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The Neural Determinants of Perceptual Decision-Making in the Human Brain

by

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A dissertation submitted to the

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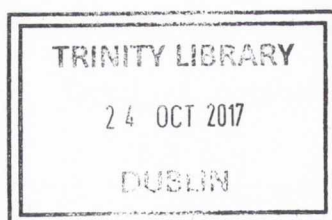


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Summary

Perceptual decision making is the process through which sensory information is translated into adaptive action. It is a fundamental brain function that is at the heart of human behaviour and is necessary for the successful performance of any cognitive task. Basic perceptual decisions are composed of at least three essential processing stages: sensory encoding, decision formation, and motor execution. In recent years, studies of animal neurophysiology have greatly elucidated the neural dynamics underpinning each of these stages. Most importantly, this body of work demonstrated that the intermediate decision stage is achieved by accumulating sensory evidence for the decision over time until a reliable quantity has been gathered. Such accumulation-to-bound dynamics accord with the long-standing predictions of mathematical models and can explain how the brain facilitates adaptive action in the face of sensory information that is often noisy. These breakthroughs generated considerable excitement across the broad field of neuroscience as they provided a framework for exploring the flow of information from sensation through to action in a comprehensive and mechanistically principled way. However, despite these advances, much is still to be learned about the brain's decision-making machinery and how it is implicated in the neurobiology of psychiatric disorders.

The scalp-recorded electroencephalogram (EEG) provides a millisecond-scale readout of human brain activity. Discrete stimuli evoke a complex pattern of temporally and spatially overlapping signals in EEG recordings which can be difficult to disentangle. This issue of global signal summation has prevented researchers from bridging the advances made in monkey neurophysiology to the study of decision-making in humans. However, a novel EEG paradigm has recently been developed that surmounts these technical limitations and provides an unprecedented facility to isolate and independently monitor the three stages of perceptual decision-making in discrete and freely-evolving electrical brain signals that can be convincingly linked to the neural mechanisms necessary for simple perceptual decisions. Most importantly, two distinct classes of decision signal have been identified. Each exhibits the same accumulation-to-bound dynamics observed in single-unit recordings – a domain-general signal known as the centro-parietal positivity (CPP) and an effector-selective motor preparation signal. The overall purpose of the present work was to capitalise on this breakthrough. This thesis

aimed to: 1) expand our understanding of the functional characteristics of neural decision variable signals under different experimental conditions and 2) establish whether the neural metrics can be used as a tool to further our understanding of clinical disorders in which there may be compromised decision-making capacities.

The CPP bears a strong resemblance to the classic P300 component of the human event-related potential; a component which continually draws widespread interest in basic and clinical neuroscience, yet its functional significance has never been conclusively established. The first aim of the thesis was to establish whether or not functional equivalence exists between the CPP and P300 components. In Chapter 2, novel analyses of signal build-up and peak dynamics, along with computational simulations, reveal that the P300, like the CPP, reflects an abstract, accumulation-to-bound decision mechanism.

To date, studies in rodents and monkeys have focussed primarily on effector-selective signals that translate the emerging decision into a specific motor plan, but the discovery of the CPP signal indicates that the human brain also houses an abstract signature of evidence accumulation that does not appear to play any direct role in action preparation. The functional dissociations between these distinct signal types have only begun to be characterised. Their dynamics during decisions with deferred actions, with or without foreknowledge of stimulus-effector mapping – a commonly studied task scenario in single-unit and functional imaging investigations – have not been established. Chapter 3 demonstrates salient distinctions in the dynamics of abstract versus effector-selective decision signals in the human brain, in terms of sustainment through response delays and contingency on foreknowledge of stimulus-response mapping.

Recent data suggests that adults with attention-deficit/hyperactivity disorder (ADHD) are impaired on perceptual decision-making tasks. However, the neural underpinnings of compromised decision-making capacities remain poorly understood and, given that it is a feature of many psychiatric disorders, there is a major imperative to determine disease-specific etiological pathways for ADHD. Chapter 4 evaluated the utility of the novel EEG metrics as a means to link decision-making performance deficits in ADHD to precise abnormalities in information processing (sensory, decision, motor) versus pre-stimulus state (attention). The chapter provides some of the first evidence that the perceptual decision-making process is not fully intact in emerging adults with ADHD and reveals that the neural metrics are a promising tool for parsing out impairments in the

constituent components of the decision-making process in brain disorders. It also highlights a number of very important methodological factors that merit consideration in future work. It shows that inter-individual variability in EEG responses is a significant issue when using the metrics to detect effects across groups such that future investigations will need to use more complex analysis techniques to harness within-subject effects.

Finally, Chapter 5 provides a discussion of the implications of this work and future challenges in this direction.

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Publications Arising from this Thesis

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Chapter 3

- **Twomey DM**, Kelly SP, O’Connell RG (2016). Abstract and Effector-Selective Decision Signals Exhibit Qualitatively Distinct Dynamics before Delayed Perceptual Reports. *Journal of Neuroscience*, 36(28): 73467352.
- **Twomey DM**, Kelly SP, O’Connell RG (2013). The temporal dynamics of decision formation and motor preparation. *Psychophysiology*, 50: S28–S28.

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Published Abstracts

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- **Twomey DM**, Kelly SP, O'Connell RG (2013). The Temporal Dynamics of Decision Formation and Motor Preparation. *Neuroscience Ireland 2013*, Cork, Ireland.

Table of Contents

Declaration.....	ii
Summary.....	iii
Acknowledgements.....	vi
Publications Arising from this Thesis.....	viii
Table of Contents.....	x
List of Figures.....	xv
List of Tables.....	xvii
Chapter 1 Conceptual Background.....	1
1.1 Introduction.....	1
1.2 Conceptual Framework for Understanding Perceptual Decision-Making 3	
1.2.1 Sequential Sampling Models of Perceptual Decision-Making.....	5
1.2.2 Summary.....	7
1.3 Neural Correlates of Decision Formation in the Primate Brain.....	7
1.3.1 Neural Correlates of Perceptual Decisions Formed within an Intentional Framework.....	7
1.3.2 Evidence for Distinct Representations of a Perceptual Decision and the Associated Motor Plan in the Monkey Brain.....	9
1.3.3 Necessity for Reciprocal Interactions between Primate and Human Work in Perceptual Decision-Making.....	12
1.3.4 Summary.....	13
1.4 Identifying Neural Correlates of Decision Formation in the Human Brain Using Functional Imaging-Based Approaches.....	14
1.4.1 Identifying Candidate Sites of Decision Formation using FMRI ...	14

1.4.2	Disentangling Effector-Selective and Domain-General Evidence Accumulation using FRMI	16
1.4.3	Challenges to the FMRI Investigations of Perceptual Decision-Making	18
1.4.4	Summary	19
1.5	Identifying Neural Correlates of Decision Formation in the Human Brain Using EEG/MEG-Based Approaches	20
1.5.1	Electroencephalography	20
1.5.2	EEG Studies of Perceptual Decision-Making	21
1.5.3	EEG-Informed fMRI Approach in Perceptual Decision-Making Research	24
1.5.4	Model-Based Approaches to the Analysis of EEG and MEG Data in Perceptual Decision-Making Research	25
1.5.5	Challenges to Model-Based EEG Analytic Approaches	26
1.5.6	Summary	27
1.6	Directly Tracing the Decision Process in Humans	28
1.6.1	Paradigm Innovations Enabling Parallel Tracking of Sensory, Decision and Motor Signals in EEG	30
1.6.2	Tracing the Three Stages of Perceptual Decision-Making in EEG	30
1.6.3	Functional Equivalence of the CPP and P300	36
1.6.4	Summary	38
1.7	Overall Summary and Objectives of Thesis	39
Chapter 2	The Classic P300 Encodes a Build-to-Threshold Decision Variable	42
2.1	Introduction	42
2.2	Methods	43
2.2.1	Participants	43
2.2.2	Experimental Tasks	43
2.2.3	Data Acquisition and Pre-processing	45

2.2.4	Statistical Analyses	50
2.3	Results	50
2.3.1	Behaviour	50
2.3.2	A Build-up Rate that Scales with the Strength of Sensory Evidence 51	
2.3.3	A Build-up Rate that Predicts Reaction Time	51
2.3.4	An Action-Triggering Threshold	51
2.3.5	P300 as a Domain General Decision Signal	53
2.3.6	Comparison with Simulated Decision Variable	55
2.3.7	RT-Linked Fronto-central Negativity Signal Overlaps with the P300 57	
2.4	Discussion	58
Chapter 3	Abstract and Effector-Selective Decision Signals Exhibit Qualitatively Distinct Dynamics before Delayed Perceptual Reports	63
3.1	Introduction	63
3.2	Materials and Methods	64
3.2.1	Participants	64
3.2.2	Random Dot Motion (RDM) Paradigm	64
3.2.3	EEG Acquisition and Pre-processing	67
3.2.4	Statistical Analyses	70
3.3	Results	71
3.3.1	Behavioural Performance	71
3.3.2	Foreknowledge of Stimulus-Effector Mapping Differentially Impacts upon Abstract and Motor-Selective Decision Signals	71
3.3.3	Impact of Evidence Strength on Abstract versus Motor-Selective Decision Signals	74
3.4	Discussion	76

Chapter 4 Pinpointing the Neural Origins of Deficient Perceptual Decision-Making in Emerging Adults with Attention-Deficit/Hyperactivity Disorder.....	79
4.1 Introduction.....	79
4.2 Causal Models of ADHD.....	80
4.2.1 Simple Causal Models.....	80
4.2.2 Dual Pathway Models of ADHD.....	86
4.2.3 Challenges to the Causal Models of ADHD.....	87
4.3 Electrophysiological Investigations of ADHD.....	88
4.3.1 Event-related Potential Studies of ADHD.....	89
4.4 Perceptual Decision-Making in ADHD.....	91
4.4.1 Behavioural Evidence.....	92
4.4.2 Electrophysiological Evidence.....	93
4.5 Aims and Objectives.....	93
4.6 Methods.....	94
4.6.1 Participants.....	94
4.6.2 Study design.....	96
4.6.3 Neuropsychological Assessments.....	97
4.6.4 Two-alternative Forced Choice Contrast Discrimination Task	104
4.6.5 EEG Acquisition and Pre-processing.....	106
4.6.6 Statistical Analyses.....	109
4.7 Results.....	110
4.7.1 Cognitive Deficits in ADHD.....	110
4.7.2 Behavioural Performance.....	112
4.7.3 Behavioural Performance and the EEG Metrics of the Perceptual Decision-Making Process.....	113
4.7.4 Perceptual Decision-Making Process and Inattentive Symptom Severity	116
4.8 Discussion.....	117

Chapter 5 General Discussion 124

5.1 Thesis Overview..... 124

5.2 Functional Characteristics of Neural Decision Variable Signals 125

5.2.1 Contributions..... 125

5.2.2 Limitations and Future Directions 130

5.3 Perceptual Decision-Making in Emerging Adults with ADHD..... 136

5.3.1 Contributions..... 136

5.3.2 Limitations and Future Directions 137

References..... 140

Appendices..... 159

List of Figures

Figure 1.1: Sequential sampling models of perceptual decision-making.	6
Figure 1.2: Intentional framework for decision-making in the monkey brain.....	9
Figure 1.3: Domain-general perceptual decision-making.....	15
Figure 1.4: Perceptual decision-making within a distributed neural network.	25
Figure 1.5: Tracing the three stages of perceptual decision-making in EEG.	32
Figure 1.6: Abstract and effector-selective neural decision variable signals.	36
Figure 1.7: Striking resemblance between the CPP and P300 components of the human ERP.	38
Figure 2.1: Schematic of the auditory oddball and visual target detection tasks.	45
Figure 2.2: The effect of bin-size on P300 amplitude variance reduction at response time relative to a permutation distribution in the two-stimulus auditory oddball experiment (z-scores averaged across subjects).	53
Figure 2.3: The P300 exhibits the critical dynamical properties of a neural decision variable across three prototypical P300 paradigms.	54
Figure 2.4: Computational modelling of an accumulation-to-bound decision process captures oddball performance and P300 dynamics.....	56
Figure 2.5: Inverse relationship between untransformed response-aligned P300 amplitude and RT is driven by a frontocentral negativity.	58
Figure 3.1: Schematic of the delayed response random dot motion task.	66
Figure 3.2: Impact of foreknowledge of stimulus-effector (S-E) mapping on abstract and effector-selective signatures of evidence accumulation in the human brain.	73
Figure 3.3: Decision variable signals as a function of coherence.....	75
Figure 4.1: Schematic representation of a cognitive dysfunction model of ADHD (adapted from Barkley, 1997) and a simplified explanation of the associated frontostriatal circuitry (adapted from Alexander et al., 1990).....	81
Figure 4.2: Schematic representation of a simple motivational model of ADHD (adapted from Sagvolden et al., 1998) and a simplified explanation of the associated frontostriatal circuitry (adapted from Alexander et al., 1990).....	83
Figure 4.3: The cognitive energetic model (Sergeant, 2000).	85

Figure 4.4 Schematic representation of the dual pathway model (Sonuga-Barke, 2002).	87
Figure 4.5: Schematic of the Sustained Attention to Response Task.	99
Figure 4.6: Schematic of the two-alternative forced choice contrast discrimination task and the neural metrics of the perceptual decision-making process.	105
Figure 4.7: No significant differences in the electrophysiological correlates of decision-making in the ADHD and Control groups.	115
Figure 5.1: The stimulus-aligned P300 component is disrupted in a wide range of clinical disorders.	128

List of Tables

Table 4.1: Summary of demographic data for the control and ADHD groups... 97

Table 4.2: Definitions of the cognitive domains and the tasks used to assess each domain. 103

Table 4.3: Summary of performance on the neuropsychological assessments for the control and ADHD groups. 112

Table 4.4: Summary of the median values used to classify participants as being of Low or High Inattentive symptom severity. 117

Table A.1: Partial correlations between accuracy on the contrast discrimination task and the selected metrics EEG metrics of the perceptual decision-making process with group, partialled out. 159

Table A.2: Partial correlations between accuracy on the contrast discrimination task and selected cognitive capacities relevant to the perceptual decision-making process with group, partialled out. 160

Table A.3: Partial correlations between Inattentive symptom severity and selected metrics EEG metrics of the perceptual decision-making process with group, partialled out. 161

Chapter 1 Conceptual Background

1.1 Introduction

Consider driving on a nice day. The traffic light turns red; you stop and spot pedestrians waiting patiently to cross the street. Effortlessly, you distinguish if one of them is your partner, your boss, or a stranger. You relate this percept to the appropriate response such that you might wave manically, give a dutiful nod, or continue about your business (Heekeren et al., 2008). This conversion of sensory information into an appropriate action is termed perceptual decision-making. Sensorimotor transformations consist of at least three essential stages: sensory encoding, decision formation, and motor execution (Sternberg, 1969). In recent years, there has been a considerable focus within the field of neuroscience on elucidating the neural principles and processes underpinning this intermediate decision formation stage since it represents such a fundamental and pervasive component of human cognitive function.

A comprehensive knowledge of how the basic elements of decision formation are realised in the brain would enhance our understanding of the neural mechanisms that underpin the more complex decisions that we encounter in everyday life (Heekeren et al., 2008). Furthermore, compromised decision-making capacities are central to a wide range of psychiatric and neurological disorders such as obsessive-compulsive disorder (OCD; Heekeren et al., 2008) and attention-deficit/hyperactivity disorder (ADHD; Mulder et al., 2010). As decision-making deficits may manifest in indistinguishable ways (such as slower or more variable reaction times, reduced accuracy), a fundamental challenge for researchers is to identify disease-specific aetiological pathways by elucidating the precise information processing stages or neural computations that are impacted by a given disorder (Kelly and O'Connell, 2015). Such knowledge would pave the way for a new and more precise understanding of how clinical brain disorders impact on decision-making in the human brain.

In recent years, a series of influential monkey neurophysiology studies have provided compelling empirical support for a mechanistic account of decision formation that is grounded in the framework of sequential sampling theory (Gold and Shadlen, 2007). The primary principle of sequential sampling models is that a ‘decision variable’ accumulates evidence over time in favour of a specific outcome and determines action upon crossing an internal decision threshold (Smith and Ratcliff, 2004). Crucially, sequential sampling offers a neural process through which accurate choice behaviour can be achieved in the face of fluctuating and noisy sensory information. Models based on these principles can account for an exceptional quantity of the effects observed in decision behaviour such as reaction time and accuracy on a broad range of cognitive tasks (Ratcliff and McKoon, 2008; Kelly and O’Connell, 2013). Additionally, the mechanistic nature of the framework makes it possible to generate very precise and testable predictions about how each parameter of the model should vary as a function of specific stimulus properties.

Sequential sampling models have received strong empirical validations through neurophysiological research on the monkey brain which has identified specific neural populations whose spiking activity encodes an accumulation-to-bound decision variable process (Hanes and Schall, 1996; Roitman and Shadlen, 2002; Ratcliff et al., 2007). This work has incited a concerted effort to identify an equivalent mechanism in the human brain using both functional imaging and neurophysiology. Recently, relatively simple paradigm innovations have enabled the parallel tracking of freely-evolving sensory evidence, decision variable, and motor signals in the human electroencephalogram (EEG). Most importantly, a goal-relevant decision signal (centro-parietal positivity [CPP]) was isolated that demonstrated the key build-to-threshold dynamics predicted by the sequential sampling models (O’Connell et al., 2012; Kelly and O’Connell, 2013). Importantly, unlike any other signal identified in either the monkey or human brain to date, the CPP was fully supramodal in nature such that it carried out its function independently of the sensory or motor requirements of the task (O’Connell et al., 2012). The present thesis will capitalise on this newfound capacity to independently and continuously monitor the three distinct stages of decision-making via the human EEG to firstly, expand our understanding of the functional characteristics of neural decision variable signals under different experimental conditions and secondly, establish whether the EEG metrics can be used as a tool to further our understanding of clinical disorders in which there may be compromised decision-making capacities.

The aim of present chapter is to provide the conceptual background of the work presented within this thesis. The literature exploring the research relevant to perceptual decision-making in ADHD, as it is relevant only to the final empirical chapter (Chapter 4), will not be considered in detail until Chapter 4. The present chapter is organised into seven main sections. In the proceeding section, an overview of the key elements of the decision process and the most important computational models of perceptual-decision making is provided. The third section discusses the neural correlates of perceptual-decision making that have been isolated in the monkey brain thus far, and highlights the necessity for reciprocal interactions between studies of animal and human participants. The fourth section offers insight into the progress that has been made in tracing the dynamics of perceptual decision formation in humans using functional imaging. The fifth section details the progress that has been made in tracing the dynamics of perceptual decision formation in humans using neurophysiological approaches such as electroencephalography (EEG) and magnetoencephalography (MEG). The sixth section focuses on recent developments in human neurophysiology that enable us to non-invasively trace sensorimotor transformations in the human brain. The seventh and final section provides an overall summary and an outline of the objectives of the thesis.

1.2 Conceptual Framework for Understanding Perceptual Decision-Making

Prior to settling on a verdict of guilty or innocent, a jury must take time to consider the available evidence for different explanations of a crime. This real-life scenario reflects a decision which can be formally defined as a deliberative process that results in a commitment to a categorical proposition (Gold and Shadlen, 2007). Before hearing the case, the jury may be biased towards accepting one version of events owing to their own particular prejudices. From an information theory perspective, such prejudice would represent a prior, that is the probability that a hypothesis is accurate before gathering any evidence about it (Gold and Shadlen, 2007). The blood of the accused at a crime scene may be cited as evidence to support the hypothesis that he or she was present at that location, evidence can thus be considered the information that influences whether, and maybe when, to commit to a specific hypothesis (Gold and Shadlen, 2007). The final component of a decision is value - the perceived costs and benefits associated with each possible outcome of the decision. A 'decision variable' is thought to represent all the

priors, evidence and value in a single theoretical quantity that builds over time and is interpreted by a decision rule to produce a decision (Gold and Shadlen, 2007). The decision rule determines how and when the decision variable is interpreted to commit to a hypothesis. One mechanism by which a decision rule may function is by applying a threshold rule on the decision variable (Gold and Shadlen, 2007).

The sequential sampling models have provided some of the most influential theoretical accounts of perceptual decision-making to date and can comprehensively account for decisions that necessitate a choice between two alternatives (Deco et al., 2013). Sequential sampling is grounded in signal detection theory and represents a logical extension of that framework. Signal detection theory suggests that a subject will convert a single observation of noisy evidence into a categorical choice within a short but fixed period of time that is not under their control (Deco et al., 2013). A major advantage of sequential sampling models over signal detection theory is that they can account for the reaction time distributions observed on a wide range of tasks (Gold and Shadlen, 2007). Sequential analysis proposes that we make decisions by integrating multiple samples of noisy stimulus information across an extended period of time with the ‘decision variable’ being updated with each new piece of evidence until a decision criterion is reached and action is triggered (Smith and Ratcliff, 2004). Thus, sequential sampling suggests that a decision has two parts: a decision between competing alternatives and another decision about whether it is time to terminate the process and commit to a choice (Gold and Shadlen, 2007).

One of the key advantages of the computational models of decision-making is that they can mechanistically account for the changes observed in behavioural measures following experimental manipulations such as varying the levels of sensory evidence, levels of prior information or speed pressure via strategic adjustments of the model parameters such as drift rate, the distance-to-boundary, or the decision criterion. In these models, drift rate indexes the rate of evidence accumulation, the distance to boundary controls the quantity of evidence required for the choice, and the amount of time spent on non-decision processes including sensory encoding and motor preparation reflects non-decision time (Poliastides et al., 2014).

1.2.1 Sequential Sampling Models of Perceptual Decision-Making

Although this thesis does not aim to adjudicate between different classes of sequential sampling models, the present section will provide a very brief overview of the key variants. The most basic models derived from sequential analysis are often called the psychological models of decision-making and they can be divided into two distinct categories based on the nature of their evidence accumulation processes (Smith and Ratcliff, 2004; Bogacz, 2007). While both categories of sequential sampling model hold that decisions are based on the accumulation of sensory evidence, they differ in the manner in which the accumulation process is thought to occur (Smith and Ratcliff, 2004; see Fig 1.1). In random-walk models, the net difference in sensory evidence for the two decision alternatives is accumulated in a single evidence total and action is triggered once the decision boundary is crossed. Conversely, in accumulator and counter models, two separate integrators accumulate the sensory evidence in favour of each response alternative and a decision is implemented when one of the integrators exceeds the decision threshold (Bogacz, 2007; see Fig 1.1). If there is mutual inhibition between the two integrators in an accumulator model, then the evidence for one response serves as evidence against the alternate response, as is the case in the diffusion model. Under these circumstances, the two classes of model predict a very similar range of behavioural data (Smith and Ratcliff, 2004).

The random-walk and accumulator and counter models can be classified into subcategories based on the temporal and incremental nature of their sensory integration processes. With respect to random-walk models, sensory integration in a single total across discrete time points is termed a random-walk process, while the same in continuous time is called a diffusion process. A diffusion process can be subject to, or void of, information decay ('leakage', Smith and Ratcliff, 2004). With respect to accumulator and counter models, the Poisson counter model represents the integration of discrete sensory evidence across continuous time in two separate totals. The popular leaky competing accumulator model reflects the accumulation of continuous evidence across continuous time in two separate totals that are mutually inhibitive (Smith and Ratcliff, 2004).

Random-walk and diffusion processes with perfect integration can both reasonably account for the reaction time distributions and accuracy data generated on a broad range of cognitive paradigms (Smith and Ratcliff, 2004). However, only diffusion

processes with imperfect integration can predict that accuracy will vary as a function of reaction time. The diffusion model optimises the speed of decisions for a required level of accuracy (Bogacz, 2007). For example, if the evidence in favour of the losing decision alternative is weak relative to that in favour of the winning alternative, then the diffusion process will integrate for a shorter period of time than if the evidence in favour of the two alternatives is similar, such that there is a higher degree of conflict between them. In the case of the latter, it would take longer for the accumulated evidence difference to cross the decision threshold (Bogacz, 2007).

Deco et al. (2013) highlighted the growing need for decision-making research to evolve from the computational and phenomenological explanations of behaviour to those that are neurophysiologically plausible. Adjudicating between competing models on the basis of behaviour fits alone is highly challenging (Ratcliff et al., 2016) but an avenue for future progress is provided by the fact that computational models of decision-making also generate very precise and testable hypotheses about the underlying neurophysiology.

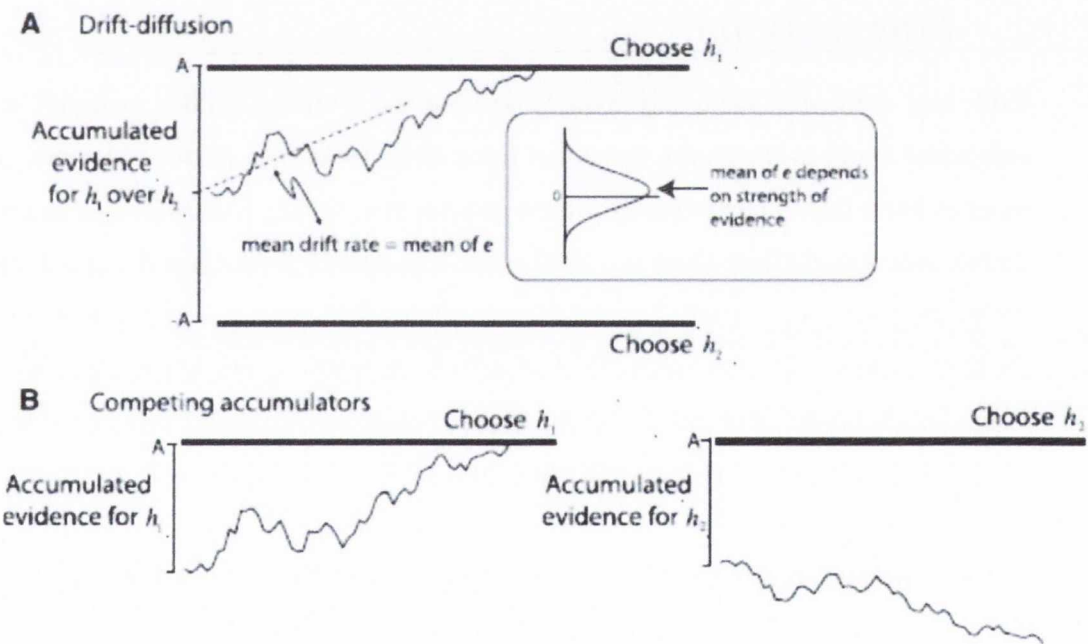


Figure 1.1: Sequential sampling models of perceptual decision-making.

A, In the drift diffusion model, noisy sensory evidence is integrated across time as a single quantity in favour or against two hypotheses, h_1 and h_2 . The decision process is bounded by an upper and lower decision threshold. Once the evidence integrates beyond either decision threshold, the appropriate choice is implemented. **B**, In the competing accumulators model, there are separate integrators for h_1 and h_2 . The two integrators

accumulate the sensory evidence in favour of each response alternative and a choice is implemented when one of the integrators exceeds the decision criterion. Adapted from Shadlen and Kiani (2013).

1.2.2 Summary

The mathematical models of decision-making have provided influential theoretical descriptions of how perceptual decisions may be implemented in the brain. The most prevalent models are grounded on sequential analysis. While the computational models of decision-making provide us with a powerful theoretical framework from which we can generate hypotheses, empirical data is needed to establish whether or not this how decisions are implemented in the human brain. There is a growing imperative in the literature to move from phenomenological explanations of behaviour to those that are neurophysiologically plausible.

1.3 Neural Correlates of Decision Formation in the Primate Brain

With the sequential sampling models serving as a strong guide, neuronal signals exhibiting build-to-threshold dynamics have been identified in several areas of the monkey brain including parietal (Roitman and Shadlen, 2002), frontal (Hanes and Schall, 1996), subcortical (Ratcliff et al., 2007) and oculomotor areas (Ratcliff and McKoon, 2008; Ding and Gold, 2010). Two key features identify these signals with the theoretical decision variable: 1) they reach fixed amplitude at response execution, indicative of a boundary-crossing effect; and 2) they build across time at rate that scales with the strength of sensory evidence, consistent with the principle of temporal integration (see Fig. 1.2).

1.3.1 Neural Correlates of Perceptual Decisions Formed within an Intentional Framework

Many perceptual decision-making studies in monkeys have used the classic random dot motion task (RDM; Newsome et al., 1989; Britten et al., 1992) in which the observer views a series of randomly interspersed dots within a circular aperture (see Fig. 1.2A). The dots are subject to random displacements from frame to frame, with the exception of a subset, which move coherently in one of two directions forming the choice alternatives. The motion discrimination decision is typically communicated with a saccade in the

direction of the coherent motion. An advantage of the paradigm is that the experimenter can precisely manipulate the strength of the sensory evidence, and hence task difficulty, by varying the percentage of dots moving coherently in one direction (Newsome et al., 1989; Britten et al., 1992).

A series of motion direction discrimination studies repeatedly demonstrated that the firing rate of motion-selective neurons in the primate middle temporal (MT) area tonically traced the quality of available sensory evidence providing a neural index of the encoding of the sensory evidence for the decision (Newsome et al., 1989; Britten et al., 1996; Gold and Shadlen, 2001; Shadlen and Newsome, 2001; Gold and Shadlen, 2007). In contrast to the tonic elevation observed in the middle temporal area, the rate of spiking activity of neurons in the oculomotor regions of the primate brain such as the lateral intraparietal (LIP) area, the frontal eye fields, the dorsolateral prefrontal cortex and the superior colliculus increased as a function of the integrated output of the middle temporal area to an action-triggering threshold. This is consistent with the theoretical ‘decision variable’ signals described by sequential sampling (Gold and Shadlen, 2001; Shadlen and Newsome, 2001; Huk and Shadlen, 2005; Gold and Shadlen, 2007). A causal role for the LIP neurons in forging perceptual decisions that are reported with a saccade was confirmed using microstimulation which successfully biased the motor response that followed the decision process (Gold and Shadlen, 2000, 2003). Similar results were obtained in somatosensory research using a vibrotactile frequency discrimination task in which monkeys had to distinguish between two stimuli of different frequencies and had to decide which of the two stimuli was at a higher frequency (Romo et al., 2002). Here, the firing rate of neurons in the somatosensory cortex encoded the momentary quality of available sensory evidence thus, providing a measure of the sensory evidence for the decision. In contrast, the spiking activity of neurons in the sensorimotor regions of the primate brain such as the prefrontal, medial, and ventral prefrontal cortices increased over time at a rate that scaled with the integrated output of somatosensory cortex and reliably triggered a perceptual report upon reaching a stereotyped level of firing. These properties closely correspond to the predictions of sequential sampling models detailed above (Romo et al., 2002).

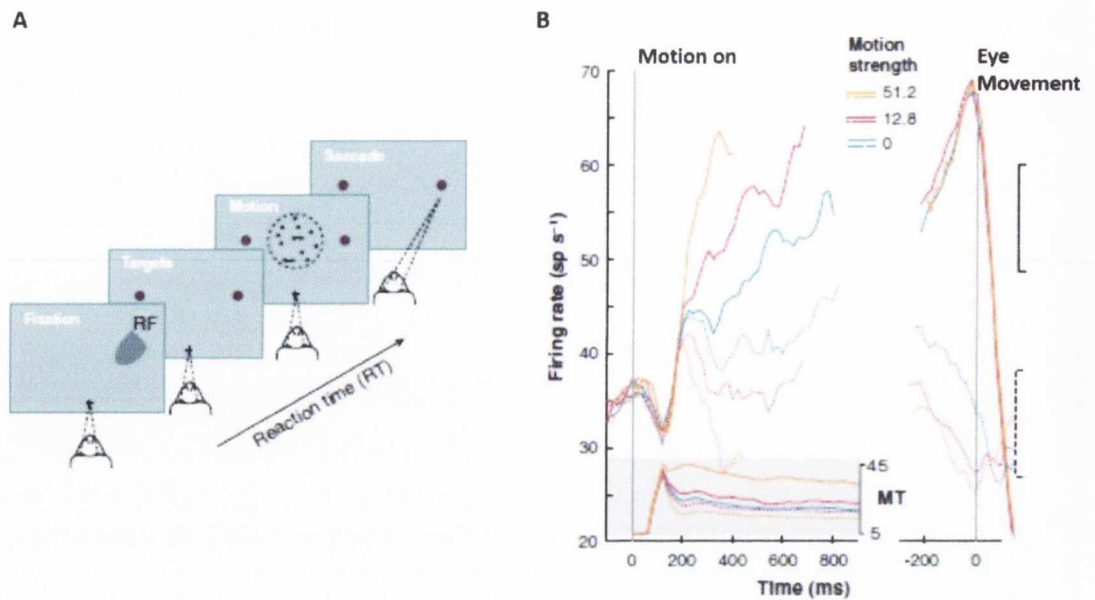


Figure 1.2: Intentional framework for decision-making in the monkey brain.

A, Reaction time version of the classic random dot motion task. The monkeys monitored a patch of dynamic random dots and had to detect and indicate the net direction of the coherent motion. The motion decision was communicated via a saccade to the peripheral target in the appropriate direction and the trial ended once the saccade was made. **B**, Fully consistent with a theoretical decision variable, the firing rate of LIP neurons builds over time at rate that scales with the strength of the sensory evidence and reaches a stereotyped amplitude at response execution. Adapted from Gold and Shadlen (2007).

1.3.2 Evidence for Distinct Representations of a Perceptual Decision and the Associated Motor Plan in the Monkey Brain

A notable feature of the single-unit recordings studies is that decision variable encoding neurons have been almost exclusively observed in effector-selective, pre-motor regions of the brain that play a direct role in preparing the action that the decision entails (Gold and Shadlen, 2001; Shadlen and Newsome, 2001; Huk and Shadlen, 2005; Gold and Shadlen, 2007). This fuelled the view that decisions are formed within an ‘intentional framework’ whereby the regions recruited to compute a perceptual decision reflect the specific motor requirements of the task (Gold and Shadlen, 2007; Shadlen and Kiani, 2013). The validity of the intentional framework has been called into question due to the fact that the monkeys learn to associate a specific sensory stimulus with a specific motor response through extensive training and operant conditioning, such that the task itself is cast as an action selection decision (Freedman and Assad, 2006; Heekeren et al., 2008;

Bennur and Gold, 2011; de Lafuente et al., 2015). Since the relationship between perceptual decision-making and action selection in monkeys has, for the most part, been assessed under conditions in which the two could not be disentangled, it is unclear whether the intentional framework plays a more general role in perceptual decision formation or whether it reflects specific task conditions in which sensory evidence can be converted directly into action (Bennur and Gold, 2011). Numerous authors have pointed out that computing a domain-general decision that can be relayed to the pre-motor regions of the brain to guide action would be a more economical and adaptive means to implement perceptual decisions than motor-selective evidence accumulation. After all, a combination of motor responses may be required following any one decision (Liu and Pleskac, 2011). In the last number of years, numerous studies have been conducted in an effort to establish the existence of such a domain-general mechanism.

Bennur and Gold (2011) sought to decouple decision formation from motor preparation. Monkeys had to detect the direction of coherent motion in a random-dot motion stimulus and, following a delay period, indicate their decision with a saccade to a coloured target. Red and green coloured targets were associated with rightward and leftward motion and always appeared at a known location, but the colour at each location was unknown until the targets appeared. Three distinct versions of the task were used that differed in terms of when the coloured targets relaying the decision-reporting information appeared. The coloured targets either appeared before (task 1), during (task 2) or after (task 3) the motion viewing (Bennur and Gold, 2011). This manipulation was used to control the time at which the decision was computed relative to when it became linked to a specific action. Irrespective of whether the stimulus-response association became known prior to, during, or after the motion viewing, a neural correlate of the decision process was observed in the LIP area (Bennur and Gold, 2011). LIP neurons exhibited selectivity for motion direction that was, for the most part, independent of the saccadic choice during motion viewing, followed by selectivity for saccadic choice that was mostly independent of motion direction at the time of the saccade (Bennur and Gold, 2011). The results suggest that perceptual decision-making and action selection are distinct neural processes that are only inextricably linked in specific behavioural contexts. Furthermore, they imply that the role played by LIP neurons in decision-making may be saccade-independent and could be linked to its selectivity for a visual feature of a stimulus such as colour or motion direction (Bennur and Gold, 2011).

