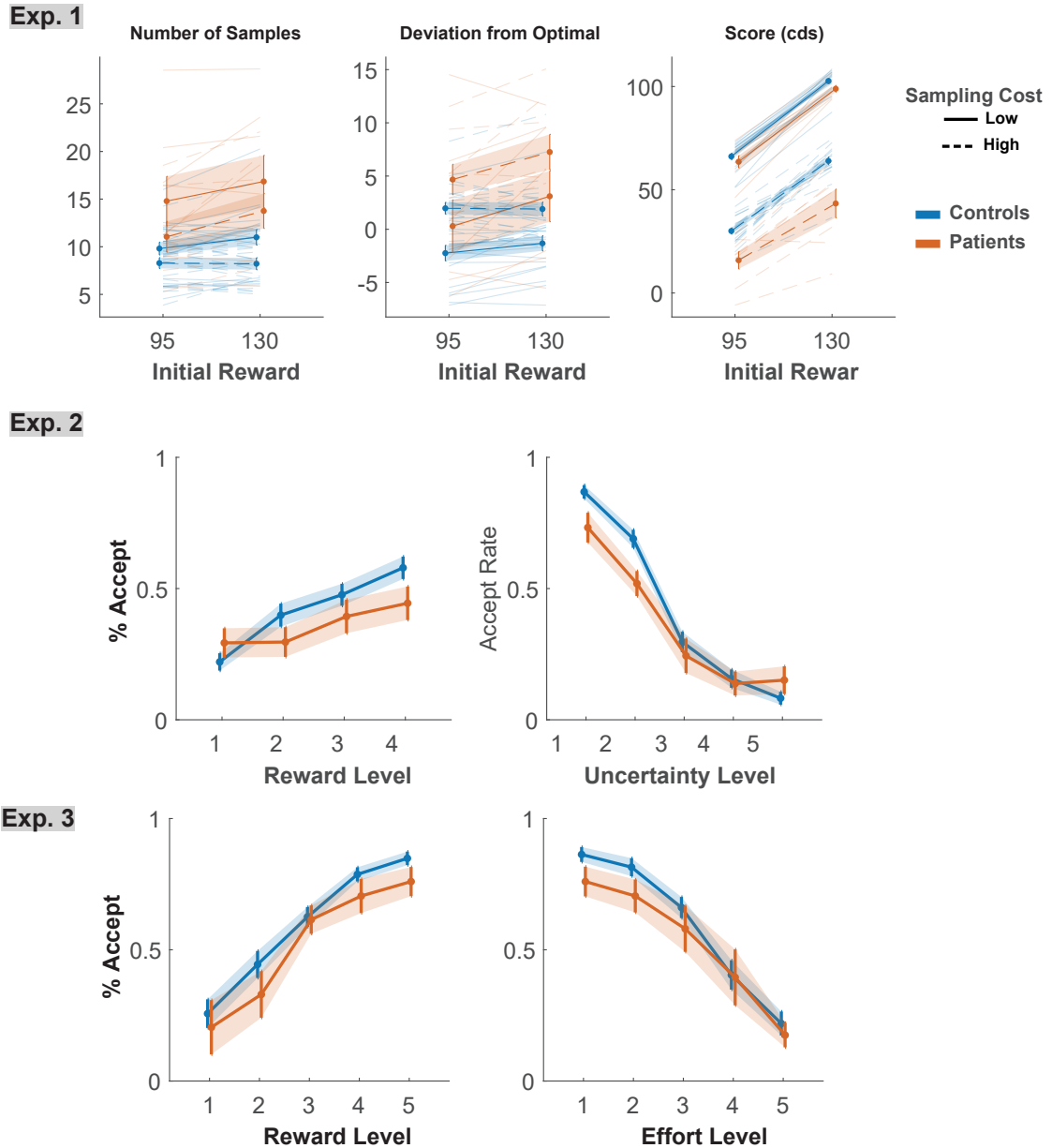


Figure A.3: **Analysis of Exps.1–3 with ALE patients from Exp. 4.** To investigate if the eight patients tested in Exp. 4 were adequate representation of the ALE group, performance was analysed after exclusion of patients who did not complete Exp. 4. The results were similar to the findings reported when the all patients included.

A.2 Chapter 6

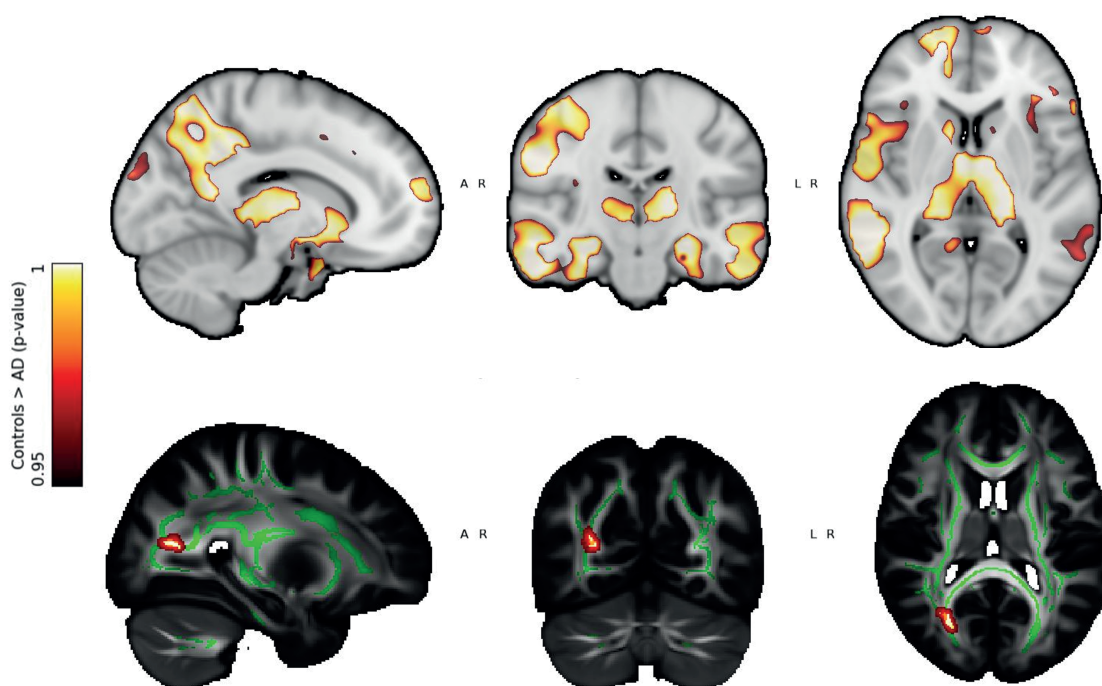


Figure A.4: **MRI structural difference between AD patients and controls.** The upper panel shows the results for voxel-based morphometry (controls > patients). AD patients had lower grey matter intensity in different brain regions including hippocampal, frontal and parietal areas. The bottom panel shows differences in diffusion functional anisotropy (FA) using tract-based spatial statistics. The images were acquired and analysed using the same acquisition and analysis pipeline applied for the UK biobank neuroimaging protocol ([Alfaro-Almagro et al., 2018](#)). VBM results were interpolated for visualisation purposes.

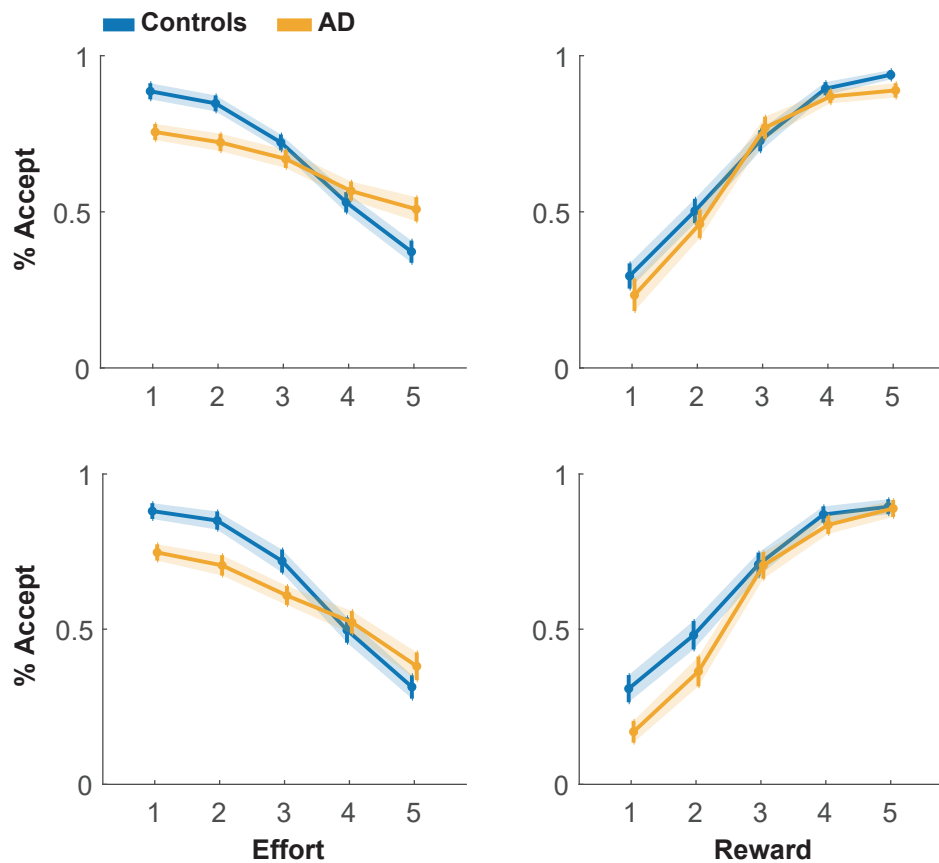


Figure A.5: **EBDM task results split by block.** The upper panel shows data from the first two blocks and bottom panel shows data from the last two blocks. Note that in these two datasets AD patients had reduced sensitivity to effort and preserved to sensitivity to reward. This indicates that effect of decay on preferences is negligible in this experiment.

B | Additional Tables

B.1 Chapter 2

	Uncertainty Score	Choices
(Intercept)	$\beta = +8.27 \times 10^{-17}$ $SE = 0.0149$ $t_{8062} = +0.00$ $p = 1.00$	$\beta = +0.356$ $SE = 0.286$ $t_{8060} = +1.24$ $p = 0.21$
<i>EE</i>	$\beta = +0.799$ $SE = 0.016$ $t_{8062} = +49.89$ $p < 0.0001$	$\beta = -2.53$ $SE = 0.135$ $t_{8060} = -18.77$ $p < 0.0001$
<i>R</i>		$\beta = +1.87$ $SE = 0.196$ $t_{8060} = +9.58$ $p < 0.0001$
<i>R:EE</i>		$\beta = +0.101$ $SE = 0.102$ $t_{8060} = +0.99$ $p = 0.32$
<i>adj - R²</i>	0.69	1.00
<i>N_{obs}</i>	8064	8064
BIC	14046.98	48710.74

Table B.1: **Fixed effects of the analysis of uncertainty score and accept-reject decisions.** Models were specified as follows. Uncertainty Score $\sim 1 + EE + (1 + EE \mid \text{participant}) + (1 + EE \mid \text{Session Order}) + (1 \mid \text{trial})$; Choice $\sim 1 + R*EE + (1 + R*EE \mid \text{participant}) + (1 + R*EE \mid \text{Session Order}) + (1 \mid \text{trial})$. A linear model was used for uncertainty scores, while a logistic one was used for choices (coded as 1 = accept, 0 = reject). To obtain standardised coefficient estimates, *R* and *EE* were z-scored.

	Exp. 1b	Exp. 2	Exp. 3	Exp. 4	Exp. 5
(Intercept)	$\beta = +2.31$ $SE = 0.0287$ $t_{4604} = +80.53$ $p < 0.0001$	$\beta = +2.33$ $SE = 0.0741$ $t_{1918} = +31.45$ $p < 0.0001$	$\beta = +2.32$ $SE = 0.0484$ $t_{1918} = +47.98$ $p < 0.0001$	$\beta = +2.41$ $SE = 0.0492$ $t_{1918} = +48.92$ $p < 0.0001$	$\beta = +2.38$ $SE = 0.0503$ $t_{1822} = +47.26$ $p < 0.0001$
R_0	$\beta = +0.0392$ $SE = 0.00554$ $t_{4604} = +7.08$ $p < 0.0001$	$\beta = +0.0339$ $SE = 0.00788$ $t_{1918} = +4.30$ $p < 0.0001$			
η_s	$\beta = -0.191$ $SE = 0.0102$ $t_{4604} = -18.64$ $p < 0.0001$		$\beta = -0.209$ $SE = 0.0223$ $t_{1918} = -9.38$ $p < 0.0001$		
$\eta_s:R_0$	$\beta = +0.00784$ $SE = 0.00685$ $t_{4604} = +1.14$ $p = 0.25$				
η_e				$\beta = +0.0871$ $SE = 0.0171$ $t_{1918} = +5.08$ $p < 0.0001$	
t_{max}					$\beta = +0.14$ $SE = 0.0125$ $t_{1822} = +11.14$ $p < 0.0001$
$adj - R^2$	0.67	0.69	0.68	0.54	0.57
N_{obs}	4608	1920	1920	1920	1824
BIC	288.78	239.07	234.35	174.31	203.75

Table B.2: Mixed effects model of the analysis of task variables on the number of samples acquired. Linear mixed-effect models all used a Poisson distribution, and were specified as follows. Exp. 1b: sample $\sim 1 + \eta_s * R_0 + (1 + \eta_s * R_0 \mid \text{participant}) + (1 \mid \text{trial})$; Exp. 2: sample $\sim 1 + R_0 + (1 + R_0 \mid \text{participant}) + (1 \mid \text{trial})$; Exp. 3: sample $\sim 1 + \eta_s + (1 + \eta_s \mid \text{participant}) + (1 \mid \text{trial})$; Exp. 4: sample $\sim 1 + \eta_e + (1 + \eta_e \mid \text{participant}) + (1 \mid \text{trial})$; Exp. 5: sample $\sim 1 + t_{max} + (1 + t_{max} \mid \text{participant}) + (1 \mid \text{trial})$.

	Exp. 1b	Exp. 2	Exp. 3	Exp. 4	Exp. 5
(Intercept)	$\beta = +0.25$ $SE = 0.025$ $t_{4604} = +9.97$ $p < 0.0001$	$\beta = +0.282$ $SE = 0.0528$ $t_{1918} = +5.34$ $p < 0.0001$	$\beta = +0.311$ $SE = 0.0477$ $t_{1918} = +6.53$ $p < 0.0001$	$\beta = +0.185$ $SE = 0.0418$ $t_{1918} = +4.42$ $p < 0.0001$	$\beta = -0.123$ $SE = 0.0485$ $t_{1822} = -2.54$ $p = 0.011$
R_0	$\beta = -0.0184$ $SE = 0.00468$ $t_{4604} = -3.94$ $p < 0.0001$	$\beta = -0.00383$ $SE = 0.00442$ $t_{1918} = -0.87$ $p = 0.39$			
η_s	$\beta = +0.122$ $SE = 0.00883$ $t_{4604} = +13.83$ $p < 0.0001$		$\beta = +0.127$ $SE = 0.0171$ $t_{1918} = +7.41$ $p < 0.0001$		
$\eta_s:R_0$	$\beta = -0.00145$ $SE = 0.00614$ $t_{4604} = -0.24$ $p = 0.81$				
η_e				$\beta = -0.00924$ $SE = 0.00745$ $t_{1918} = -1.24$ $p = 0.21$	
t_{max}					$\beta = +0.18$ $SE = 0.0154$ $t_{1822} = +11.71$ $p < 0.0001$
$adj - R^2$	0.59	0.62	0.65	0.53	0.63
N_{obs}	4608	1920	1920	1920	1824
BIC	-1333.54	-670.99	-369.33	-876.64	-30.15

Table B.3: **Fixed effects of the analysis of task variables on the inter-sampling interval (ln-transformed).** Linear mixed-effect models were specified as follows. Exp. 1b: $\ln ISI \sim 1 + \eta_s * R_0 + (1 + \eta_s * R_0 \mid \text{participant}) + (1 \mid \text{trial})$; Exp. 2: $\ln ISI \sim 1 + R_0 + (1 + R_0 \mid \text{participant}) + (1 \mid \text{trial})$; Exp. 3: $\ln ISI \sim 1 + \eta_s + (1 + \eta_s \mid \text{participant}) + (1 \mid \text{trial})$; Exp. 4: $\ln ISI \sim 1 + \eta_e + (1 + \eta_e \mid \text{participant}) + (1 \mid \text{trial})$; Exp. 5: $\ln ISI \sim 1 + t_{max} + (1 + t_{max} \mid \text{participant}) + (1 \mid \text{trial})$.