Freedman and Assad (2006) also provided evidence that more abstract representations of decisions can be observed in the monkey oculomotor system (Li and Krishnamurthy, 2015). In this study, two monkeys were trained to classify 12 directions of visual motion into two distinct categories that were separated by a category boundary. After training, the firing rate of the neurons in area LIP strongly reflected category such that the monkeys responded more similarly to motion directions of the same category even when those motion directions were dissimilar and discriminated between similar motion directions that belonged to different categories (Freedman and Assad, 2006). MT neurons did not demonstrate the same pattern of responding, such that they remained highly direction selective but did not become category selective (Freedman and Assad, 2006). When the monkeys were re-trained to categorise the same stimuli into two new categories, the selectivity of the LIP neurons adapted to encode motion direction relative to the new category classifications. Thus, Freedman and Assad (2006) not only demonstrated that LIP activity can reflect arbitrary, learned visual categories, but that these learned visual representations can be plastic (Li and Krishnamurthy, 2015).

In a recent study, de Lafuente et al. (2015) further demonstrated that the monkey oculomotor system may play a more general role in decision-making (Li and Krishnamurthy, 2015). On a trial-by-trial basis, monkeys detected the direction of coherent motion in a random-dot motion stimulus and were subsequently cued to report their decision with either a saccade or a reach movement while neuronal firing was recorded in both the LIP and medial intraparietal (MIP) regions of the brain. MIP neurons signal the spatial location of stimuli that may be the target of reach movements. MIP neurons represented the evolving decision when the monkey communicated it with a reach movement but, not a saccade. However, on hand-movement trials, *both* LIP and MIP neurons traced evidence accumulation. These findings suggest that parallel decision mechanisms exist in the parietal cortex. Furthermore, the very fact that two distinct brain regions can support similar computations indicates that the neural mechanisms underpinning decision-making may be more general than previously thought (de Lafuente et al., 2015).

When the decision and motor processes were dissociated, decision-related activity was still observed in the pre-motor regions of the brain (Bennur and Gold, 2011; de Lafuente et al., 2015). Under these circumstances, the oculomotor neurons continued to represent the sensory evidence for the decision but ceased to exhibit a deterministic, accumulation-to-threshold relationship with behaviour. These data reveal that LIP

neurons can be saccade-independent (Bennur and Gold, 2011; de Lafuente et al., 2015) and may have a general role in forging perceptual decisions that is linked to select features of the visual stimulus (Freedman and Assad, 2006; Bennur and Gold, 2011).

1.3.3 Necessity for Reciprocal Interactions between Primate and Human Work in Perceptual Decision-Making

The insights garnered from the monkey neurophysiological research described above has had a number of important implications for decision-making research in general. The studies convincingly demonstrate that it is possible to parse the constituent components of sensorimotor transformations and provide strong empirical support for a specific mechanistic model of the decision-making process. The body of work also elegantly demonstrated how a theoretical decision variable signal may be directly encoded in the firing rates of neurons in association cortex and facilitated a characterisation of the microcircuitry of perceptual decision-making that would have been impossible using non-invasive assays (Kelly and O'Connell, 2015). Importantly, it motivated an effort to identify equivalent mechanisms in the human brain using non-invasive recordings on a much more macroscopic scale (Philiastides et al., 2006; Philiastides and Sajda, 2006; Donner et al., 2009; O'Connell et al., 2012; Van Vugt et al., 2014). Given the significant difference in the resolution of invasive and non-invasive recording techniques, the correspondence, if any, between response patterns observed in single-unit recordings and those recorded from the scalp remains unclear (Philiastides et al., 2014). However, both levels of analysis are necessary to understand decision formation (Philiastides et al., 2014). For example, functional imaging and neurophysiological methods provide us with a picture of the entire brain that could not be achieved using single-cell recordings such that we can study perceptual decision-making at the systems level, explore simultaneously active processes at different levels of the sensorimotor system, and determine the role played by a wider network of brain regions in decision-making (e.g. the attentional network; Heekeren et al., 2008; Philiastides et al., 2014; Kelly and O'Connell, 2015)

On a more basic level, studying decision-making in humans is important as decision formation, even when based on the simplest of perceptions, may be fundamentally different in primates and humans. Humans may have evolved a more abstract decision-making network than monkeys to facilitate a more flexible link between decision and action (Heekeren et al., 2008; Kelly and O'Connell, 2015). Furthermore, it

is more feasible to interrogate the higher-order aspects of decision-making such as the speed-accuracy trade-off in humans than in monkeys, as they can be issued more complex instructions. In the proceeding sections, an overview will be provided of the contribution made by non-invasive assays such as functional imaging and neurophysiology (EEG and MEG) to our understanding of the neurobiology of perceptual decision-making.

1.3.4 Summary

A series of motion discrimination studies revealed that perceptual decisions that are tightly coupled with a motor response are encoded in pre-motor regions of the monkey brain, providing compelling support for the idea that perceptual decisions are forged within an intentional framework. However, it was unclear how these structures would contribute to the decision process in more complex behavioural scenarios where the decision was not tantamount to selecting a response. A series of single-unit recording studies revealed that even when the decision and motor processes were fully dissociated, decision-related activity was still observed in the pre-motor regions of the brain (Bennur and Gold, 2011; de Lafuente et al., 2015). In these studies, the oculomotor neurons continued to represent the sensory evidence for the decision but no longer exhibited a deterministic, accumulation-to-threshold relationship with behaviour. These findings indicate that perceptual decision-making and action selection are distinct neural processes that only appear to be inextricably linked in particular behavioural contexts. Furthermore, they reveal that LIP neurons can be saccade-independent (Bennur and Gold, 2011; de Lafuente et al., 2015) and may play a more general role in decision-making (Freedman and Assad, 2006; Bennur and Gold, 2011).

The progress in monkey neurophysiological research in isolating effector-selective neural decision variable signals motivated a search for equivalent mechanisms in the human brain using functional imaging, EEG and MEG. While non-invasive methods cannot characterise the neural mechanisms underpinning perceptual decision-making with the same level of detail as single-unit recordings; they provide an overview of the whole brain which makes it possible to explore multiple levels of the ‘sensorimotor and decision architecture simultaneously’ (Kelly and O’Connell, 2015). Exploring the neural substrates of decision-making in humans is important in its own right as decision-making may be markedly different for humans as they can be issued more complex instructions and higher-order aspects of decision-making can be studied.

1.4 Identifying Neural Correlates of Decision Formation in the Human Brain Using Functional Imaging-Based Approaches

A series of human brain imaging studies have attempted to establish a comprehensive map of the brain regions involved in decision formation (e.g. Pleger et al., 2006; Ploran et al., 2007; Heekeren et al., 2008; Ivanoff et al., 2008; Donner et al., 2009; Liu and Pleskac, 2011; Filimon et al., 2013). Much of this work has focused on determining whether decisions are directly formed within an intentional framework or if specific brain regions compute decisions in a domain-general fashion that is independent of motor planning. Functional magnetic resonance imaging (fMRI) is one of the most commonly used neuroimaging technique in this area; it measures changes in blood flow within the brain, thought to reflect the energy used by neighbouring cells, i.e., neuronal activity. FMRI has exceptional spatial resolution but has poor temporal resolution (~1 Hz) and is expensive, immobile, and noisy.

1.4.1 Identifying Candidate Sites of Decision Formation using FMRI

Animal neurophysiology has provided a wealth of evidence to suggest that decisions are formed within an ‘intentional framework’ whereby the regions that compute a perceptual decision reflect the particular motor requirements of the task (Gold and Shadlen, 2007; Shadlen and Kiani, 2013). However, the vast majority of complex decisions that we encounter in every-day life are not associated with a pre-defined response and it is unclear how an effector-selective decision mechanism would operate under such conditions. Many researchers have claimed that the dorsolateral prefrontal cortex may house an abstract decision variable signal that computes the decision independently of the response (Heekeren et al., 2004; Heekeren et al., 2006; Liu and Pleskac, 2011; Philiastides et al., 2011)

In an early event-related fMRI study, Heekeren et al. (2004) instructed participants to discriminate between greyscale images of faces and houses (see Fig 1.3). It was assumed that activation in a domain-general decision region should correlate with the difference between the output signals of face- and house- selective sensory regions and should exhibit a larger blood oxygen-level dependent (BOLD) response for easy relative to difficult discriminations on the basis that stronger sensory evidence should drive higher rates of neural firing. Numerous brain regions including the left posterior

portion of the dorsolateral prefrontal cortex, the posterior cingulate cortex and the superior frontal gyrus exhibited a greater BOLD response for easy relative to difficult discriminations. However, the activation in the left posterior portion of the dorsolateral prefrontal cortex was the only activation that also co-varied with the difference signal between face- and house- selective regions in the ventral temporal cortex (see Fig 1.3). Accordingly, it was concluded that this sub-region of the dorsolateral prefrontal cortex may be a critical cog in the domain-general perceptual decision-making network. This assertion was supported by a later study from the same group in which participants were cued prior to the onset of the stimulus to communicate the direction of the coherent motion with either a saccade or a button press (Heekeren et al., 2006). Irrespective of the modality of the decision reporting action, the decision was encoded in the dorsolateral prefrontal cortex.

Philiastides et al. (2011) went one step further and demonstrated that the relationship between the dorsolateral prefrontal cortex and domain-general perceptual decision-making may extend beyond a correlational link. Low frequency repetitive transcranial magnetic stimulation (1 Hz) was applied to the posterior portion of the dorsolateral prefrontal cortex as participants completed a protracted version of a face-versus-car categorisation task. The ‘virtual lesion’ disrupted the ongoing decision process as evidenced by reduced accuracy and increased reaction time in the stimulation condition relative to the sham condition (no stimulation). The behavioural effects were directly linked to a reduced drift rate in the diffusion model (Philiastides et al., 2011).

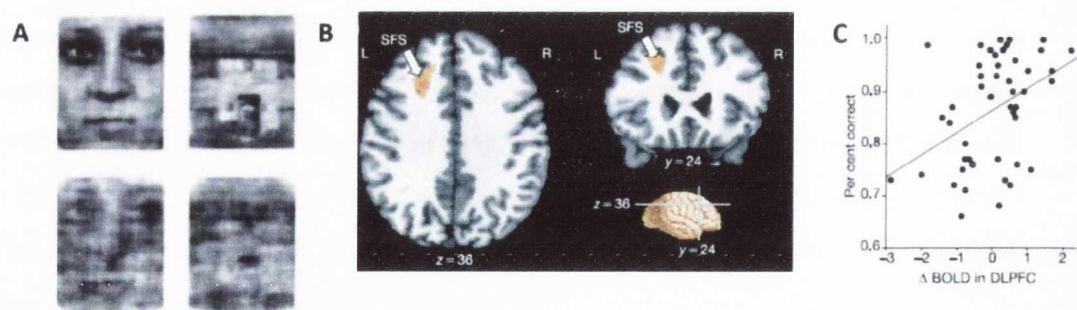


Figure 1.3: Domain-general perceptual decision-making.

A, In Heekeren et al. (2004), participants had to decide whether the image presented on screen was a face or a house; the images could either be easy or difficult to discriminate. **B**, The superior frontal sulcus (SFS), posterior to Brodmann’s area 8/9 in the mid-dorsolateral prefrontal cortex was identified as a possible site of domain-general decision

formation in the human brain. **C**, Task-related changes the superior frontal sulcus predicted task-performance. Adapted from Heekeren et al., (2004).

Other researchers also provided evidence that sub-regions of the dorsolateral prefrontal cortex may be implicated in domain-general decision-making (Ho et al., 2009; Liu and Pleskac, 2011; Filimon et al., 2013). Inconsistent with the assumptions of Heekeren et al. (2004) and Heekeren et al. (2006), Ho et al., (2009) predicted that a decision-encoding region should exhibit two critical properties: 1) a greater and more temporally extended BOLD response on difficult relative to easy trials and 2) a temporally delayed onset of the BOLD response on difficult relative to easy trials. With these assumptions in mind, Ho et al., (2009) highlighted a role for a sub-region of the right insula in domain-general decision-formation. The discrepancy in the two sub-regions of dorsolateral prefrontal cortex implicated in decision formation can likely be explained by the different classification criteria used in the two studies.

1.4.2 Disentangling Effector-Selective and Domain-General Evidence Accumulation using FRMI

Echoing the findings in monkeys, human perceptual decisions that are tightly coupled with a pre-defined effector are encoded in the effector-selective regions of the brain involved in the preparation of the decision-reporting action (Tosoni et al., 2008; Ho et al., 2009; Filimon et al., 2013). For example, Tosoni et al. (2008) trained participants to associate a visual stimulus (face or place) with a specific motor response (eye or hand-pointing movement). In this study, the authors concluded that the decision was encoded in the posterior parietal cortex, an effector-selective brain region involved in motor preparation as the task related activity in this region was modulated at the moment in which decisions were being formed by the level of sensory evidence, by the location of the target and by the sequel of the decision in the absence of useful sensory evidence (Tosoni et al., 2008).

It may be the case that the recruitment of brain regions external to the sensorimotor cortex in decision-making may be contingent on the degree to which the stimulus-response associations are conditioned (Ho et al., 2009). Accordingly, a very popular line of enquiry in neuroimaging research has been to manipulate the extent to which decision formation and motor preparation can occur in parallel, often on a trial-by-trial basis (Liu and Pleskac, 2011; Filimon et al., 2013). The main objective of this line

of work was to elucidate whether different neural systems compute decisions that are embodied and decisions that are implemented independently of the decision-reporting action. With this in mind, Liu and Pleskac (2011) hypothesised that the mode of evidence accumulation (sensory-selective versus effector-selective) used to form a decision may be context-dependent. Sensory-selective evidence accumulation was defined as integrating evidence for a specific stimulus feature such as the direction of coherent motion (Liu and Pleskac, 2011). The hypothesis was tested using a motion discrimination paradigm which participants performed with and without foreknowledge of the responding modality (saccade versus button press). It was assumed that a decision-encoding region would exhibit a larger BOLD response for difficult relative to easy discriminations. Irrespective of response modality, where participants did not have foreknowledge of the decision-reporting action, an fMRI signature of decision formation was observed in the anterior insula and the inferior frontal sulcus. Conversely, when the decision was mapped onto a particular motor response, the sensorimotor regions of the brain such as the frontal eye field and intraparietal sulcus appeared to house the decision process. Liu and Pleskac (2011) concluded that the extent to which the decision is embodied will govern the type of accumulation strategy that we use. We may use motor-selective evidence accumulation when the decision can be treated as an issue of action selection, but we may need to use more abstract, sensory-selective evidence accumulation when the decision is independent of the response (Liu and Pleskac, 2011).

Filimon et al. (2013) also demonstrated that motor-selective and domain-general decisions are differentially implemented in the human brain using data from a face-versus-house categorisation task which participants performed with and without foreknowledge of the modality of responding (saccade versus button press). Acknowledging the contradictory assumptions in the literature regarding the pattern of activation that a BOLD response should exhibit as a function of sensory evidence strength in a domain-general decision region, they simply assumed that it should exhibit increased effective connectivity with the regions of the brain encoding the sensory evidence for the decision prior to the onset of motor preparation (Filimon et al., 2013). The investigation revealed that a domain-general decision variable may be housed in the left inferior sulcus and in the intraparietal sulcus for effector-selective decisions (Filimon et al., 2013).

Tosoni et al. (2014) provided further support for the notion that motor-dependent and motor-independent neural signatures of evidence accumulation can be observed

within a single experimental design. Echoing their earlier work (Tosoni et al., 2008), arbitrary associations were trained between visual stimuli (male versus female face) and specific motor responses (saccade versus hand-pointing). However, this time the visual stimuli were gradually unmasked to maximise the temporal separation between decision formation and motor preparation. Motor-selective and motor-independent neural signatures of evidence accumulation were observed in the parietal reach region and the posterior intraparietal sulcus, respectively. However, the intraparietal sulcus was not labelled a domain-general decision-encoding region as it demonstrated spatial-selectivity for targets presented in the contralateral hemi-field (Tosoni et al., 2014).

Echoing the findings in monkey neurophysiology, fMRI investigations of decision-making using flexible stimulus-effector mapping have strongly challenged the generalisability of the intentional framework such that perceptual decisions only appear to be implemented within the sensorimotor network when the stimulus-response mappings are tightly coupled through extensive training and operant conditioning. However, the sensorimotor system is well positioned to make a critical contribution to the decision-making process as it can access information such as action costs that are imperative for choice selection. The sensorimotor system may communicate with the frontal or parietal regions of the brain to form a ‘distributed consensus’ about the choice at hand (Cisek, 2012; Tosoni et al., 2014).

1.4.3 Challenges to the FMRI Investigations of Perceptual Decision-Making

It is clear from this snapshot of the neuroimaging literature alone that there have been substantial inconsistencies in the number and location of brain regions that have been claimed to house decision variables in fMRI research (Heekeren et al., 2004; Heekeren et al., 2006; Pleger et al., 2006; Ploran et al., 2007; Ivanoff et al., 2008; Ho et al., 2009; Kayser et al., 2010; Liu and Pleskac, 2011; Filimon et al., 2013). As the limited temporal resolution of fMRI precludes direct observation of the characteristic build-to-threshold dynamics that define decision variable signals, neuroimaging studies often rely on assumptions about the activation patterns that a decision formation region should exhibit which has resulted in inconsistencies in the criteria used to classify decision-encoding regions across studies. The most popular approach to identifying a decision-region has been based on their relationship with trial difficulty (Heekeren et al., 2004; Heekeren et

al., 2006; Pleger et al., 2006; Liu and Pleskac, 2011). However, other studies have also applied alternative and additional criteria including a steeper build-to-threshold for stronger evidence (Ho et al., 2009) and increased effective connectivity between sensory and decision regions during decision formation (Filimon et al., 2013). As the decision dynamics cannot be directly traced using fMRI, it is impossible to determine whether these candidate structures actually compute the decision or whether they are simply relay stations that convert the output received from an abstract decision variable housed elsewhere in the brain into the appropriate motor response (Ho et al., 2009). Establishing how decision signals behave post-decision will be essential in order to inform the accurate predictions for fMRI research (Filimon et al., 2013; Kelly and O’Connell, 2015). This information can potentially be acquired using electrophysiology and is a central focus of Chapter 3 of the present thesis.

1.4.4 Summary

The search for neural signatures of evidence accumulation in fMRI research has produced significant inconsistencies in the number and location of brain regions that have been claimed to house decision variable signals. To name a few, the dorsolateral prefrontal cortex (Heekeren et al., 2004; Heekeren et al., 2006), posterior parietal cortex (Tosoni et al., 2008), intraparietal sulcus (Kayser et al., 2010; Liu and Pleskac, 2011), inferior frontal gyrus/sulcus (Liu and Pleskac, 2011; Filimon et al., 2013) and insula (Ho et al., 2009; Liu and Pleskac, 2011) have all been cited as candidate decision-encoding regions. The inconsistencies in the decision-making regions identified across studies is driven by the fact that the limited temporal resolution of fMRI precludes direct observations of the critical dynamics that define decision variable signals and so neuroimaging studies often invoke qualitative assumptions about the activation patterns that a decision formation region should exhibit. Determining the post-threshold dynamics of decision signals will be key to informing the accurate predictions for fMRI research in the future. Studies manipulating the extent to which decision formation and motor preparation could occur simultaneously revealed that motor-selective and domain-general neural signatures of evidence accumulation could be isolated within a single experimental design. Effector-selective evidence accumulation appears to be employed when the decision can be treated as an issue of action selection, however; more domain-general evidence accumulation is used when the decision is independent of action.

1.5 Identifying Neural Correlates of Decision Formation in the Human Brain Using EEG/MEG-Based Approaches

Perceptual decision-making in the context of sequential sampling has also been explored extensively using neurophysiological (EEG and MEG) techniques. As EEG was the method of choice in all of the studies presented in this thesis, its functional basis is detailed very briefly in the proceeding section.

1.5.1 Electroencephalography

EEG reflects the summed electrical activities of populations of pyramidal neurons, with some input from glial cells (da Silva, 2009). Pyramidal neurons are excitatory in nature and their activity can produce electrical and magnetic fields that are measurable via electrodes applied to the scalp (da Silva, 2009). Electrical brain activity can be analysed from a number of different perspectives. Stimulus, motor, or cognitive events induce changes in the voltage of the EEG which are known as event-related potentials (ERPs). The traditional ERP technique has exceptional temporal but, poor spatial resolution the implications of which for ERP research exploring decision-making are discussed in greater detail in section 1.5.2 below. EEG can also provide useful information about the dynamics of brain oscillations. EEG signals can be decomposed into their time-frequency representations to measure changes in signal power and phase that are related to sensory, cognitive and motor events. Neuronal oscillations are typically classified into five distinct frequency bands according to the natural frequencies of the brain and each individual frequency band has been linked to a specific cognitive process (e.g. Başar et al., 2001; da Silva, 2013): delta (1–3 Hz), theta (3–8 Hz), alpha (8–14 Hz), beta (14–30 Hz) and gamma (30–70 Hz).

MEG has also been extensively used to deconstruct the neural underpinnings of perceptual decision-making in the human brain (Donner et al., 2009; de Lange et al., 2013; Van Vugt et al., 2014). MEG is a non-invasive technique that is very similar to EEG in that it measures the magnetic aspect of the electric fields elicited by neurons (da Silva, 2013). As the skull is transparent to magnetism, the magnetic fields are not blurred by the skull which gives it a superior spatial resolution to EEG (Luck, 2014). However, MEG is more expensive than EEG and is much less portable (Luck, 2014).

1.5.2 EEG Studies of Perceptual Decision-Making

Human neurophysiological research exploring the perceptual decision-making process commenced over five decades ago, long before the sequential sampling models became a key player in the field. One specific component of the ERP, the centro-parietal P300 ('P3' or P3b') was functionally associated with decision-making and a series of early ERP studies demonstrated that its characteristics are consistent with the theoretical decision variable as described by the sequential sampling models. However, at that time a direct link was not forged between the P300 and the sequential sampling models of decision-making. The present section will provide a brief overview of the key studies which intimated that the P300 may reflect a neural signature of evidence accumulation.

Using an auditory signal detection task in which participants had to decide whether or not an acoustic signal at threshold level had been added to continuous background noise, Hillyard et al. (1971) showed that the P300 was closely related to the participant's perceptual reports. Most notably, the P300 was only elicited by task-relevant stimuli that required a decision such that it was extinguished when a passive version of the task comprised of the same stimuli was employed. Furthermore, a greater amplitude P300 was observed for detected stimuli (hits) relative to misses, errors, and false alarms (Hillyard et al., 1971). The relationship between the P300 and goal-relevance was probed further by Rohrbaugh et al. (1974) using a visual target detection task which required the participants to temporally integrate visual information. More specifically, two identical grids of illuminated squares could be intercalated to yield either horizontal or vertical stripes. The two stimuli were presented sequentially but were separated by a variable inter-stimulus interval and the orientation of the stripe could not be determined until the second stimulus appeared. In this case, greater P300 amplitude was observed in response to the second stimulus which permitted the choice to be made, providing further support for the idea that the P300 is only elicited by task-relevant stimuli that necessitate a decision. Rohrbaugh et al. (1974) surmised that the P300 may reflect a poststimulus process such as decision-making. On a semantic categorisation task, Kutas et al. (1977) demonstrated that the peak latency of the P300 was tightly linked to reaction time such that the component was thought to reflect stimulus evaluation time that is independent of the response. McCarthy and Donchin (1981) later provided support for the idea that the latency of the P300 is determined by processes involved in stimulus evaluation or categorisation. Their data also revealed that reaction time was affected by

both stimulus discriminability and stimulus-response compatibility, but the peak latency of the P300 was only affected by stimulus discriminability. This observation added further weight to the idea that the P300 largely carries out its role independently of response selection and execution.

A number of more recent studies have also suggested that the P300 may in some way be related to the perceptual decision-making process. For example, Vanrullen and Thorpe (2001) employed an animals-versus-vehicles categorisation task to show that visual categorisation of a naturalistic scene involves two distinct mechanisms with different time courses. An early component (75-80 ms) represented the visual category of the stimulus, but did not have an influence on- or correlate with the subject's choice behaviour until much later on the trial (150 ms). Most notably, the authors concluded that the later 'P300-like' component was a category-independent correlate of the decision such that it represented decision-related activity (Vanrullen and Thorpe, 2001).

Verleger et al. (2005) assessed whether the P300 may be directly related to a decision process that mediates between perceptual analysis and response initiation. The authors hypothesised that if the P300 does indeed reflect the intermediate stage between perceptual processing and response preparation, that P300 amplitudes should be comparable in the stimulus- and response-aligned waveforms. This should be the case irrespective of reaction time and that P300 latencies would vary across reaction time in both the stimulus- and the response-aligned signals (Verleger et al., 2005). An analysis of ERP components elicited by both visual and auditory stimuli confirmed each of these predictions. The authors concluded that the P300 may have a role in monitoring whether the decision to classify a stimulus is appropriately converted into adaptive action (Verleger et al., 2005).

While this body of work was successful in associating the P300 with perceptual decision-making, it failed to link the signal to a specific neural mechanism in the brain. It follows that no consensus regarding its precise functional significance emerged and that the dominant accounts of the signal are primarily descriptive rather than mechanistic. There are a number of important factors which may have contributed to this critical link not being established that merit further discussion. Firstly, early human neurophysiologists exploring perceptual decision-making conceived of the P300 as a unitary event rather than a dynamic process that gradually evolves over time to directly impact upon perceptual performance. Therefore, there has been a strong disconnect in how human and monkey neurophysiologists considered the neural underpinnings of the

perceptual decision-making process and this explains why the dynamical properties central to the function of a decision variable, such as evidence-dependent build-up rate and a threshold-crossing relationship with reaction time, went unexplored in P300 research.

Furthermore, although the traditional ERP technique, in theory, has the requisite temporal resolution to resolve the essential dynamical properties of a decision variable such that it has long been hailed as a promising means to differentiate the distinct stages underpinning sensorimotor transformations it is especially susceptible to the issues posed by global signal summation (Hillyard & Kutas, 1983). Global signal summation refers to the fact that signals that are simultaneously active will also overlap spatially at the level of the task making them difficult to disentangle and measure independently. This problem is exacerbated by the traditional use in ERP paradigms (as described above) of punctate stimuli whose sudden onset results in a rapid and complex pattern of scalp signals reflecting the distinct stages of sensory, perceptual, and motor processing (Van Rullen & Thorpe, 2001; Philiastides et al., 2006; Philiastides & Sajda, 2006). Therefore, the complex spatio-temporal pattern of scalp signals evoked in traditional ERP research obscure the more gradually evolving processes relevant to decision formation. As discussed in the sections below, the more recent generation of neurophysiologists have tried to integrate methods from both animal neurophysiology and computational neuroscience to not only overcome the global summation problem but also to isolate signals that can be unambiguously identified with specific neural mechanisms.

The growing movement towards using complementary approaches to investigate decision-making is exemplified very nicely in a series of studies carried out by Philiastides and colleagues (Philiastides et al., 2006; Philiastides and Sajda, 2006). In these studies, a traditional ERP technique was combined with a machine learning technique to obtain a spatiotemporal pattern of activity that discriminates between stimulus categories (face-versus-car) and between levels of difficulty (manipulated by the percentage phase coherence of the images; Philiastides and Sajda, 2006). On the face-versus-house perceptual categorisation task, two components that were predictive of decision accuracy were identified: an early (170 ms) and late (300 ms) component that were thought to reflect early perceptual processing and post-sensory evidence, respectively.

In a follow-up study using the same behavioural task, a cortical correlate of task difficulty (D220) intermediate to the early and late component was identified and the

functional significance of all three components was interrogated further in a second experiment. In the new paradigm, participants were cued at trial-onset to either discriminate between the faces and cars or to categorise the image based on its colour (green or red; Philiastides et al., 2006). While the early sensory component was present on all trials, the two later components were absent on the colour discrimination trials; owing possibly to the simplicity of the decision (Philiastides et al., 2006). This observation was taken as further evidence that the N170 component represented an early perceptual process that had no direct relationship to the eventual decision and that the D220 component represented a top-down influence on decision-making (owing to that fact that it was absent during an easy colour discrimination; Philiastides et al., 2006). While the authors explicitly stated that the late component was unlikely to represent the process of evidence accumulation to threshold, they proceeded to discuss it in light of the drift diffusion model. More specifically, they acknowledged that it was highly predictive of behavioural accuracy; it shifted in time as a function of decision difficulty and that its duration increased when decision difficulty increased. Additionally, it was strongly correlated with both reaction time variance and the drift rates computed in their diffusion model simulations (Philiastides et al., 2014). Based on the totality of these observations, it was intimated that the late component corresponded to the mean drift rate in a diffusion model and that it represented ‘post-sensory evidence that is fed into the diffusion process that ultimately determines the decision’ (Philiastides et al., 2006). While this work certainly provided valuable insights into the electrophysiological correlates of decision formation, the validity of the findings may be undermined by the fact that a machine learning approach was used. This point is discussed in greater detail in section 1.5.5 below.

1.5.3 EEG-Informed fMRI Approach in Perceptual Decision-Making Research

In another elegant example of how complementary methodologies can be used to investigate perceptual decision-making, Philiastides and Sajda (2007) used the information derived from their previous EEG studies to guide the analysis of functional imaging data collected using the same behavioural task. This EEG-informed fMRI approach enabled them to establish cortical regions that correlated with each of the three EEG components and in doing so they demonstrated that the processes underpinning

perceptual decision-making may occur within a highly distributed neural network (Philiastides and Sajda, 2007; see Fig. 1.4).

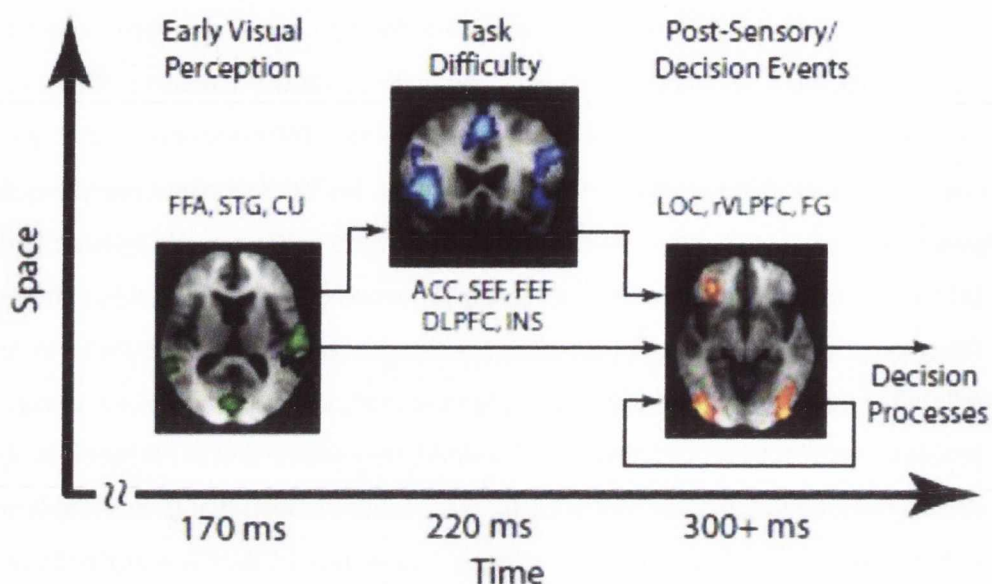


Figure 1.4: Perceptual decision-making within a distributed neural network.

In a series of studies conducted by Philiastides and colleagues, an early, difficulty, and late EEG component thought to be related to visual processing, a top-down attentional mechanism modulated by task difficulty, and post-sensory evaluation were identified (Philiastides et al., 2006; Philiastides and Sajda, 2006). An EEG-informed fMRI analysis was used to locate cortical regions that correlated with each of the three components and revealed that the processes underpinning perceptual decision-making may occur within a highly distributed neural network. Taken from Philiastides and Sajda (2007).

1.5.4 Model-Based Approaches to the Analysis of EEG and MEG Data in Perceptual Decision-Making Research

Model-based approaches have also been applied to neurophysiological data to explore the constituent components of the perceptual decision-making process. Van Vugt et al. (2014) used a combined modelling-electrophysiological approach to explore whether oscillatory activity in the EEG may encode evidence accumulation for motion discrimination decisions. A generalised linear model was developed in which the expected integration dynamics were correlated with the EEG time series to identify the electrodes that displayed a pattern of activation predicted by the drift diffusion model (Van Vugt et al., 2014). The approach was very much akin to that used in functional

imaging research to locate voxels exhibiting a hypothesised pattern of activation such as a greater BOLD response when sensory evidence is strong relative to when it is weak (Van Vugt et al., 2014). The analysis revealed that evidence integration dynamics may be reflected in oscillatory activity in the theta frequency range (4–9 Hz) measured over parietal electrodes. While the predicted evidence accumulation dynamics also correlated with activity in other frequency ranges, a strong relationship was only observed between the decreases in theta-band activity and individual differences in the parameters of the drift diffusion model fitted to individual's behavioural data (Van Vugt et al., 2014).

Model-based approaches have also been taken to the analysis of MEG data. For example, Hunt et al. (2012) conducted a model-based analysis of MEG data to determine the mechanisms underlying cortical activity during value-guided choices. More specifically, they analysed a biophysically plausible network model of decision-making to generate predictions about the expected temporal dynamics of neural signals that transform value-related input into a categorical choice (Hunt et al., 2012). The model predictions were subsequently applied to source-reconstructed MEG which led to the identification of signals in the parietal and prefrontal regions of the brain that matched well with the model such they were attributed a role in computing value comparisons (Hunt et al., 2012). Value correlates that matched poorly with the biophysical model were identified in other brain regions and these signals were thought to play a role in distinct computational processes that co-vary with value (Hunt et al., 2012). The authors highlighted that the application of this powerful biophysical modelling approach may not be limited to decision-making research and that it may be used to investigate other cognitive operations such as working memory.

1.5.5 Challenges to Model-Based EEG Analytic Approaches

While model-based and machine learning approaches to the analysis of EEG and MEG data have made a critical contribution to our understanding of the how decisions are forged in the brain, the approaches are subject to a number of significant limitations. For example, model-based analysis approaches rely on certain models and the assumptions on which they are based. It follows that the validity of model-based research is contingent on the validity of the model itself. In cognitive neuroscience the validity of a given model is typically assessed based on its capacity to provide a good account of the behavioural data. However, it can be difficult to determine how unique the model is in its goodness

of fit and also whether the model accurately reflects the underlying neural processes. As is the case in fMRI research, model-based analyses of neural data also rely heavily on qualitative assumptions about the processes and signals under investigation. In animal neurophysiology decision variable signals can be directly traced using single-unit recordings. However, human decision-making research relies on non-invasive techniques that do not allow us to directly probe the signals and so many of the predictions of decision-making models are assumed rather than actually empirically tested. Therefore, there is a strong disconnect between the model-based analytic approaches used in human research and the direct neural signal observations used in animal neurophysiology.

1.5.6 Summary

Perceptual decision-making from a sequential sampling perspective has also been explored comprehensively using EEG and MEG. While these techniques are not limited by poor temporal resolution, EEG is subject to global signal summation which makes it difficult to disentangle temporally overlapping but functionally distinct signals on the scalp. It follows that complex data processing techniques and transformations are often adopted in EEG research to overcome this issue. One such machine learning approach led to the identification of three EEG components relevant to the perceptual decision-making process. A late component was not explicitly linked to a decision variable but was considered in light of the mathematical models of decision-making such that it was thought to be analogous to the mean drift rate in a diffusion model. An EEG-informed fMRI analysis located the cortical regions that correlated with each of the three components and revealed that the processes underpinning perceptual decision-making may occur within a highly distributed neural network. Model-based approaches have also been successfully applied to neurophysiological data to identify the oscillatory activity that best captures evidence accumulation and to isolate the mechanisms underpinning cortical activity during value-guided choices. While model-based and machine learning analytic techniques have taught us a lot about the decision-making machinery in the brain, they are also subject to a number of significant limitations. For example, the validity of a model-based analytic approach is dependent of the validity of the model itself and it is unclear whether a given model accurately captures the underlying neural processes. Many of the predictions of decision-making models are assumed as opposed to tested as we

cannot directly observe the neural decision signals in the human brain. This reduces the extent to which concrete links can be made between animal and human neurophysiology.

1.6 Directly Tracing the Decision Process in Humans

As previously mentioned, the single-unit recordings employed in animal neurophysiology enable researchers to directly trace and probe the neural signatures of evidence accumulation. Of course we do not have this luxury when exploring perceptual decision-making in the human brain and many fMRI and EEG analysis techniques rely on qualitative assumptions about the behaviour of the underlying neural signals. The inability to directly monitor decision variable signals in the human brain has prevented us from bridging between the advances made in animal neurophysiology to the study of decision-making in humans. The present section details some recent basic paradigm innovations that have made it possible to continuously monitor the three stages of perceptual decision-making in discrete and freely evolving electrical brain signals. Additionally, the functional characteristics of these electrical brain signals that can be convincingly linked to the neural mechanisms necessary for simple perceptual decisions are discussed in greater detail.

As is the case in animal neurophysiology many studies investigating perceptual decision-making in humans use the classic random-dot motion task. As the random-dot motion paradigm relies on protracted sequential sampling it is ideally-suited to studying perceptual decision-making (Newsome et al., 1989; Britten et al., 1992). Furthermore, it is the paradigm for which the strongest data exist and was critical to the successful identification of neural signals that perform the role of a decision variable in monkeys (Newsome et al., 1989; Gold and Shadlen, 2001; Shadlen and Newsome, 2001). A variant of the random-dot motion task was used in a ground-breaking MEG study by Donner et al. (2009) which showed for the first time that it was possible to directly trace decision-related activity in humans. More specifically, Donner et al. (2009) isolated build-to-threshold dynamics in lateralised beta-band activity (12–36 Hz) which indexed the emerging motor plan associated with a perceptual decision (Donner et al., 2009). Here, participants searched for coherent motion embedded in random dot motion that was only present on one half of trials. The perceptual report was made following a delay period which was designed to disentangle the neural activity associated with motor preparation and response execution (Donner et al., 2009). Analysis indicated that oscillatory activity

in the gamma frequency range (64–100 Hz) in the motion-sensitive, visual middle temporal area indexed the strength of the sensory evidence for the decision. While lateralised beta-band activity displayed a choice-predictive, gradual-build up during stimulus viewing that reflected the temporal integral of the gamma-band activity in the middle temporal area. These data were consistent with the idea that lateralised beta-band activity accumulated the evidence passed on by sensory cortex towards a motor plan for the decision or, at the very least, that motor preparation in primary motor cortex and dorsal premotor cortex is driven by the outcome of a temporal integration process housed elsewhere in the brain (Donner et al., 2009).

In an MEG study de Lange et al. (2013) probed whether or not choice-selective motor signals are affected by prior expectations during a visual motion discrimination task. Participants completed a variant of the random dot motion task in which a cue was presented at trial-onset. The cue was either predictive or non-predictive (neutral) of the upcoming direction of coherent motion (de Lange et al., 2013). It was shown that inducing prior expectations about the upcoming motion direction not only biased the participant's perceptual performance, they also biased choice-selective motor cortical oscillations in the 8-30 Hz frequency range prior to the onset of the visual stimulus. Given that the bias manifested itself pre-stimulus (prior to the onset of evidence accumulation), it was hypothesised that inducing prior expectations may affect the decision process by modulating the starting-point of evidence integration (de Lange et al., 2013). Interestingly, on neutral trials where participants did not receive any information about the upcoming motion direction, spontaneous biases in choice-selective activity were observed over motor cortex. These spontaneous biases were at least in part driven by the choice on the previous trial (de Lange et al., 2013). Finally, de Lange et al. (2013) demonstrated that the build-up rate of the response-aligned lateralised beta signal scaled with the strength of the motion coherence lending further support to the idea that these choice-selective motor signals can be equated with motor-selective decision variable signals.

This MEG work was the first to analyse freely-evolving brain signals using an approach borrowed from monkey neurophysiology and it represented an important first step in bridging the gap between animal and human decision-making research. Importantly, the studies revealed parallels between the decision-making machinery in the

human and monkey brains. Echoing the findings in monkey neurophysiology, the MEG studies demonstrated that motor-selective decision signals in the human brain trace the evidence accumulation process when the decision can be converted into an emerging motor plan. Additionally, motor-selective decision signals exhibit the same choice-predictive, build-to-threshold dynamics in both species.

1.6.1 Paradigm Innovations Enabling Parallel Tracking of Sensory, Decision and Motor Signals in EEG

Recently, two EEG studies implemented basic paradigm innovations that made it possible to continuously monitor the three stages of perceptual decision-making in discrete and freely evolving electrical brain signals (O'Connell et al., 2012; Kelly and O'Connell, 2013). Instead of the discrete, sudden-onset stimuli typically used in ERP research, the targets in the studies were defined by a seamless or gradual change in a single feature (e.g. direction of coherent motion) of a continuously presented stimulus (random dot motion kinetogram). This approach eliminated the complex pattern of early transient sensory evoked potentials typically elicited by discrete stimuli and resulted in a long decision process that could be traced from evidence onset to response execution (O'Connell et al., 2012; Kelly and O'Connell, 2013). Secondly, the use of a unimanual button-press as the decision-reporting response provided a well-established neural metric of lateralised motor preparation in the form of the lateralised readiness potential (LRP; Coles et al., 1988) and β -band activity (Pfurtscheller and Da Silva, 1999). The design innovations were implemented on two separate tasks: a gradual-change detection task (O'Connell et al., 2012) and a two-alternative motion discrimination task (Kelly and O'Connell, 2013).

1.6.2 Tracing the Three Stages of Perceptual Decision-Making in EEG

In the first of these studies, participants continuously monitored an annular visual pattern that flickered at a high frequency and were instructed to detect and report a gradual, linear reduction in contrast using a right-hand button press (see Fig. 1.5A). The steady-state visual evoked potential (SSVEP; Di Russo et al., 2007) elicited by the flicker represented the sensory signal and provided a 'neural read' out of the sensory encoding for the decision while left-hemisphere beta provided a neural signature of lateralised motor preparation (O'Connell et al., 2012; see Fig. 1.5). With well-defined neural signatures of

sensory encoding and decision formation identified in the EEG, it was possible to parse out and directly trace decision formation from the onset of evidence accumulation to response execution via a centro-parietal positive potential (CPP). The CPP exhibited a gradual build-up that corresponded to the temporal integral of the SSVEP trace, and reliably reached a fixed amplitude immediately prior to response execution, consistent with an action-triggering threshold effect. Importantly, the build-up rate and peak latency of the CPP precisely accounted for the timing and accuracy of the perceptual reports across trials (see Fig. 1.5C). Additional paradigm manipulations revealed that the CPP could be disrupted mid-flight during decision formation by transient perturbations in the evidence and that it plays a domain-general in decision formation. It displayed the same dynamics irrespective of the sensory (auditory versus visual) or motor requirements of the task (counting versus button-press; O'Connell et al., 2012). Left-hemisphere beta also exhibited the defining features of a neural decision variable signal: a gradual-build with incoming sensory evidence and a boundary-crossing effect that precisely predicted the timing and accuracy of the perceptual reports (see Fig. 1.5C). Although left-hemisphere beta and the CPP shared these critical characteristics they differed in one important way. When the necessity for an overt motor response (button-press) was removed, left-hemisphere beta ceased to encode a decision variable, suggesting that this motor-selective signal does not play a general role in decision formation (O'Connell et al., 2012).

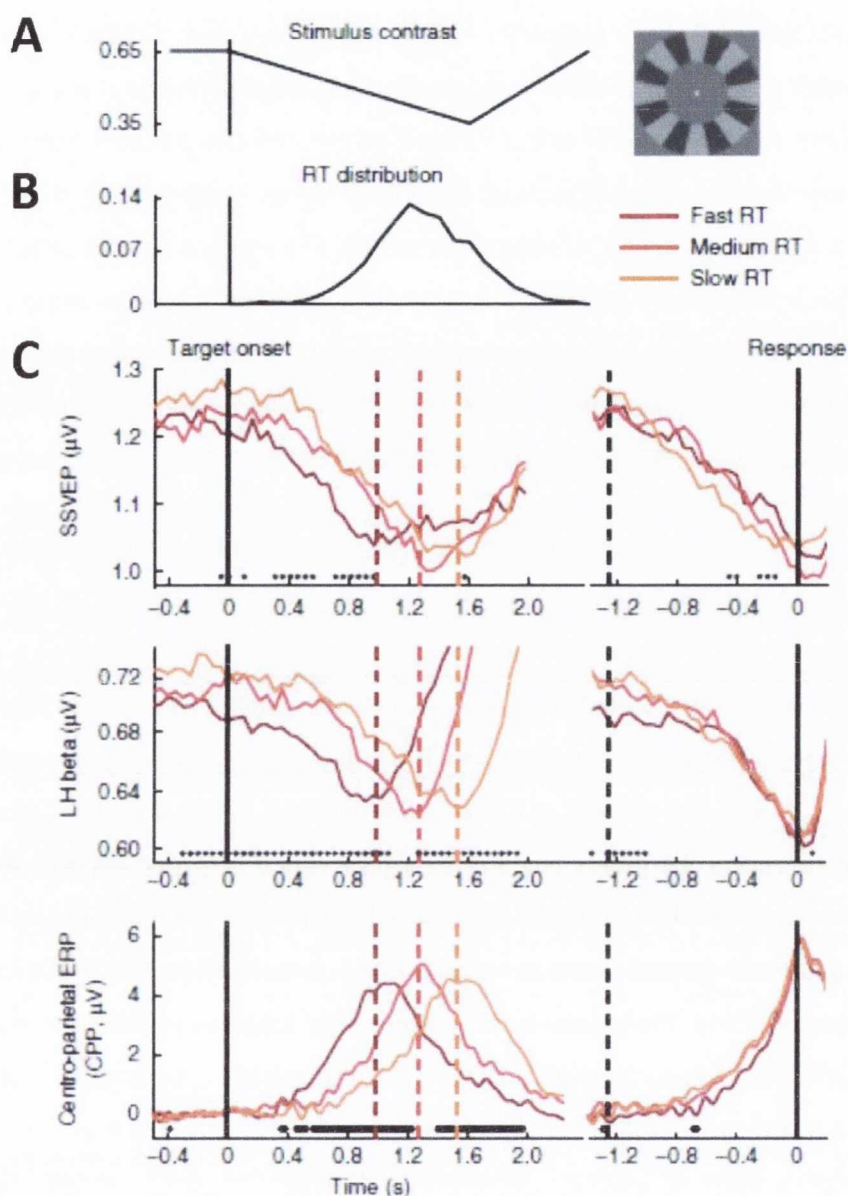


Figure 1.5: Tracing the three stages of perceptual decision-making in EEG.

A, Participants continuously monitored a flickering visual pattern and had to detect intermittent targets defined by a gradual, linear decrease in intensity. **B**, Grand average reaction time distribution. The single-trial EEG data were sorted and divided into three equally-sized reaction time bins. **C**, SSVEP (sensory signal), left-hemisphere β -band activity (motor signal) and the centro-parietal positivity potential (CPP; decision variable signal) plotted as a function of reaction time in the stimulus- (left) and the response-aligned (right) waveforms. Taken from O'Connell et al. (2012).

Kelly and O'Connell (2013) extended this work using a continuous version of the random dot motion paradigm. As in the original study (O'Connell et al., 2012), transient

sensory deflections at evidence onset were eliminated by introducing a seamless transition from incoherent to coherent motion (target onset). Here, participants were instructed to use their left hand to indicate leftward motion and their right hand to indicate rightward motion so that lateralised motor preparation could be captured in the LRP signal (Coles et al., 1988). Kelly and O'Connell (2013) demonstrated that the CPP not only exhibited a deterministic, accumulation-to-bound relationship to motion discrimination decisions but that the build-up rate of the signal scaled with the strength of the sensory evidence (motion coherence); consistent with the principle of temporal integration at the heart of the sequential sampling framework.

The LRP demonstrated the same accumulation-to-bound dynamics as the CPP including a similar dependence of build-up rate on sensory evidence strength. (Kelly & O'Connell, 2013) As the LRP provided a measure of limb-selective motor preparation that was on the same temporal scale as the domain-general CPP, it was possible to monitor the two signals in parallel to determine the sequence of processing in perceptual decision-making. It was shown that evidence accumulation in the abstract signal significantly preceded that in the motor preparation signal which provided support for the idea that decision variables housed in the effector-selective regions may be the recipients of input from a domain-general decision variable that is housed elsewhere in the brain (Kelly and O'Connell, 2013). Furthermore, the considerable build-up observed in the LRP prior to the CPP reaching a decision criterion argued against a hierarchical interpretation of decision-making (Sternberg, 1969) and provided support for the idea that there is a continuous flow of sensory information through the motor system during decision formation (Resulaj et al., 2009). Rather curiously, all research to date indicates that the CPP and LRP are both evidence accumulation signals that play the same role in decision-making. However, it would be uneconomical for the brain to house two signals that carry out the exact same function in cognition. Perhaps there are additional important functional dissociations between the neural signatures of evidence accumulation that have yet to be discovered.

On both the gradual detection and motion discrimination tasks, the response-aligned decision signal accumulated sensory evidence to a stereotyped threshold, consistent with predictions drawn from the mathematical models of perceptual decision-making and mirroring observations in monkey neurophysiology (O'Connell et al., 2012;

Kelly and O'Connell, 2013). The result was not replicated by Philiastides et al. (2014) who took a combined modelling-electrophysiological approach to the analysis of data collected on a face-versus-car perceptual categorisation task with four different levels of sensory evidence strength (manipulated by the percentage phase coherence of each image). Similar to previous studies from the same group, a machine learning approach was used to obtain a spatiotemporal of activity that discriminates between the highest and lowest levels of sensory evidence in the stimulus- and response-aligned waveforms (Philiastides et al., 2006; Philiastides and Sajda, 2006; Philiastides et al., 2014). In this study, the stimulus-aligned component exhibited a gradual-build-up rate that scaled with the strength of sensory evidence (Philiastides et al., 2014). However, unexpectedly the response-aligned component continued to co-vary positively with the strength of sensory evidence and did not reach a stereotyped amplitude at decision commitment (Philiastides et al., 2014). Echoing the analysis approach taken by Kelly and O'Connell (2013) they subsequently converted the data to current source density and still found no convergence at a common boundary. An additional regression analysis with the impact of sensory evidence factored out indicated that while single-trial component amplitude was only weakly correlated with the rate of evidence accumulation it reliably and independently predicted choice-accuracy. Based on this observation, the authors concluded that component amplitude at choice commitment may represent the effect of post-sensory, decision signals such as those related to decision confidence (Philiastides et al., 2014).

Philiastides et al. (2014) suggested that the boundary-crossing effect observed in Kelly and O'Connell (2013) may have been task specific. In particular, they highlighted that the paradigm could be considered a departure from those typically used to study evidence accumulation as most tasks only include a discrimination component as opposed to a detection *and* a discrimination component (detect coherent motion embedded in the incoherent motion and discriminate the direction of the coherent motion; Philiastides et al., 2014). It was concluded that the combined detection and discrimination aspect of the paradigm may have resulted in additional cognitive processes being recruited, leading to the stereotyped amplitude at decision commitment (Philiastides et al., 2014). However, the lack of boundary-crossing effect in the Philiastides et al. (2014) work may have been driven by a number of additional critical factors. Firstly, it may have been obscured by the 0.5 Hz high-pass filter applied to the data. High-pass filtering would have attenuated the signal amplitude and this is particularly pertinent here as the attenuation would have

been even more pronounced for a longer latency component such as the CPP. Additionally, as a machine-learning approach was used to isolate the decision-related component, it is likely that this component also captured decision-correlated signals on the scalp other than the CPP. Finally, they used discrete trials with a relatively short deadline for responding such that subjects may have implemented a ‘collapsing bound’ to ensure that their response was made prior to the deadline. A collapsing bound strategy would not have been possible in the continuous paradigms used by O’Connell et al. (2012) and Kelly and O’Connell (2013) in which the timing of evidence onset was completely unpredictable and in which there could be long delays (>10 seconds) between targets. These issues are discussed in further detail in Chapter 5. Nevertheless, the above work highlights that there is much still to be learned about how these distinct neural signals behave under different experimental conditions.

Philiastides et al. (2014) proposed that the CPP may be linked to decision confidence and indeed an alternative functional interpretation of the CPP could be that rather than directly encoding the decision, it encodes decision confidence with builds in parallel to the integrated evidence (Urai and Pfeffer, 2014). However, the very fact that the CPP reaches a fixed amplitude immediately prior to response execution, irrespective of sensory evidence strength and reaction time, appears inconsistent with this interpretation as these factors are known to have a systematic effect on decision confidence (Kiani and Shadlen, 2009; Yeung and Summerfield, 2012). Future empirical investigations will need to address the issues raised by Philiastides et al. (2014) and Urai and Pfeffer (2014) and indeed this is discussed in greater detail in Chapter 5.

Finally, it is important to note that the CPP’s complete independence from response preparation and execution appears to be a truly unique feature of the signal and a single-unit equivalent of the CPP has yet to be discovered in animal neurophysiology. Although, not addressed in the present thesis, this is an important outstanding question that merits further investigation.

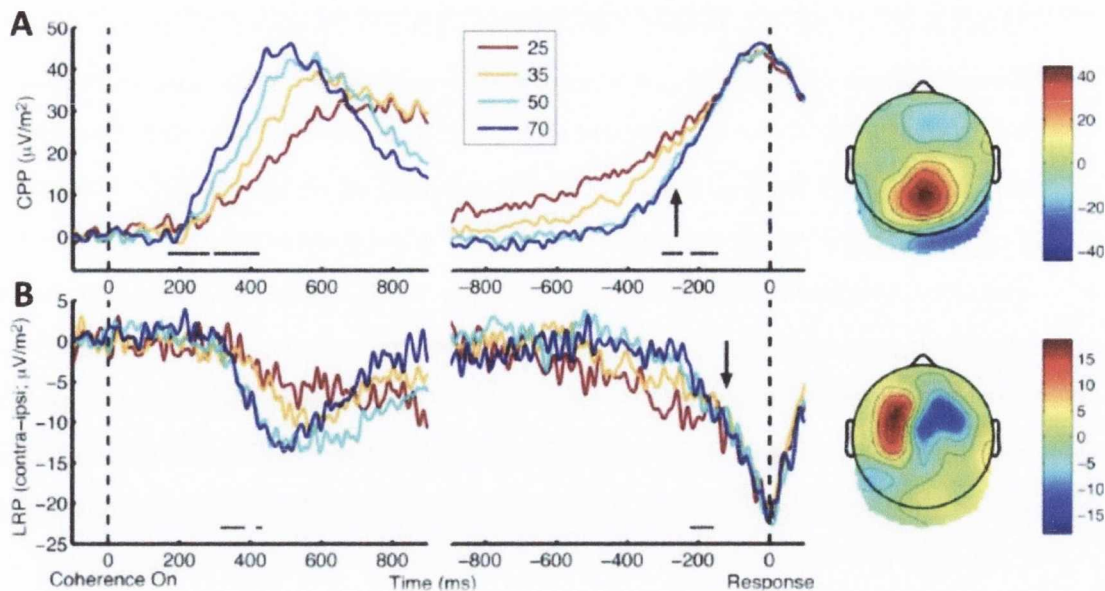


Figure 1.6: Abstract and effector-selective neural decision variable signals.

A, CPP waveforms aligned to stimulus onset (left), response execution (middle) and signal scalp topography (colour bar represents signal amplitude, right). **B**, LRP waveforms aligned to stimulus onset (left), response execution (middle) and scalp topography of the difference between left and right motion trials at response execution. Both the abstract and effector-selective decision variable signals exhibited the defining features of a theoretical decision variable signal predicted by the sequential sampling models. The arrows indicate the moment at which each signal reached half of its peak amplitude (signal onset) and reveal that evidence accumulation in the domain-general CPP reliably preceded that in the effector-selective LRP. This suggested that the CPP may serve as an intermediate between sensory encoding and response execution. Taken from Kelly and O'Connell (2013).

1.6.3 Functional Equivalence of the CPP and P300

The P300 component has arguably been the single most intensively studied human brain signal across a five-decade period. There are two primary reasons why this particular signal has attracted such enduring interest. The first is that it is elicited by virtually all cognitive tasks and covaries closely with performance within and across subjects. The second is that it is highly sensitive to a wide variety of brain disorders. For example, it provides one of the most robust electrophysiological indices of cognitive aging and dementia (Polich et al., 1990; Santosh et al., 1994; Mavrogiorgou et al., 2002; Prox et al., 2007; Verleger et al., 2013). While these features clearly render the P300 a major signal

of interest, to date its overall contribution to our understanding of the normal and abnormal brain has been very limited because its precise functional significance has never been established. Numerous explanatory accounts have been proposed over the years, several of which have achieved dominance within the field, but none have received conclusive empirical validation. For example, the P300 has been variously linked to the encoding of stimulus significance (Kutas et al., 1977), decision confidence (Hillyard et al., 1971; Squires et al., 1973), uncertainty or surprise (Duncan-Johnson and Donchin, 1977; Mars et al., 2008), to playing a role in context updating (Coles et al., 1988), neuroinhibition (Polich, 2007), event-categorisation (Kok, 2001), orienting and response potentiation (Nieuwenhuis et al., 2005; Nieuwenhuis et al., 2011), and context closure (Verleger, 1988).

It has been noted in the literature that the P300 bears a striking resemblance to the recently discovered CPP, in that they are both goal-relevant, positive deflections that reach a stereotyped zenith at response execution (O'Connell et al., 2012) and that a strong correlation exists between their topographic distributions and peak amplitudes across subjects (O'Connell et al., 2012; see Fig. 1.7). The considerable shared properties of the two components hint that the P300 may also reflect a dynamically evolving neural signature of decision formation and indeed this is not the first time that the P300 has been functionally linked to decision-making. As discussed in section 1.5.2, from the advent of its discovery, the P300 was linked to decision-making (Sutton et al., 1965) as it was elicited solely by task-relevant stimuli that necessitated a decision (Sutton et al., 1965; Hillyard et al., 1971; Rohrbaugh et al., 1974), it was larger for detected versus undetected stimuli (Hillyard et al., 1971); its peak latency varied very closely with reaction time (Kutas et al., 1977; McCarthy and Donchin, 1981). However, the characterisation of the P300 as a neural signature of decision formation has been entirely overlooked by the literature to date and thus the question of whether it displays the dynamical properties central to the function of a decision variable, such as evidence-dependent build-up rate and a threshold-crossing relationship with reaction time, has never been addressed. For example, the two most influential models of the P300 (Donchin and Coles, 1988 Context Updating hypothesis and; Nieuwenhuis et al., 2011 Locus Coeruleus Orienting hypothesis) are predicated on the assumption that it onsets after the decision making process has been completed. The aim of Chapter 2 is to determine whether the P300 actually forges the decision itself. Establishing that the P300 is a neural decision variable

would directly contradict the dominant accounts in the field and would demand a re-evaluation of both the analytic techniques and interpretations of results in previous basic and clinical research. Furthermore, it would provide critical evidence supporting a new and comprehensive mechanistic explanation of the P300 that could reconcile all of its key functional characteristics and would have far reaching consequences both for clinical and basic studies of the P300 itself, and for research on the neurobiology of human decision-making in general. It would place the P300 at the forefront of what has become a burgeoning research focus on the neural signals mediating human decision making, and in so doing would establish a concrete link to animal electrophysiology: research of a kind that is extremely rare.

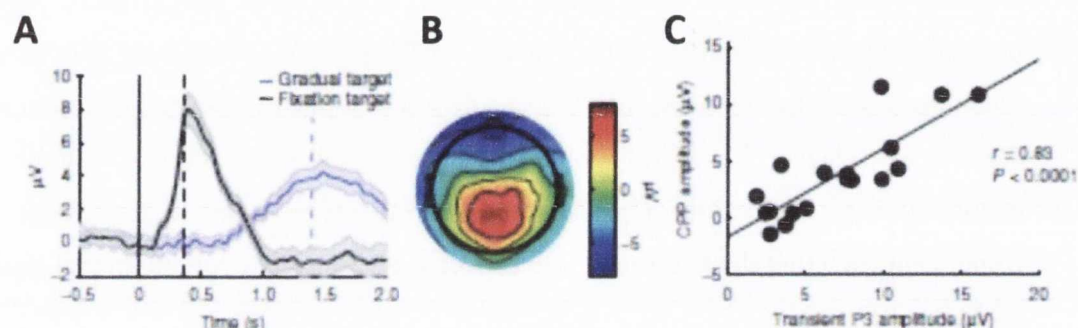


Figure 1.7: Striking resemblance between the CPP and P300 components of the human ERP.

A, Grand average stimulus-aligned waveforms for the P300 evoked by transient fixation targets and for the CPP evoked by the gradual contrast decreases. **B**, The P300 has an almost identical centro-parietal topographic distribution to that of the CPP. **C**, A very strong correlation exists between the peak amplitude of the two components across subjects. Taken from O'Connell et al. (2012).

1.6.4 Summary

The random dot motion task was critical to the identification of neural decision variable signals in the monkey brain and variants of the paradigm were used in ground-breaking MEG work that showed for the first time that was possible to directly trace accumulation-to-bound, decision-related activity in the human brain. Recently, basic paradigm innovations were implemented that made it possible to directly trace the three stages of perceptual decision-making in the EEG. A signal (CPP) that exhibited the defining characteristics of a neural decision variable was discovered. Importantly, the CPP not

only predicted the timing and accuracy of perceptual reports, but carried out its role in a domain-general manner such that it displayed consistent dynamics irrespective of the sensory or motor requirements of the task. A follow-up study demonstrated that evidence accumulation at the abstract level significantly preceded that at the motor preparatory level which provided support for the idea that the CPP serves as an intermediate between sensory encoding and response execution. Furthermore, the significant build-up observed in the motor-selective decision signal prior to the CPP reaching threshold provided support for a heterarchical interpretation of perceptual decision-making. Not all empirical data are consistent with the idea that scalp recorded decision signals reach a stereotyped amplitude at decision commitment such that it has been suggested that the boundary-crossing effect may have been specific to the experimental design used. Alternate interpretations of the functional significance of the CPP have also been offered in the literature: rather than directly encoding the decision, it has been hypothesised to reflect decision confidence. However, the proposition is not entirely consistent with the existing empirical data. Finally, the CPP bears a striking resemblance to the classic P300 component such that the latter may also reflect a dynamically evolving neural signature of decision formation.

1.7 Overall Summary and Objectives of Thesis

The purpose of this chapter was to provide a detailed review of the relevant literature on the mathematical models of perceptual decision-making, the progress made in identifying the neural correlates of perceptual decision-making in both primates and humans, and on the recent developments in neurophysiology that have enabled us to non-invasively trace the three distinct stages of perceptual decision-making in humans.

Monkey neurophysiology has made significant advances in demonstrating that a decision variable may be directly encoded in the firing rates of neurons in association cortex. This remarkable progress in characterising the microcircuitry of perceptual decision-making in monkeys incited a concerted effort to identify analogous mechanisms in the human brain using non-invasive recording techniques such as functional imaging, EEG and MEG. While these non-invasive assays provide a global picture of the brain during decision-making, they often preclude direct observation of the build-to-threshold dynamics that are characteristic of decision variable processes. This limits our capacity to make definitive judgements regarding the role that specific brain signals play in

decision-making. As a result, there has been a notable inconsistency in the quantity and location of brain regions that have been attributed a role in decision formation. Recent paradigm innovations that enable the parallel tracking of sensory evidence, decision variable, and motor signals in electrophysiological signals have provided an unprecedented facility to comprehensively probe the decision-making network and to elucidate the precise nature of evidence accumulation in the human brain (Kelly and O'Connell, 2015). The present thesis will capitalise on this newfound capacity to access the three distinct stages of decision-making via the human EEG to expand our knowledge of how the process operates under different experimental conditions and how it may be compromised in brain disorders.

Thus, the empirical work within this thesis is divided into two parts. The first part (Chapter 2 and Chapter 3) is comprised of electrophysiological investigations that explore a potential role for the classic P300 component in perceptual decision-making and probe possible functional dissociations between abstract versus motor-selective decision variables signals in the human brain. The second part of the thesis (Chapter 4) constitutes an effort to use the novel EEG metrics to identify a disease specific aetiological pathway in ADHD by pinpointing the precise neural computation(s) in perceptual decision-making that are impacted upon by the disorder.

The P300 potential continually draws widespread interest in basic and clinical neuroscience, yet its functional significance has never been established. The aim of Chapter 2 will be to determine the extent to which the classic P300 component exhibits the characteristic dynamics properties of the decision variable signals predicted by sequential sampling models and recently observed in primate and human electrophysiology.

Neural signatures of evidence accumulation have been isolated in a variety of brain regions. While animal neurophysiology has largely concentrated on motor-selective decision signals that translate the emerging decision into a specific motor plan, recent research on the human brain has isolated abstract neural signatures of decision formation. The functional distinctions between the two distinct classes of decision variable signal have yet to be determined. Chapter 3 of the present thesis aims to provide such critical knowledge by exploring the dynamics of abstract versus effector-selective decision

signals, in terms of sustainment through response delays and contingency on the knowledge of stimulus-response mapping.

Chapter 4 will provide a brief overview of the research relevant to perceptual decision-making in ADHD and evaluates the utility of the new EEG metrics to inform our understanding of compromised decision-making capacities in this prevalent neuropsychiatric disorder. As decision-making deficits may manifest in indistinguishable ways such as reduced accuracy or slower reaction times, a real challenge for research is to identify disease-specific aetiological pathways by shedding light on the exact neural computations that are affected by a given disorder (Kelly & O'Connell, 2015). Chapter 4 aims to link perceptual performance deficits in ADHD to precise abnormalities in information processing (sensory, decision, motor) versus pre-stimulus state (attention). Possible relationships between performance deficits in ADHD and cognitive capacities relevant to decision-making are also considered.

Finally, Chapter 5 will provide a general discussion of the findings in this thesis, their respective implications, and suggestions for future research.

Chapter 2 The Classic P300 Encodes a Build-to-Threshold Decision Variable

2.1 Introduction

The centro-parietal P300 component has drawn relentless interest since its initial discovery in 1965 (Sutton et al., 1965) due to its apparent relevance to a wide variety of cognitive operations and its disruption in a number of prominent brain disorders (Polich et al., 1990; Santosh et al., 1994; Mavrogiorgou et al., 2002; Prox et al., 2007; Verleger et al., 2013). Yet despite intensive investigation, a consensus regarding the precise functional significance of the P300 has failed to emerge. Numerous explanatory accounts have been proposed, variously implicating the encoding of stimulus significance (Kutas et al., 1977), decision confidence (Hillyard et al., 1971; Squires et al., 1973), uncertainty or surprise (Duncan-Johnson and Donchin, 1977; Mars et al., 2008), or asserting a role in context updating (Coles et al., 1988), neuroinhibition (Polich, 2007), event-categorisation (Kok, 2001), orienting and response potentiation (Nieuwenhuis et al., 2005; Nieuwenhuis et al., 2011), or context closure (Verleger, 1988). However, no single model has received conclusive empirical validation and this lack of clarity has greatly limited the P300's utility as an interpretable neuro-cognitive marker both in basic and clinical research.

Early research on the P300 systematically examined its sensitivity to variations in perceptual performance within a signal detection framework (Hillyard et al., 1971; Squires et al., 1973). These studies established that the P300 is larger when evoked by detected versus undetected stimuli, that its peak latency varies with reaction time, and that it is sensitive to experimental manipulations impacting on stimulus evaluation. This initially prompted a view that the P300 was linked in some way to the neural process through which sensory information is translated into adaptive action, i.e., perceptual decision-making (Smith et al., 1970; Rohrbaugh et al., 1974). But whether and how the P300 might itself contribute to forming decisions was never established. Today, the two most influential accounts of the P300 (Coles et al., 1988; Nieuwenhuis et al., 2005) propose that it has no direct role in decision formation but reflects a process that is triggered by the outcome of decision making. However, in recent years, our understanding of the neural mechanisms underpinning perceptual decision making has expanded

through a combination of mathematical modelling and single-unit recording studies (Smith and Vickers, 1988; Smith and Ratcliff, 2004; Gold and Shadlen, 2007; Shadlen and Kiani, 2013). A key insight from this work is that perceptual decisions arise from a process of sequential sampling and accumulation of sensory evidence and models founded on these principles offer a clear set of empirically verifiable predictions regarding the dynamics that a neural decision variable signal should exhibit. In the present chapter, a series of critical analyses were conducted to verify the extent to which each of these predictions is met by the classically-evoked P300 using data from oddball and target detection paradigms.

2.2 Methods

In order to comprehensively probe the P300's role in decision formation, the data from three experiments was analysed; each of which involved separate participant samples and employed a distinct target detection paradigm (four-stimulus auditory oddball, two-stimulus auditory oddball and visual target detection task).

2.2.1 Participants

Fifteen participants completed the four-stimulus auditory oddball experiment. One was excluded due to poor accuracy (detection accuracy < than 50%) yielding a final sample of 14 participants (five male, two left-handed), with a mean age of 29 years ($SD = 5.8$). The two-stimulus auditory oddball sample consisted of 33 participants with five excluded due to excessive artefacts in the EEG data (< 50 trials remaining) yielding a final sample of 28 participants (13 male, two left-handed), with a mean age of 23.1 years ($SD = 4.2$). 15 participants (six female, one left-handed), with a mean age of 21.7 years ($SD = 4.3$) completed the visual target detection paradigm. All participants had normal or corrected-to-normal vision, no history of psychiatric illness or head injury and provided written informed consent in advance of testing. All procedures were approved by the Trinity College Dublin ethics committee and in accordance with the Declaration of Helsinki.

2.2.2 Experimental Tasks

The four-stimulus auditory oddball stimuli were presented through headphones using the Presentation software suite (Neurobehavioural Systems, San Francisco, CA) and consisted of sinusoidal tones of 60 ms duration. Participants were instructed to make a

speeded right index finger mouse click to target tones (either 530 Hz, 590 Hz or 680 Hz, 6.7% of trials each) while ignoring the presentation of non-target tones (500 Hz). The three different frequencies of target tone were used to manipulate the amount of sensory evidence available for the decision on each trial and were selected based on the observation at pilot testing that they produced significant differences in accuracy. For example, it would have been more difficult to differentiate between a 530 Hz target tone and 500 Hz standard tone than between a 680 Hz target tone and 500 Hz standard tone. A total of 1500 tones were presented with an interstimulus interval (ISI) that varied pseudorandomly between 1 and 2 s. The stimuli were ordered such that at least 2 non-target tones were presented between targets, leaving a minimum inter-target interval of 3 s. Participants completed a practice session to ensure they were well acquainted with the instructions prior to beginning and were seated at a distance of ~50 cm from a 20-in. LED monitor (Dell P2011H; Dell Inc., Ireland) with their head supported by a chin rest. Participants completed ten three and a half minute blocks of the task.

Task instructions and testing conditions in the two-stimulus auditory oddball experiment were identical to those in the four-stimulus auditory oddball experiment (see Murphy et al., 2011). However, the targets were 1 kHz tones while the non-target tones were presented at 500 Hz. The targets were pseudorandomly distributed throughout the task and comprised 20% of the total number of trials. A total of 890 tones were presented with an interstimulus interval (ISI) that varied pseudorandomly between 2.1 and 2.9 s. The stimuli were arranged such that at least three non-target tones separated the targets, leaving a minimum inter-target interval of 8s. The total duration of the task was 37 minutes with no breaks

The visual target detection experiment was conducted as part of a separate study (O'Connell et al., 2012). Participants were seated ~50 cm from an LCD monitor with a 120-Hz frame rate and made a speeded button press to transient (100 ms) size increases (from an initial 5 pixels to a target of 10 pixels) in a white central fixation square that was continuously presented for four minutes at a time. For reasons not relevant to the present experiment (see O'Connell et al., 2012), the fixation square was surrounded by a 20 Hz flickering annular pattern (inner radius = 1.14° , outer radius = 3.1°) that consisted of light and dark radial segments that alternated with two cycles per quadrant. The annulus underwent periodic, task-irrelevant decreases in contrast (from 65 to 35% over 1.6 s) and

participants were instructed to ignore the annulus at all times (data presented in O'Connell et al., 2012 indicate that this instruction was obeyed). Between 23 and 27 fixation targets were presented per block at random times following each contrast change. Participants completed two blocks of the task. O'Connell et al. (2012) demonstrated that the visual targets elicited a typical P300 component. Here, a novel set of analyses that were not reported in that paper are presented.