	Exp. 1b	Exp. 2	Exp. 3	Exp. 4	Exp. 5
(Intercept)	$\beta = -1.51$ $SE = 0.0248$ $t_{4604} = -60.97$ $p < 0.0001$	$\beta = -1.52$ $SE = 0.0418$ $t_{1918} = -36.45$ $p < 0.0001$	$\beta = -1.5$ $SE = 0.0349$ $t_{1918} = -42.90$ $p < 0.0001$	$\beta = -1.54$ $SE = 0.039$ $t_{1918} = -39.57$ $p < 0.0001$	$\beta = -1.43$ $SE = 0.0216$ $t_{1822} = -66.02$ $p < 0.0001$
R_0	$\beta = +0.00228$ $SE = 0.00632$ $t_{4604} = +0.36$ $p = 0.72$	$\beta = -0.00104$ $SE = 0.00714$ $t_{1918} = -0.15$ $p = 0.88$			
η_s	$\beta = +0.0173$ $SE = 0.00681$ $t_{4604} = +2.54$ $p = 0.011$		$\beta = +0.0286$ $SE = 0.0072$ $t_{1918} = +3.97$ $p < 0.0001$		
$\eta_s:R_0$	$\beta = -0.00966$ $SE = 0.00776$ $t_{4604} = -1.24$ $p = 0.21$				
η_e				$\beta = +0.0065$ $SE = 0.00707$ $t_{1918} = +0.92$ $p = 0.36$	
t_{max}					$\beta = -0.000163$ $SE = 0.00799$ $t_{1822} = -0.02$ $p = 0.98$
$adj - R^2$	0.19	0.26	0.21	0.24	0.07
N_{obs}	4608	1920	1920	1920	1824
BIC	3978.99	1105.14	958.39	985.56	994.65

Table B.4: **Fixed effects of the analysis of task variables on the information extraction rate (ln-transformed).** Linear mixed-effect models were specified as follows. Exp. 1b: $\ln \alpha \sim 1 + \eta_s * R_0 + (1 + \eta_s * R_0 \mid \text{participant}) + (1 \mid \text{trial})$; Exp. 2: $\ln \alpha \sim 1 + R_0 + (1 + R_0 \mid \text{participant}) + (1 \mid \text{trial})$; Exp. 3: $\ln \alpha \sim 1 + \eta_s + (1 + \eta_s \mid \text{participant}) + (1 \mid \text{trial})$; Exp. 4: $\ln \alpha \sim 1 + \eta_e + (1 + \eta_e \mid \text{participant}) + (1 \mid \text{trial})$; Exp. 5: $\ln \alpha \sim 1 + t_{max} + (1 + t_{max} \mid \text{participant}) + (1 \mid \text{trial})$.

	Exp. 1b	Exp. 2	Exp. 3	Exp. 4	Exp. 5
(Intercept)	$\beta = +0.214$ $SE = 0.00675$ $t_{4606} = +31.73$ $p < 0.0001$	$\beta = +0.205$ $SE = 0.00689$ $t_{1918} = +29.69$ $p < 0.0001$	$\beta = +0.214$ $SE = 0.00793$ $t_{1918} = +26.98$ $p < 0.0001$	$\beta = +0.209$ $SE = 0.00806$ $t_{1918} = +25.90$ $p < 0.0001$	$\beta = +0.263$ $SE = 0.00902$ $t_{1822} = +29.15$ $p < 0.0001$
$\ln ISI$	$\beta = +0.0762$ $SE = 0.0075$ $t_{4606} = +10.16$ $p < 0.0001$	$\beta = +0.0988$ $SE = 0.00931$ $t_{1918} = +10.62$ $p < 0.0001$	$\beta = +0.0639$ $SE = 0.0127$ $t_{1918} = +5.02$ $p < 0.0001$	$\beta = +0.0963$ $SE = 0.0127$ $t_{1918} = +7.60$ $p < 0.0001$	$\beta = +0.0695$ $SE = 0.0102$ $t_{1822} = +6.81$ $p < 0.0001$
$adj - R^2$	0.22	0.28	0.21	0.26	0.11
N_{obs}	4608	1920	1920	1920	1824
BIC	-10743.20	-4277.37	-4285.17	-4555.20	-3698.71

Table B.5: **Fixed effects of the relationship between inter-sampling interval and information extraction rate.** For each experiment, the linear mixed-effect model was specified as follows: $\alpha \sim 1 + ISI + (1 \mid \text{trial}) + (1 + ISI \mid \text{Exp. cond.}) + (1 + ISI \mid \text{participant})$. ISI : Inter-sampling interval.

	Raw ratings	Z-scored ratings
(Intercept)	$\beta = +28.9$ $SE = 3.07$ $t_{1150} = +9.42$ $p < 0.0001$	$\beta = -0.537$ $SE = 0.0976$ $t_{1150} = -5.50$ $p < 0.0001$
block	$\beta = +0.873$ $SE = 0.21$ $t_{1150} = +4.16$ $p < 0.0001$	$\beta = +0.153$ $SE = 0.0259$ $t_{1150} = +5.90$ $p < 0.0001$
$adj - R^2$	0.98	0.34
N_{obs}	1152	1152

Table B.6: **Mixed effects Model – analysis of fatigue development in Exp. 1.** For each column, the linear mixed-effect model was specified as follows: Fatigue $\sim 1 + \text{block} + (1 + \text{block} \mid \text{participant})$. The first model used raw fatigue ratings, while the second used z-scored fatigue ratings as the dependent variable.

	Raw ratings	Z-scored ratings
(Intercept)	$\beta = -585$ $SE = 223$ $t_{43} = -2.63$ $p = 0.012$	$\beta = -40.8$ $SE = 32.4$ $t_{43} = -1.26$ $p = 0.21$
Exp. Duration	$\beta = +145$ $SE = 58.1$ $t_{43} = +2.50$ $p = 0.016$	$\beta = +10$ $SE = 8.45$ $t_{43} = +1.19$ $p = 0.24$
w_0	$\beta = -16.4$ $SE = 6.98$ $t_{43} = -2.35$ $p = 0.023$	$\beta = -1.53$ $SE = 1.02$ $t_{43} = -1.51$ $p = 0.14$
w_α	$\beta = +8.86$ $SE = 2.83$ $t_{43} = +3.13$ $p = 0.0032$	$\beta = +0.87$ $SE = 0.412$ $t_{43} = +2.11$ $p = 0.041$
w_{speed}	$\beta = -5.99$ $SE = 3.27$ $t_{43} = -1.83$ $p = 0.07$	$\beta = -0.712$ $SE = 0.476$ $t_{43} = -1.50$ $p = 0.14$
$adj - R^2$	0.31	0.14
N_{obs}	48	48

Table B.7: **Robust multiple linear regressions of the relationship between task-induced fatigue and model-derived cognitive effort cost.** For each column, the robust multiple linear regression was specified as follows: $\Delta\text{Fatigue} \sim 1 + \ln \text{Exp.Duration} + w_0 + \ln w_\alpha + \ln w_{speed}$. $\ln$ -transforms were applied to obtain a more normal distribution of the independent variables. The first model used raw fatigue ratings, while the second used z-scored fatigue ratings as the dependent variable. The Δ symbol refers to the difference between the average rating within the last block of active search and the 3 blocks of exposure (used as a measure of baseline fatigue).