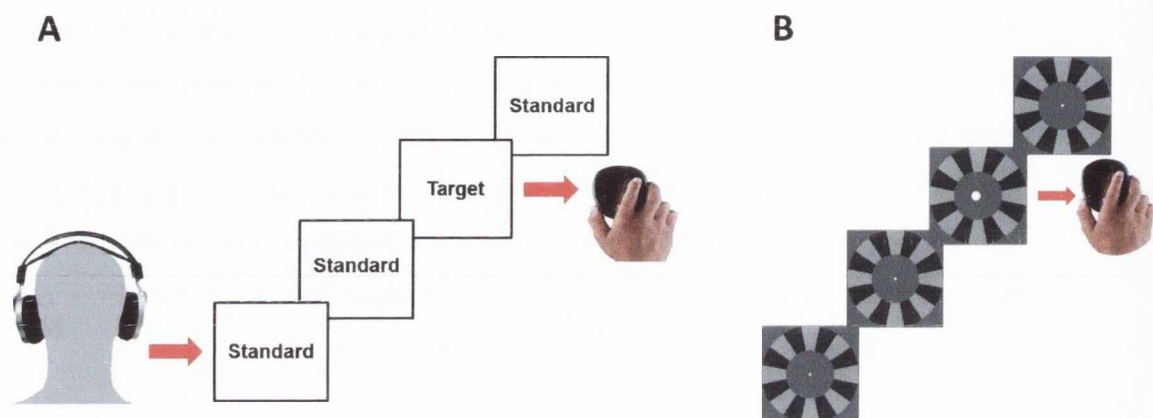


Figure 2.1: Schematic of the auditory oddball and visual target detection tasks.

A, In the four-stimulus auditory oddball task, participants made a speeded right-index mouse press to targets that were either 530 Hz, 590 Hz or 680 Hz tones (6.7% of trials each) while ignoring non-target tones that were presented at 500 Hz. In the two-stimulus auditory oddball, the task instructions were identical but the targets were 1 kHz tones (20% of trials) and the non-target tones were presented at 500 Hz. **B**, In the visual target detection task, participants made a speeded button press to transient (100 ms) size increases (from an initial 5 pixels to a target of 10 pixels) in a white central fixation square that was continuously presented for four minutes at a time. Participants were instructed to ignore the flickering annular pattern surrounding the white fixation square at all times as it was irrelevant to the present experiment.

2.2.3 Data Acquisition and Pre-processing

Continuous EEG data were acquired using an Active Two system (BioSemi, The Netherlands) from 128 scalp electrodes (64 electrodes in two-stimulus auditory oddball experiment) and digitised at 512 Hz. The Active Two system replaces the 'ground' electrodes used in conventional EEG systems with two electrodes: 1) a Common Mode Sense (CMS) active electrode and 2) a Driven Right Leg (DRL) passive electrode. The

CMS and DRL electrodes form a feedback circuit, which pushes the average potential of the participant as close as possible to the analog-to-digital converter reference in the analog-to-digital box.

In all three experiments, vertical and horizontal eye movements were recorded using two vertical electrooculogram (EOG) electrodes placed above and below the left eye and two horizontal electrodes placed at the outer canthus of each eye, respectively. Data were analysed using custom scripts in MATLAB (MathWorks, Natick, MA), drawing on EEGLAB (Delorme and Makeig, 2004) routines for reading in data files and spherical spline interpolation of noisy channels. EEG data were re-referenced offline to the average reference and low-pass filtered below 35 Hz using a direct form II, second order Butterworth infinite impulse response filter. The 'filtfilt' function in MATLAB was implemented to allow for a non-causal, zero-phase filtering approach, which would have eliminated any non-linear phase distortion associated with the use of an infinite impulse response filter. No high-pass filter was applied either on- or offline. Trials were rejected if the bipolar vertical EOG signal (upper minus lower) exceeded an absolute value of 200 μV or if any scalp channel exceeded 100 μV at any time during the epoch.

EEG data were segmented into epochs centred on target onset using windows of -500 to 1500 ms (four-stimulus oddball), -500 to 1200 ms (two-stimulus oddball) and -500 to 1250 ms (visual target detection) relative to target onset. The epochs were then baseline-corrected relative to the 100ms interval prior to target onset in the two- and four-stimulus auditory oddball experiments and relative to the 500ms prior to target onset in the visual target detection experiment. In all three experiments, response-aligned traces were derived by extracting epochs from -500 to 50 ms relative to the response on each trial. P300 amplitude and build-up rate were measured from electrodes centred on the region of maximum positive amplitude identified in the grand average scalp topography for each experiment; depending on the montage density and focus, a similar spatial area encompassed a varying number of electrodes (four-stimulus oddball: cluster of four electrodes anterior to Pz; two-stimulus oddball: electrode Pz; visual target detection experiment: cluster of six electrodes centred on Pz). All single-trial EEG data were converted to current source density (CSD; Kayser and Tenke, 2006) to counteract spatial overlap between the P300 and a functionally distinct fronto-central negativity (see Fig. 2.5 and Kelly and O'Connell, 2013).

Signal analysis

Traditionally the P300 has been measured in terms of its peak amplitude and latency in the stimulus-aligned average waveform. However, sequential sampling models and primate electrophysiology offer detailed predictions regarding the dynamics that a decision variable signal should exhibit that call for a more comprehensive analysis of the P300 waveforms as described below.

A Build-up Rate that Scales with the Strength of Sensory Evidence and Predicts Reaction Time

A strong prediction of sequential sampling models is that the build-up rate of a decision variable signal should scale with the strength of sensory evidence, consistent with temporal integration. A further prediction is that RT variability results in large part from variation in the build-up rate of the decision variable, either across trials (Reddi and Carpenter, 2000; Brown and Heathcote, 2008), within trials (Link and Heath, 1975; Palmer et al., 2005) or both (Ratcliff and McKoon, 2008), even when the sensory evidence has identical statistics across trials. Initially, the extent to which the build-up rate of the P300 scales with evidence strength was examined using data from the four-stimulus auditory oddball task which incorporates three distinct levels of target discrimination difficulty. Following the application of artefact rejection procedures, the average number of target trials remaining for each participant, per level of target detection difficulty was (mean $\pm$ SD): 530 Hz: 76.3 ± 18.8 ; 590 Hz: 89.9 ± 9.3 ; 680 Hz: 88.7 ± 11.1). The build-up rate of the P300 was measured as the slope of a straight line fitted to the unfiltered stimulus- and response-aligned ERP waveforms for each target type.

Previously collected data from a two-stimulus auditory oddball task that was continuously performed for approximately 38 minutes ensuring that there was substantial trial-to-trial variability in RT was analysed (Murphy et al., 2011) to conduct a detailed test of the influence of P300 build-up rate on detection times when evidence is held constant. Using the auditory oddball data each participant's RT distribution was split into equal-sized fast, medium and slow reaction time bins and the grand average signal time courses aligned to both the target onset and response execution for each bin was plotted (Fig. 2.3B). Following artefact rejection, a mean number of 46 ($SD = 9.4$) target trials remained per participant, per RT bin. To verify whether any relationships between the P300 and decision making were modality independent a similar analysis of the visual

target detection dataset was conducted. As there were fewer trials available for analysis in the visual target detection experiment, each participant's RT distribution was divided into two equal sized fast and slow bins based on a median split. Across participants a mean number of 21 target trials (± 2.2) remained in each RT bin, following the application of artefact rejection procedures.

The time intervals used for P300 slope measurement were as follows: stimulus-aligned P300 slope was measured across intervals of 200 to 350 ms in the two- and four-stimulus auditory oddball experiments respectively. The slope of the response-aligned P300 was measured across a window of -250 to 0 ms centred on response execution in the two-stimulus auditory oddball and visual detection experiments. A smaller interval of -250 to -50 ms centred on response execution was used to measure the build-up rate of the P300 in the four-stimulus auditory oddball experiment due to the observed conversion of build-up rates immediately prior to response execution (see Figure 2.3 A).

To enable a finer characterisation of the signal dynamics and their relationship to RT in the two-stimulus oddball data, single-trial measures of ERP slope and amplitude relative to decision report were isolated. The single-trial data were denoised using a 20 Hz low-pass filter. Single-trial P300 build-up rate was measured as the slope of a straight line fitted to the filtered waveform across an interval of 200 to 350 ms. Single-trial P300 peak amplitude was defined as the maximum voltage within a broad latency range of 260 to 800 ms on each trial. The single-trial measurements of P300 build-up rate and amplitude were regressed onto RT for each subject and the resultant beta weights were subject to a *t*-test against zero.

An Action-Triggering Threshold

An additional defining feature of a decision variable signal in the context of reaction time tasks is that it reliably triggers action upon reaching a fixed threshold level. It was verified whether the P300 exhibits such characteristics using all three datasets. The threshold-crossing effect is most appropriately tested on the variance of peak amplitude at response-aligned waveforms, which should, theoretically, be zero for an accumulation process with a fixed threshold in the absence of measurement and background neural noise. However, since the dominant approach in the literature has been to measure the P300 relative to stimulus onset, the RT-threshold relationship in the stimulus-aligned waveforms was also examined to allow for a direct comparison with previous studies. The peak amplitude of

the P300 was defined as the largest positive peak within an appropriate interval in the stimulus- and response aligned traces based on inspection of the grand-average waveforms. In the stimulus-aligned averages, P300 amplitude was measured across time windows of 300 to 550 ms, 310 to 420 ms and 300 to 450 ms in the four-stimulus oddball, two-stimulus oddball and the visual target detection experiments respectively. In the response-aligned average, the peak amplitude of the P300 was measured across a -30 to 0 ms interval centred on response execution in all three experiments. As a further test of the threshold-crossing effect on RT, trial-to-trial variance in P300 amplitude measured immediately in advance of response initiation (-100 to 50 ms) in the two-stimulus auditory oddball data was compared, to a null distribution of the same variance metric computed when RTs were randomly re-assigned to trials. 500 permutations were used for each individual subject and variance values were calculated for P300 amplitudes in bins of five trials, grouped after trials were sorted in order of ascending RT. These values were representative of the values obtained for larger bin sizes (see Fig. 2.2). The variance metric for the unshuffled data was then expressed as a z-score with respect to the null distribution for each subject, and these z-scores were tested against zero.

Comparison with Simulated Decision Variable

To further illustrate how P300 dynamics can be explained by a decision variable process that accumulates noisy sensory evidence to a fixed decision bound, a reduced diffusion model was fitted to the RT distributions of the four-stimulus auditory oddball task and the resultant mean decision variable trajectories over time were simulated (Fig. 2.4A). RT data for each of the three oddball difficulty levels in the four-stimulus auditory oddball experiment were pooled across subjects. Since misses were few and depended on the variable inter-target interval, these trials were omitted from the model fit for simplicity, thus leaving just the trials that contribute to the stimulus- and response-locked P300 waveforms. The model was fit to all data at once, and included a constant non-decision time component T_{er} accounting for delays due to processes other than the evidence accumulation process, a within-trial noise parameter s which quantified the standard deviation of a Gaussian noise process comprising the sole source of within-condition, across-trial variability in RT, and drift rate parameters v_1 , v_2 , and v_3 , one for each of the three oddball difficulty levels. Thus, there were 5 free parameters in total and only drift rate was allowed to vary across difficulty levels. The decision bound a was a scaling parameter, fixed at a value of 1 for all conditions. The fit was performed by minimizing

a chi-square error statistic using a bounded simplex algorithm. The same number of trials as in the real data were simulated, in each of which a random diffusion process with the best-fit parameters from the behavioural fit and approximately the same 2-ms temporal resolution as the EEG was played out from T_{er} until reaching the decision bound a . To enable comparison with the ERP data, it was necessary to additionally model the return path of the decision variable from bound to starting point after each bound-crossing. For this a gradual decay back to baseline at a mean rate that was fixed across all conditions and that roughly matched the post-response decline of the observed, response-locked P300 was implemented.

2.2.4 Statistical Analyses

Where Analyses of Variance (ANOVAs) were used for statistical analyses and sphericity was violated in factors with three or more levels, the Greenhouse-Geisser or the Huynh-Feldt corrected degrees of freedom are reported (the correction applied was contingent on the degree of violation). The impact of target discrimination difficulty on the build-up rate and amplitude of the P300 was established using two separate one-way repeated measures ANOVAs. Four separate one-way repeated measures ANOVAs were conducted to investigate within-subject relationships between RT and the build-up rate and amplitude of the P300 in the two-stimulus oddball and visual target detection data. Furthermore, in the two-stimulus oddball data, each participant's single-trial signal slope and amplitude measures were regressed against their single-trial RT and the resulting beta values were subjected to a t -test against 0.

2.3 Results

2.3.1 Behaviour

As expected, in the four-stimulus auditory oddball, the manipulation of target detection difficulty had a significant impact on both detection accuracy ($F_{(1, 13)} = 6.7, p = 0.02$; 530 Hz target (mean $\pm$ SD): $87.1 \pm 17.5\%$; 590 Hz targets: $99.4 \pm 1.1\%$; 680 Hz targets: $99.8 \pm 0.056\%$) and RT ($F_{(1.3, 16.4)} = 73.7, p = 0.0001$; 530 Hz targets: 533.3 ± 50.9 ms; 590 Hz targets: 455.2 ± 43.9 ms; 680 Hz targets: 416.6 ± 44.3 ms). Targets in the two-stimulus-oddball were rarely missed (accuracy (mean $\pm$ SD): $99.7\% \pm 0.9$) and RTs were 460.9 ms

± 107.7 . Visual targets were detected with $100 \pm 0\%$ accuracy, a mean RT of 366 ± 23 ms and 0.05 ± 0.26 false alarms.

In the following set of analyses, the extent to which the classic P300 bears the defining characteristics of a decision variable signal as predicted by mathematical models and primate neurophysiology was examined.

2.3.2 A Build-up Rate that Scales with the Strength of Sensory Evidence

The grand average signal time courses aligned to target onset and response execution were plotted for each level of target detection difficulty in the four-stimulus oddball data (Fig. 2.3A). As expected, the build-up rate of the P300, which was measured as the slope of a straight line fitted to the unfiltered ERP waveform of each participant, increased in proportion to the strength of sensory evidence, such that stronger sensory evidence was associated with a steeper rate of rise. This effect was significant in both the stimulus ($F_{(2, 26)} = 4.8, p = 0.02$) and the response-aligned traces ($F_{(2, 26)} = 3.8, p = 0.04$; Fig. 2.3A).

2.3.3 A Build-up Rate that Predicts Reaction Time

To examine the relationship between P300 build-up rate and RT, each participant's RT distribution was split into equal-sized fast, medium and slow reaction time bins and the grand average signal time courses aligned to both the target onset and response execution for each bin were plotted (Fig. 2.3B) in the two-stimulus oddball data. Consistent with a decision variable signal, the slope of the response-aligned P300 reliably differentiated RT bins such that faster build-up was associated with faster RTs ($F_{(2, 54)} = 8.8, p = 0.001$). In a further analysis, single-trial measurements of P300 build-up rate were regressed onto RT for each subject and a t -test revealed that the resultant beta weights were significantly more negative than would be expected by chance ($t_{(27)} = -4.02, p = 0.0001$).

2.3.4 An Action-Triggering Threshold

Analysis of the response-aligned traces in the two-stimulus auditory oddball task revealed that P300 peak amplitude did not vary as a function of RT bin in the grand average ($F_{(2, 54)} = 0.1, p = 0.9$) or at the single-trial level ($t_{(27)} = -1.1, p = 0.3$). Furthermore, trial-to-trial variance in amplitude measured immediately in advance of response initiation was significantly lower than a permutation distribution derived by randomly reassigning

reaction times to trials over repeated iterations ($t_{(27)} = -2, p = 0.03$, one-tailed; Fig. 2.2). In contrast, the amplitude of the P300 in the stimulus-aligned average decreased as a function of RT ($F_{(2,54)} = 4.3, p = 0.02$). This effect can be explained by the fact that a signal whose peak is most precisely time-locked to the response will exhibit reduced amplitude in the stimulus-aligned average in proportion with the temporal variability of the response. Indeed, the amplitude reduction was most pronounced in the slowest RT bin, whose intra-subject variability ((mean $\pm$ SD) 100.53 ms $\pm$ 38) was substantially greater than that of the medium (19.43 ms $\pm$ 6.9) or fast (27.89 ms $\pm$ 10.6) bins. Analysis of the response-aligned averages in the four-stimulus oddball task also confirmed that P300 peak amplitude was insensitive to sensory evidence strength ($F_{(2,26)} = 0.1, p = 0.9$).

Inspection of the average waveforms revealed that the peak latency of the P300 coincides with response execution whereas the crossing of the decision threshold and the initiation of the response must occur sometime earlier. A plausible explanation for this overshoot effect is that it reflects sensory information that had already entered the processing pipeline at the time of decision commitment (Resulaj et al., 2009). This is an interesting phenomenon worthy of further investigation and there is already compelling evidence to suggest that this additional post-commitment information plays an important role in the correction or countermanding of erroneously executed actions (Resulaj et al., 2009).

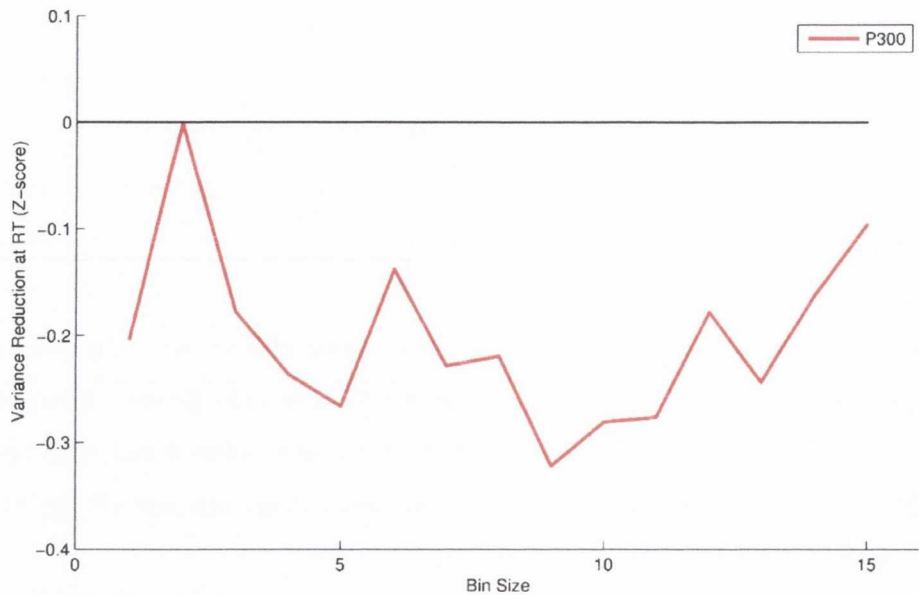


Figure 2.2: The effect of bin-size on P300 amplitude variance reduction at response time relative to a permutation distribution in the two-stimulus auditory oddball experiment (z-scores averaged across subjects).

2.3.5 P300 as a Domain General Decision Signal

To verify the generality of the P300 dynamics identified above in the auditory domain, analyses were conducted to establish whether equivalent build-to-threshold dynamics could be demonstrated in the visual target detection task. Each participant’s RT distribution was divided into equal-sized fast ($M = 315.7 \pm 18.7$ ms) and slow ($M = 409.2 \pm 14.8$ ms) RT bins (there were insufficient trials available for a three-bin analysis). Despite the modest differences in mean RT across bins (Fig. 2.3C), the dynamics of the response-aligned visual P300 were consistent with those observed in the auditory domain: its rate of rise reliably differentiated RT bins such that a faster build-up rate resulted in faster RTs ($F_{(1,14)} = 7.4, p = 0.02$) and its peak amplitude did not vary as a function of RT ($F_{(1,14)} = 1.1, p = 0.3$; see Fig. 2.3C). Thus, the P300 component exhibited equivalent accumulation-to-bound dynamics across the two sensory modalities.

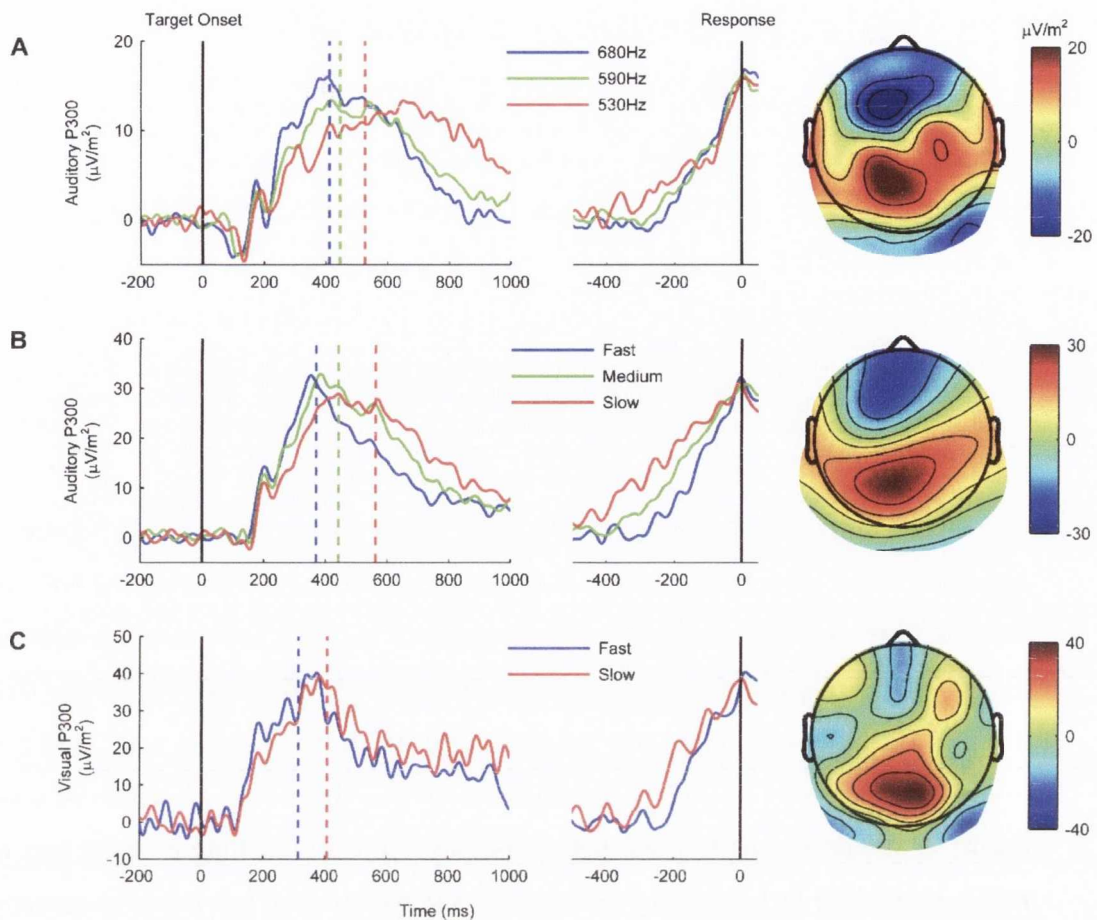


Figure 2.3: The P300 exhibits the critical dynamical properties of a neural decision variable across three prototypical P300 paradigms.

P300 waveforms aligned to stimulus-onset (left column), response execution (middle column) and signal scalp topographies across a time window of -25 to 25 ms centred on response execution (right column). In all panels, the coloured vertical lines denote mean RT for each condition. Single-trial EEG data were converted to current source density (CSD) to minimise the projection of motor preparation signals to centro-parietal electrodes. **A**, The build-up rate of the response-aligned P300 in the four-stimulus auditory oddball task increased in proportion to the strength of sensory evidence (oddball pitch above non-target tone), consistent with temporal integration. **B**, In the two-stimulus auditory oddball task, the response-aligned auditory P300 for three equal-sized reaction time (RT) bins exhibited a gradual build-up rate that scaled with RT and reached a stereotyped zenith at response execution. **C**, In the visual target detection paradigm, the response-aligned visual P300 for two equal-size RT bins exhibited equivalent accumulation-to-bound dynamics to those observed in B, confirming the supramodal nature of the P300.

2.3.6 Comparison with Simulated Decision Variable

A reduced diffusion model comprising five free parameters was fitted to the RT distributions of the four-stimulus auditory oddball task and the resultant mean decision variable trajectories over time were simulated. This minimalistic model accounted well for the observed RT distributions (Fig. 2.4B). Decision variable trajectories were then simulated using the best-fitting parameter values, incorporating a gradual decline (fixed across difficulty levels) to baseline after reaching threshold. As Figure 2.4 C illustrates, the model waveforms recapitulate all of the key qualitative features observed in the P300 data (Fig. 2.3A) including (i) a build-up rate dependence on target difficulty, (ii) a stereotyped amplitude at response execution, (iii) an inverse relationship between peak amplitude in the stimulus-aligned average and target difficulty reflecting the influence of reaction time variability, and (iv) a convergence of build-up rates across conditions for the last 100ms prior to response execution. This last phenomenon reflects the fact that due to high within-trial noise, the time at which the decision bound is crossed is often determined by a brief positive signal fluctuation (see Mazurek et al., 2003 for a similar result). It should be emphasised that the purpose in this modelling exercise was not to achieve a precise fit to both the behavioural and neural data, but rather to demonstrate that a model with even the bare minimum of free parameters (three for any given evidence level, compared to, for example, nine in current versions of the drift diffusion model (Vandekerckhove and Tuerlinckx, 2008)), can reproduce the most salient characteristics of the P300 observed in this study.

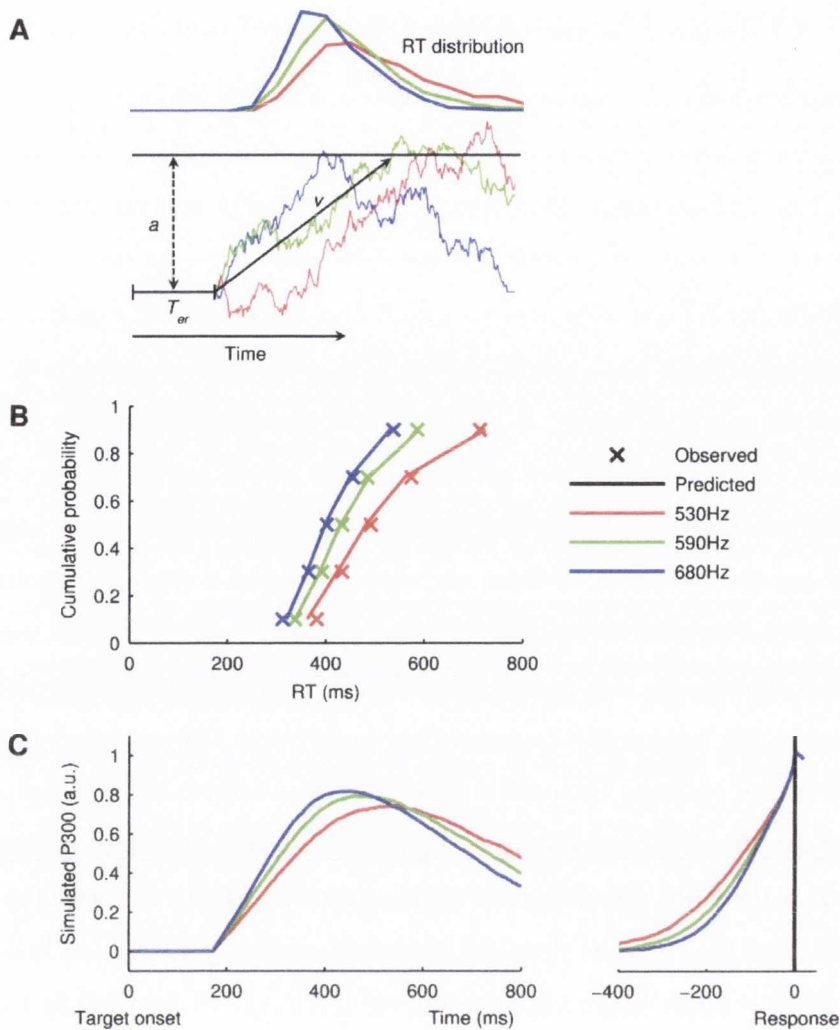


Figure 2.4: Computational modelling of an accumulation-to-bound decision process captures oddball performance and P300 dynamics.

A, Three sample paths of the modelled decision process (bottom) and RT histograms from the four-stimulus auditory oddball task (top). For each target difficulty level, noisy evidence is accumulated at a mean rate that is parameterised by drift rate (v) and a detection response is triggered when the path reaches the decision bound. In order to facilitate modelling of the neural waveforms, the process does not terminate upon reaching the bound but, subject to the ongoing within-trial-noise, returns gradually to baseline at a fixed rate. **B**, Predicted and observed RT quantiles for each of the three target difficulty levels. **C**, Simulated decision variable waveforms aligned to target (left) and response (right) onset.

2.3.7 RT-Linked Fronto-central Negativity Signal Overlaps with the P300

Without CSD transformation, a significant relationship between P300 build-up rate and RT was still observed in the analysis of the response-aligned averages ($F_{(2, 54)} = 6.7, p = 0.003$; Fig. 2.5) and single-trials ($t_{(27)} = -3.4, p = 0.002$) in the two-stimulus oddball data. However, there was a non-significant trend towards an inverse relationship between P300 amplitude and RT bin ($F_{(11.4, 46.3)} = -2.9, p = 0.07$) that reached significance in the single-trial analysis ($t_{(27)} = -2.3, p = 0.04$). An additional series of analyses were conducted to explore its origins. Plotting a topography of the mean difference in ERP amplitude between fast and slow RT bins revealed that the amplitude-RT relationship was greatest over fronto-central electrodes (electrodes Fz and FCz, see Fig. 2.5B) and observation of the averaged waveforms at these electrodes revealed a distinct, negative-going signal (Fig. 2.5C), that extended across the target epoch and reached a maximum negativity at response execution. The peak amplitude of the fronto-central negativity (FCN) was defined as the largest negative peak within a 430 to 800 ms interval in the stimulus-aligned grand average. The peak amplitude of the response-aligned signal and the rate of rise of the stimulus- and response-aligned traces were measured across the same time interval as the P300. Crucially, this fronto-central negativity was found to be functionally distinct from the P300: its slope did not reliably differentiate RT bin in the stimulus ($F_{(2, 54)} = 0.6, p = 0.54$) or the response-aligned ($F_{(1.6, 43.1)} = 1.1, p = 0.3$) averages or at the single-trial level ($t_{(27)} = -0.9, p = 0.4$). Instead, there was a strong relationship between FCN amplitude at decision report and RT at the average (stimulus-aligned: $F_{(2, 54)} = 9.1, p = 0.001$; response-aligned: $F_{(1.6, 43.9)} = 10.1, p = 0.001$) and single-trial levels ($t_{(27)} = -4.6, p = 0.000008$). In fact, a similar fronto-central negativity impinging on the P300 has been reported in previous studies (Verleger et al., 2013), and Kelly and O'Connell (2013) recently demonstrated that an identical RT-linked signal overlapped with the CPP. The fact that CSD transformation, which reduces the overlap between distinct topographical foci, eliminated any relationship between P300 amplitude and RT indicates that it was purely the product of spatial overlap with the FCN.

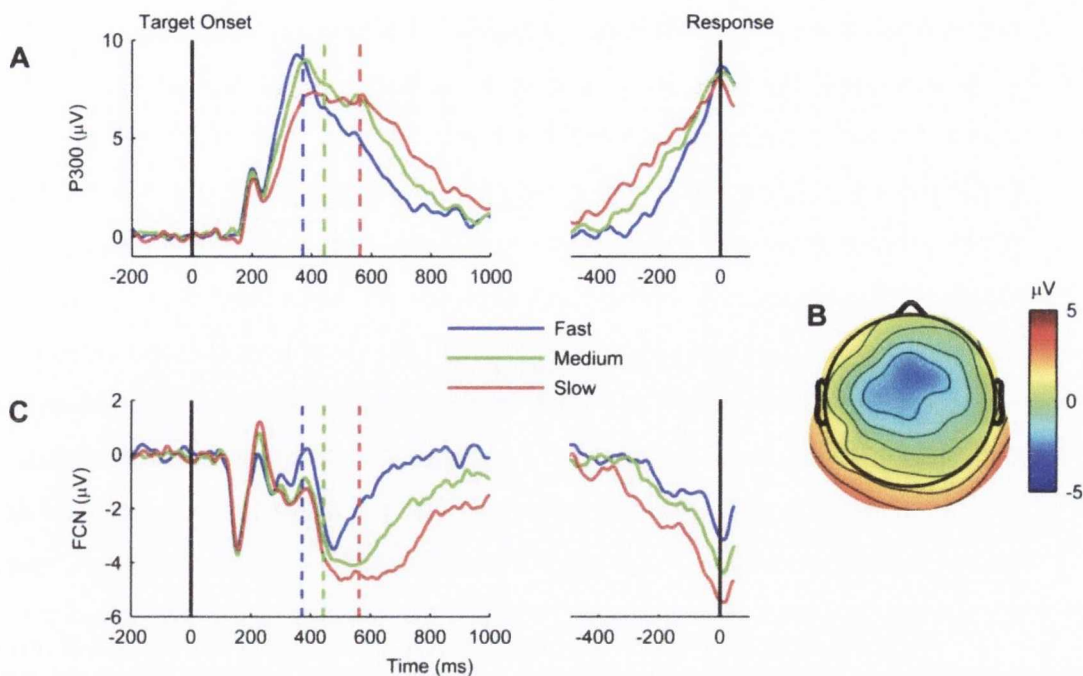


Figure 2.5: Inverse relationship between untransformed response-aligned P300 amplitude and RT is driven by a frontocentral negativity.

P300 (upper panel) and FCN (lower panel) waveforms aligned to stimulus-onset (left column), response execution (middle column) and a signal scalp topography of the mean difference in ERP amplitude between the fast and slow RT bins (right column). In all panels, the coloured vertical lines denote mean RT for each RT bin. **A**, In the two-stimulus auditory oddball experiment, prior to CSD transformation, there was a subtle negative relationship between the amplitude of the response-aligned P300 and RT. **B**, The topography of the mean difference in ERP amplitude between fast and slow RT bins indicated that the amplitude-RT effect was greatest over fronto-central electrodes. **C**, Plotting the average waveform at these electrodes revealed a negative-going component that was functionally distinct from the P300 and reached more negative amplitudes at RTs for slower trials.

2.4 Discussion

The empirical data and computational modelling converge to establish that the classic P300 exhibits all of the characteristic dynamical properties of the ‘decision variable’ signals predicted by sequential sampling models and recently observed in primate and human electrophysiology (Shadlen and Kiani, 2013; Kelly and O’Connell, 2014): a gradual evidence-dependent build-up whose rate determines reaction time and a

boundary-crossing effect at response execution. The findings also suggest that the P300 reflects the same neural process as another, recently reported human decision variable signal. When participants perform tasks that involve slow, deliberative perceptual decisions, a topographically similar but temporally extended centro-parietal positivity (CPP) exhibits a gradual, evidence-dependent build-up to a fixed threshold level that precisely determines the timing and accuracy of perceptual reports across trials (O'Connell et al., 2012; Kelly and O'Connell, 2013). This study thus establishes the equivalence of the P300 and the CPP. In so doing, it provides confirmation that the sequential sampling and accumulation of evidence is not exclusively implemented during difficult, temporally extended discriminations necessitated by typical perceptual decision making paradigms, but is equally apparent during rapid detections of punctate stimuli.

In addition to the P300, a distinct, negative-going signal that extended across the entire target epoch and reached a maximum negativity at response execution was also observed in the data. Here, this fronto-central negativity was shown to be functionally distinct from the P300 in that its slope did not reliably differentiate RT bin in the stimulus- or the response-aligned averages or at the single-trial level. Instead, the FCN amplitude at decision report was shown to be strongly associated with RT at both the average and single-trial levels. As mentioned above, a similar fronto-central negativity impinging on the P300 has been reported in other studies (Verleger et al., 2013), and Kelly and O'Connell (2013) recently demonstrated that an identical RT-linked signal overlapped with the CPP. While this anterior negativity does not appear to have a direct role in the perceptual decision-making process; it may reflect either a contingent negative variation or a *bereitschaftspotential*, two frontocentral negativities associated with the anticipation or preparation of a volitional movement (Brunia and van Boxtel, 2001). Given that the FCN is consistently observed on tasks of perceptual decision-making; its exact contribution, if any, to the perceptual decision-making process should be examined in a dedicated empirical investigation.

One of the shortcomings of sudden-onset, discrete trial presentation, which is often favoured in ERP research, is that the stimuli elicit strong early sensory-evoked components that may partly obscure the dynamics of an unfolding decision process. This is a particular concern when comparing decision-related activity across experimental conditions that affect reaction time because the extent of such signal overlap may vary as

a function of reaction time. Nevertheless, the fact that the P300 exhibited a stereotyped amplitude across evidence levels and RT in the present study indicates that although sensory-locked components are mixed in to the early part of the ERP waveforms, they do not hinder the observation of key dynamical characteristics of the decision variable. Moreover, the close correspondence between the observed P300 and the simulated decision variable waveforms provides a strong indication that interference from overlapping sensory-locked components does not account for the results.

By identifying the P300 as a neural decision variable, this study places it at the heart of a comprehensive theoretical framework that can account for its cardinal functional characteristics, thus calling for a re-interpretation of the prevailing explanatory accounts. Perhaps the most influential of these has been the ‘context updating’ hypothesis (Coles et al., 1988), which proposes that the P300 reflects the revision of the current mental model of the task environment when an unexpected stimulus is identified. While this proposal is consistent with a range of key experimental effects pertaining to the P300, most notably its sensitivity to subjective probability, it rests on the assumption that the signal is only evoked after the stimulus and its probability have been evaluated. These data directly contradict this assumption because they show that, rather than being triggered by the completion of stimulus identification, the P300 traces the identification process itself. This marks a departure from the traditional conception of ERP components as unitary processes that unfold in a stereotyped way in relation to a discrete eliciting event, and instead highlights the important mechanistic insights that can be gleaned from the finer dynamics of their trajectories.

The decision variable account of the P300 is novel not just in its details but more fundamentally in its nature. Whereas constructs such as context updating (Coles et al., 1988) and context closure (Verleger, 1988) are qualitative ones, removed from computational realization, the sequential sampling framework is a mechanistic one that makes concrete, empirically verifiable predictions regarding signal dynamics. For example, in addition to accounting for dynamical aspects such as the variable build-up rate and boundary-crossing effect observed here, sequential sampling models can explain the well-established inverse relationship between the amplitude of the P300 and stimulus probability. Specifically, this would reflect a strategic adjustment to the quantity of evidence required to trigger commitment to a particular decision (i.e. the start-to-

threshold distance) in accordance with prior information (Smith and Vickers, 1988; Smith and Ratcliff, 2004). Another influential and more mechanistic theory has been that the P300 is a cortical manifestation of the phasic locus-coeruleus/noradrenergic (LC/NE) orienting and response potentiation (Nieuwenhuis et al., 2011). This hypothesis is drawn primarily from the observation of numerous similarities in the antecedent conditions that drive the LC/NE phasic response and the P300, as well as evidence from pharmacological (Glover et al., 1988; Pineda and Westerfield, 1993; Swick et al., 1994; Pineda et al., 1997) and pupillometric studies (Friedman et al., 1973; Murphy et al., 2011). However, as with context updating, a core component of this model is that the orienting response, and therefore the P300, serves to facilitate neural processes that are triggered by the outcome of the decision making process. While these data call for a very different interpretation of the P300 they do not exclude a supportive role for the LC/NE system in its potentiation (de Gee et al., 2014). One long-standing proposal that these data do support, is that the peak latency of the P300 indexes the duration of stimulus evaluation processes (Kutas et al., 1977; Duncan-Johnson, 1981) but, for the first time, this study identifies the specific neural mechanism that underpins this relationship.

Consideration of the analytic methods used in previous P300 studies points to reasons why accumulation-to-bound characteristics have been overlooked. The observation that the P300 was primarily sensitive to experimental manipulations bearing on stimulus evaluation (Duncan-Johnson and Donchin, 1977; Kutas et al., 1977; Duncan-Johnson, 1981; Coles et al., 1988) motivated its measurement in stimulus-aligned average waveforms, an approach that has been adopted in the overwhelming majority of studies. These results indicate that analysis of the stimulus-aligned waveform obscures the critical boundary-crossing effect at response execution due to the impact of reaction time variability on the trial-averaged peak; an effect that is clearly apparent for both the P300 (Fig. 2.3) and simulated decision variable waveforms (Fig. 2.4C). Another issue has been that the P300, or 'P3b,' bears spatiotemporal overlap with a distinct frontal process 'P3a' that scales with stimulus novelty. The P3a and P3b have in some instances been grouped together in terms of their hypothesised underlying mechanisms (Nieuwenhuis et al., 2005) and may be difficult to tell apart particularly when tasks involve viewing of stimuli with high-level semantic content such as verbal material (Fabiani et al., 1986) or emotionally valent stimuli (Keil et al., 2002). While P3a/P3b overlap is not an issue in tasks with minimal novelty such as those used in the present study, the insights obtained on how P3b

dynamics relate to stimulus identification and responding may be exploited in experimental designs with higher-level or more varied stimuli to facilitate separation of the two processes.

In the present chapter, the empirical and computational modelling data converged to determine that the P300 exhibits the defining features of a dynamically evolving neural decision variable signal as predicted by the sequential sampling models and as recently observed in both the monkey and human brain (O'Connell et al., 2012; Kelly and O'Connell, 2013; Shadlen and Kiani, 2013). In doing so, the present chapter confirmed the functional equivalence of the CPP and P300 components and offered important new insights into the decision-making machinery in the human brain. The findings indicated that the temporal integration of sensory evidence is not only employed during difficult, temporally extended decisions that characterise decision-making paradigms, but that an accumulation to bound-process also underpins rapid detections of discrete stimuli. Notably, the CPP and left-hemisphere beta also share a number of important characteristics including an evidence-dependent build-up rate, consistent with the principle of temporal integration, and a boundary-crossing effect that precisely predicts the timing and accuracy of perceptual reports. However, it has been shown that the signals differ in at least one important way. While the CPP is a domain-general decision variable signal that carries out its function independently of the sensory or motor requirements of the task, left-hemisphere beta ceases to encode a decision variable when the necessity for an overt motor response is removed, suggesting that it does not play a general role in decision-making. It is likely that additional undiscovered functional dissociations exist between the two neural signatures of evidence accumulation. Chapter 3 explicitly tested this assumption by exploring the dynamics of the abstract and motor-selective decision signals in response to experimental manipulations such as enforcing a delay period between the decision and the response and varying the participant's foreknowledge of stimulus-response mapping.

Chapter 3 Abstract and Effector-Selective Decision Signals Exhibit Qualitatively Distinct Dynamics before Delayed Perceptual Reports

3.1 Introduction

Single-unit recordings in rodents and monkeys have identified neural populations whose spiking activity integrates sensory evidence during perceptual decision formation and triggers the decision-reporting action upon reaching a threshold level (Shadlen and Kiani, 2013). More recently, human electrophysiology studies have indicated that such build-to-threshold ‘decision variable’ signals may fall into at least two categories - effector-selective signals that track decision formation when the decision entails a specific action (e.g. limb-selective beta-band activity; Donner et al., 2009; O’Connell et al., 2012; de Lange et al., 2013) and a domain-general signal that represent decisions independently of specific sensory or motor requirements (the centro-parietal positivity, CPP; O’Connell et al., 2012; Kelly and O’Connell, 2013). Although it has been verified that these signal types differ in the most obvious way, in that effector-selective preparation signals are absent when no responses are required while the CPP remains (O’Connell et al., 2012), much is yet to be elaborated on their functional distinctions.

A notable feature of effector-selective signals in single-unit and non-invasive recordings is that they maintain an elevated level of activity during the interval between commitment and action when the decision report must be delayed until the appearance of a response cue (Shadlen and Newsome, 2001; Donner et al., 2009). This observation has directly informed the model assumptions employed in many functional neuroimaging studies to isolate domain-general decision regions (Heekeren et al., 2004; Heekeren et al., 2006; Pleger et al., 2006). However, it has yet to be determined if the CPP exhibits the same properties. Maintaining a sustained level of motor preparation would facilitate the

rapid execution of the decision-reporting action but the benefits of sustainment for a domain general decision process are less clear. One possibility is that sustainment of domain-general decision signals may only be beneficial when a choice cannot be immediately mapped to a specific action such as when participants must await a response cue to learn the appropriate stimulus-response association.

The present chapter sought to address these questions using a delayed-response variant of a prototypical perceptual discrimination task which participants performed with and without foreknowledge of the correct decision reporting action. The data indicate that domain-general and effector-selective decision signals exhibit qualitatively different dynamics during the interval between choice and action.

3.2 Materials and Methods

3.2.1 Participants

Twenty-five participants took part in the study. Two participants were excluded due to excessive artefacts in their EEG data (< 50% trials remaining), yielding a final sample of 23 participants (9 male, 1 left-handed), aged 24.6 ± 6.2 years (mean $\pm$ SD). All participants had normal or corrected-to-normal vision, no history of psychiatric illness or head injury and provided written informed consent in advance of testing. All procedures were approved by the Trinity College Dublin ethics committee in accordance with the Declaration of Helsinki.

3.2.2 Random Dot Motion (RDM) Paradigm

A discrete-trial version of a flickered motion discrimination task modelled on the classic RDM task (Newsome et al., 1989; Britten et al., 1992; Kelly and O'Connell, 2013) in which participants judged the direction of motion in a patch of moving dots (see Fig. 3.1) was used. Participants made a simultaneous left and right mouse button click to initiate each trial upon which the dot kinetogram appeared. Initially the dots moved incoherently for a period of 1400 ms after which they underwent an instantaneous transition to either leftward or rightward coherent motion. The stimulus disappeared after a further 1600 ms and was replaced by a response cue. The initial period of incoherent motion was introduced to ensure that sensory potentials evoked by stimulus onset would not impinge on activity associated with the decision making process. Participants were made aware of

this feature and informed that coherent motion would appear after 1400 ms on every trial. Motion direction and coherence (20% or 30%) were varied independently and randomly across trials. The response cue always took the form of a centrally presented 'S' or 'M' with font size of 5 mm. Participants performed the task under three experimental conditions in which the stimulus-effector (S-E) mapping was manipulated.

In the first condition (No S-E) coherent motion was incidental to the requirements of the task. Participants were instructed to maintain central fixation, ignore the kinetogram and make a speeded left or right hand button press solely on the basis of the response cue, where 'M' indicated a left press and 'S' a right press. In the two remaining conditions participants were required to judge the direction of coherent motion, and whether or not the evolving perceptual decision could be directly translated into a specific motor plan was manipulated. In the Varied S-E condition the stimulus-response association was withheld from the participant until the appearance of the response cue. An 'M' cue indicated that leftward motion should be reported with a left hand press and rightward motion with a right hand press while an 'S' cue indicated the reverse mapping, i.e., a left hand press for rightward motion and a right hand press for leftward motion. In the fixed S-E mapping condition, participants always indicated leftward motion with a left hand press and rightward motion with a right hand press and the cue simply indicated the number of presses required (M = one press, S = two presses). This variation in the number of required button clicks was introduced to ensure that participants would be obliged to determine the identity of the response cue in all conditions before responding. In all conditions, participants were advised to respond as quickly as possible once the response cue appeared, with the trial ending as soon as the press was made. If the press was made prior to the onset of the response cue participants were informed that it was 'Too Fast' however, if it was made more than 1200 ms following the appearance of the response cue they were informed that it was 'Too Slow'. At the end of each trial participants were advised as to whether their decision report was 'Correct', 'Wrong' or 'Too Slow'. Additional feedback pertaining to the number of trials responded to correctly out of a maximum of 30 was provided at the end of each block to promote effort maintenance.

Testing took place in a dark, sound attenuated room, with participants seated at a distance of approximately 50 cm from the visual display. Participants always completed

the No S-E condition first to ensure that they were unaware of the presence of coherent motion and this was confirmed at follow-up. The Fixed and Varied S-E mapping conditions were completed in counterbalanced order. Each participant completed 5 blocks of 30 trials per condition. Visual stimuli were presented against a black background on a 51 cm CRT monitor with a refresh rate of 85 Hz and a resolution of 1024 × 768 Hz. Participants were instructed to fixate on a centrally presented 5 × 5 pixel white point for the duration of the task in all conditions. The RDM stimulus was presented within an 8 degree aperture centred on fixation. During incoherent motion, an average of 118, 6 × 6 pixel white dots were placed randomly and independently within the circular aperture on each of a sequence of 58.8 Ms frames played at 17 frames per second. This resulted in an on-off flicker at the same rate, giving rise to a steady-state visual-evoked potential (SSVEP) at 17 Hz in the EEG. During coherent motion, a proportion of the dots were randomly selected on each frame to be displaced by a fixed distance of 0.353 degrees in either the leftward or rightward direction on the following frame, resulting in a motion speed of 6 degrees per second.

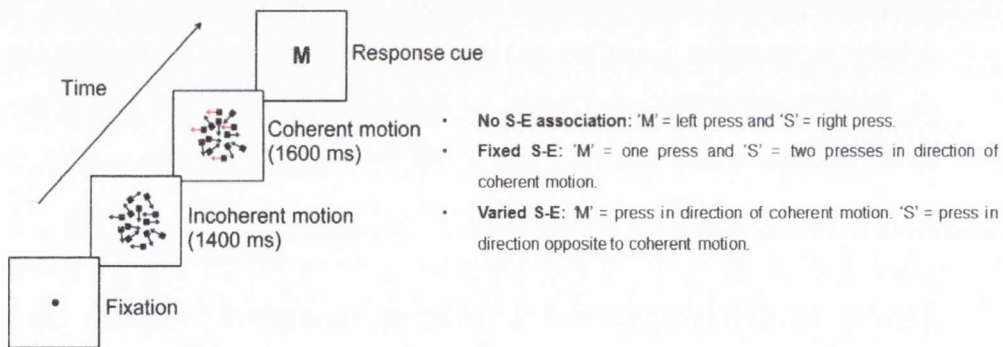


Figure 3.1: Schematic of the delayed response random dot motion task.

In the No S-E condition participants were instructed to ignore the kinetogram and make a speeded left or right hand button press solely on the basis of the response cue. In the Varied S-E condition the stimulus-response association was withheld until the appearance of the response cue. An ‘M’ cue indicated that leftward motion should be reported with a left hand press and rightward motion with a right hand press while an ‘S’ cue indicated the reverse mapping, i.e., a left hand press for rightward motion and a right hand press for leftward motion. In the Fixed S-E condition, participants always indicated leftward motion with a left hand press and rightward motion with a right hand press and the cue simply indicated the number of presses required (M = one press, S = two presses).

3.2.3 EEG Acquisition and Pre-processing

Continuous EEG data were acquired using an ActiveTwo system (BioSemi, The Netherlands) from 128 scalp electrodes and digitised at 512 Hz. Vertical and horizontal eye movements were recorded using two vertical electrooculogram (EOG) electrodes placed above and below the left eye and two horizontal electrodes placed at the outer canthus of each eye, respectively. Data were analysed using custom scripts in MATLAB (Mathworks, Natick, MA), drawing on EEGLAB (Delorme and Makeig, 2004) routines for reading in data files and spherical spline interpolation of noisy channels. The continuous recordings at all channels were detrended in order to minimise the influence of slow drifts and were low-pass filtered below 35 Hz using a Hamming-windowed sinc finite impulse response (FIR) filter. For all of the principal analyses, the EEG data were segmented into epochs of -412 to 1700 ms. The epochs were baseline-corrected relative to the 117 ms (two SSVEP cycles) interval preceding coherent motion onset. Trials were rejected if the bipolar vertical EOG signal (upper minus lower) exceeded an absolute value of $200\ \mu\text{V}$ or if any scalp channel exceeded $100\ \mu\text{V}$ at any time during the epoch. Response-aligned traces were also extracted in the period spanning from -400 to 100 ms relative to response execution and any trials with artefacts within this time-range were excluded from this analysis. To remove the steady state signal evoked by the on-off flicker of the stimulus which was irrelevant to the present study, a 17 Hz notch filter was applied to the segmented EEG data for the ERP analysis. The filter was applied using a zero phase-shift Butterworth infinite impulse response (IIR) filter with a passband below 16 Hz and -60 dB response at 16.5 Hz, and a passband above 18 Hz and -60 dB response at 17.5 Hz. As was the case in Chapter 2, the single-trial EEG data were converted to current source density (CSD; Kayser and Tenke, 2006) to increase spatial selectivity and to reduce the spatial blurring effects of volume conduction. This transformation was applied to minimise the projection of a negativity at fronto-central electrodes to the more posterior centro-parietal electrodes (Kelly and O'Connell, 2013). Since the signal topography, onset latency, build-up rate, peak amplitude and latency of the signal did not differ for leftward versus rightward motion (all $p > 0.05$); trials were collapsed across motion direction in all CPP analyses.

Measurement of electrophysiological decision signals

The domain-general CPP was measured at a single centro-parietal electrode centred on the region of maximum component amplitude identified in the grand-average stimulus-

aligned topography collapsing the Fixed and Varied S-E mapping conditions (see Fig. 3.2C). Due to a strong a priori expectation that the CPP would be absent in the No S-E mapping condition based on previous findings (O'Connell et al., 2012), these trials were excluded from the topography for the purposes of channel selection. The CPP bears many parameters that impact on the timing and accuracy of decisions (O'Connell et al., 2012; Kelly and O'Connell, 2013), including onset latency, rate of rise, peak amplitude and peak latency, which have been posited to index the start time and rate of evidence accumulation and the level and timing of its cessation, respectively (Kelly and O'Connell, 2015).

CPP onset latency was calculated using the Schwarzenau et al. (1998) regression-based method, which defines signal onset as the 'break-point' between two intersecting lines that are fit to the ERP waveform, one fitted to the baseline and another to the rising slope of the ERP (see Cespon et al., 2013 for a similar approach). This method was applied separately to each participant's average stimulus-aligned waveform that was denoised by low-pass filtering the data below 6 Hz using a zero phase-shift, fourth-order Butterworth IIR filter (Spencer, 2005). The rate of rise of the stimulus-aligned CPP was measured as the slope of a straight line fitted to the unfiltered ERP waveform, using the interval 100 to 400 ms post-evidence onset. Average stimulus- and response-aligned CPP peak amplitude per participant was measured as the maximum trial-average signal amplitude within windows of 350 to 600 ms and -100 to 100 ms relative to evidence-onset and response execution on each trial, respectively. Peak latency was measured as the time at which this maximum signal amplitude occurred in the same interval in the averaged trace of each condition and subject. Topographical differences in the CPP within a time window of 350 to 600 ms post-evidence onset, on left and right motion trials and in the Fixed and Varied S-E mapping conditions were assessed using a non-parametric randomization test known as a paired TANOVAs (topographic ANOVAs (TANOVAs); Murray et al., 2008), implemented using Cartool software (<http://www.fbmlab.com/cartool-software/>). Specifically, a TANOVAs tests for differences in global dissimilarity of EEG activity between two conditions by assessing if the topographies are significantly different from each other on a timepoint-by-timepoint basis (Murray et al., 2008). Finally, the area under the curve (AUC) of each participant's stimulus-aligned CPP waveforms, collapsed across the Fixed and Varied S-E mapping conditions, was measured using the trapezoid method with unit spacing in MATLAB (MathWorks, Natick, MA). This additional measure was included to generate predictions

for fMRI research since the BOLD response is assumed to scale with the integrated neural activity for a given time interval (Kayser et al., 2010).

Power estimates for all β analyses were calculated using the Fast Fourier Transform, integrating across the 8–30 Hz range but excluding the single frequency bin at precisely 17 Hz (stimulus flicker frequency). To ensure that SSVEP power was fully contained in this omitted frequency bin data segments of exactly 7 cycles of the 17-Hz SSVEP (i.e., 412 ms) with no tapering were used. β power was thus measured in each of a series of time segments taken in 58.82-ms steps, comprising a Short Time Fourier Transform (STFT). In order to identify channels exhibiting the strongest effector-selective activity, a grand-average topography was generated from the interval -200 ms to 0 with respect to response, with right button press trials subtracted from left button press trials collapsed across all conditions (Fig. 3.2A). Based on inspection of this topography, the standard left- and right-hemisphere motor sites C3 and C4 were selected for β -band amplitude measurements. Stimulus- and response-aligned β -band lateralisation was calculated by subtracting amplitude values at the electrode ipsilateral to the responding hand from those at the electrode contralateral to the responding hand (contra-ipsi). Thus, more negative β lateralisation values were indicative of greater preparation of the responding hand. The impact of motion coherence on the build-up rate of the stimulus-aligned β -trace was measured in the Fixed S-E mapping condition as the slope of a straight line fitted to the lateralisation time course, using the interval 200 to 500 ms post-evidence onset.

A single-trial surface plot was generated to examine the single-trial dynamics of the CPP (curved black line). For this analysis, the stimulus-aligned CPP waveforms were denoised by low-pass filtering the data below 6 Hz using a zero phase-shift fourth-order Butterworth IIR filter (Spencer, 2005), and were pooled across S-E mapping condition (Fixed and Varied), motion direction, coherence and participants. The CPP waveforms were subsequently sorted according to the signal's single-trial peak latency within a window of 200 to 1600 ms post-evidence onset and were smoothed over bins of 100 trials with a Gaussian weighted moving average (Fig. 3.2E).

3.2.4 Statistical Analyses

A one-way repeated measures ANOVA was used to examine the impact of S-E mapping on RT. As the data were not normally distributed the effect of this same manipulation on accuracy rates was measured using three separate, non-parametric Wilcoxon signed-rank tests. The impact of coherence on accuracy and RT were measured using a Wilcoxon signed-rank test and a paired-samples *t*-test, respectively. As the CPP was absent in the No S-E condition, a series of paired-samples *t*-tests was used to explore the relationship between foreknowledge of S-E mapping and the onset latency, build-up rate, peak amplitude and latency of the stimulus-aligned CPP in the two motion discrimination conditions (Fixed and Varied S-E). Two paired TANOVAs were employed to identify possible topographical differences in the CPP as a function of motion direction and S-E mapping condition (Fixed and Varied). The impact of foreknowledge of S-E mapping on stimulus- and response-aligned effector-specific motor preparation signal was examined using two one-way repeated measures ANOVAs. The effect of foreknowledge of S-E mapping on the peak amplitude of the response-aligned CPP was established using an additional one-way repeated measures ANOVA.

To measure the impact of coherence on the build-up rate, peak amplitude and AUC of the stimulus-aligned CPP in the average waveform collapsed across S-E mapping conditions (Fixed and Varied) and aligned to coherent motion onset, a series of paired-samples *t*-tests were employed. Two additional paired-samples *t*-tests were used to determine the impact of coherence on the build-up rate and AUC of stimulus-aligned β -band lateralisation in the Fixed S-E mapping condition. Finally, the impact of coherence on mean β -band lateralisation and the peak amplitude of the response-aligned CPP at response execution was assessed using two paired-samples *t*-tests. Where ANOVAs were used for statistical analyses and sphericity was violated in factors with three or more levels, the Greenhouse-Geisser or the Huynh-Feldt corrected degrees of freedom are reported (the correction applied was contingent on the degree of violation). False discovery rate corrections (Benjamini and Hochberg, 1995; Benjamini and Yekutieli, 2001) were applied to the timepoint-by-timepoint *t*-tests in order to correct for multiple comparisons. Outlying participants were excluded from specific analyses if their values within that analysis were a distance of more than three times the interquartile range or more than 2.5 standard deviations from the mean.

3.3 Results

3.3.1 Behavioural Performance

RT varied significantly across the three experimental conditions (with respect to coherent motion onset: mean $\pm$ SD; Fixed S-E: 2095 ± 65 ms; Varied S-E: 2184 ± 71 ms; No S-E: 2138 ± 52 ms; $F_{(2,44)} = 28.4$, $p = 0.0001$) such that participants responded significantly faster in the Fixed S-E condition relative to the Varied S-E ($p = 0.0001$) and No S-E mapping conditions ($p = 0.001$) and in the No S-E condition relative to Varied S-E condition ($p = 0.01$). Accuracy levels did not vary across conditions (Fixed S-E: $95.9 \pm 3.9\%$; Varied S-E: $95.1 \pm 4.4\%$; No S-E: $97.4 \pm 2.4\%$). There was no significant difference in accuracy rates between any pair of S-E conditions (all $p > 0.1$). Participants were more accurate (Low: $94.4 \pm 4.8\%$; High: $96.7 \pm 3.4\%$; $Z = -3.2$ $p = 0.001$) and had faster RTs (Low: 2152 ± 65 ms; High: 2126 ± 62 ms; $t_{(22)} = 6.6$, $p = 0.0001$) when coherence was high relative to when it was low.

3.3.2 Foreknowledge of Stimulus-Effector Mapping Differentially Impacts upon Abstract and Motor-Selective Decision Signals

To explore the influence that foreknowledge of S-E mapping has on neural signatures of decision formation each participant's trials were collapsed across levels of coherence and the average signal time courses aligned to the onset of coherent motion, the cue and response execution were plotted for each mapping condition separately (see Fig. 3.2).

Consistent with observations of effector-selective decision neurons in the monkey and human brain (Fixed S-E; Shadlen and Newsome, 2001; Donner et al., 2009; de Lange et al., 2013), limb-selective β -band activity exhibited a building lateralisation upon evidence onset and then a sustained lateralisation up until the appearance of the response cue when the decision-reporting effector was known in advance. A one-way repeated measures ANOVA indicated a main effect of Condition ($F_{(2, 42)} = 4.9$, $p = 0.01$), with significantly more stimulus-aligned β -band lateralisation in the Fixed relative to the Varied and No S-E mapping conditions (Fixed S-E vs. Varied S-E: $p = 0.01$; Fixed S-E vs. No S-E: $p = 0.03$; Varied S-E vs. No S-E: $p = 0.7$; Fig. 3.2B). Running t -tests against zero spanning the interval from 0 to 1441 ms confirmed significant and sustained lateralisation in the Fixed S-E condition only (16 out of 24 time points, $p < 0.05$; all $p > 0.05$ for the Varied and No S-E conditions; see Fig. 3.2B, left).

Coherent motion onset only elicited a CPP when it was relevant to the task at hand (i.e., Fixed and Varied S-E). A series of *t*-tests against zero spanning the interval from 0 to 1600 ms confirmed that the CPP was absent in the No S-E condition (all $p > 0.05$; O'Connell et al., 2012; Fig. 3.2D, left). In addition, the stimulus-aligned CPP was entirely unaffected by the presence or absence of foreknowledge regarding the decision reporting effector with neither its topography, onset latency, build-up rate, peak amplitude nor peak latency differing between the Fixed and Varied S-E mapping conditions ($p > 0.1$; Fig. 3.2D, left). Inspection of the stimulus-aligned waveforms elicited in the two motion discrimination conditions (Fixed and Varied S-E) indicated that the CPP did not remain at an elevated level during the interval prior to the response cue but descended towards baseline levels upon reaching its peak. A single-trial surface plot (Fig. 3.2E), sorted as a function of single-trial CPP peak latency confirmed that the CPP returned toward baseline upon reaching its peak amplitude. This plot also highlights that the apparent slow return to baseline levels in the grand-average waveforms is largely the product of the temporal dispersion of CPP peaks, consistent with the variable decision times typically observed on random dot motion tasks. Analysis of the response-aligned waveforms confirmed that β -lateralisation reached a comparable level prior to response execution ($F_{(2, 42)} = 0.82$, $p = 0.45$; Fig. 3.2B, right). The appearance of the response cue elicited an additional positive going signal over centro-parietal electrodes that likely reflects a second decision process for identification of the cue letter (Fig. 3.2D, middle). Analysis of this second signal, in a response-aligned average waveform indicated that there were no differences in amplitude across S-E mapping conditions (Fig. 3.2D, right; $F_{(2, 44)} = 2.1$, $p = 0.14$).

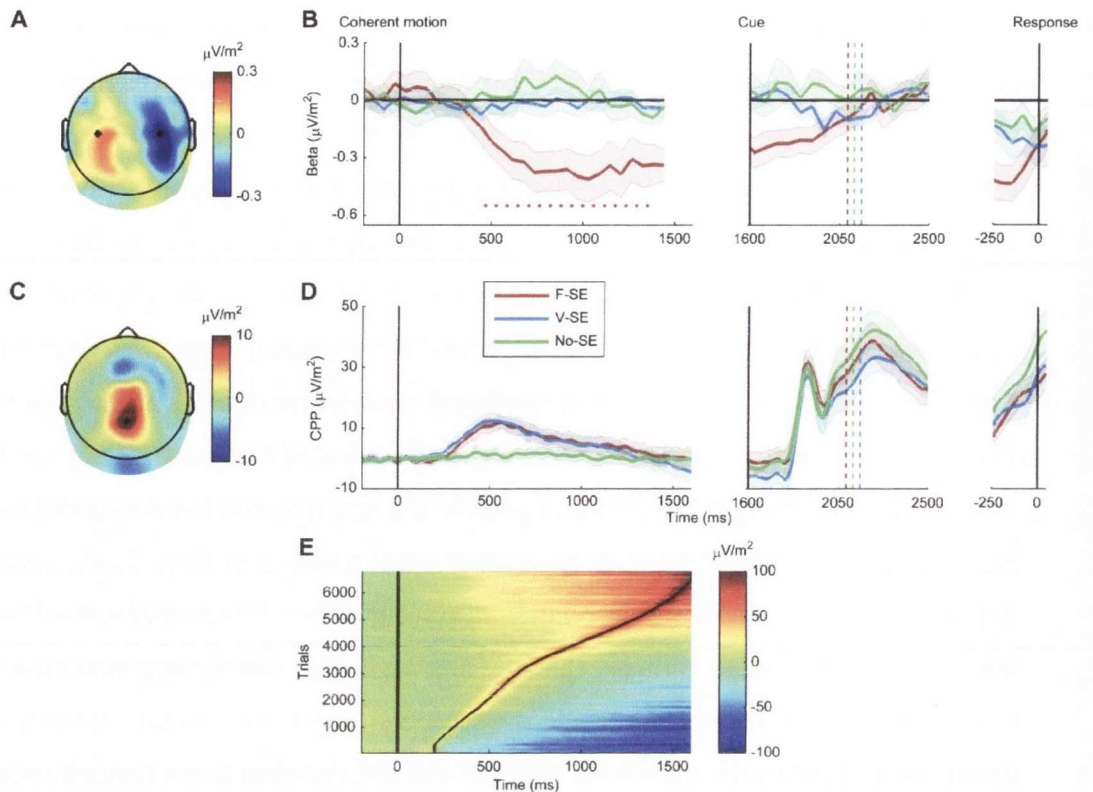


Figure 3.2: Impact of foreknowledge of stimulus-effector (S-E) mapping on abstract and effector-selective signatures of evidence accumulation in the human brain.

In **B** and **D**, the error bars indicate the standard error of the mean (SEM) across subjects and the colour bar represents signal amplitude. The coloured vertical lines denote mean RT for each condition. **A**, Grand average signal topography of the difference between trials on which participants responded with a left versus right button click (collapsing across the three S-E mapping conditions) across a window of -200 to 0 ms centred on response execution. **B**, β -band lateralisation traces (8 – 16 and 18 – 30 Hz) measured as the average difference in amplitude over motor regions contralateral minus ipsilateral to the responding hand, aligned to coherent motion onset (left), cue (middle) and response execution (right). Markers running along the bottom of the plot indicate the time points at which the lateralised β -band traces deviated significantly from zero ($p < 0.05$); a significant and sustained lateralisation with respect to the hand of eventual response was only observed across the decision timeframe when the decision-reporting effector was known in advance. **C**, Grand-average signal scalp topography of the Fixed and Varied S-E mapping conditions across a time window of 400 to 550 ms centred on target onset. **D**, CPP waveforms aligned to the onset of coherent motion (left), cue (middle) and response execution (right). **E**, Single-trial CPP surface plot sorted from the earliest to latest CPP peak latencies (curved black line; right) in the two motion discrimination conditions

shows that the CPP did not remain at an elevated level post-decision but descended towards baseline levels upon reaching its peak. Although there was considerable variability in the time at which the CPP reached its peak, it consistently returned to baseline levels shortly afterwards. While the abstract and effector-selective signals appear to accumulate sensory evidence in a similar way, they are dissociable in terms of their post-decision dynamics.

3.3.3 Impact of Evidence Strength on Abstract versus Motor-Selective Decision Signals

To explore the influence that sensory evidence strength has on neural signatures of decision formation the average signal time courses aligned to the onset of coherent motion, the cue and response execution were plotted for each level of coherence separately (see Fig. 3.3). For each signal trials were collapsed across conditions that showed equally strong build-up in the above analyses (CPP: Fixed and Varied S-E; β -lateralisation: Fixed S-E only). In keeping with previous reports (Kelly and O'Connell, 2013), the build-up rate of the CPP increased in proportion to the strength of sensory evidence, such that stronger coherence was associated with a steeper rate of rise ($t_{(22)} = -3.97, p = 0.00006$). The amplitude of the coherent motion-aligned signal peak increased with coherence ($t_{(22)} = -2.5, p = 0.02$; Fig. 3.3A, left), an effect that is consistent with the impact of evidence strength on the variability of decision times (Kelly and O'Connell, 2013). That is, to the extent that the peak latency of the CPP marks the end of evidence accumulation, greater cross-trial variability in decision times for lower coherences would result in greater temporal jitter in peak latency and hence yield smaller grand average signal amplitudes (Luck, 2014).

Efforts to identify human brain regions that play a domain-general role in decision formation have frequently relied on assumptions regarding the impact that varying sensory evidence should have on the BOLD response in a decision making region. One common prediction has been that the amplitude of the BOLD response in a decision region should distinguish between high and low evidence trials (Heekeren et al., 2004; Heekeren et al., 2006; Liu and Pleskac, 2011), although there has been disagreement regarding the direction of that relationship. Since the BOLD response is assumed to scale with the integrated neural activity for the corresponding time-period (Kayser et al., 2010),

the area under the CPP curve was measured over the interval spanning from 0 to 1600 ms. This analysis indicated no significant effect of coherence ($t_{(22)} = 0.18, p = 0.86$).

In contrast to the CPP and one previous report using a reaction time version of the random dot paradigm (de Lange et al., 2013), the rate of β -band lateralisation in the Fixed S-E mapping condition did not increase in proportion to the strength of sensory evidence ($t_{(21)} = -0.39, p = 0.697$; Fig. 3.3B). Analysis of the response-aligned waveforms revealed that the CPP and β -lateralisation reached a fixed amplitude prior to response execution irrespective of sensory evidence strength (CPP: $t_{(22)} = -0.4, p = 0.97$, β -band lateralisation: $t_{(21)} = -1.1, p = 0.28$; see Fig. 3.3A,B, right).

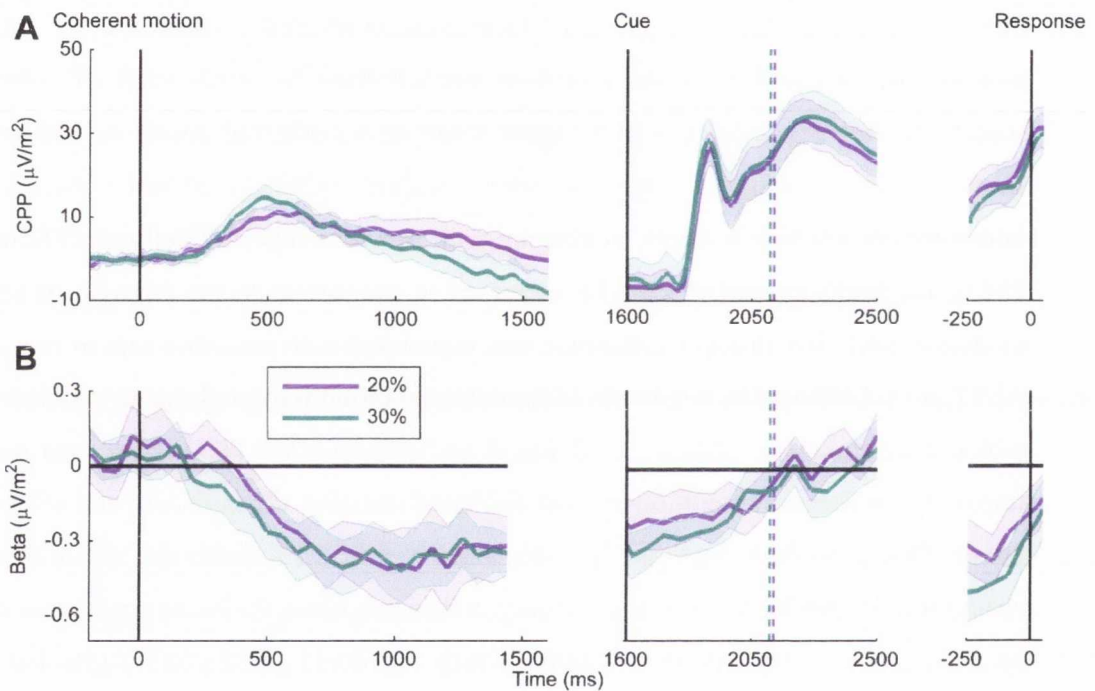


Figure 3.3: Decision variable signals as a function of coherence.