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	S	score	EE	Error	ISI
(Intercept)	$\beta = +2.18$ $SE = 0.0817$ $t_{2272} = +26.72$ $p < 0.0001$	$\beta = +65.7$ $SE = 1.39$ $t_{2272} = +47.32$ $p < 0.0001$	$\beta = +20.3$ $SE = 2.12$ $t_{2272} = +9.57$ $p < 0.0001$	$\beta = +2.06$ $SE = 0.0873$ $t_{2272} = +23.64$ $p < 0.0001$	$\beta = +1.5$ $SE = 0.0902$ $t_{2272} = +16.67$ $p < 0.0001$
ALE	$\beta = +0.153$ $SE = 0.116$ $t_{2272} = +1.32$ $p = 0.19$	$\beta = -7.93$ $SE = 1.96$ $t_{2272} = -4.04$ $p < 0.0001$	$\beta = -0.683$ $SE = 2.99$ $t_{2272} = -0.23$ $p = 0.82$	$\beta = +0.162$ $SE = 0.123$ $t_{2272} = +1.32$ $p = 0.19$	$\beta = -0.211$ $SE = 0.128$ $t_{2272} = -1.65$ $p = 0.10$
ALE: R_0	$\beta = +0.0247$ $SE = 0.0251$ $t_{2272} = +0.98$ $p = 0.33$	$\beta = -1.66$ $SE = 1.06$ $t_{2272} = -1.56$ $p = 0.12$	$\beta = -0.952$ $SE = 0.819$ $t_{2272} = -1.16$ $p = 0.25$	$\beta = -0.0265$ $SE = 0.0376$ $t_{2272} = -0.70$ $p = 0.48$	$\beta = -0.0393$ $SE = 0.027$ $t_{2272} = -1.45$ $p = 0.15$
ALE: η_s	$\beta = +0.0318$ $SE = 0.0247$ $t_{2272} = +1.29$ $p = 0.20$	$\beta = -3.66$ $SE = 1.84$ $t_{2272} = -2.00$ $p = 0.046$	$\beta = -0.924$ $SE = 0.665$ $t_{2272} = -1.39$ $p = 0.16$	$\beta = -0.0277$ $SE = 0.0318$ $t_{2272} = -0.87$ $p = 0.38$	$\beta = -0.0719$ $SE = 0.0337$ $t_{2272} = -2.14$ $p = 0.033$
ALE: $\eta_s:R_0$	$\beta = +0.0542$ $SE = 0.0202$ $t_{2272} = +2.68$ $p = 0.0074$	$\beta = -0.403$ $SE = 1.04$ $t_{2272} = -0.39$ $p = 0.70$	$\beta = -0.881$ $SE = 0.602$ $t_{2272} = -1.46$ $p = 0.14$	$\beta = -0.0463$ $SE = 0.0302$ $t_{2272} = -1.53$ $p = 0.13$	$\beta = -0.0273$ $SE = 0.0231$ $t_{2272} = -1.18$ $p = 0.24$
R_0	$\beta = +0.0231$ $SE = 0.018$ $t_{2272} = +1.29$ $p = 0.20$	$\beta = +17.6$ $SE = 0.751$ $t_{2272} = +23.45$ $p < 0.0001$	$\beta = -0.169$ $SE = 0.579$ $t_{2272} = -0.29$ $p = 0.77$	$\beta = +0.0104$ $SE = 0.0266$ $t_{2272} = +0.39$ $p = 0.70$	$\beta = +0.00487$ $SE = 0.0191$ $t_{2272} = +0.25$ $p = 0.80$
η_s	$\beta = -0.111$ $SE = 0.0177$ $t_{2272} = -6.25$ $p < 0.0001$	$\beta = -18.7$ $SE = 1.3$ $t_{2272} = -14.41$ $p < 0.0001$	$\beta = +2.07$ $SE = 0.47$ $t_{2272} = +4.40$ $p < 0.0001$	$\beta = +0.0919$ $SE = 0.0225$ $t_{2272} = +4.09$ $p < 0.0001$	$\beta = +0.12$ $SE = 0.0238$ $t_{2272} = +5.04$ $p < 0.0001$
$\eta_s:R_0$	$\beta = -0.0301$ $SE = 0.0145$ $t_{2272} = -2.07$ $p = 0.038$	$\beta = -0.654$ $SE = 0.732$ $t_{2272} = -0.89$ $p = 0.37$	$\beta = +0.477$ $SE = 0.426$ $t_{2272} = +1.12$ $p = 0.26$	$\beta = +0.0211$ $SE = 0.0213$ $t_{2272} = +0.99$ $p = 0.32$	$\beta = +0.0135$ $SE = 0.0164$ $t_{2272} = +0.83$ $p = 0.41$
$adj - R^2$	0.79	0.71	0.58	0.27	0.71
N_{obs}	2280	2280	2280	2280	2280
AIC	295.84	19913.90	16521.03	4656.47	1163.69

Table B.8: **Active Search – Generalised mixed effects models of the effect of the disease (ALE) on performance.** Models were specified as follows. Predicted variable $\sim 1 + \text{group}*\eta_s + \text{group}*R_0 + \eta_s*R_0 + \text{group}:\eta_s:R_0 + (1 + \eta_s*R_0 | \text{participant})$. S: Raw number of samples. EE: Expected Error (Uncertainty). Error: Distance to the hidden circle. ISI: Inter-Sampling Interval.

(Intercept)	$\beta = +0.244$ $SE = 0.00934$ $t_{566} = +26.11$ $p < 0.0001$
ALE	$\beta = -0.026$ $SE = 0.0131$ $t_{566} = -1.98$ $p = 0.048$
ALE:ISI	$\beta = -0.00165$ $SE = 0.0128$ $t_{566} = -0.13$ $p = 0.90$
ISI	$\beta = +0.0122$ $SE = 0.00905$ $t_{566} = +1.35$ $p = 0.18$
$adj - R^2$	0.25
N_{obs}	570
AIC	-1256.45

Table B.9: **Active Search – Generalised mixed effect the effect of ALE on efficiency (α) in the condition with high sampling cost and high initial reward reserve, i.e., the condition where ALE patients over-sampled more than controls.** Model was specified as follows. : $\alpha \sim 1 + \text{group} * \text{ISI} + (1 | \text{trial}) + (1 + \text{ISI} | \text{participant})$.

Condition (R/η_s)	Controls	ALE
<i>Low/Low</i>	$\beta = -2.24$ $SE = 0.715$ $t_{1136} = -3.14$ $p = 0.0018$	$\beta = -1.6$ $SE = 1.23$ $t_{1136} = -1.30$ $p = 0.19$
<i>Low/High</i>	$\beta = +1.97$ $SE = 0.543$ $t_{1136} = +3.63$ $p = 0.00029$	$\beta = +3.14$ $SE = 0.81$ $t_{1136} = +3.88$ $p = 0.00011$
<i>High/Low</i>	$\beta = -1.32$ $SE = 0.689$ $t_{1136} = -1.92$ $p = 0.06$	$\beta = -0.277$ $SE = 1.34$ $t_{1136} = -0.21$ $p = 0.84$
<i>High/High</i>	$\beta = +1.9$ $SE = 0.625$ $t_{1136} = +3.04$ $p = 0.0024$	$\beta = +4.74$ $SE = 1.05$ $t_{1136} = +4.52$ $p < 0.0001$
$adj - R^2$	0.86	0.84
N_{obs}	1140	1140
AIC	4273.50	5545.49

Table B.10: **Active Search – Deviation from optimal number of samples..** Models were specified as follows: $Deviation \sim Condition + (Condition | participant)$. R : Initial reward reserve. η_s : Sampling cost.

	Controls	ALE
(Intercept)	$\beta = -1.67$ $SE = 0.0721$ $t_{1138} = -23.12$ $p < 0.0001$	$\beta = -1.9$ $SE = 0.0881$ $t_{1138} = -21.57$ $p < 0.0001$
ISI	$\beta = +0.137$ $SE = 0.0463$ $t_{1138} = +2.96$ $p = 0.0032$	$\beta = +0.26$ $SE = 0.054$ $t_{1138} = +4.82$ $p < 0.0001$
$adj - R^2$	0.22	0.27
N_{obs}	1140	1140
BIC	570.28	858.72

Table B.11: **Active Search – Relationship between inter-sampling interval and information extraction rate.** Models were specified as follows: $\alpha \sim 1 + ISI + (1 | trial) + (1 + ISI | condition) + (1 + ISI | participant)/$

	Reward against uncertainty
(Intercept)	$\beta = -0.423$ $SE = 0.323$ $t_{3748} = -1.31$ $p = 0.19$
ALE	$\beta = -0.402$ $SE = 0.457$ $t_{3748} = -0.88$ $p = 0.38$
ALE:EE	$\beta = +0.336$ $SE = 0.442$ $t_{3748} = +0.76$ $p = 0.45$
ALE:R	$\beta = -0.983$ $SE = 0.275$ $t_{3748} = -3.58$ $p = \mathbf{0.00035}$
ALE:R:EE	$\beta = +0.162$ $SE = 0.17$ $t_{3748} = +0.95$ $p = 0.34$
EE	$\beta = -2.73$ $SE = 0.313$ $t_{3748} = -8.72$ $p < \mathbf{0.0001}$
R	$\beta = +1.41$ $SE = 0.198$ $t_{3748} = +7.16$ $p < \mathbf{0.0001}$
R:EE	$\beta = +0.0659$ $SE = 0.125$ $t_{3748} = +0.53$ $p = 0.60$
$adj - R^2$	0.93
N_{obs}	3756
AIC	2938.44

Table B.12: **Generalised mixed effects model examining the effect of group (ALE vs. controls) on choices under uncertainty.** Model was specified as follows: $\text{choice} \sim 1 + \text{group} * R + \text{group} * EE + R * EE + \text{group}:R:EE + (1 + R * EE | \text{participant})$. Control group was set as the reference group. *EE*: Expected Error. *R*: Reward. *ALE*: Autoimmune Limbic Encephalitis.