Error bars indicate SEM across subjects and the coloured vertical lines denote mean RT for each coherence level. **A**, CPP waveforms collapsed across the motion discrimination conditions (Fixed and Varied S-E), aligned to coherent motion onset (left), cue (middle) and response execution (right) and plotted separately over time for the two coherence levels. **B**, Lateralised β -band waveforms in the Fixed S-E mapping condition, aligned to coherent motion onset (left), cue (middle) and response execution (right) for both coherence levels.

3.4 Discussion

These data indicate that effector-selective and domain-general decision signals exhibit qualitatively distinct dynamics in delayed-response scenarios. Limb-selective β -band activity maintained a representation of the decision until the response cue appeared but only when the stimulus-effector association was known in advance. In contrast, the CPP was unaffected by such foreknowledge and, in all cases, returned toward baseline levels after reaching its peak. The findings highlight the functional independence of abstract and effector-selective signatures of evidence accumulation and have important implications for neurophysiological and neuroimaging investigations of perceptual decision-making.

A number of single-unit neurophysiology studies have demonstrated that sub-populations of neurons within the lateral intraparietal area (LIP), continue to exhibit activity that discriminates the categorical alternatives even when the appropriate stimulus-response mapping is withheld until a response cue (Freedman and Assad, 2006; Bennur and Gold, 2011) or when hand movements are used to report decisions instead of saccades (de Lafuente et al., 2015). In at least one study (Bennur and Gold, 2011), this category-selective activity appears to dissipate over time when the stimulus-response mapping is unknown, similar to the CPP under similar conditions. However, under conditions where the stimulus-response mapping is known in advance, LIP neurons coding for the saccade target location invariably do exhibit sustained activity up to the point of response execution; yet, the CPP returns to baseline under this condition in our data. Thus, the CPP's independence from the process of action preparation and execution appears to be a unique characteristic and highlights a key functional distinction from single-unit decision signals.

Efforts to isolate brain regions that are directly involved in decision formation from other task-activated structures using fMRI have relied on assumptions that are inspired by observations from computational modelling and animal electrophysiology. One of the most common criteria for classifying decision structures has been a BOLD response that scales with evidence strength across trials (Heekeren et al., 2004; Heekeren et al., 2006; Pleger et al., 2006; Tosoni et al., 2008; Ho et al., 2009; Liu and Pleskac, 2011). The current chapter offers insight into the validity of these criteria as it used a delayed-response paradigm that is typical of those used in fMRI studies. Contrary to the evidence-scaling assumption, although the initial rate-of-rise of the CPP was sensitive to

the strength of sensory evidence, its integrated activity across the trial duration was not (Heekeren et al., 2004; Heekeren et al., 2006; Pleger et al., 2006; Liu and Pleskac, 2011). Thus, to the extent that ERPs relate to BOLD activity, one implication of the current findings is that contrasts based on these predictions will not necessarily produce differential activation of domain-general evidence accumulation regions when decision reports are withheld until the appearance of a response cue. In the present experiment, the influence of evidence strength on the build-up rate of the CPP was cancelled out in an integrated activity measure by its slow post-peak rate of decrease, although a larger discrepancy in build-up rates, driven by larger differences in coherence levels, would likely have yielded significant differences. In contrast, a well-established EEG index of motor preparation exhibited clear sustainment prior to the response cue when the stimulus-response mapping was known in advance. This result demonstrates that it cannot always be assumed that effector-selective and domain-general decision regions will exhibit the same dynamics across experimental conditions.

In contrast with previous reports (de Lange et al., 2013), β -band lateralisation failed to show any modulation by evidence strength. This non-significant result should not be interpreted as evidence that such a relationship is entirely absent, particularly given the relatively small differences in coherence levels in this study. However, this observation is noteworthy in light of previous reports that the relationship between coherence and the slopes of LIP responses is diminished (Roitman and Shadlen, 2002) or absent (Rao et al., 2012) under delayed response conditions. It is plausible that delayed decision reporting significantly loosens the coupling between evidence integration and motor preparation, so that even dynamical dependencies as fundamental as that related to coherence fail to exhibit parallels across signal types. This issue will need to be addressed in a future, dedicated investigation, however.

While β -band activity maintained a representation of the chosen action during the interval between decision and response when the stimulus-effector mapping was known in advance, neither β nor the CPP performed this role when the requisite effector could not be determined until presentation of the response cue. The question of how choice representations are actually maintained in delayed response scenarios will require further investigation to address (Shadlen and Kiani, 2013; Tsetsos et al., 2015).

The present chapter examined possible functional distinctions between the two distinct classes of decision variable signal during decisions with deferred actions with and without foreknowledge of stimulus-effector mapping. Salient distinctions were reported in the dynamics of abstract versus motor-selective decision signals, in terms of sustainment through response delays and contingency on foreknowledge of stimulus-response mapping. The present data also revealed that although the initial rate-of-rise of the CPP was sensitive to the strength of sensory evidence, its integrated activity across the trial duration was not. This finding is at direct odds with the evidence-scaling assumption that is most frequently used to classify domain-general decision structures in neuroimaging investigations of decision-making. Therefore, Chapter 3 not only revealed fundamental functional dissociations between abstract and effector-selective evidence accumulation mechanisms in the human brain but also highlighted the need for cross-talk between electrophysiological and functional neuroimaging studies of perceptual decision making. Using these new neural measurements that can be directly linked to perceptual performance, Chapters 2 and 3 made a significant contribution to our understanding of the decision-making architecture by providing additional insights into the functional characteristics of neural decision variable signals under differing experimental conditions. However, despite these advances in knowledge, much is still to be learned about the brain's decision-making machinery and particularly how it is implicated in the neurobiology of psychiatric disorders. Chapter 4 aimed to determine whether the neural metrics of the decision-making process can be used as a tool to enhance our understanding of clinical disorders which may be characterised by compromised decision-making capacities.

Chapter 4 Pinpointing the Neural Origins of Deficient Perceptual Decision-Making in Emerging Adults with Attention-Deficit/Hyperactivity Disorder

4.1 Introduction

ADHD is a prevalent neuropsychiatric developmental disorder that is characterised by a constellation of symptoms including inattention, impulsivity and hyperactivity (Visser et al., 2016). Inattention is defined as an inability to pay sufficient attention to detail or to sustain attention across an extended period of time and excessive distractibility. Hyperactivity refers to excessive movements, talking, restlessness and fidgeting. Impulsivity can be described as an inability to inhibit behaviour, which results in a tendency to interrupt and intrude upon others (American Psychiatric Association, 2013). ADHD is one of the most common diagnoses in educational and child mental health settings. As of 2011–2012, approximately 6.4 million U.S. children aged between 4 and 17 years old (11%) were reported to have a diagnosis of ADHD, a 42% increase since 2003 (Visser et al., 2016). While it was long considered a disorder of childhood, a growing body of evidence suggests that although certain ADHD symptoms diminish as a function of increasing age, others persist in to adulthood (Davidson, 2007; Cross-Villasana et al., 2015). More specifically, a wealth of longitudinal data indicates that as people get older the symptoms of hyperactivity-impulsivity diminish but the symptoms of inattention remain (Achenbach et al., 1995; Hart et al., 1995). This observation tallies with clinical research which suggests that inattentive symptoms are the most prevalently observed in adults with ADHD (Murphy and Barkley, 1996), with an empirical investigation by Millstein et al. (1997) indicating that inattention remained a persistent clinical feature in over 90% of a clinically-referred sample of adults with ADHD who showed a reduction in the hyperactive-impulsive symptoms. The decrease in ADHD symptoms in adulthood may reflect an amelioration of the disorder however, it may also reflect an issue of measurement namely, a diminished sensitivity of ADHD diagnostic criteria with age (Davidson, 2007). This issue has been the subject of considerable debate in the literature (see Davidson, 2007 for further discussion).

4.2 Causal Models of ADHD

Individuals with ADHD often experience difficulty in tailoring their behaviour appropriately to meet social and environmental demands. For example, they may find it challenging to await their turn in conversation or be easily distracted such that they find it difficult to focus on the task at hand. Hyperactive-impulsive and inattentive symptoms of this nature are thought to be driven by impairments in higher-order cognitive processes however, despite extensive empirical investigation the psychopathophysiology of ADHD remains very poorly understood (Sonuga-Barke, 2005). While numerous explanatory accounts of ADHD have been proposed in the literature no one model has received conclusive empirical validation and it follows that the neural underpinnings of the dysfunction(s) that cause ADHD have yet to be determined (Barkley, 1997; Sonuga-Barke, 2005).

Although this thesis does not aim to adjudicate between different causal models of ADHD, to provide context for the empirical work presented within this chapter, the present section will provide an overview of the key variants. Initial explanatory accounts of ADHD centred on single, common core dysfunctions (Sonuga-Barke, 2005). A number of simple causal models have been especially influential. The first class of models, known as the cognitive dysfunction models focus primarily on executive dysfunction that is driven by defective inhibitory control (e.g. Morton and Frith, 1995; Barkley, 1997). The second class of models, referred to as motivation-based dysfunction models are centred on defective communication of delayed rewards driven by impaired motivational processes (Sagvolden et al., 1998). A more recent model, the cognitive energetic model proposed by Sergeant (2000) attempts to link cognitive process dysfunction to physiological state dysfunction to account for the symptoms of ADHD. A groundbreaking empirical investigation by Solanto et al. (2001) revealed that inhibitory deficits (cognitive models) and delay aversion mechanisms (motivational models) have an independent but, equally pivotal role in predicting ADHD. Thus, a dual pathway model was devised which incorporated the two uncorrelated constructs in an effort to better explain the defining characteristics of ADHD.

4.2.1 Simple Causal Models

The cognitive dysfunction models have long been considered the dominant explanatory accounts of ADHD (Sonuga-Barke, 2005). Built on the modelling framework proposed

by Morton and Frith (1995), Barkley’s unified theory of ADHD also known as the behaviour inhibition model represents one of the most dominant cognitive dysfunction models (see Fig. 4.1). In this particular model the symptoms of ADHD are thought to be caused by a disruption of neuro-cognitive control systems which results in inhibitory-based deficits in executive function (Barkley, 1997; Sonuga-Barke, 2005). A number of studies have shown that children with ADHD exhibit some deficits in performance on tasks that tap into response inhibition and the constituent components of executive function (Clark et al., 2000; Sergeant et al., 2002) and a body of work exploring the neurobiological basis of ADHD has provided a functional basis for the model. More specifically, a combination of neuroimaging (Castellanos, 1997), pharmacological and genetic studies (see Levy and Swanson, 2001 for review) have indicated that the deficits in inhibitory-based executive function may be driven by an impairment in frontostriatal circuitry, namely in one of the proximate ganglia-thalamocortical circuits (Alexander et al., 1990), a simplified version of which is shown in Figure 4.1B.

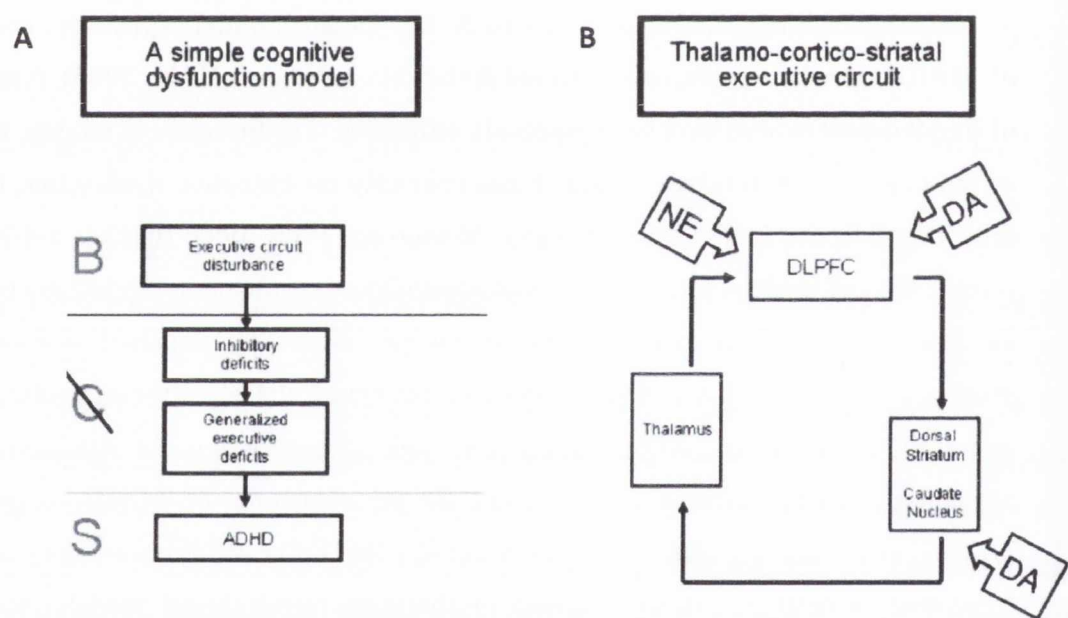


Figure 4.1: Schematic representation of a cognitive dysfunction model of ADHD (adapted from Barkley, 1997) and a simplified explanation of the associated frontostriatal circuitry (adapted from Alexander et al., 1990).

B, C and S represent biology, cognition and symptoms respectively. The slashed C represents cognitive deficit; NE, norepinephrine; DA dopamine, DLPFC, dorsolateral prefrontal cortex. Taken from Sonuga-Barke (2005).

An alternative explanatory account of ADHD can be found in the motivation-based dysfunction models (e.g. Sagvolden et al., 1998). The motivational models represent a departure from the cognitive theories described above in that suboptimal rewards processes are proposed to be the core dysfunction driving ADHD symptoms (Sagvolden et al., 1998). Figure 4.2 demonstrates one such model which extends the basic conceptualisation of Sagvolden et al. (1998). In this model, ADHD reflects the sequel of a neurobiological impairment in the power and efficiency with which the causal relationship between present actions and future rewards is communicated (Sonuga-Barke, 2005). The deficit causes a decrease in the control wielded by future rewards on current behaviour. That is, there is a decrease in the subjective value of the future reward and marked increase in the extent to which it is discounted (Sagvolden et al., 1998). This motivation-based dysfunction model finds some support in data which shows that children with ADHD not only experience difficulty engaging in a task for a long period of time but, that they are extremely sensitive to enforced delay periods and find it challenging to wait for a motivationally salient outcome (Sonuga-Barke et al., 1996; Tripp and Alsop, 2001)

The literature suggests that the inability to wait is divorced from the response inhibition impairments associated with executive function. That is, children are capable of waiting even when it entails inhibition, but they sometimes opt not to wait in circumstances where waiting does not entail inhibition (Sonuga-Barke, 1994). Notably, the site of neural dysfunction underpinning both inhibitory-based executive deficits and impaired signalling of delayed rewards appears to be in the frontostriatal regions of the brain. Although it is likely that the motivational and/or affective circuits play a much more pronounced role in the thalamocortical-basal ganglia circuit implicated in the inability to wait for delays (Barkley, 1997; Sonuga-Barke, 2005). An additional interesting neurobiological parallel can be drawn – dopamine is the critical neuromodulator of the two distinct thalamocortical circuits implicated in the cognitive dysfunction and motivation-based dysfunction models (Sonuga-Barke, 2005).

contingent on the energetic state of the child (Sergeant, 2000). The model is comprised of three distinct but interrelated levels (see Fig. 4.3). The first level reflects the mechanisms relevant to information processing: encoding, search and decision and motor organisation. The second level consists of three energetic pools: effort, arousal and activation (Sergeant, 2000). Effort is defined as having sufficient energy to meet the task demands and it may be used when the current state of the organism fails to meet the energetic state needed to meet the task demands (Sergeant, 2000). Arousal is phasic responding which is tightly aligned to stimulus processing. Conversely, tonic changes in physiological activity are thought to reflect activation which is the next pool on level two (Sergeant, 2000). The final level of the cognitive energetic model is an executive function mechanism which plays a role in planning, monitoring, error detection and correction.

Empirical evidence supporting the cognitive energetic model is drawn from behavioural studies that manipulate event rate that is, the speed at which stimuli are presented. A study by Chee et al. (1989) demonstrated that children with ADHD perform poorly when event rates are slow relative to when they are fast. Furthermore, on a Go/No-go task with three different rates of stimulus presentation, van der Meere et al. (1995) showed that children with ADHD made more commission errors (failing to withhold to the No-go target) in the fast and slow conditions relative to the medium speed conditions. Together these findings support the idea that inhibitory deficits in ADHD may be directly related to an inability to modulate one's own state or to allocate the requisite energy to meet task demands (Sergeant, 2000). The cognitive energetic model represents a valiant effort to comprehensively link psychological and physiological constructs to account for the defining features of ADHD. However, the utility of the model is undermined by the lack of direct measures of the energetic pools. Additionally, future research will be required to clarify the link between cognitive process dysfunction and physiological state dysfunction in ADHD (Sergeant, 2005).

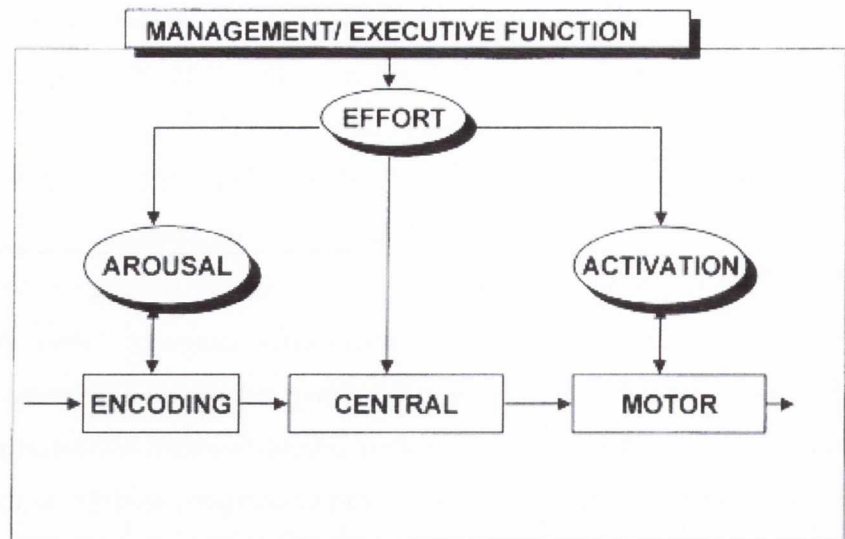


Figure 4.3: The cognitive energetic model (Sergeant, 2000).

Traditionally speaking ADHD has been conceptualised as a disorder that is the product of one core dysfunction. Accordingly, the cognitive and motivational models have been considered as competitive rather than complementary accounts of ADHD. A critical empirical investigation by Solanto et al. (2001) sought to directly assess which of the two theoretical accounts could best resolve the deficits observed in ADHD. The explanatory power of both classes of models was tested in school-age children with a diagnosis of combined ADHD (Solanto et al., 2001). Here, the children performed a stop-signal task, in which a prepotent response already initiated is stopped after a stop signal in addition to a choice reaction time task, in which they had to choose either a small, but immediate reward or a large, but delayed reward. Interestingly, the data revealed that there was no significant association between inhibitory failures and delay aversion. Furthermore, performance on both tasks was independently associated with ADHD and together the two measures enabled approximately 90% of children with ADHD to be accurately categorised. These data strongly suggested that inhibitory failures and delay aversion are two important but wholly independent features of ADHD (Solanto et al., 2001) and provided an impetus for developing a dual pathway model which could incorporate the two processes. The dual pathway models of ADHD are described in greater detail in the proceeding section.

4.2.2 Dual Pathway Models of ADHD

A recent dual pathway model (Sonuga-Barke, 2002, 2003) describes ADHD as the developmental outcome of two separate developmental processes (see Fig. 4.4). One pathway of the model describes ADHD as the sequel of disordered motivational processes that are modulated by the development of maladaptive delay aversion during early childhood (Sonuga-Barke, 2002). The second pathway of the model characterises ADHD as a disorder that is driven by inhibitory-deficits in executive function. Each of the two pathways is comprised of a number of elements that are expressed at distinct conceptual levels (Sonuga-Barke, 2002). The first component in the model is developmental outcome. Developmental outcome can be thought of as the behavioural symptoms of ADHD and task engagement (Sonuga-Barke, 2002). The model proposes that developmental outcomes are underpinned by psychological processes that are either core or secondary features of ADHD. For example, inhibitory-deficits of executive function would be classed as a core feature of ADHD and cognitive and behavioural dysfunction would be described as its secondary manifestation (Sonuga-Barke, 2002). The dual pathway model also proposes that delay aversion and inhibitory-deficits in executive function are not on the same conceptual level. Delay aversion is thought to be shaped by disruptions in reward processes in the brain and by factors in the child's early environment (Sonuga-Barke, 2002). In terms of the functional basis of the model, it is hypothesised that the dysregulation of the thought and action pathway stems from the frontal and pre-frontal higher order control circuits, with projections to the basal ganglia and into the striatum. The dysregulation of the motivational pathway is thought to be driven by impairments in the reward circuits and particularly in the ventral-striatal network. The neural circuits thought to underpin each pathway are both associated with the meso-limbic branch of the dopamine system. The model proposes that deficits in two pathways contribute to the delay aversion impairment which ultimately produces the symptoms of ADHD (Sonuga-Barke, 2002). Future research will be required to better characterise the connection between the two functionally distinct mechanisms and to further interrogate the possible existence of multiple independent pathways in ADHD.

AD/HD AS A DISORDER OF THE REGULATION
OF THOUGHT AND ACTION

AD/HD AS A MOTIVATIONAL STYLE WITH
ACQUIRED COGNITIVE CHARACTERISTICS

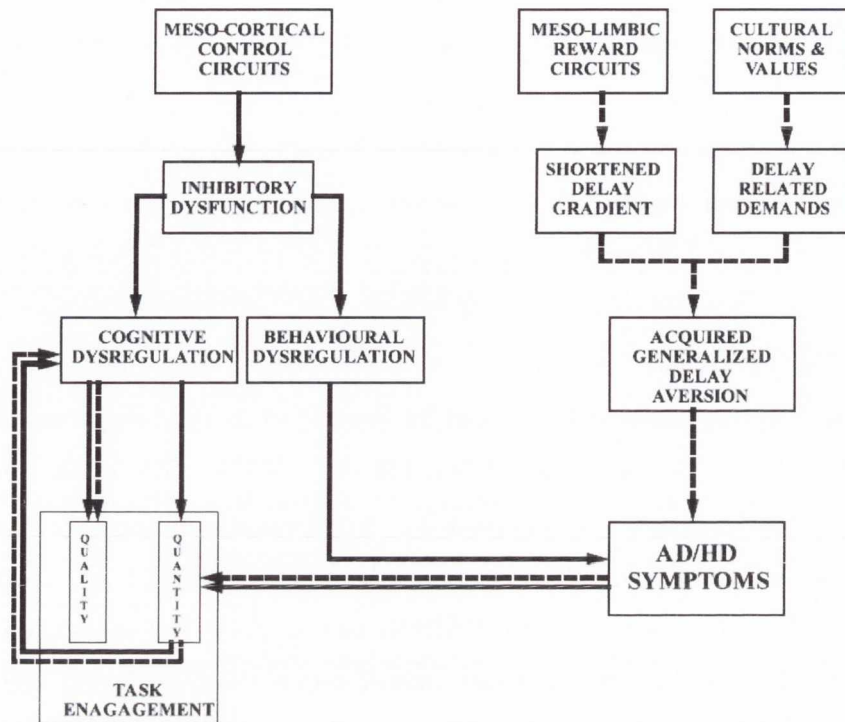


Figure 4.4 Schematic representation of the dual pathway model (Sonuga-Barke, 2002).

4.2.3 Challenges to the Causal Models of ADHD

The casual models of ADHD provide useful explanatory accounts of the condition from which we can generate testable predictions about the behavioural symptoms. However, there is a strong need for models of ADHD to evolve from phenomenological explanations of the disorder to those that are mechanistic and neurophysiologically plausible. For example, many of the causal models of ADHD propose that disruptions to specific neural circuits modulate the behavioural symptoms however; the causes or mechanisms that lend to such insults have yet to be identified. Furthermore, the distinctive contribution and interaction between genetic and environmental factors in determining the insults to the neural pathways and in mediating the role of neuromodulators in the models is yet to be determined (Sonuga-Barke, 2005). Additionally given the complexity of the neuropsychiatric disorder, it is likely that a single pathway or indeed a dual pathway account may not be exhaustive such that other undiscovered pathways may have a role in shaping the behavioural symptoms (Nigg, 2005). As the above section details a wide range of different models each with unique neurobiological origins have been proposed

to account for the defining characteristics of ADHD. Future research is required to determine whether these models can be reconciled to construct a unifying theory of ADHD.

ADHD is a highly heterogeneous disorder that is defined by different neuropsychological subtypes (Nigg, 2005). A meta-analysis of the neuroimaging literature by Nigg (2005) revealed that there is also consistent variation in the neural underpinnings of cognitive operations in individuals with and without a diagnosis of ADHD. The findings of the meta-analysis are inconsistent with work that implicates the same brain regions across studies with different clinical group compositions (Nigg, 2005). Equally, they do not support simple theoretical accounts of ADHD assuming that the disorder is the product of select deficits in isolated brain regions (Nigg, 2005). One possible avenue for future progress would be to capitalise on the recent advances in our understanding of the critical brain-behaviour relationships that underpin cognition to identify different pathophysiological subtypes of ADHD. For example, the novel EEG paradigm described in the preceding chapters could be used to link the independent contribution of each of the three stages of the perceptual decision-making process to poorer perceptual performance in ADHD. Pinpointing the neural underpinnings of ADHD will be critical to generating a more precise clinical phenotype and therefore, more targeted treatment options (Nigg, 2005; Sonuga-Barke, 2005).

4.3 Electrophysiological Investigations of ADHD

Behavioural investigations provide valuable insight into cognitive dysfunctions in ADHD. While an overt behavioural measure such as reduced accuracy reveals that processing may be impaired in a clinical disorder; it tells us nothing about the contribution made by each distinct stage(s) of information processing to the observed deficit. By providing a window into the sensory and cognitive processes, ERPs provide a level of analysis additional to behavioural measures, allowing for an examination of typical and atypical processes in the brain (Barry et al., 2003b). As alluded to in the preceding section, this type of information is fundamental in clinical research where disorders are highly heterogeneous or characterised by shared cognitive deficits such that it is difficult to generate a neuropsychological profile that distinguishes ADHD from other disorders such as autism spectrum disorder (Nigg, 2005; Sonuga-Barke, 2005). As it was long considered a disorder of childhood many of the electrophysiological investigations of

ADHD have been carried out in child and adolescent populations. As very few studies have used adult populations, much of the literature discussed in the following sections reflects a younger population than was used in the present empirical work. The literature suggests that children, adolescents and adults with ADHD exhibit the same electrophysiological abnormalities but, that the measured effects may decline with increasing age (Bresnahan and Barry, 2002). A very brief overview of electrophysiological investigations of cognition in ADHD is provided below.

4.3.1 Event-related Potential Studies of ADHD

A complex range of ERP deficits have been associated with ADHD (Barry et al., 2003a). Most relevant to the present thesis, empirical investigations have examined the impact of the disorder on early sensory and later P300 components on a wide variety of tasks examining attention and inhibitory control (Johnstone et al., 2013). EEG studies of ADHD employing oddball tasks have reliably shown that children and adolescents in the patient group exhibit atypical early sensory ERP components relative to the healthy age-matched controls. For example, Brown et al. (2005) showed that children with the hyperactive-inattentive subtype of ADHD demonstrated reduced N1 and P2 amplitude in response to both target and non-target stimuli on visual and auditory oddball tasks. In adolescents with co-morbid conduct disorder and ADHD, on a single-stimulus oddball task, Du et al. (2006) found a delayed P2 and N2 latency in the clinical group relative to the healthy age-matched controls. On a similar vein, Senderecka et al. (2012) demonstrated that children with the combined subtype of ADHD had greater P2 and attenuated N2 amplitudes in response to both target and non-target stimuli in an auditory oddball task. This snapshot of the literature strongly suggests that the sensory stage of information processing is affected by ADHD. However, given that an abundance of research suggests that early sensory components are modulated by attention (see Luck et al., 2000 for a review), it remains to be determined whether the deficits in ADHD occur at the sensory stage or whether they are the product of deficient attentional allocation. Traditionally speaking, questions of this nature are difficult to address as the tests used to assess cognition recruit a complex chain of neural processes that are difficult to disentangle using standard non-invasive techniques such as the ERP technique. Therefore, there is a glaring need to develop paradigms within which the discrete neural

mechanisms required for task performance can be both clearly defined and independently measured.

Arguably the most robust electrophysiological correlate of impaired cognitive processing in ADHD can be found in the P300 complex which encompasses two functionally distinct signals – the frontal and parietal P300 components often labelled the ‘P3a’ and ‘P3b’ respectively. Chapter 2 of the present thesis demonstrated functional equivalence between the parietal P300 (P300) and the CPP such that it is thought to reflect an accumulation-to-bound decision variable signal. While, the frontal P300 is a fronto-central ‘novelty’ signal that is elicited by unexpected stimuli and is thought to reflect an attention orientating mechanism (Polich and Criado, 2006). A reasonably consistent pattern of results has emerged in the literature such that children and adolescents with ADHD reliably exhibit attenuated stimulus-aligned frontal and parietal P300 amplitude on a wide variety of tasks that tap into selective attention and inhibitory control (Brandeis et al., 2002; Lawrence et al., 2005; Spronk et al., 2008; Doehnert et al., 2010).

Brown et al. (2005) demonstrated that children with the hyperactive-inattentive subtype of ADHD exhibited reduced stimulus-aligned P300 amplitude in response to both target and non-target stimuli on visual and auditory oddball tasks. The authors subsequently showed that children with both the hyperactive-inattentive and combined subtypes of ADHD also had reduced stimulus-aligned P300 amplitude on a multi-modal oddball task (Brown et al., 2005). A similar pattern of results was observed in adolescents with co-morbid conduct disorder and ADHD. Here on a single-stimulus oddball task, the patient group demonstrated an abnormal stimulus-aligned P300 response in the form of a delayed latency and attenuated component amplitude (Du et al., 2006). Senderecka et al. (2012) also demonstrated that children with the combined subtype of ADHD exhibited reduced stimulus-aligned P300 amplitude in response to target stimuli on an auditory oddball task. Mirroring the pattern of results observed for the P300, a number of studies have also indicated that both children and adolescents with ADHD demonstrate an attenuated stimulus-aligned frontal P300 component in response to novel distractor stimuli (Gumenyuk et al., 2005; Keage et al., 2006). The findings are much more equivocal when it comes to P300 latency. A proportion of studies using the oddball tasks have reported that P300 latency does not reliably discriminate ADHD (e.g. Johnstone and Barry, 1996) while others have reported shorter (e.g. Loiselle et al., 1980) or longer P300 latencies (e.g. Winsberg et al., 1997; Du et al., 2006) in the clinical group. The atypical frontal P300 component is thought to index disrupted attentional orientating or allocation

in ADHD (Barry et al., 2003a; Johnstone et al., 2013). While the abnormal parietal P300 responses that characterise the disorder have variously been interpreted as deficiencies in attentional or resource allocation, in stimulus evaluation or in the discrimination and classification of stimuli (Barry et al., 2003a; Johnstone et al., 2013). Accordingly, this lack of consensus surrounding the functional significance of the P300 has greatly limited its interpretability as a neuro-cognitive marker of ADHD.

The new mechanistic theory of the P300 as a dynamically evolving neural decision variable signal provided in Chapter 2 has significant implications for the interpretation of this neural signal in clinical research. After all, it reveals that there is a whole host of reasons as to why the stimulus-aligned P300 amplitude might be diminished in ADHD. For example, evidence accumulation may have started at a later time, evidence may have been accumulated at a slower and more variable rate, or because a reduced decision threshold necessitated less evidence accumulation to trigger action. To date, the relative contribution of each of these critical characteristics of the P300 to the diminished component amplitude had been overlooked due to a reliance on tasks involving discrete stimuli and a narrow focus on stimulus-aligned peak amplitude measurements which overlooks the dynamic and progressive nature of this neural signal.

4.4 Perceptual Decision-Making in ADHD

As detailed in the section 4.1 above, many explanatory accounts of ADHD focus on higher order aspects of cognition such as executive function, response inhibition and reward processes. It is generally assumed that more basic neural processes such as perceptual decision-making are fully intact. However, this assumption awaits conclusive validation and the electrophysiological evidence presented in the section above suggests that sensory and decision processes as indexed by sensory-evoked potentials and the P300, respectively, may actually be impaired in ADHD. This is a concern since efficient perceptual decision making is an essential component for any cognitive task. For example, a commonly used paradigm in ADHD research is the Go/No-go paradigm which is intended to measure response inhibition. On this task the participant must respond to one type of stimulus (Go) with a button-press as quickly as possible while, withholding the same response to an alternative No-go stimulus. Any impairment that impacts on the ability to quickly and accurately translate sensory information into appropriate action would impact on performance on such a task and thus it is not necessarily the case that

errors on the Go/No-go paradigm are solely attributable to response inhibition. Indeed most neuropsychological research in ADHD is predicated on the assumption that individuals with ADHD are as capable of making a timely and accurate perceptual decision as healthy controls (Mulder et al., 2010). However, it remains to be determined whether or not this is the case and recent data suggests that perceptual decision-making may be compromised in ADHD (Mulder et al., 2010; Cross-Villasana et al., 2015).

4.4.1 Behavioural Evidence

Very few empirical investigations have explored the integrity of the perceptual decision-making process in ADHD. One exception to the rule is a behavioural study by Mulder et al. (2010) which used a variant of the random-dot motion task to show that children with ADHD cannot optimise the speed-accuracy trade-off as effectively as typically developing children (Mulder et al., 2010). More specifically, although those with ADHD demonstrated a strong preference for speed, they did not make more mistakes than the healthy age-matched controls in either the speed or accuracy conditions. Indeed, the impact of the suboptimal speed-accuracy trade-off on performance really only became apparent in the speed sessions. Here, although the children with ADHD were just as accurate as the controls they scored fewer points overall. Therefore, the smaller strategic adjustment of the decision boundary was not optimal in terms of maximising reward outcomes. Based on these observations, Mulder et al. (2010) concluded that children with ADHD did not optimise the speed-accuracy trade-off not because they were incapable of making rapid decisions but because they could not appropriately adjust the decision boundary to optimise task performance (Mulder et al., 2010). To determine whether the optimisation of decision behaviour was directly related to the ADHD behavioural phenotype, Mulder et al. (2010) assessed whether the decision parameters were predictive of ADHD symptoms. A regression analysis revealed a strong negative linear relationship between the speed-accuracy trade-off and both self-reported and teacher ratings of impulsivity/hyperactivity symptoms (Mulder et al., 2010). Therefore, impairments in basic perceptual decision-making processes may represent a contributing factor to a defining symptom of ADHD.

4.4.2 Electrophysiological Evidence

Further support for the idea that basic perceptual decision-making deficits may be at the heart of ADHD can be found in a recent study by Cross-Villasana et al. (2015). In this study the exceptional temporal resolution of the ERP technique was exploited to link the slower reaction times observed in adult ADHD with delays in both the attentional and response selection stages of information processing as indexed by a posterior contralateral negativity and the lateralised readiness potential components, respectively. A correlation between the latencies of the posterior contralateral negativity and the ADHD symptom ratings indicated that this attentional signal could serve as a neurocognitive marker of ADHD. Despite this mounting evidence that individuals with ADHD exhibit performance deficits on basic perceptual decision-making tasks that can be linked to the symptoms of ADHD, the neural underpinnings of compromised decision-making capacities remain poorly understood and given that it is a feature of numerous psychiatric disorders, there is a major imperative to determine disease-specific etiological pathways for ADHD. The search for such pathways has been hindered by the fact that the paradigms used to test perceptual decision-making often evoke a complex chain of neural processes that make it difficult to disentangle the respective contributions of the distinct stages of neural information processing to task performance using non-invasive techniques such as functional imaging and EEG (Cross-Villasana et al., 2015; Kelly and O'Connell, 2015).

4.5 Aims and Objectives

In the present chapter a novel contrast discrimination paradigm was used to probe possible perceptual decision-making deficits in emerging adults with ADHD. The EEG paradigm provided access to clearly-defined and independently measured neural metrics of the perceptual decision-making process that could in turn be directly linked to overt behavioural performance on the task. It was hypothesised that ADHD would impact on at least one or more stages of the perceptual decision-making process such that:

1. Emerging adults with ADHD would demonstrate poorer perceptual performance on a contrast discrimination task relative to healthy age-matched controls.
2. The performance deficit would be underpinned by an abnormal pattern of brain activity such that there would be measurable group differences in one or more of the electrophysiological indices of sensory encoding, decision formation, response execution and attentional allocation.

3. The performance deficit would be correlated with specific parameters (build-up rate, peak amplitude and latency) of the sensory, decision, motor preparation and attentional signals.
4. Well-established cognitive deficits in ADHD would correlate with perceptual performance and with certain parameters (build-up rate, peak amplitude or latency) of the sensory, decision, motor preparation and attentional signals. This hypothesis was included to determine whether the highly simplified perceptual decision-making task used in the present chapter actually taps into a fundamental mental process that is common to a wide variety of cognitive tasks.
5. Consistent with a wealth of literature demonstrating a reduced stimulus-aligned P300 component in ADHD – the patient group would exhibit attenuated CPP amplitude.
6. The attenuated CPP amplitude would be directly linked to a slower or more variable accumulation of sensory evidence or to a reduced decision threshold.

4.6 Methods

4.6.1 Participants

24 ‘emerging’ adults with ADHD (9 females, 3 left-handed) and 24 controls (14 female, 1 left-handed) participated in this study (see Table 4.1 for a summary). There was no significant difference between the two groups in mean age, gender, handedness, years in education or full scale IQ as measured using ten subsets of the Wechsler Adult Intelligence Scale (WAIS-IV^{UK}, block design, similarities, digit span, matrix reasoning, vocabulary, arithmetic, symbol search, visual puzzles, information, coding; all $p > 0.1$). The demographic data for the two participant groups are summarised in Table 4.1. All participants had normal or corrected-to-normal vision and were withdrawn from any stimulant medication 36 hours prior to testing, where relevant. Written informed consent was obtained from all participants prior to testing, where participants were under the age of 18 years old, written informed consent was obtained from the parent or guardian in addition to the minor’s written assent. All procedures were approved by the ethical review boards of the Linn Dara Child and Adolescent Mental Health Service, Ballyfermot and Trinity College Dublin in accordance with the Declaration of Helsinki.

Recruitment and screening

The participants with ADHD were referred by a psychiatrist following their attendance at the outpatient clinics of the Child and Adolescent Mental Health Service or else were recruited through support groups or via advertisements on social media and at Dublin Universities. Patients volunteered for the present study following a telephone call. A detailed investigation of current symptom levels as well as a retrospective assessment of childhood symptoms was undertaken. To achieve a retrospective diagnosis of ADHD in childhood or to achieve a diagnosis in adulthood, each patient must have met 6 of the 9 DSM-IV criteria on either the inattention or hyperactivity/impulsivity axis at the time of assessment. Additionally, each patient had to report persistent ADHD symptoms from childhood to adulthood and have experienced moderate to severe levels of impairment across a range of different settings attributable to the symptoms of ADHD. Of the sample recruited, seven patients were taking psychostimulant medication, five had taken stimulant medication in the past but had ceased and twelve were stimulant-naïve.

Healthy controls were recruited via advertisements on social media and at Dublin Universities and received €45 as a defrayal of expenses. Prior to being included in the study all participants were screened in an extensive telephone interview in which detailed information was obtained about the participant's personal and family history of ADHD, learning disability, psychiatric, neurological or medical disorders, use of medication and substances. Also, prior to testing all participants completed a number of psychiatric measures, including the Conners Adult ADHD Rating Scale (CAARS-S: L, Conners et al., 1999) or the Conners 3 ADHD Rating Scale (Conners 3 S: L, Conners, 2008) if the participant was under the age of 18 years old, a Substance Use Questionnaire (Molina and Pelham Jr, 2003) and the Wender Utah Rating Scale, a retrospective measure of ADHD symptoms in childhood (WURS; Ward et al., 1993). Self-reported comorbid Axis I disorders in the patient group included current depression ($N = 7$), anxiety disorder ($N = 4$), oppositional defiant disorder ($N = 1$). Two control and four ADHD participants were using cannabis recreationally (more than once a month).

Exclusion criteria

Participants were excluded from the study if they reported any previous history of psychosis, organic brain disorder, photosensitive epilepsy, serious head injury or learning disability. Controls were only included if they had no family history of ADHD and if they were not suspected of having ADHD based on the screening tests. The cut-off for inclusion

of controls was a self-rated T-score of less than 65 (95th percentile) on each of the three DSM-IV symptom subscales of the CAARS or a self-rated T-score of less than 66 (95th percentile) on each of the DSM-IV Inattention and Impulsivity/Hyperactivity symptom subscales of the Conners 3, and a self-rated score of less than 36 on the WURS. A cut-off score in excess of 36 on the WURS has been found to correctly identify 96% of adults with ADHD and 96% of normal participants (Ward et al., 1993). The ADHD group was required to have a self-rated T-score greater than 65 on one of the three DSM-IV CAARS subscales or a self-rated T-score of greater than 66 on either of the DSM-IV Inattention and Impulsivity/Hyperactivity symptom subscales of the Conners 3, in addition to a self-rated score of more than 36 on the WURS (see Table 4.1).

4.6.2 Study design

All participants presented at Trinity College Dublin for two separate testing sessions. In the initial session, written informed consent or, where relevant, assent was obtained in addition to some basic demographic information. Participants then completed a number of measures, including the Conners Adult ADHD Rating Scale (CAARS-S: L, Conners et al., 1999) or the Conners 3 ADHD Rating Scale (Conners 3 S: L, Conners, 2008) if the participant was under the age of 18 years old, a Substance Use Questionnaire (Molina and Pelham Jr, 2003) and the Wender Utah Rating Scale (Ward et al., 1993). Participants were then administered the ten core subsets of the WAIS-IV^{UK} (Wechsler, 2010; Block Design, Similarities, Digit Span, Matrix Reasoning, Vocabulary, Arithmetic, Symbol Search, Visual Puzzles, Information and Coding).

In a second session which typically occurred 7 to 14 days following the first session, a number of additional neuropsychological assessments were administered to the participant including: pen and paper versions of the Stroop Colour and Word test (Golden and Freshwater, 2002), the Trail Making Test, parts A and B (Battery, 1944) and a computerised version of the Sustained Attention to Response Task (SART; Robertson et al., 1997). Participants were then taken to the EEG laboratory where 128-channel EEG data were recorded while they completed a two-alternative forced choice contrast discrimination task (see Fig. 4.6).

Table 4.1: Summary of demographic data for the control and ADHD groups.

	ADHD	Control	<i>t</i>	<i>p</i>
	Mean (<i>SD</i>)	Mean (<i>SD</i>)		
N	24 (9 female)	24 (14 female)		
Age	20.0 (3.1)	19.96 (2.3)	$t_{(46)} = 0.05$	0.96
Full scale IQ	109.1 (19.7)	114.5 (13.2)	$t_{(40.1)} = 1.1$	0.3
Years in education	14.96 (2.1)	15.7 (2.4)	$t_{(46)} = 1.2$	0.3
WURS (raw score)	58.4 (14.6)	21.0 (7.8)	$t_{(35.1)} = 9.9$	0.0001***
CAARS DSM-IV Inattention (T)	80.4 (8.3)	48.5 (7.3)	$t_{(35)} = 12.5$	0.0001***
CARRS DSM-IV Hyperactive-Impulsive (T)	66.3 (10.7)	40.8 (7.2)	$t_{(35)} = 8.5$	0.0001***
CAARS DSM-IV Total (T)	78.3 (8.6)	44.4 (7.3)	$t_{(35)} = 12.9$	0.0001***
CAARS DSM-IV ADHD Index (T)	63.3 (7.9)	42.95 (4.9)	$t_{(35)} = 8.8$	0.0001***
Conners DSM-IV-TR Inattention (T)	74.7 (13.9)	46.8 (5.8)	$t_{(6.94)} = 4.5$	0.003**
Conners DSM-IV-TR Impulsivity/Hyperactivity (T)	72.3 (11.7)	50.2 (8.6)	$t_{(9)} = 3.5$	0.007**
Conners DSM-IV-TR Conduct Disorder (T)	62.0 (18.4)	48.6 (10.8)	$t_{(9)} = 1.4$	0.19
Conners DSM-IV-TR Oppositional Defiant Disorder (T)	63.8 (16.5)	47.2 (10.0)	$t_{(9)} = 1.97$	0.08
Conners ADHD Index (% Probability)	82.0 (15.1)	24.4 (15.7)	$t_{(9)} = 9.9$	0.0001***

*Denotes the level of statistical significance: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

4.6.3 Neuropsychological Assessments

A number of neuropsychological assessments were administered to all participants, including: a computerised version of the Sustained Attention to Response Task (SART; Robertson et al., 1997), the Stroop Colour and Word test (Golden and Freshwater, 2002), the Trail Making Test, parts A and B (Batterly, 1944) and the ten core subsets of the

WAIS-IV^{UK} (Wechsler, 2010; Block Design, Similarities, Digit Span, Matrix Reasoning, Vocabulary, Arithmetic, Symbol Search, Visual Puzzles, Information and Coding).

Sustained Attention to Response Task

All participants performed one 5.5-minute block of the Fixed version of the SART (Robertson et al., 1997; see Fig. 4.5) in which the stimuli were presented sequentially from '1' through '9' on a 51 cm CRT monitor with a refresh rate of 100 Hz and a resolution of 1024 × 768 Hz. Over the course of the block, 450 digits were presented, representing 50 runs of the 1–9 sequence. Digit font sizes varied between 100, 120, 140, 160 and 180 in Arial font. Digits were presented 0.25° above a central white fixation cross on a gray background. The task specifications were programmed and stimuli were delivered using the Presentation software package (Neurobehavioral Systems). For each trial, a digit was presented for 300 ms followed by an Inter-Stimulus-Interval (ISI) of 800 ms. Participants were instructed to respond with a left mouse button press with their right forefinger upon presentation of each digit (Go trials) with the exception of the 50 occasions when the digit 3 (No-go target) appeared where they were required to withhold their response. Participants were asked to time their button press to the offset of each stimulus as this type of 'response-locking' has been shown to reduce inter-individual variability and eliminate speed-accuracy trade-offs (Manly et al., 2000). The behavioural measures of performance on this task included: errors of commission (failing to withhold to the No-go target), errors of omission (failing to respond to a Go stimulus), reaction time (Go Targets), and reaction time variability as measured by the coefficient of variation (standard deviation of reaction time divided by mean reaction time).

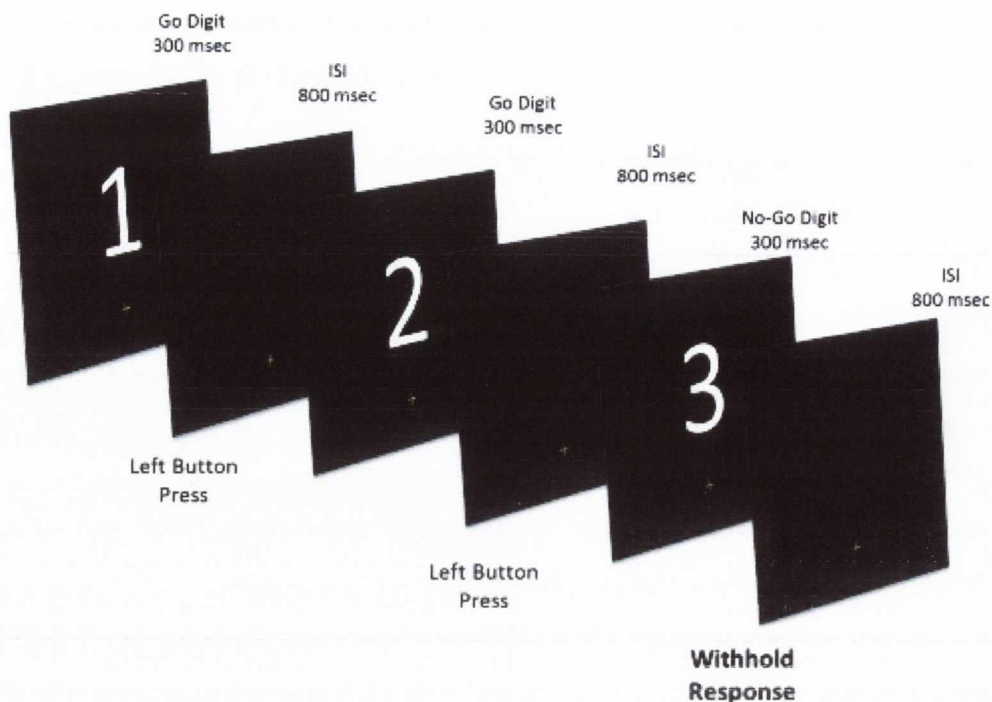


Figure 4.5: Schematic of the Sustained Attention to Response Task.

In the SART, participants were instructed to respond to each digit (Go trials) with the exception of 50 occasions when the digit 3 (No-go target) appeared and they were required to withhold their response.

Wechsler Adult Intelligence Scale

Participants completed the ten core subsets of the WAIS-IV^{UK} (Wechsler, 2010; Block Design, Similarities, Digit Span, Matrix Reasoning, Vocabulary, Arithmetic, Symbol Search, Visual Puzzles, Information and Coding). This assessment was employed not only to measure full scale IQ but to yield a measure of cognitive function on four key domains that may be of relevance to the perceptual decision-making process. Specifically, the test framework for the WAIS-IV^{UK} is divided into four index scales that provide a measure of: Verbal Comprehension, Perceptual Reasoning, Working Memory and Processing Speed (Wechsler, 2010). Each of the four index scales is described in greater detail below.

- 1) ***Verbal Comprehension Index*** – consisted of three core subsets of the WAIS-IV^{UK} (Similarities, Vocabulary and Information). In the Similarities subtest the examinee was presented with two words that represent common objects or concepts and were asked to describe the manner in which they were similar. In the Vocabulary subtest for picture items, the examinee named the objects

presented visually and for verbal items, the examinee defined words that were presented both visually and orally. In the Information subtest, the examinee was asked to answer questions that addressed a broad range of general knowledge topics (Wechsler, 2010).

- 2) ***Perceptual Reasoning Index*** was comprised of three core subsets of the WAIS-IV^{UK} (Block Design, Matrix Reasoning and Visual Puzzles). In the Block Design subset, the examinee viewed a model and a picture or else a picture only and recreated the design using red and white blocks within a specified time limit. In the Matrix Reasoning subtest, the participant viewed an incomplete matrix or series and was required to select the response option that accurately completed the matrix or series. In the Visual Puzzles subset, the participant was shown a completed puzzle and was asked to select the three response options that when combined, accurately reconstructed the puzzle (Wechsler, 2010)
- 3) ***Working Memory Index*** reflected two core subsets of the WAIS-IV^{UK} (Digit Span and Arithmetic). The Digit Span subtest consists of the Digit Span Forwards, Backwards and Sequencing. In the Digit Span Forwards, the participant was read a sequence of numbers and was asked to regale the numbers in that exact sequence. In the Digit Span Backwards, the participant was read a sequence of numbers and was asked to regale the numbers in reverse order. In the Digit Span Sequencing, the participant was read a sequence of numbers and was asked to recall them in ascending order. In the Arithmetic subtest, the examinee had to mentally solve a series of arithmetic problems that became progressively more difficult within a specified period of time (Wechsler, 2010).
- 4) ***Processing Speed Index*** consisted of two core subsets of the WAIS-IV^{UK} (Symbol Search and Coding). In the Symbol Search subset, the participant scanned a search group and indicated whether or not one of the symbols in the target group matched those in the search group, within a specified time limit. In the Coding subset, the participant used a key to copy symbols that were paired with numbers within a pre-determined time limit (Wechsler, 2010).

For the purposes of interpretation, the raw score of each subtest on a given index were scaled and summed to provide a single measure of performance for each of the four index scales.

The Trail-Making Test (Parts A and B)

Both parts of the Trail Making Test consisted of 25 circles distributed over a sheet of paper. In Part A, the circles were numbered 1–25, and the participant was instructed to draw lines to connect the numbers in ascending order. In Part B, the circles included both numbers (1–13) and letters (A–L); as in Part A, the participant was advised to draw lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). Prior to commencing each part of the assessment the experimenter would demonstrate the test to the participant using a sample sheet. Once familiar with the task instructions, the participant was instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. No time limit was imposed and performance was simply measured as the time it took, in seconds, for the ‘trail’ to be completed on each part of the assessment. If the participant made an error, the experimenter would verbally highlight it and allow for it to be corrected such that errors only affected the participant’s score in that the correction of errors is included in the completion time for the task (Battery, 1944).

The Golden Stroop Colour and Word Test

All participants were administered a standardised version of the Golden Stroop Colour and Word Test (Golden and Freshwater, 2002) which consisted of three pages in a single booklet. Each page was comprised of 100 items, presented in five columns of 20 items. The Word page consisted of the words “RED”, “GREEN”, and “BLUE” arranged randomly and printed in black ink on a white 8.5 × 11 sheet of paper. No word followed itself within a colour. Participants were advised to read the words on a column-by-column basis as quickly as possible within a 45 second word limit. If they made a mistake, the experimenter said “No” which signalled to the participant that they needed to correct the error and to proceed without stopping until the time limit had elapsed.

The Colour page consisted of 100 items, all written as “XXXX”, printed in red, green, or blue ink. No colour was permitted to follow itself in a column, or to match the corresponding item on the Word page. Participants were instructed to name the colours on a column-by-column basis as quickly as possible within a 45 second limit. The Colour-Word page consisted of words from the Word page printed in Colours from the Colour page. The two pages were blended item for item and in no case did the word and colour it was printed in match one another. This time the participants were asked to name the colour of the ink the words were printed in, ignoring the word that was printed for each

item on a column-by-column basis as quickly as possible within a 45 second time limit. On all three tests, if the participant finished the entire page within the 45 second time limit they were instructed to begin again and to continue reading until they were advised to stop.

The Stroop Test yields three basic measures of performance: raw Word, Colour and Colour-Word scores which reflected the number of items completed on each of the stimulus sheets. Although, errors are not explicitly counted on this task they do result in an overall lower score as the participant must repeat and correct any item that was incorrect. A raw Interference score was also calculated by subtracting the predicted Colour-Word score from the uncorrected raw Colour-Word score. For the purposes of interpretation all raw scores were subsequently converted to T-scores.

Table 4.2: Definitions of the cognitive domains and the tasks used to assess each domain.

Cognitive Domain	Functional Definition	Tasks Measuring Domain
Response Inhibition	Ability to inhibit prepotent response in order to make correct but, less common response.	SART Stroop Colour-Word test
Selective Attention	Ability to maintain goal-directed focus on one aspect of the environment while ignoring irrelevant aspects.	The Trail-Making Test (Part B) Processing Speed Index of the WAIS-IV ^{UK} (Symbol Search and Coding) The Stroop Colour-Word test
Sustained Attention	Ability to maintain an alert, goal-directed focus in the absence of exogenous stimulation.	SART
Perceptual Reasoning	Capacity to examine an issue, call upon visual-motor and visual-spatial skills, organise thoughts, create solutions, and then test them.	Perceptual Reasoning Index of WAIS-IV ^{UK} (Block Design, Matrix Reasoning and Visual Puzzles).
Processing Speed	Ability to focus attention and quickly scan, discriminate between, and sequentially order visual information.	The Trail-Making Test (Parts A and B) Processing Speed Index of WAIS-IV ^{UK} (Coding and Symbol Search).
Verbal Comprehension	General verbal skills, including verbal fluency, ability to understand and use verbal reasoning and verbal knowledge.	Verbal Comprehension Index of the WAIS-IV ^{UK} (Similarities, Vocabulary and Information).
Working Memory	Ability to maintain task-relevant information online for brief periods of time and to manipulate or use that information to guide subsequent behaviour.	Working Memory Index of WAIS-IV ^{UK} (Digit Span and Arithmetic).

4.6.4 Two-alternative Forced Choice Contrast Discrimination Task

Continuous EEG data were recorded while participants completed a discrete-trial two-alternative forced choice contrast discrimination task. Participants monitored a circular pattern stimulus (inner radius = 1° , outer radius = 6°) centred on fixation which consisted of two overlaid gratings tilted at -45° and $+45^\circ$ relative to the vertical midline for a relative contrast increase in either the left-tilted or right-tilted grating (see Fig. 4.6). A simultaneous left and right mouse button click was made to initiate each trial upon which time a centrally-presented fixation point and circular pattern stimulus appeared. Following a delay period which varied on a trial-by-trial basis (800, 1200 or 1600 ms), in which the stimulus contrast was held constant at 50%, the contrast level of one pattern increased from 50% to 72.5% while, the contrast level of the other pattern decreased by the same increment over a 100 ms period. The simultaneous increase and decrease in contrast was implemented to ensure that the overall net contrast remained the same therefore, avoiding the generation of a substantial visual evoked potential. On detecting the contrast change, participants were advised to make a mouse-press in the direction in which the tilted-pattern became 'stronger' as quickly as possible with the target remaining on screen for a total 2000 ms even if a press was made. Feedback pertaining to the number of trials responded to correctly out of a maximum of 30 was provided at the end of each block to promote effort maintenance.

Testing took place in a dark, sound attenuated room, with participants seated with their head supported by a headrest, at a distance of approximately 57 cm from the visual display. Participants always completed two practice blocks of the task to ensure they were well acquainted with the targets and instructions prior to commencing. Each participant completed ten, 2.5 minutes blocks of the task (30 trials per block). This resulted in total testing time of 35 minutes including breaks were necessary. The visual stimuli were presented against a black background on a 51 cm CRT monitor with a refresh rate of 100 Hz and a resolution of 1024×768 Hz.

The contrast discrimination task facilitated the independent measurement of a number of neural metrics that could be directly linked to behavioural performance (see Fig. 4.6). For example, the left-tilted and right-tilted gratings were phase reversed at 20 Hz and 25 Hz, respectively to facilitate measurement of a distinct steady-state visual evoked potential (SSVEPs) to each. A subtraction of the two SSVEPs provided a neural measure of the participant's representation of the 'sensory evidence' on each trial that is,

how much more intense one grating was relative to the other. As in previous chapters, the CPP provided a neural signature of abstract evidence accumulation. Preparation of the decision-reporting action (mouse press) was captured via β -band activity over premotor cortex. Finally, the magnitude of α -band activity recorded over parieto-occipital electrodes was employed as a measure of attentional engagement during the performance of the task (Kelly and O'Connell, 2013).

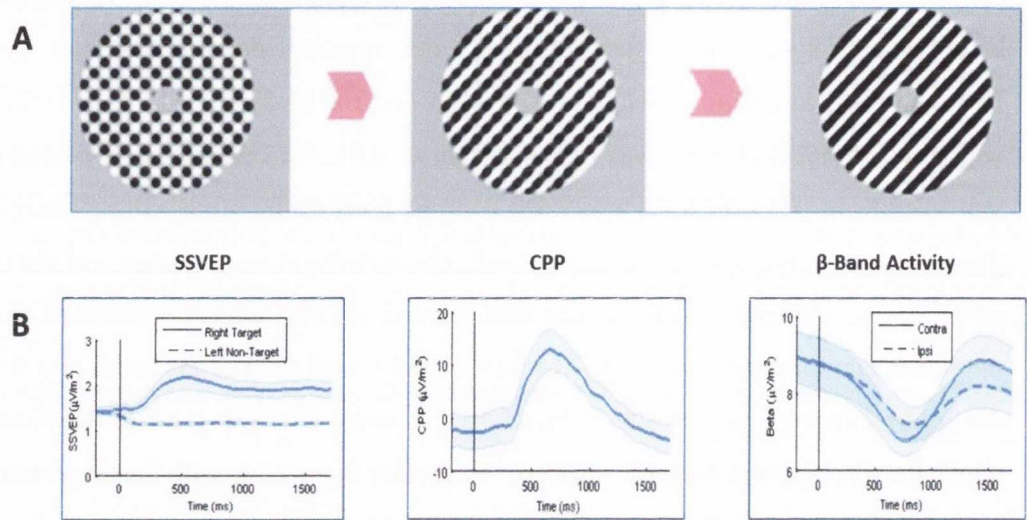


Figure 4.6: Schematic of the two-alternative forced choice contrast discrimination task and the neural metrics of the perceptual decision-making process. **A**, Participants monitored a circular pattern stimulus centred on fixation which consisted of superimposed left and right-tilted gratings. Following a delay period which varied on a trial-by-trial basis (800, 1200 or 1600ms), in which the stimulus contrast was held constant at 50%, the contrast level of one tilted grating increased from 50% to 72.5% while, the contrast level of the other pattern decreased by the same increment over a 100 ms period. Here, the stimulus is captured during an emerging right-tilted pattern (middle and right). Upon detecting the contrast increase, participants made a press in this direction. **B**, Sensory evidence (left), central accumulator (middle) and motor preparation (right) signals can be traced in parallel on the task. The SSVEP increases and decreases in response to a rightward target and a leftward non-target grating respectively. The fidelity with which sensory evidence is encoded in primary visual cortex is measured by calculating the difference in SSVEP amplitude generated by the two gratings. The β -band trace exhibits a gradual desynchronisation upon evidence onset that is more pronounced over electrodes contralateral to the chosen hand.

4.6.5 EEG Acquisition and Pre-processing

Continuous EEG data were acquired using an ActiveTwo system (BioSemi, The Netherlands) from 128 scalp electrodes and digitised at 512 Hz while participants performed the two-alternative forced choice contrast discrimination task. Vertical and horizontal eye movements were recorded using two vertical electrooculogram (EOG) electrodes placed above and below the left eye and two horizontal electrodes placed at the outer canthus of each eye, respectively. Data were analysed using custom scripts in MATLAB (MathWorks, Natick, MA), drawing on EEGLAB (Delorme and Makeig, 2004) routines for reading in data files and spherical spline interpolation of noisy channels. The continuous recordings at all channels were detrended in order to minimise the influence of slow drifts. The data were low-pass filtered below 35 Hz using a zero phase-shift Butterworth infinite impulse response (IIR) filter with a 35 Hz cut-off and were high-pass filtered using a zero phase-shift IIR filter with a 0.03 Hz cut-off. For all of the principal analyses, the EEG data were segmented into epochs of -400 to 2000 ms relative to target onset irrespective of the delay period. The epochs were baseline-corrected relative to the -80 to 20 ms interval centred on stimulus onset. Trials were rejected if the bipolar vertical EOG signal (upper minus lower) exceeded an absolute value of $200 \mu\text{V}$ or if any scalp channel exceeded $100 \mu\text{V}$ at any time during the epoch up to and including the 100 ms period following the response. Response-aligned traces were extracted in the period spanning from -400 to 450 ms relative to response execution. As was the case in Chapters 2 and 3, the single-trial EEG data were converted to current source density (Kayser and Tenke, 2006) to increase spatial selectivity and to reduce the spatial blurring effects of volume conduction. As in previous chapters, this transformation was applied to minimise the projection of a negativity at fronto-central electrodes to the more posterior centro-parietal electrodes (Kelly and O'Connell, 2013). As the build-up rate, peak or mean amplitude of the stimulus and response-aligned signals did not differ for leftward versus rightward contrast increases in either group ($p > 0.05$); trials were collapsed across target direction in all SSVEP, CPP and α -band analyses.

Measurement of electrophysiological sensory evidence, central accumulator, motor preparation and attentional signals

The SSVEPs were measured at frequencies of 20 and 25 Hz (stimulus flicker frequency) using the discrete Fast Fourier Transform (FFT) over a window of exactly 8 and 10 cycles

of each (400 ms) to attenuate spectral leakage. To limit the influence of noise, the amplitude at each SSVEP peak was divided by the average of the immediately adjacent upper and lower frequencies. As the left-tilted and right-tilted gratings were phase reversed at 20 Hz and 25 Hz, respectively, this facilitated the measurement of a distinct SSVEP to each grating on each trial. The fidelity with which sensory evidence was encoded in primary visual cortex was measured by calculating the difference in SSVEP amplitude generated by the two gratings on each trial. More specifically, for leftward targets, the 25 Hz non-target SSVEP was subtracted from the 20 Hz target SSVEP and for rightward targets, the 20 Hz non-target SSVEP was subtracted from the 25 Hz target SSVEP to yield a difference SSVEP waveform. The difference SSVEPs were measured as the average spectral amplitude at a cluster of six parieto-occipital electrodes centred on the region of maximum amplitude identified in the grand-average stimulus-aligned topography collapsing across target direction and the ADHD and control groups (see Fig. 4.7A, left). As there was no significant difference in the mean spectral amplitude of the stimulus- and response-aligned difference SSVEP waveforms for leftward versus rightward targets, trials were collapsed across target direction for all further analyses ($p > 0.1$). For each group and participant, the average difference SSVEP time courses were plotted relative to evidence onset and response execution (see Fig. 4.7A, middle and right). To examine the influence that ADHD has on sensory encoding, stimulus- and response-aligned SSVEP amplitude was measured as the mean trial-average spectral amplitude within windows of 137 to 534 ms and -205 to 195 ms relative to evidence-onset and response execution on each trial, respectively.

The CPP was measured at four centro-parietal electrodes centred on the region of maximum component amplitude identified in the grand-average response-aligned topography collapsing across the ADHD and control groups (see Fig. 4.7B, left). As discussed in Chapter 2, the CPP possesses a number of parameters that have been shown to influence the timing and accuracy of perceptual reports (O'Connell et al., 2012; Kelly and O'Connell, 2013). Most relevant to the present chapter, the rate of rise, peak amplitude and peak latency are thought to represent the rate of evidence accumulation and the level and timing of its cessation, respectively (Kelly and O'Connell, 2015). The rate of rise of the stimulus- and response-aligned CPP was measured as the slope of a straight line fitted to the unfiltered ERP waveform, using the intervals of 400 to 500 ms and -200 to 0 ms relative to evidence-onset and response execution, respectively. Average stimulus- and response-aligned CPP peak amplitude per participant was

measured as the maximum trial-average signal amplitude within windows of 500 to 700 ms and -100 to 0 ms relative to evidence-onset and response execution on each trial, respectively. Peak latency was measured as the time at which this maximum signal amplitude occurred in the same interval in the averaged trace of each group and subject.

Power estimates for all β analyses were calculated using the standard FFT, integrating across the 8–30 Hz range but excluding the frequency bins at precisely 20 and 25 Hz (stimulus flicker frequency). As before, data segments of 400 ms with no tapering were used. β power was thus measured in each of a series of time segments taken in 50-ms steps, comprising a Short Time Fourier Transform (STFT). In order to identify channels exhibiting the strongest effector-selective activity, a grand-average topography was generated from the interval -205 to 195 ms with respect to response, with right button press trials subtracted from left button press trials and collapsed across group (Fig. 4.7C, left). Based on inspection of this topography, the standard left- and right-hemisphere motor sites C3 and C4 were selected for β -band amplitude measurements. Stimulus and response-aligned β -band activity ipsilateral and contralateral to the responding hand was measured as the spectral amplitude at a single electrode ipsilateral and contralateral to the responding hand, respectively. Lower amplitude β values were indicative of greater motor preparation. The impact of group on the stimulus and response-aligned β -trace was determined by measuring the average spectral amplitude within windows of -156 to 244 ms and -205 to 195 ms relative to evidence-onset and response execution, respectively. The stimulus-aligned measurement window was tailored to capture possible motor preparation prior to evidence onset.

Power estimates for all the α -band analyses were also calculated using the standard FFT, integrating across the 8–12 Hz frequency range and as before, data segments of 400 ms with no tapering were used. α power was measured in each of a series of time segments taken in 50-ms, comprising an STFT. To identify channels demonstrating the strongest α activity, a grand-average topography was generated for the -205 to 195 ms interval centred on evidence onset and was collapsed across group. Based on inspection of this topography, a cluster of six parieto-occipital electrodes were selected for the α -band amplitude measurements (see Fig. 4.7D, left). For each group and participant, pre-target α -band activity was calculated as the average spectral amplitude within a window of -205 to 195 ms relative to evidence-onset. To explore post-target α -band activity as a function of group, average stimulus- and response-aligned α -band amplitude per participant was measured as the mean trial-average signal amplitude within

windows of -10 to 390 ms and -205 to 195 ms relative to evidence-onset and response execution on each trial, respectively.

4.6.6 Statistical Analyses

A series of independent samples *t*-tests were employed to explore possible differences between the ADHD and control groups on the neuropsychological assessments and in their behavioural performance on the two-alternative forced choice contrast discrimination task. Independent samples *t*-tests were also used to determine the impact of group on the EEG metrics of the perceptual decision-making process including the build-up rate, peak amplitude and latency of the CPP and mean spectral amplitude of α -band activity and the average difference SSVEP amplitude. A series of two-way mixed ANOVAs with the between-subjects factor of Group (Control, ADHD) and the within-subjects factor of Hemisphere (Contralateral, Ipsilateral) were used to examine the influence of Group on contralateral and ipsilateral β -band desynchronisation.

A series of two-way ANOVAs with the factors Group (Control, ADHD) and Inattentive Symptom Severity (Low Inattentive, High Inattentive) were used to examine the relationship between Inattentive symptom severity and the EEG metrics of the decision-making process as described above. Two-way mixed ANOVAs with the between-subjects factors of Group (Control, ADHD) and Inattentive Symptom Severity (Low Inattentive, High Inattentive) and the within-subjects factor of Hemisphere (Contralateral, Ipsilateral) were used to establish the influence of Group and Inattentive Symptom Severity on contralateral and ipsilateral β -band desynchronisation.

To further probe the extent to which perceptual performance deficits in ADHD could be related to the EEG metrics of the perceptual decision-making process or to the cognitive capacities of sustained attention, response inhibition and processing speed, a number of Bonferroni adjusted partial correlations controlling for group were employed (Holm, 1979). To examine the degree to which Inattentive symptom severity was associated with either accuracy or indeed the EEG metrics of the perceptual decision-making process, additional Bonferroni adjusted partial correlations controlling for group were used.

Where Independent samples *t*-tests were used for statistical analyses and Levene's Test for Equality of Variance was significant such that homogeneity of variance between the two groups could not be assumed ($p < 0.05$), the corrected values are reported. Where

the data were not normally distributed the non-parametric equivalent of the independent samples *t*-test, the Mann-Whitney U test was used. Where ANOVAs were used for statistical analyses and sphericity was violated in factors with three or more levels, the Greenhouse-Geisser or the Huynh-Feldt corrected degrees of freedom are reported (the correction applied was contingent on the degree of violation). One control participant was excluded from all EEG analyses due to excessive artefacts in their EEG data (< 50% trials remaining). Outlying participants within each group were excluded from specific analyses if their values within that analysis were a distance of more than three times the interquartile range.

4.7 Results

4.7.1 Cognitive Deficits in ADHD

To test the hypothesis that emerging adults with ADHD would demonstrate deficits across multiple cognitive domains relevant to the perceptual decision-making process, group differences in the SART, the Verbal Comprehension, Perceptual Reasoning, Working Memory and Processing Speed indices of the WAIS-IV^{UK}, the Trail-Making Test (parts A and B) and the Stroop Word, Colour and Colour-Word tests were examined. Descriptive and inferential statistics are summarised in Table 4.3.

Response Inhibition

The SART and Stroop Colour-Word test were employed to assess response inhibition. Emerging adults with ADHD demonstrated deficits in response inhibition on the SART, registering significantly slower reaction time on Go-Trials and by making significantly more errors of commission and omission than controls. However, the ADHD group did not exhibit significantly greater RT variability on Go-Trials relative to the control group. Participants with ADHD also had a significantly lower score on the Stroop Colour-Word Test than those in the control group.