	Effort-based choices
(Intercept)	$\beta = +1.96$ $SE = 0.442$ $t_{4739} = +4.43$ $p < 0.0001$
ALE	$\beta = -0.137$ $SE = 0.622$ $t_{4739} = -0.22$ $p = 0.83$
ALE:Effort	$\beta = +0.306$ $SE = 0.467$ $t_{4739} = +0.66$ $p = 0.51$
ALE:Reward	$\beta = -0.48$ $SE = 0.37$ $t_{4739} = -1.30$ $p = 0.19$
ALE:Reward:Effort	$\beta = -0.22$ $SE = 0.408$ $t_{4739} = -0.54$ $p = 0.59$
Effort	$\beta = -2.82$ $SE = 0.334$ $t_{4739} = -8.45$ $p < 0.0001$
Reward	$\beta = +2.97$ $SE = 0.267$ $t_{4739} = +11.12$ $p < 0.0001$
Reward:Effort	$\beta = -0.281$ $SE = 0.292$ $t_{4739} = -0.96$ $p = 0.34$
$adj - R^2$	0.97
N_{obs}	4747
AIC	2775.57

Table B.13: **Generalised mixed effects models examining effect of group (ALE vs. controls) on effort-based decision making.** Models were specified as follows. Effort-based choices: $\text{choice} \sim 1 + \text{group} * \text{Reward} + \text{group} * \text{Effort} + \text{Reward} * \text{Effort} + \text{group} : \text{Reward} : \text{Effort} + (1 + \text{Reward} * \text{Effort} | \text{participant})$. Control group was set as the reference group. ALE: ALE: Autoimmune Limbic Encephalitis group.

Parameter	Rhat	n_eff	mean	sd	2.5%	50%	97.5%
Intercept	1.0	2906	1.6	0.5	0.6	1.6	2.5
Reward	1.0	6786	2.8	0.3	2.2	2.8	3.5
Effort	1.0	5174	-2.7	0.4	-3.5	-2.7	-2.0
Reward:Effort	1.0	7592	-0.2	0.3	-0.8	-0.2	0.4
ALE	1.0	3097	0.0	0.6	-1.3	-0.0	1.3
Reward:ALE	1.0	6647	-0.3	0.4	-1.1	-0.3	0.5
Effort:ALE	1.0	4945	0.2	0.5	-0.8	0.2	1.1
Reward:Effort:ALE	1.0	7563	-0.2	0.4	-1.0	-0.2	0.5

Table B.14: **Baysian mixed effects modelling of apples choice data – Posterior summary statistics.** Model was specified as follows: $\text{choice} \sim 1 + \text{group} * R + \text{group} * EE + R * EE + \text{group}:R:EE + (1 + R * EE | \text{participant})$. To improve convergence and guard against over-fitting, mildly informative conservative priors were specified.

	Exp. 1 & 2	Exp. 4
(Intercept)	$\beta = -0.00398$ $SE = 0.0903$ $t_{3752} = -0.04$ $p = 0.96$	$\beta = -0.0106$ $SE = 0.174$ $t_{2306} = -0.06$ $p = 0.95$
EEbest	$\beta = +0.647$ $SE = 0.0502$ $t_{3752} = +12.88$ $p < 0.0001$	$\beta = +0.476$ $SE = 0.0873$ $t_{2306} = +5.45$ $p < 0.0001$
LE	$\beta = -0.009$ $SE = 0.127$ $t_{3752} = -0.07$ $p = 0.94$	$\beta = +0.028$ $SE = 0.281$ $t_{2306} = +0.10$ $p = 0.92$
LE:EEbest	$\beta = -0.0546$ $SE = 0.0711$ $t_{3752} = -0.77$ $p = 0.44$	$\beta = -0.0226$ $SE = 0.141$ $t_{2306} = -0.16$ $p = 0.87$
$adj - R^2$	0.58	0.71
N_{obs}	3756	2310
AIC	7645.65	3940.63

Table B.15: **Generalised mixed effects model of the effect of the group (ALE vs. controls) on flexibility of uncertainty estimation.** Models were specified as follows: $\text{Uncertainty Score} \sim 1 + \text{group} * EE + (1 + EE | \text{participant}) + (1 | \text{trial})$.

	EBDM under uncertainty
(Intercept)	$\beta = +1.93$ $SE = 0.579$ $t_{4184} = +3.34$ $p = 0.00084$
LE	$\beta = -1.03$ $SE = 0.927$ $t_{4184} = -1.12$ $p = 0.26$
LE:Uncertainty ₁	$\beta = +1.09$ $SE = 0.875$ $t_{4184} = +1.25$ $p = 0.21$
LE:Uncertainty ₁ : z_q Effort	$\beta = -0.257$ $SE = 0.239$ $t_{4184} = -1.08$ $p = 0.28$
LE:Uncertainty ₁ : Reward	$\beta = +0.568$ $SE = 0.272$ $t_{4184} = +2.09$ $p = 0.036$
LE:Uncertainty ₁ : Reward : z_q Effort	$\beta = -0.123$ $SE = 0.24$ $t_{4184} = -0.51$ $p = 0.61$
LE: z_q Effort	$\beta = +1.24$ $SE = 0.415$ $t_{4184} = +2.99$ $p = 0.0028$
LE:Reward	$\beta = -1.41$ $SE = 0.499$ $t_{4184} = -2.83$ $p = 0.0046$
LE:Reward: z_q Effort	$\beta = -0.146$ $SE = 0.209$ $t_{4184} = -0.70$ $p = 0.48$
Uncertainty ₁	$\beta = -1.9$ $SE = 0.545$ $t_{4184} = -3.49$ $p = 0.0005$
Uncertainty ₁ : z_q Effort	$\beta = +0.251$ $SE = 0.164$ $t_{4184} = +1.53$ $p = 0.13$
Uncertainty ₁ : Reward	$\beta = -0.671$ $SE = 0.186$ $t_{4184} = -3.61$ $p = 0.0003$
Uncertainty ₁ : Reward : z_q Effort	$\beta = +0.0537$ $SE = 0.164$ $t_{4184} = +0.33$ $p = 0.74$
z_q Effort	$\beta = -1.45$ $SE = 0.269$ $t_{4184} = -5.38$ $p < 0.0001$
Reward	$\beta = +1.73$ $SE = 0.327$ $t_{4184} = +5.31$ $p < 0.0001$
Reward: z_q Effort	$\beta = +0.207$ $SE = 0.141$ $t_{4184} = +1.47$ $p = 0.14$
$adj - R^2$	0.99
N_{obs}	4200
AIC	3352.10

Table B.16: **Generalised mixed effects model of the effect of the group (LE vs. controls) effort-based decisions under uncertainty.** Models were specified as follows. EBDM under Uncertainty: choice $\sim 1 + \text{group} * \text{Uncertainty} + \text{group} * \text{Reward} + \text{Uncertainty} * \text{Reward} + \text{group} * \text{Effort} + \text{Uncertainty} * \text{Effort} + \text{Reward} * \text{Effort} + \text{group} : \text{Uncertainty} : \text{Reward} + \text{group} : \text{Uncertainty} : \text{Effort} + \text{group} : \text{Reward} : \text{Effort} + \text{Uncertainty} : \text{Reward} : \text{Effort} + \text{group} : \text{Uncertainty} : \text{Reward} : \text{Effort} + (1 + \text{Uncertainty} * \text{Reward} + \text{Uncertainty} * \text{Effort} + \text{Reward} * \text{Effort} + \text{Uncertainty} : \text{Reward} : \text{Effort} | \text{participant})$.

B.3 Chapter 4

	Samples	EE _{end}	Score	Deviation from Optimal	Expected Value
(Intercept)	$\beta = +2.18$ $SE = 0.0489$ $t_{3232} = +44.58$ $p < 0.0001$	$\beta = +2.83$ $SE = 0.0693$ $t_{3232} = +40.84$ $p < 0.0001$	$\beta = +66$ $SE = 0.886$ $t_{3232} = +74.49$ $p < 0.0001$	$\beta = -0.48$ $SE = 0.432$ $t_{3232} = -1.11$ $p = 0.27$	$\beta = +63.3$ $SE = 0.697$ $t_{3232} = +90.81$ $p < 0.0001$
SCI	$\beta = +0.194$ $SE = 0.0691$ $t_{3232} = +2.81$ $p = 0.005$	$\beta = -0.261$ $SE = 0.0981$ $t_{3232} = -2.66$ $p = 0.0078$	$\beta = -2.33$ $SE = 1.25$ $t_{3232} = -1.86$ $p = 0.06$	$\beta = +2.32$ $SE = 0.611$ $t_{3232} = +3.79$ $p = 0.00015$	$\beta = -0.197$ $SE = 0.985$ $t_{3232} = -0.20$ $p = 0.84$
SCI: R_0	$\beta = +0.0216$ $SE = 0.0196$ $t_{3232} = +1.11$ $p = 0.27$	$\beta = -0.0266$ $SE = 0.0322$ $t_{3232} = -0.83$ $p = 0.41$	$\beta = -0.0693$ $SE = 0.618$ $t_{3232} = -0.11$ $p = 0.91$	$\beta = +0.203$ $SE = 0.206$ $t_{3232} = +0.99$ $p = 0.32$	$\beta = +0.0954$ $SE = 0.47$ $t_{3232} = +0.20$ $p = 0.84$
SCI: η_s	$\beta = -0.0356$ $SE = 0.0237$ $t_{3232} = -1.50$ $p = 0.13$	$\beta = +0.0586$ $SE = 0.0304$ $t_{3232} = +1.93$ $p = 0.05$	$\beta = -1.47$ $SE = 1.07$ $t_{3232} = -1.37$ $p = 0.17$	$\beta = -0.755$ $SE = 0.303$ $t_{3232} = -2.49$ $p = 0.013$	$\beta = -2.86$ $SE = 1.01$ $t_{3232} = -2.82$ $p = 0.0048$
SCI: η_s : R_0	$\beta = +0.0189$ $SE = 0.0138$ $t_{3232} = +1.37$ $p = 0.17$	$\beta = -0.0347$ $SE = 0.0231$ $t_{3232} = -1.50$ $p = 0.13$	$\beta = +0.261$ $SE = 0.678$ $t_{3232} = +0.38$ $p = 0.70$	$\beta = +0.128$ $SE = 0.155$ $t_{3232} = +0.83$ $p = 0.41$	$\beta = -0.0395$ $SE = 0.535$ $t_{3232} = -0.07$ $p = 0.94$
R_0	$\beta = +0.0147$ $SE = 0.014$ $t_{3232} = +1.05$ $p = 0.30$	$\beta = -0.00661$ $SE = 0.0227$ $t_{3232} = -0.29$ $p = 0.77$	$\beta = +18.1$ $SE = 0.437$ $t_{3232} = +41.41$ $p < 0.0001$	$\beta = +0.0735$ $SE = 0.145$ $t_{3232} = +0.50$ $p = 0.61$	$\beta = +17.6$ $SE = 0.332$ $t_{3232} = +52.95$ $p < 0.0001$
η_s	$\beta = -0.111$ $SE = 0.017$ $t_{3232} = -6.52$ $p < 0.0001$	$\beta = +0.12$ $SE = 0.0215$ $t_{3232} = +5.60$ $p < 0.0001$	$\beta = -18.4$ $SE = 0.76$ $t_{3232} = -24.22$ $p < 0.0001$	$\beta = +2.25$ $SE = 0.214$ $t_{3232} = +10.48$ $p < 0.0001$	$\beta = -17.9$ $SE = 0.717$ $t_{3232} = -24.92$ $p < 0.0001$
η_s : R_0	$\beta = -0.0243$ $SE = 0.0101$ $t_{3232} = -2.41$ $p = 0.016$	$\beta = +0.0289$ $SE = 0.0163$ $t_{3232} = +1.77$ $p = 0.08$	$\beta = -0.247$ $SE = 0.479$ $t_{3232} = -0.52$ $p = 0.61$	$\beta = -0.18$ $SE = 0.109$ $t_{3232} = -1.64$ $p = 0.10$	$\beta = -0.271$ $SE = 0.378$ $t_{3232} = -0.72$ $p = 0.47$
$adj - R^2$	0.77	0.44	0.72	0.82	0.89
N_{obs}	3240	3240	3240	3240	3240
AIC	1.16	4887.34	27724.93	13242.21	24174.45

Table B.17: **Active Search – Generalised mixed effects models investigating the effect of the group (SCI vs. controls) on performance.** Models were specified as follows: Response variable $\sim 1 + \text{group} * \eta_s + \text{group} * R_0 + \eta_s * R_0 + \text{group} : \eta_s : R_0 + (1 + \eta_s * R_0 | \text{participant})$. SCI: subjective cognitive impairment. R_0 : initial credit. η_s : sampling cost. EE_{end} : uncertainty before committing to decisions.

R_0/η_s	Mean	Controls vs. SCI
95/1	$Controls = 9.8346$ $SCI = 12.5333$	$t(52) = -2.9219$ $SD = 3.3937$ $p = 0.0051$
95/5	$Controls = 8.2074$ $SCI = 9.3259$	$t(52) = -1.7567$ $SD = 2.3395$ $p = 0.0849$
130/1	$Controls = 10.6000$ $SCI = 13.3753$	$t(52) = -3.2560$ $SD = 3.1318$ $p = 0.0020$
130/5	$Controls = 8.0321$ $SCI = 9.8494$	$t(52) = -2.9422$ $SD = 2.2694$ $p = 0.0049$

Table B.18: **Active Search – Number of samples obtained per condition.** R_0 : initial credit reserve. η_s : sampling cost.

R_0/η_s	Controls	SCI	Controls vs. SCI
95/1	$\beta = -2.98$ $SE = 0.47$ $t_{1616} = -6.34$ $p < 0.0001$	$\beta = +0.0148$ $SE = 0.757$ $t_{1616} = +0.02$ $p = 0.98$	$Mean_{Controls} = -2.9802$ $Mean_{SCI} = -2.9802$ $t(52) = -3.2984$ $p = 0.0018$
95/5	$\beta = +1.87$ $SE = 0.334$ $t_{1616} = +5.61$ $p < 0.0001$	$\beta = +3.1$ $SE = 0.48$ $t_{1616} = +6.47$ $p < 0.0001$	$Mean_{Controls} = +1.8741$ $Mean_{SCI} = +3.1037$ $t(52) = -2.0644$ $p = 0.0440$
130/1	$\beta = -2.47$ $SE = 0.523$ $t_{1616} = -4.73$ $p < 0.0001$	$\beta = +0.672$ $SE = 0.627$ $t_{1616} = +1.07$ $p = 0.28$	$Mean_{Controls} = -2.4741$ $Mean_{SCI} = +0.6716$ $t(52) = 3.7820$ $p = 0.0004$
130/5	$\beta = +1.66$ $SE = 0.337$ $t_{1616} = +4.93$ $p < 0.0001$	$\beta = +3.55$ $SE = 0.457$ $t_{1616} = +7.77$ $p < 0.0001$	$Mean_{Controls} = +1.6617$ $Mean_{SCI} = +3.5531$ $t(52) = -3.2668$ $p = 0.0019$
$adj - R^2$	0.83	0.77	
N_{obs}	1620	1620	
AIC	6117.11	7013.05	

Table B.19: **Active Search – Deviation from optimal ($s - s^*$) for each condition.** R_0 : initial credit reserve. η_s : sampling cost. s : number of samples obtained. s^* : optimal number of samples.

	Subjective Uncertainty	
(Intercept)	$\beta = +0.0335$ $SE = 0.0961$ $t_{5396} = +0.35$ $p = 0.73$	$\beta = -0.000125$ $SE = 0.0663$ $t_{5394} = -0.00$ $p = 1.00$
<i>EE</i>	$\beta = +0.652$ $SE = 0.0435$ $t_{5396} = +14.99$ $p < 0.0001$	$\beta = +0.651$ $SE = 0.0307$ $t_{5394} = +21.17$ $p < 0.0001$
SCI	$\beta = -0.067$ $SE = 0.136$ $t_{5396} = -0.49$ $p = 0.62$	
SCI: <i>EE</i>	$\beta = -0.00185$ $SE = 0.0615$ $t_{5396} = -0.03$ $p = 0.98$	
<i>EE</i> :Affective Burden		$\beta = +0.0142$ $SE = 0.0112$ $t_{5394} = +1.26$ $p = 0.21$
Affective Burden		$\beta = -0.00308$ $SE = 0.0116$ $t_{5394} = -0.27$ $p = 0.79$
ACE-III		$\beta = +0.125$ $SE = 0.0627$ $t_{5394} = +1.98$ $p = 0.047$
Age		$\beta = -0.0161$ $SE = 0.0628$ $t_{5394} = -0.26$ $p = 0.80$
$adj - R^2$	0.73	0.73
N_{obs}	5400	5400
AIC	8824.97	8823.82

Table B.20: **Active Search. Generalised mixed effects models investigating the effect of the group (SCI vs. controls) and affective burden on uncertainty estimation.** Models were specified as follows: Subjective Uncertainty $\sim 1 + \text{group} * EE + (1 + EE | \text{participant}) + (1 | \text{trial})$. Subjective Uncertainty $\sim 1 + \text{Burden} * EE + \text{age} + \text{ACE-III} + (1 + EE | \text{participant}) + (1 | \text{trial})$. *EE*: Experimentally defined expected error. ACE-III: Addenbrook's Cognitive Examination score.

	Passive Choices	
(Intercept)	$\beta = -0.416$ $SE = 0.281$ $t_{5392} = -1.48$ $p = 0.14$	$\beta = -0.391$ $SE = 0.188$ $t_{5390} = -2.08$ $p = 0.037$
<i>EE</i>	$\beta = -2.77$ $SE = 0.225$ $t_{5392} = -12.31$ $p < 0.0001$	$\beta = -2.69$ $SE = 0.158$ $t_{5390} = -17.00$ $p < 0.0001$
<i>R</i>	$\beta = +1.12$ $SE = 0.193$ $t_{5392} = +5.80$ $p < 0.0001$	$\beta = +1.06$ $SE = 0.138$ $t_{5390} = +7.69$ $p < 0.0001$
<i>R:EE</i>	$\beta = -0.0493$ $SE = 0.103$ $t_{5392} = -0.48$ $p = 0.63$	$\beta = +0.0249$ $SE = 0.0724$ $t_{5390} = +0.34$ $p = 0.73$
group	$\beta = +0.029$ $SE = 0.397$ $t_{5392} = +0.07$ $p = 0.94$	
group: <i>EE</i>	$\beta = +0.167$ $SE = 0.318$ $t_{5392} = +0.53$ $p = 0.60$	
group: <i>R</i>	$\beta = -0.103$ $SE = 0.272$ $t_{5392} = -0.38$ $p = 0.71$	
group: <i>R:EE</i>	$\beta = +0.169$ $SE = 0.14$ $t_{5392} = +1.21$ $p = 0.23$	
<i>EE</i> :Affective Burden		$\beta = -0.0665$ $SE = 0.092$ $t_{5390} = -0.72$ $p = 0.47$
ACE-III		$\beta = -0.144$ $SE = 0.169$ $t_{5390} = -0.85$ $p = 0.39$
Age		$\beta = +0.245$ $SE = 0.169$ $t_{5390} = +1.45$ $p = 0.15$
Affective Burden		$\beta = -0.151$ $SE = 0.0773$ $t_{5390} = -1.96$ $p = 0.05$
<i>R:EE</i> :Affective Burden		$\beta = +0.0916$ $SE = 0.0676$ $t_{5390} = +1.36$ $p = 0.17$
<i>R</i> :Affective Burden		$\beta = +0.0766$ $SE = 0.0726$ $t_{5390} = +1.06$ $p = 0.29$
<i>adj</i> - R^2	0.96	0.96
N_{obs}	5400	5400
AIC	3959.72	3958.60

Table B.21: **Generalised mixed effects model investigating effects of group (SCI vs. controls) and affective burden effect in passive decision making under uncertainty.** Models were specified as follows: $\text{choice} \sim 1 + \text{group} * R + \text{group} * EE + R * EE + \text{group} : R : EE + (1 + R * EE | \text{participant})$. $\text{Choice} \sim 1 + \text{Burden} * R + \text{Burden} * EE + R * EE + \text{Burden} : R : EE + \text{Age} + \text{ACE-III} (1 + R * EE | \text{participant})$. *R*: reward on offer. *EE*: uncertainty of offer represented by dot configurations and computed as expected localisation error. SCI: subjective cognitive impairment group. ACE-III: Addenbrook's Cognitive Examination score.

	<i>ISI</i>	α
(Intercept)	$\beta = +1.58$ $SE = 0.0495$ $t_{3232} = +31.98$ $p < 0.0001$	$\beta = +0.236$ $SE = 0.00812$ $t_{3232} = +29.03$ $p < 0.0001$
SCI	$\beta = -0.297$ $SE = 0.07$ $t_{3232} = -4.24$ $p < 0.0001$	$\beta = +0.00702$ $SE = 0.0115$ $t_{3232} = +0.61$ $p = 0.54$
SCI: R_0	$\beta = -0.0221$ $SE = 0.0247$ $t_{3232} = -0.90$ $p = 0.37$	$\beta = -0.00195$ $SE = 0.00372$ $t_{3232} = -0.52$ $p = 0.60$
SCI: η_s	$\beta = -0.0161$ $SE = 0.0265$ $t_{3232} = -0.61$ $p = 0.54$	$\beta = +0.00172$ $SE = 0.00389$ $t_{3232} = +0.44$ $p = 0.66$
SCI: η_s : R_0	$\beta = -0.0274$ $SE = 0.0165$ $t_{3232} = -1.66$ $p = 0.10$	$\beta = -0.00117$ $SE = 0.00309$ $t_{3232} = -0.38$ $p = 0.71$
R_0	$\beta = -0.0199$ $SE = 0.0175$ $t_{3232} = -1.14$ $p = 0.26$	$\beta = -0.00108$ $SE = 0.00263$ $t_{3232} = -0.41$ $p = 0.68$
η_s	$\beta = +0.125$ $SE = 0.0187$ $t_{3232} = +6.70$ $p < 0.0001$	$\beta = +0.0036$ $SE = 0.00275$ $t_{3232} = +1.31$ $p = 0.19$
η_s : R_0	$\beta = +0.0153$ $SE = 0.0117$ $t_{3232} = +1.31$ $p = 0.19$	$\beta = +0.00113$ $SE = 0.00219$ $t_{3232} = +0.52$ $p = 0.60$
$adj - R^2$	0.64	0.18
N_{obs}	3240	3240
AIC	1059.49	-6438.06

Table B.22: **Active Search – Generalised mixed effects models investigating the effect of the group (SCI vs. controls) on sampling speed (ISI) and efficiency (α).** Models were specified as follows. Inter-sampling Interval: $ISI \sim 1 + \text{group} * \eta_s + \text{group} * R_0 + \eta_s * R_0 + \text{group} : \eta_s : R_0 + (1 + \eta_s * R_0 | \text{participant})$; Information extraction rate: $\alpha \sim 1 + \text{group} * \eta_s + \text{group} * R_0 + \eta_s * R_0 + \text{group} : \eta_s : R_0 + (1 + \eta_s * R_0 | \text{participant})$.

R_0/η_s	Mean	Controls vs. SCI
95/1	$Controls = 1.4917$ $SCI = 1.2056$	$z = 3.7195$ $ranksum = 958$ $p = \mathbf{0.0002}$
95/5	$Controls = 1.7119$ $SCI = 1.4485$	$z = 3.0275$ $ranksum = 918$ $p = \mathbf{0.0025}$
130/1	$Controls = 1.4214$ $SCI = 1.1458$	$t(52) = 4.4093$ $SD = 0.2296$ $p = \mathbf{0.0001}$
130/5	$Controls = 1.7028$ $SCI = 1.3404$	$z = 3.8060$ $ranksum = 963$ $p = \mathbf{0.0001}$

Table B.23: **Active Search – Inter-sampling interval per condition.** R_0 : initial credit reserve. η_s : sampling cost.

	Controls	SCI
(Intercept)	$\beta = +0.152$ $SE = 0.0168$ $t_{1618} = +9.01$ $p < \mathbf{0.0001}$	$\beta = +0.174$ $SE = 0.0173$ $t_{1618} = +10.06$ $p < \mathbf{0.0001}$
ISI	$\beta = +0.0541$ $SE = 0.0109$ $t_{1618} = +4.97$ $p < \mathbf{0.0001}$	$\beta = +0.0524$ $SE = 0.0125$ $t_{1618} = +4.21$ $p < \mathbf{0.0001}$
$adj - R^2$	0.23	0.20
N_{obs}	1620	1620
AIC	-3296.91	-3258.57

Table B.24: **Active Search. Speed efficiency trade-off.** Models were specified as follows: $\alpha \sim 1 + ISI + (1 + ISI | \text{participant}) + (1 + ISI | \text{condition}) + (1 | \text{trial})$.

Analysis Unit	Statistic	p-unc	p-FDR	p-FWE
Cluster 1	TFCE = 67.62	0.000035	0.001779	0.003000
Connection Hipp l - IC r	T(40) = 4.43	0.000071	0.015860	
Connection Hipp r - IC l	T(40) = 4.39	0.000081	0.015860	
Connection Hipp l - IC l	T(40) = 3.90	0.000355	0.046208	
Connection aPaHC r - IC r	T(40) = 3.59	0.000898	0.087543	
Cluster 2	TFCE = 65.51	0.000035	0.001779	0.003000
Connection pPaHC l - IC r	T(40) = 4.67	0.000034	0.015860	
Connection pPaHC l - IC l	T(40) = 4.54	0.000050	0.015860	
Cluster 3	TFCE = 44.23	0.000389	0.013084	0.035000
Connection Amygdala r - SensoriMotor Lateral (R)	T(40) = 4.26	0.000120	0.018653	
Connection Amygdala l - SensoriMotor.Lateral (L)	T(40) = 3.12	0.003366	0.138196	
Connection Amygdala l - SensoriMotor.Lateral (R)	T(40) = 2.91	0.005808	0.174246	

Table B.25: **ROI to ROI resting functional connectivity with potential outliers (three SCI individuals and one control with values above or below $Q3 + 1.5IQR$) excluded.** PaHC: para-hippocampus. Hipp: hippocampus. IC: insular cortex. unc: uncorrected. FWE: family-wise error. FDR: false discovery rate.

B.4 Chapter 5

	Effort-based choices
(Intercept)	$\beta = +1.87$ $SE = 0.291$ $t_{10242} = +6.41$ $p < 0.0001$
group	$\beta = -0.201$ $SE = 0.411$ $t_{10242} = -0.49$ $p = 0.63$
group:Effort	$\beta = +0.423$ $SE = 0.319$ $t_{10242} = +1.33$ $p = 0.19$
group:Reward	$\beta = +0.42$ $SE = 0.347$ $t_{10242} = +1.21$ $p = 0.23$
group:Reward:Effort	$\beta = -0.426$ $SE = 0.301$ $t_{10242} = -1.41$ $p = 0.16$
Effort	$\beta = -2.42$ $SE = 0.226$ $t_{10242} = -10.71$ $p < 0.0001$
Reward	$\beta = +3.16$ $SE = 0.244$ $t_{10242} = +12.94$ $p < 0.0001$
Reward:Effort	$\beta = +0.75$ $SE = 0.211$ $t_{10242} = +3.55$ $p = 0.00039$
$adj - R^2$	1.00
N_{obs}	10250
AIC	5230.85

Table B.26: **Effort-based decision making – Generalised mixed effects models examining effect of reward and effort on choices as well as differences between SCI group and controls.** Models were specified as follows. Effort-based choices: $\text{choice} \sim 1 + \text{group} * \text{Reward} + \text{group} * \text{Effort} + \text{Reward} * \text{Effort} + \text{group} : \text{Reward} : \text{Effort} + (1 + \text{Reward} * \text{Effort} | \text{participant})$.

	Effort-based choices, apathy model
(Intercept)	$\beta = +1.79$ $SE = 0.31$ $t_{5113} = +5.75$ $p < 0.0001$
ACE	$\beta = +0.0395$ $SE = 0.294$ $t_{5113} = +0.13$ $p = 0.89$
Age	$\beta = +0.46$ $SE = 0.303$ $t_{5113} = +1.52$ $p = 0.13$
AMI	$\beta = +0.0471$ $SE = 0.326$ $t_{5113} = +0.14$ $p = 0.89$
AMI:Effort	$\beta = +0.503$ $SE = 0.228$ $t_{5113} = +2.21$ $p = 0.027$
AMI:Reward	$\beta = -0.0246$ $SE = 0.283$ $t_{5113} = -0.09$ $p = 0.93$
AMI:Reward:Effort	$\beta = +0.265$ $SE = 0.209$ $t_{5113} = +1.27$ $p = 0.21$
BDI	$\beta = +0.681$ $SE = 0.345$ $t_{5113} = +1.97$ $p = 0.049$
Gender	$\beta = -0.146$ $SE = 0.31$ $t_{5113} = -0.47$ $p = 0.64$
Effort	$\beta = -2.07$ $SE = 0.227$ $t_{5113} = -9.11$ $p < 0.0001$
Reward	$\beta = +3.69$ $SE = 0.283$ $t_{5113} = +13.05$ $p < 0.0001$
Reward:Effort	$\beta = +0.233$ $SE = 0.206$ $t_{5113} = +1.13$ $p = 0.26$
$adj - R^2$	0.99
N_{Obs}	5125
AIC	2619.71

Table B.27: **Generalised mixed effects models investigating the effect of apathy in SCI.** Models were specified as follows. Effort-based choices, apathy model: $\text{choice} \sim 1 + \text{Age} + \text{Gender} + \text{ACE} + \text{BDI} + \text{AMI} * \text{Reward} + \text{AMI} * \text{Effort} + \text{Reward} * \text{Effort} + \text{AMI} : \text{Reward} : \text{Effort} + (1 + \text{Reward} * \text{Effort} | \text{participant})$.

Analysis Unit	Statistic	p-unc	p-FDR	p-FWE
Cluster 1/1	TFCE = 35.32	0.002	0.089	0.039
DefaultMode.LP (R) (47,-67,29)-FrontoParietal.PPC (L) (-46,-58,49)	T(23) = 3.87	0	0.168	
DefaultMode.MPFC (1,55,-3)-FrontoParietal.LPFC (L) (-43,33,28)	T(23) = 3.57	0.001	0.177	
DefaultMode.LP (L) (-39,-77,33)-FrontoParietal.PPC (L) (-46,-58,49)	T(23) = 3.01	0.003	0.438	
DefaultMode.LP (R) (47,-67,29)-FrontoParietal.PPC (R) (52,-52,45)	T(23) = 2.80	0.005	0.438	
DefaultMode.LP (L) (-39,-77,33)-FrontoParietal.LPFC (R) (41,38,30)	T(23) = 2.63	0.007	0.541	
DefaultMode.LP (R) (47,-67,29)-FrontoParietal.LPFC (L) (-43,33,28)	T(23) = 2.53	0.009	0.569	
DefaultMode.MPFC (1,55,-3)-Language.IFG (L) (-51,26,2)	T(23) = 2.44	0.011	0.569	
DefaultMode.MPFC (1,55,-3)-FrontoParietal.LPFC (R) (41,38,30)	T(23) = 2.40	0.013	0.569	
DefaultMode.LP (L) (-39,-77,33)-FrontoParietal.LPFC (L) (-43,33,28)	T(23) = 2.07	0.025	0.673	
DefaultMode.MPFC (1,55,-3)-Language.pSTG (L) (-57,-47,15)	T(23) = 1.93	0.033	0.726	
DefaultMode.LP (R) (47,-67,29)-FrontoParietal.LPFC (R) (41,38,30)	T(23) = 1.65	0.057	0.775	
DefaultMode.PCC (1,-61,38)-FrontoParietal.PPC (L) (-46,-58,49)	T(23) = 1.65	0.057	0.775	

Table B.28: Cluster information showing network connectivity associated with with apathy and effort sensitivity.

B.5 Chapter 6

	Effort-based choices
(Intercept)	$\beta = +1.75$ $SE = 0.259$ $t_{8983} = +6.74$ $p < 0.0001$
group	$\beta = -0.557$ $SE = 0.358$ $t_{8983} = -1.56$ $p = 0.12$
group:Effort	$\beta = +1.42$ $SE = 0.261$ $t_{8983} = +5.44$ $p < 0.0001$
group:Reward	$\beta = -0.585$ $SE = 0.345$ $t_{8983} = -1.70$ $p = 0.09$
group:Reward:Effort	$\beta = -0.476$ $SE = 0.286$ $t_{8983} = -1.66$ $p = 0.10$
Effort	$\beta = -2.52$ $SE = 0.193$ $t_{8983} = -13.02$ $p < 0.0001$
Reward	$\beta = +3.17$ $SE = 0.251$ $t_{8983} = +12.62$ $p < 0.0001$
Reward:Effort	$\beta = +0.386$ $SE = 0.207$ $t_{8983} = +1.87$ $p = 0.06$
$adj - R^2$	1.00
N_{obs}	8991
AIC	5642.40

Table B.29: Effort-based decision making – Generalised mixed effects models examining effect of reward and effort on choices as well as differences between AD group and controls. Models were specified as follows. Effort-based choices: $\text{choice} \sim 1 + \text{group} * \text{Reward} + \text{group} * \text{Effort} + \text{Reward} * \text{Effort} + \text{group} : \text{Reward} : \text{Effort} + (1 + \text{Reward} * \text{Effort} | \text{participant})$.

	Effort-based choices, Decision Time model
(Intercept)	$\beta = +0.836$ $SE = 0.0459$ $t_{8905} = +18.19$ $p < 0.0001$
group	$\beta = +0.285$ $SE = 0.065$ $t_{8905} = +4.38$ $p < 0.0001$
group:Effort	$\beta = -0.0234$ $SE = 0.0121$ $t_{8905} = -1.93$ $p = 0.05$
group:Reward	$\beta = +0.00137$ $SE = 0.0134$ $t_{8905} = +0.10$ $p = 0.92$
group:Reward:Effort	$\beta = -0.0258$ $SE = 0.00925$ $t_{8905} = -2.79$ $p = 0.0053$
Effort	$\beta = +0.0457$ $SE = 0.00855$ $t_{8905} = +5.34$ $p < 0.0001$
Reward	$\beta = -0.0156$ $SE = 0.00945$ $t_{8905} = -1.66$ $p = 0.10$
Reward:Effort	$\beta = +0.05$ $SE = 0.00653$ $t_{8905} = +7.67$ $p < 0.0001$
$adj - R^2$	0.47
N_{obs}	8913
AIC	6274.54

Table B.30: **Generalised mixed effects models investigating decision time (DT) differences.** Models were specified as follows. Effort-based choices, Decision Time model: $\ln DT \sim 1 + \text{group} * \text{Reward} + \text{group} * \text{Effort} + \text{Reward} * \text{Effort} + \text{group} : \text{Reward} : \text{Effort} + (1 + \text{Reward} * \text{Effort} | \text{participant})$.