Selective Attention

The Trail-Making Test (Part B), the Processing Speed Index of the WAIS-IV^{UK} and the Stroop Colour-Word test were used to measure selective attention in this study. While, there were no significant group differences in performance on the Trail-Making Test (Part

B), participants with ADHD had significantly lower scores on the Processing Speed Index and the Stroop Colour-Word Test, respectively.

Sustained Attention

The SART was used to measure sustained attention. Emerging adults with ADHD demonstrated deficits in sustained attention on the SART, registering significantly slower reaction time on Go-Trials and by making significantly more errors of commission and omission than controls. However, the ADHD group did not exhibit significantly greater RT variability on Go-Trials relative to the control group.

Perceptual Reasoning

There were no significant group differences in Perceptual Reasoning as measured by the Perceptual Reasoning Index of the WAIS-IV^{UK}.

Processing Speed

The Trail-Making Test (Parts A and B) and the Processing Speed Index of the WAIS-IV^{UK} were used to assess processing speed. While, emerging adults with ADHD did not perform significantly worse on the Trail-Making Test (Parts A and B), they did register a significantly lower score on the Processing Speed Index relative to healthy controls.

Verbal Comprehension

There were no significant group differences in Verbal Comprehension as measured by the Verbal Comprehension Index of the WAIS-IV^{UK}.

Working Memory

There were no significant group differences in Working Memory as measured by the Working Memory Index of the WAIS-IV^{UK}.

Table 4.3: Summary of performance on the neuropsychological assessments for the control and ADHD groups.

	ADHD Mean (SD)	Control Mean (SD)	<i>t</i>	<i>p</i>
SART: Mean Go RT (ms)	308.6 (158.3)	226.5 (49.1)	<i>U</i> = 2.9	0.004**
SART: Coefficient of Variation	0.7 (0.3)	0.6 (0.3)	<i>t</i> ₍₄₆₎ = 1.6	0.12
SART: Commission Errors (%)	22.97 (13.4)	13.6 (7.6)	<i>t</i> _(36.4) = 2.95	0.005**
SART: Omission Errors (%)	5.3 (3.8)	3.3(2.6)	<i>t</i> _(41.0) = 2.2	0.04*
Verbal Comprehension Index of WAIS-IV ^{UK}	38.4 (11.0)	41.2 (8.63)	<i>t</i> _(42.6) = 0.9	0.4
Perceptual Reasoning Index of WAIS-IV ^{UK}	33.1 (10.1)	32.7 (7.3)	<i>t</i> _(41.9) = 0.196	0.9
Working Memory Index of WAIS- IV ^{UK}	21.8 (6.2)	24.3 (5.4)	<i>t</i> ₍₄₆₎ = 1.3	0.2
Processing Speed Index of WAIS- IV ^{UK}	19.5 (4.7)	22.9 (4.8)	<i>t</i> ₍₄₆₎ = 2.8	0.007**
Trail-Making Part A (s)	20.97 (5.4)	19.0 (3.9)	<i>t</i> ₍₄₆₎ = 1.4	0.2
Trail-Making Part B (s)	47.98 (18.8)	42.7 (22.9)	<i>t</i> ₍₄₆₎ = 0.9	0.4
Stroop Word Test (T)	44.1 (9.6)	50.8 (8.9)	<i>t</i> ₍₄₆₎ = 2.5	0.02*
Stroop Colour Test (T)	42.0 (8.96)	50.5 (9.6)	<i>t</i> ₍₄₆₎ = 3.2	0.003**
Stroop Colour-Word Test (T)	51.2 (8.8)	56.5 (9.6)	<i>t</i> ₍₄₆₎ = 2.0	0.049*
Stroop Interference (T)	59.7 (6.9)	58.98 (5.8)	<i>t</i> ₍₄₆₎ = 0.57	0.57

*Denotes the level of statistical significance: **p* < 0.05, ***p* < 0.01, ****p* < 0.001.

4.7.2 Behavioural Performance

On the two-alternative forced choice task, emerging adults with ADHD registered slower RTs than the Control group participants but the result did not reach statistical significance (mean ± SD; ADHD: 877.6 ± 182.0 ms; Controls: 831.6 ± 137.9 ms; *t*₍₄₆₎ = 0.99, *p* = 0.3). Furthermore, there was no significant difference between the two groups in intra-individual RT variability as measured by the coefficient of variation (ADHD: 0.32 ± 0.03; Controls: 0.31 ± 0.04; *t*₍₄₆₎ = 0.84, *p* = 0.4). Although accuracy rates were high on this task; the ADHD group was significantly less accurate than the control group (ADHD:

93.5 $\pm$ 5.1%; Controls: 96.3 $\pm$ 2.98%; $U = 2.1$, $p = 0.03$). As participants may have exhibited slower and more variable responding on trials on which the press was incorrect, the mean RT and coefficient of variation were calculated for the two groups on all trials on which there was a response, irrespective of correctness. This analysis indicated that on all responded to trials; emerging adults with ADHD were neither significantly slower, nor more variable in their responding than those in the control group (Mean RT: $t_{(46)} = 0.96$, $p = 0.3$; Coefficient of variation: $t_{(46)} = 0.82$, $p = 0.4$).

To test the hypothesis that the reduced accuracy would be specifically related to deficits in cognitive capacities relevant to the perceptual decision-making process, partial correlations were conducted between accuracy, sustained attention, processing speed and response inhibition, while controlling for the effects of group. Accuracy was correlated with processing speed as measured by the Processing Speed Index of the WAIS-IV^{UK} ($r = 0.30$, $p = 0.04$) and the Trail-Making Test Parts A ($r = -0.29$, $p < 0.04$) and B ($r = -0.47$, $p = 0.001$). No relationship survived the Bonferroni correction (all $p > 0.00625$; see Appendix B). A retrospective power analysis indicated that seventy-six participants would have been required to detect a statistically significant effect given a Pearson's r -value of -0.47 and a p -value of 0.00625 .

4.7.3 Behavioural Performance and the EEG Metrics of the Perceptual Decision-Making Process

The following set of analyses were tailored to determine whether emerging adults with ADHD demonstrated abnormalities in the perceptual decision-making process as indexed by the aforementioned EEG metrics relative to the healthy controls. Furthermore, the analysis also probed whether specific abnormalities in the EEG or in the cognitive capacities relevant to the perceptual decision-making process, if any, could be linked to the reduced accuracy observed on the two-alternative forced choice contrast discrimination task.

Sensory encoding in ADHD relative to Controls

Visual inspection of the stimulus- and response-aligned traces revealed that mean SSVEP difference amplitude was smaller in the ADHD group relative to the healthy age-matched controls. Although this result was in the expected direction such that emerging adults with ADHD may have encoded the sensory information for the decision less effectively than the controls; the result failed to reach statistical significance such that average SSVEP

difference amplitude did not differ as a function of Group in the grand average (stimulus-aligned: $t_{(43)} = 0.35$, $p = 0.73$; response-aligned: $t_{(43)} = -0.36$, $p = 0.71$; see Fig. 4.7A).

Domain-general and motor-selective decision signals in ADHD relative to Controls

Analysis of the stimulus- and response aligned traces revealed that the CPP build-up rate, peak amplitude and latency did not vary as a function of Group in the grand-average (stimulus-aligned: build-up rate, $t_{(45)} = 0.85$, $p = 0.398$; peak amplitude, $t_{(45)} = 0.35$, $p = 0.73$; peak latency, $t_{(45)} = 1.00$, $p = 0.32$; response-aligned: build-up rate, $t_{(45)} = 0.47$, $p = 0.64$; peak amplitude, $t_{(45)} = 0.35$, $p = 0.73$; peak latency, $t_{(45)} = 0.8$, $p = 0.42$; see Fig. 4.7B).

The effector-selective decision signal exhibited a gradual desynchronisation upon evidence onset that reached a peak over electrodes contralateral to the chosen hand which coincided with response execution for both groups (see Fig. 4.7C). Visual inspection of the stimulus-aligned β -band time courses plotted contralateral and ipsilateral to the responding hand indicated greater desynchronisation immediately following evidence onset for those with ADHD. However, a two-way mixed ANOVA indicated no main effect for Group ($F_{(1,45)} = 0.12$, $p = 0.73$), such that there was not significantly more early β -band desynchronisation for the ADHD relative to the control group. Additionally, there was no main effect for Hemisphere such that mean β -band amplitude measured at electrodes contralateral and ipsilateral to the responding hand was at a similar level ($F_{(1,45)} = 0.075$, $p = 0.79$). There was also no interaction between Group and Hemisphere ($F_{(1,45)} = 2.1$, $p = 0.16$). Analysis of the response-aligned waveforms confirmed that β -desynchronisation reached a comparable level immediately prior to response execution for both groups ($F_{(1,45)} = 0.011$, $p = 0.92$), but that there was significantly more β -desynchronisation contralateral to the responding hand at response ($F_{(1,45)} = 73.1$, $p = 0.0001$). There was no significant interaction between Group and Hemisphere ($F_{(1,45)} = 0.34$, $p = 0.56$).

Attentional engagement in ADHD relative to Controls

To examine the influence that ADHD may have on attentional engagement during the performance of a perceptual decision-making task, each participant's trials were collapsed and the grand average α time courses aligned to the onset of the contrast change and response execution were plotted for each group separately (see Fig. 4.7D). While emerging adults with ADHD exhibited greater average α -band amplitude immediately

prior to evidence onset and indeed less α -band desynchronisation across trial duration which would have been conducive to poorer perceptual performance (Ray and Cole, 1985; Klimesch et al., 1998), neither result reached statistical significance (pre-target α : $t_{(30.9)} = 0.71, p = 0.49$; post-target α : $t_{(30.7)} = 0.72, p = 0.49$). Furthermore, analysis of the response-aligned traces revealed that there was no significance group difference in the average α -band amplitude at response execution ($t_{(30.6)} = 0.89, p = 0.38$, see Fig. 4.7D).

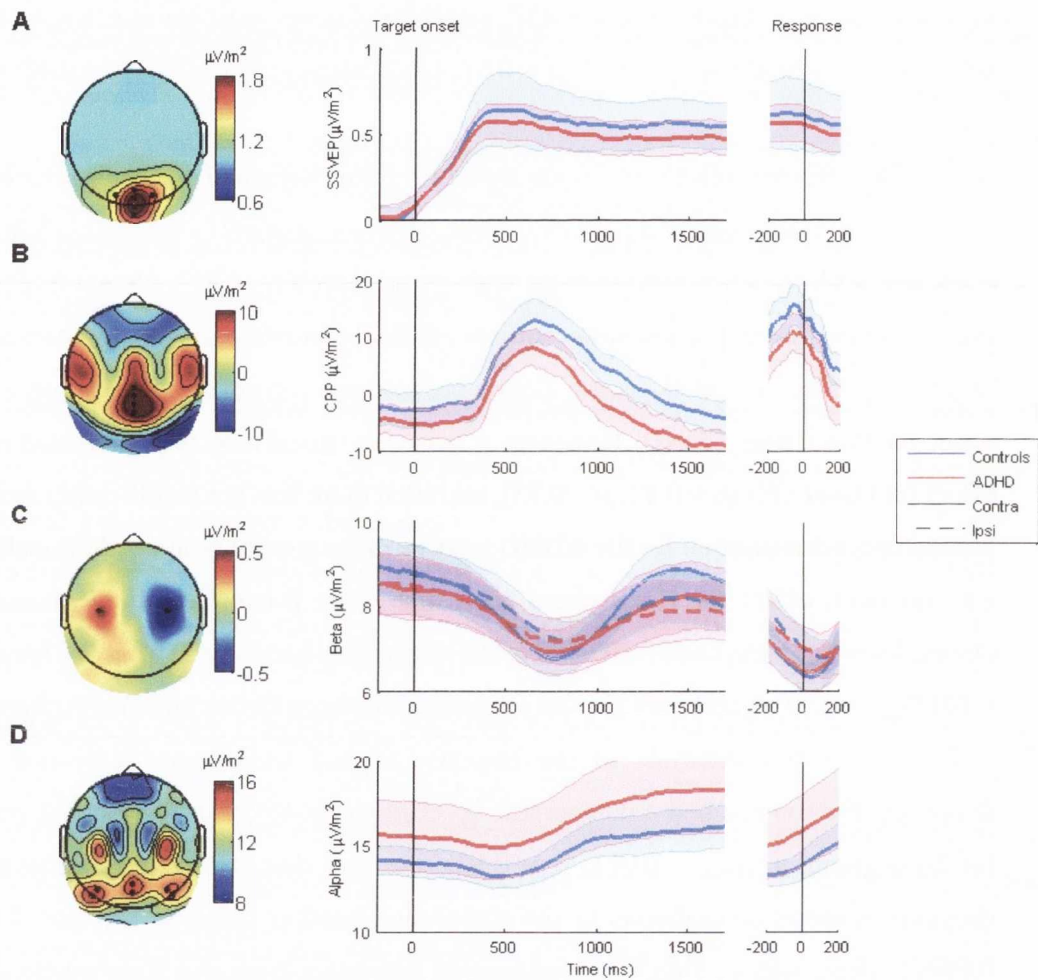


Figure 4.7: No significant differences in the electrophysiological correlates of decision-making in the ADHD and Control groups.

In all panels, the error bars represent the standard error of the mean (SEM) across subjects and the colour bars represent signal amplitude. **A**, Grand-average signal scalp topography of the control and ADHD groups (collapsing across leftward and rightward targets) across a time window of -205 to 1900 ms centred on evidence onset (left) and the average SSVEP difference waveforms aligned to the onset of the target (middle), and response execution (right). **B**, Grand-average signal scalp topography of the control and ADHD

groups across a time window of -205 to 195 ms centred on response execution (left) and CPP waveforms aligned to the onset of the target (middle), and response execution (right). **C**, Grand average signal topography of the difference between trials on which participants responded with a left versus right button click across a window of -205 to 195 ms centred on response execution (left) and β -band traces ($8-19$, $21-24$ and $26-30$ Hz) measured as the average amplitude over motor regions contralateral and ipsilateral to the responding hand (middle and right). **D**, Grand-average signal scalp topography of the control and ADHD groups across a time window of -205 to 195 ms centred on evidence onset (left) and α -band traces ($8-12$ Hz) aligned to the onset of the target (middle) and response execution (right).

To further test the hypothesis that reduced accuracy on the two-alternative forced choice discrimination task would be specifically related to the EEG metrics of the perceptual decision-making process, a series of Bonferroni adjusted partial correlations controlling for group (Holm, 1979) were conducted between accuracy and the peak amplitude and slope of the response-aligned CPP, stimulus-aligned pre- and post-target α -band amplitude, stimulus-aligned β -band desynchronisation, and stimulus-aligned SSVEP amplitude. As accuracy was non-normally distributed with a negative skew it was reflected, $\log^{10}$ transformed and reflected back prior to the correlation analyses. No significant relationship emerged between accuracy and any of the selected EEG measures either prior to or following the Bonferroni correction (all $p > 0.0071$; see Appendix A).

4.7.4 Perceptual Decision-Making Process and Inattentive Symptom Severity

As the ADHD predominantly Inattentive subtype (ADHD-I) is the most frequent diagnosis in adults with ADHD (Davidson, 2007), the possibility that impairments in perceptual decision-making may be directly related to the severity of Inattentive symptoms was considered. Individuals in the control and ADHD groups were classified as either High or Low on Inattentive symptoms based on their T-scores on the CAARS-S: L, DSM-IV Inattentive Symptoms subscale (> 18) or Conners 3 S: L, DSM-IV Inattentive Symptoms subscale (< 18). A median split was conducted separately for the adults and minors within each group (see Table 4.4 for further details). The influence of Inattentive symptom severity on the EEG metrics of the perceptual decision-making process was determined using the same approach as described above.

Table 4.4: Summary of the median values used to classify participants as being of Low or High Inattentive symptom severity.

	Low Inattentive	High Inattentive
Control	Minor: < 46.00 (<i>N</i> = 2)	Minor: ≥ 46.00 (<i>N</i> = 3)
	Adult: < 51.00 (<i>N</i> = 8)	Adult: ≥ 51.00 (<i>N</i> = 10)
ADHD	Minor: < 74.5 (<i>N</i> = 3)	Minor: ≥ 74.5 (<i>N</i> = 3)
	Adult: < 77.5 (<i>N</i> = 8)	Adult: ≥ 77.5 (<i>N</i> = 10)

Impact of inattentive symptom severity on EEG metrics of perceptual decision-making

A comprehensive analysis of the neural signals indicated that the key measurements of the SSVEP, the CPP, β -band activity, and α -band activity did not differ significantly as a function of Group or Inattentive symptom severity in either the stimulus- or the response-aligned grand-average waveforms (all $p > 0.1$).

To assess whether Inattentive symptom severity would be related to accuracy on the contrast discrimination task or to the EEG metrics of the perceptual decision-making process, a series of Bonferroni adjusted partial correlations controlling for group (Holm, 1979) were conducted between Inattentive symptom severity and accuracy, the peak amplitude and slope of the response-aligned CPP, stimulus-aligned pre- and post-target α -band amplitude, stimulus-aligned β -band desynchronisation and stimulus-aligned SSVEP amplitude. A composite variable was created using each participant’s T-score on either the DSM-IV Inattentive Symptoms subscale (> 18) or the Conners 3 S: L, DSM-IV Inattentive Symptoms subscale. As Inattentive symptom severity was non-normally distributed, it was $\log^{10}$ transformed prior to the correlation analyses. No significant relationship emerged between Inattentive symptom severity and accuracy ($r = -0.02$, $p = 0.9$) or any of the selected EEG measures prior to or following Bonferroni correction (all $p > 0.0071$; see Appendix C).

4.8 Discussion

The present chapter provides some of the first evidence that even very elementary sensorimotor transformations are impacted by ADHD. Individuals with ADHD exhibited a marked performance deficit in the form of reduced accuracy relative to the healthy age-matched controls. Despite a comprehensive analysis of the electrophysiological data - the reduced accuracy effect could not be linked to a specific abnormality in either the

information processing stream or in pre-stimulus state. Individuals with ADHD exhibited deficits across multiple cognitive domains relevant to the perceptual decision-making process and it is noteworthy that the accuracy effect was specifically related to neuropsychological test measures of sensory-motor integration and processing speed, prior to correcting for multiple comparisons. The results tentatively suggest that basic perceptual processing may be affected by ADHD and lend weight to an emerging doubt surrounding the conceptualisation of the brain disorder as a higher-order cognitive deficit. After all, basic decision processes are intrinsic to almost all paradigms employed in ADHD research (Mulder et al., 2010).

Only one previous study has directly examined the integrity of perceptual decision making in ADHD (Mulder et al., 2010) and it relied on behavioural analyses alone. Application of the drift diffusion model by Mulder et al. (2010) demonstrated that children with ADHD have difficulty regulating the speed and accuracy of their perceptual decisions such that, although they showed a strong preference for making fast responses in general, their accuracy levels did not differ between the speed and accuracy emphasis conditions. In the speed sessions although the ADHD group were as accurate as the controls, they did not adapt their decision threshold to maximise reward outcomes. Echoing Mulder et al. (2010), the current data also reveal that a degree of specificity exists in perceptual decision-making impairments such that those with ADHD do not perform poorly on all aspects of a task. Here, emerging adults with ADHD were less accurate but had similar albeit marginally slower reaction times and comparable intra-individual reaction time variability. The discrepancy in findings between the two studies highlights that it cannot be assumed that individuals with ADHD will perform similarly across different tests of perceptual decision-making. It seems that the presence or absence of a given performance deficit may be mediated by a number of important factors such as sensory modality, task demands, age and ADHD subtype or severity.

A visual inspection of the neural data also indicated that the perceptual decision-making process may be differentially implemented in ADHD relative to in healthy controls however none of the group comparisons reached statistical significance (see Fig. 4.7). It is likely that the low level of task difficulty is an important contributing factor to the relatively weak behavioural and electrophysiological group differences. After all, the lack of discrepancies between the two groups in reaction time and in intra-individual reaction time variability along with the high rates of accuracy strongly suggest that the contrast discrimination task may not have been challenging enough to tap into possible

impairments in the perceptual decision-making process in ADHD. For example, Cross-Villasana et al. (2015) note that deficits in the attentional and response selection stages of information processing in ADHD may only be observed in task scenarios that place considerable demands on both processing stages. Lending support to this idea, in a comprehensive meta-analysis, Schoechlin and Engel (2005) conclude that ADHD patients exhibit more pronounced information processing deficits in complex attention tasks that include distractor stimuli and complex stimulus-response mapping. Although the contrast discrimination task used in this experiment is perfectly placed to parse out impairments in the constituent components of the perceptual decision-making process in ADHD, future work would benefit from using a more taxing version of the paradigm in which the contrast changes are more difficult to detect.

Indeed, the error bars reflecting the standard error of the mean revealed that there was substantial variability in the EEG responses measured across subjects in both groups which likely contributed in no small way to the lack of statistical significance (see Fig 4.7). This variability in the EEG responses is likely to be independent of the perceptual decision-making process itself but, may be driven, at least in part by individual differences in the size, shape and folding of the cortex across subjects. The very fact that the cortex is folded, forming gyri and sulci, insinuates that some population of neurons possess atypical dendrites that are perpendicular to the skull (da Silva, 2009). The orientation of neurons with respect to the skull is a fundamental factor in governing the EEG signals that are recorded outside the skull (da Silva, 2009). It follows that anatomical differences in cortex will result in interindividual differences in the EEG traces measured. A number of other studies employing within-subjects designs have shown that the EEG metrics of the decision process are sensitive to various experimental manipulations (see O'Connell et al., 2012; Kelly and O'Connell, 2013; Loughnane et al., 2016). However, the present work is the first empirical investigation not only to use the EEG metrics to probe decision-making in a clinical disorder but to use them to compare processing across two different groups. The findings or lack thereof in this experiment suggests that interindividual variability in the EEG responses represents a much more pronounced issue when using the framework to compare across groups as opposed to within-subjects. It is noteworthy that a prospective power analysis indicated that a sample size of 25 participants per group would be sufficient to detect an effect size of 0.25 which matches previous comparable EEG studies conducted by both our (O'Connell et al., 2009) and indeed other groups (Cross-Villasana et al., 2015). Although the present sample consisted

of 24 participants per group it is possible that a larger sample with greater statistical power may have diluted the impact of the highly variable EEG signals and yielded additional statistically significant findings. Future studies availing of the framework may want to avail of experimental designs that can be used to harness within-subject effects for group comparisons. For example, future studies could collect a high volume of single-trial data for each subject and use regression-based analyses in which the resultant β coefficients could be used for group comparisons.

Nevertheless, a discussion of the non-significant electrophysiological patterns is provided in the interests of generating hypotheses for future work. In fact, group differences were evident in sensory encoding, decision formation (slower CPP build-up) motor preparation and attentional engagement, as indexed by the SSVEP, the CPP, β -band activity and α -band activity, respectively, and the differences were all in a direction that is consistent with the behavioural observations. Firstly, individuals with ADHD exhibited diminished SSVEP amplitude which suggests that they may have been less faithful in their encoding of the sensory information for the decision than the controls. Although not directly comparable, the SSVEP deficits observed here are consistent with ERP studies using simple target detection paradigms (oddball tasks) showing that individuals with ADHD exhibit suboptimal sensory processing as indexed by atypical sensory-evoked potentials (Brown et al., 2005; Du et al., 2006; Senderecka et al., 2012). The ADHD group also demonstrated higher pre-target α -band amplitude and reduced α -band desynchronisation across trial duration which is consistent with the diminished attentional engagement that characterises the disorder, particularly in adult populations (Ray and Cole, 1985; Klimesch et al., 1998). As Chapter 2 demonstrated the functional equivalence of the CPP and P300 components, it is noteworthy to discuss the present CPP findings in light of the vast P300 literature. An abundance of empirical investigations have demonstrated that the stimulus-aligned P300 is reliably diminished in children and adolescents with ADHD relative to healthy age-matched controls (Brown et al., 2005; Du et al., 2006; Senderecka et al., 2012). The present data suggest that a number of important group differences exist in the CPPs measured in the patient and the control groups. Firstly, the rate of evidence accumulation (build-up rate) appears to be affected by ADHD such that the patient group exhibited a slower build-to-threshold. Secondly, fully consistent with the findings reported in the P300 literature, the stimulus- and the response-aligned peak amplitude of the CPP was attenuated in emerging adults with ADHD such that less sensory evidence was accumulated for the decision prior to triggering action. In terms of

the drift diffusion model - the pattern of behavioural results observed for the ADHD group could be reasonably explained by a lower decision threshold which would enable fast but, more error prone responses.

Although the individuals with ADHD demonstrated a greater stimulus-aligned β -band desynchronisation immediately following evidence onset, it reached a comparable level for both groups at response execution. In terms of the drift diffusion model, the earlier desynchronisation observed in the ADHD group may reflect a shift in the starting point of evidence accumulation such that the patients are closer to the decision threshold before the evidence has even appeared. From a drift diffusion perspective, this interpretation would reasonably account for the fast but, more error prone responses observed in the ADHD group. The interpretation is also akin to the idea that 'urgency signals' exist in the brain that trigger decisions based on less and less evidence as time passes (Hawkins et al., 2015). Rather interestingly although the reduced accuracy was not correlated with any of the selected EEG measures it was related to poorer sensory-motor integration and processing as measured using traditional neuropsychological tests. This suggests that deficits in cognitive processes very relevant to perceptual decision-making are in some way related to performance deficits on tests of decision-making. Finally, surprisingly neural differences did not emerge as a function of Inattentive symptom severity; a correlation analysis confirmed that it was not related to accuracy on the contrast discrimination task or indeed any of the EEG response measurements.

The work presented within this chapter tallies with existing data from Cross-Villasana et al. (2015) in that it suggests that the performance deficits observed in ADHD may be the product of deficits at multiple stages of information processing. The present data also reveal that sensory encoding, decision formation, motor preparation and attentional engagement may all be affected by the disorder. Using a visual compound search paradigm, Cross-Villasana et al. (2015) showed that slower reaction times in adult ADHD are driven by the summation of information processing delays at the attentional and response selection stages as indexed by a posterior contralateral negativity and the lateralised readiness potential components, respectively. Although the results in this chapter must be interpreted with caution given the lack of statistical significance they do offer, albeit limited, insight into neural underpinnings of ADHD sensorimotor transformations.

Two recent EEG studies have shown that individuals with ADHD demonstrate greater trial-by-trial variability in task-evoked EEG responses. Saville et al. (2015)

demonstrated that the parietal P300 response was more variable in individuals with ADHD on a working memory task. Luu et al. (2004) also showed that frontal-midline theta signals were more variable in individuals with ADHD on a response-choice task (Luu et al., 2004). Gonen-Yaacovi et al. (2016) demonstrated that individuals with ADHD exhibited elevated trial-by-trial variability in EEG responses to both auditory and visual stimuli and also that the increased trial-by-trial variability in ADHD was evident prior to and following stimulus presentation and on trials on which there was no stimulus. This strongly suggests that both ongoing and stimulus-evoked neural activity is more variable or noisy in individuals with ADHD (Gonen-Yaacovi et al., 2016). Rather than being a nuisance variable, elevated neural variability may reflect a pathophysiological feature of the disorder. Future analysis of the present data should aim to establish whether emerging adults with ADHD exhibited elevated trial-by-trial variability in their EEG responses and whether elevated variability in EEG metrics of the perceptual decision-making process can be directly linked to the performance deficits observed in ADHD.

Of course, the present experiment was also subject to a number of basic limitations. For example, 50% of the patients were not stimulant-naïve. As is the case in many other clinical studies, the possibility that the behavioural and/or EEG effects are in some way affected by the long-term effects of stimulant medication cannot be excluded. Furthermore, while control subjects were only included in the study if they did not have a personal or family history of psychiatric disorder there is nothing to say that some of them would not go on to develop psychiatric symptoms in the future.

The present chapter provides some of the first evidence that that flow of information from sensation through to action may be compromised in emerging adults with ADHD. Those with ADHD were not impaired on all aspects of task performance showing only reduced accuracy relative to their healthy age-matched peers. The performance deficit could not be linked to specific neural abnormalities in either the information processing stream or in pre-stimulus state. The present chapter reveals that the framework is a promising tool for parsing out impairments in the constituent components of the decision-making process in brain disorders and highlights a number of very important factors that merit consideration in future work. Firstly, the lack of behavioural differences between the two groups in reaction time and reaction time variability in conjunction with the very high accuracy rates suggests that a more challenging version of the paradigm would have been needed to successfully tap into decision-making deficits in ADHD. Furthermore, while the EEG metrics of the decision-

making process are sensitive enough to parse out effects in a within-subjects design – the current data highlights that interindividual variability in EEG responses becomes a much larger issue when using the framework to compare across groups. Where at all possible, more complex analysis techniques that can harness within-subjects effects should be used in place of between-subjects comparisons. Although not explicitly tested in the present study, future work should explore the relationship between variability in the EEG metrics of the perceptual decision-making process and performance deficits. It may be the case that elevated variability in the EEG responses may not be a nuisance variable but, may be a more general feature of the neuropathology that defines ADHD.

Chapter 5 General Discussion

5.1 Thesis Overview

Perceptual decision-making is a critical cognitive operation that is central to human behaviour and is essential for the successful completion of any cognitive task. Monkey neurophysiology has demonstrated, in exquisite detail, the neural dynamics underpinning each stage of the perceptual decision-making process. The significant progress in characterising the microcircuitry of perceptual decision-making in monkeys motivated a sustained effort to identify equivalent mechanisms in the human brain using non-invasive assays such as functional imaging, EEG, and MEG (Heekeren et al., 2008; Kelly and O'Connell, 2015). The exceptional temporal resolution of EEG marked it as a particularly promising tool for exploring decision-making. However, discrete stimuli with a sudden onset evoke a complex pattern of scalp signals in the EEG recordings that overlap in space and time and can be difficult to tease apart. It follows that for many years the issue of global signal summation prevented researchers in the human domain from mirroring the advances made in monkey neurophysiology (Kelly and O'Connell, 2015).

The present thesis capitalised on the development of a new EEG paradigm that surmounted the problems caused by global signal summation and provided a faculty for directly monitoring the three essential stages of perceptual decision-making in freely-evolving electrical brain signals. This breakthrough provided researchers with an unprecedented opportunity to probe aspects of the perceptual decision-making process that were previously far beyond the reach of empirical investigation in humans using non-invasive assays (O'Connell et al., 2012). As the empirical work within the present thesis is divided into two major strands, the discussion of the relative contributions and limitations of each of these strands is discussed separately in the present chapter. The central aim of Chapters 2 and 3 of the thesis was to use these neural measurements that can be directly tied to perceptual performance to achieve a finer understanding of how decisions are implemented under different experimental conditions. More specifically, it was hoped that additional knowledge about the functional characteristics of neural decision variable signals could be gleaned from exploring their dynamics in response to various experimental manipulations such as using discrete stimuli, enforcing a delay period between the decision and the response and varying the participant's foreknowledge

of stimulus-response mapping. The main ambition of Chapter 4 was to establish whether these EEG metrics of decision-making can be used as a tool to advance our understanding of brain disorders which may be characterised by compromised decision-making capacities.

5.2 Functional Characteristics of Neural Decision Variable Signals

5.2.1 Contributions

The P300 component of the human ERP has long been linked to perceptual decision-making and it was recently noted in the literature that a striking resemblance exists between the P300 and CPP components (O'Connell et al., 2012; Kelly and O'Connell, 2015). The P300 component has been the subject of rigorous experimental investigation across a five-decade period, owing to its apparent relevance to a whole host of cognitive operations and its sensitivity to many brain disorders (Polich et al., 1990; Santosh et al., 1994; Mavrogiorgou et al., 2002; Prox et al., 2007; Verleger et al., 2013). Furthermore, while research on ERPs has been justifiably criticised for being poorly integrated with other fields of enquiry, the P300 component has stood out as a clear exception having been the subject of studies that span a remarkably diverse range of disciplines such as non-human primate electrophysiology (Meyer and Olson, 2011), rodent electrophysiology (Ehlers et al., 2014), functional neuroimaging (Campanella et al., 2013), transcranial magnetic stimulation (Sadeh et al., 2011), computational modelling (Fischer and Ullsperger, 2013), brain-computer interface (Akram et al., 2014), clinical research (Stevens et al., 2007) and theoretical and empirical work on consciousness (Dehaene et al., 2003). Yet despite intensive investigation, a consensus regarding the precise functional significance of the signal has failed to emerge. The P300 has been variously attributed a role in the encoding of stimulus significance (Kutas et al., 1977), decision confidence (Hillyard et al., 1971; Squires et al., 1973), uncertainty or surprise (Duncan-Johnson and Donchin, 1977; Mars et al., 2008), in context updating (Coles et al., 1988), neuroinhibition (Polich, 2007), event-categorisation (Kok, 2001), orienting and response potentiation (Nieuwenhuis et al., 2005; Nieuwenhuis et al., 2011), and context closure (Verleger, 1988). The inability to pinpoint a particular function for the P300 has placed a major barrier to progress in exploiting this signal as an informative neural metric in basic and clinical research. The main aim of Chapter 2 was to provide a resolution to

this long-standing debate through the combination of novel electrophysiological analysis techniques and computational simulations.

Key analyses of the P300 elicited by transient auditory and visual targets revealed that it reaches a stereotyped amplitude immediately prior to response execution and that its rate of rise scales with target detection difficulty and accounts for trial-to-trial variance in reaction time. Furthermore, computational simulations of an accumulation-to-bound decision process faithfully captured P300 dynamics when its parameters were set by model fits to the reaction time distributions. To date, these critical characteristics had been overlooked due to a reliance on tasks involving punctate stimuli and an almost exclusive focus on stimulus-aligned peak amplitude measurements which overlooks the dynamic and progressive nature of this neural signal. Therefore, the empirical and computational modelling data in Chapter 2 converge to establish that the P300 exhibits the defining features of a dynamically evolving neural decision variable signal as predicted by the sequential sampling models and as recently observed in both the monkey and human brain (O'Connell et al., 2012; Kelly and O'Connell, 2013; Shadlen and Kiani, 2013). This definitive evidence supporting a new and comprehensive mechanistic explanation of the P300 will have far reaching consequences not only for past and future studies of the P300 itself but equally for research on the neurobiology of human decision making in general.

The findings in Chapter 2 confirm that the CPP and classic P300 are functionally equivalent which implies that the temporal integration of sensory evidence is not only employed during difficult, protracted discriminations central to typical decision-making paradigms, but is equally observable during quick detections of punctate stimuli. Establishing a functional equivalence with the CPP has important implications for interpreting previous and future findings pertaining to the P300. A feature of the CPP that sets it apart from all previously reported build-to-threshold decision variable signals is that it traces decision formation in a way that is abstracted from the specific sensory or motor requirements of the task (O'Connell et al., 2012). It has also been shown that the build-up of the CPP reliably precedes that of motor-selective decision signals. Together, these characteristics strongly imply that the signals are an intermediate step between sensory encoding and motor preparation, and provide support for a heterarchical interpretation of perceptual decision-making.

The data presented in Chapter 2 are particularly pertinent to clinical research as the peak amplitude and latency of the stimulus-aligned P300 component have both been shown to be reliably disrupted in a wide range of neurologic and psychiatric populations (Polich and Herbst, 2000; see Fig 5.1 for a summary). Chapter 2 reveals that the dynamics of the P300 are far richer than traditionally conceived. Where the P300 has traditionally been measured in terms of its peak amplitude and latency, the analyses reveal that it bears a number of additional parameters that have independent influences on the timing and accuracy of decisions. These include the latency of its onset, marking the start of evidence accumulation, and its rate of rise, indexing the rate of evidence accumulation. Chapter 2 also demonstrates that each of these distinct parameters can be directly measured from the P300. These observations have major implications for the interpretation of P300 data because they reveal that there are multiple different reasons why the stimulus-aligned P300 peak might be delayed in a particular clinical population or experimental condition: because evidence accumulation started at a later time, because evidence was accumulated at a slower and more variable rate, or because of an elevated decision threshold necessitating accumulation over a longer interval. By embedding the P300 within the sequential sampling framework, it is possible to generate very precise and testable predictions about how each of these parameters should vary as a function of specific stimulus properties such as probability and discriminability. A key aim of Chapter 4 of the present thesis was to evaluate the utility of the framework as a tool for advancing our understanding of how the decision-making process may be disrupted in a prevalent brain disorder – ADHD.

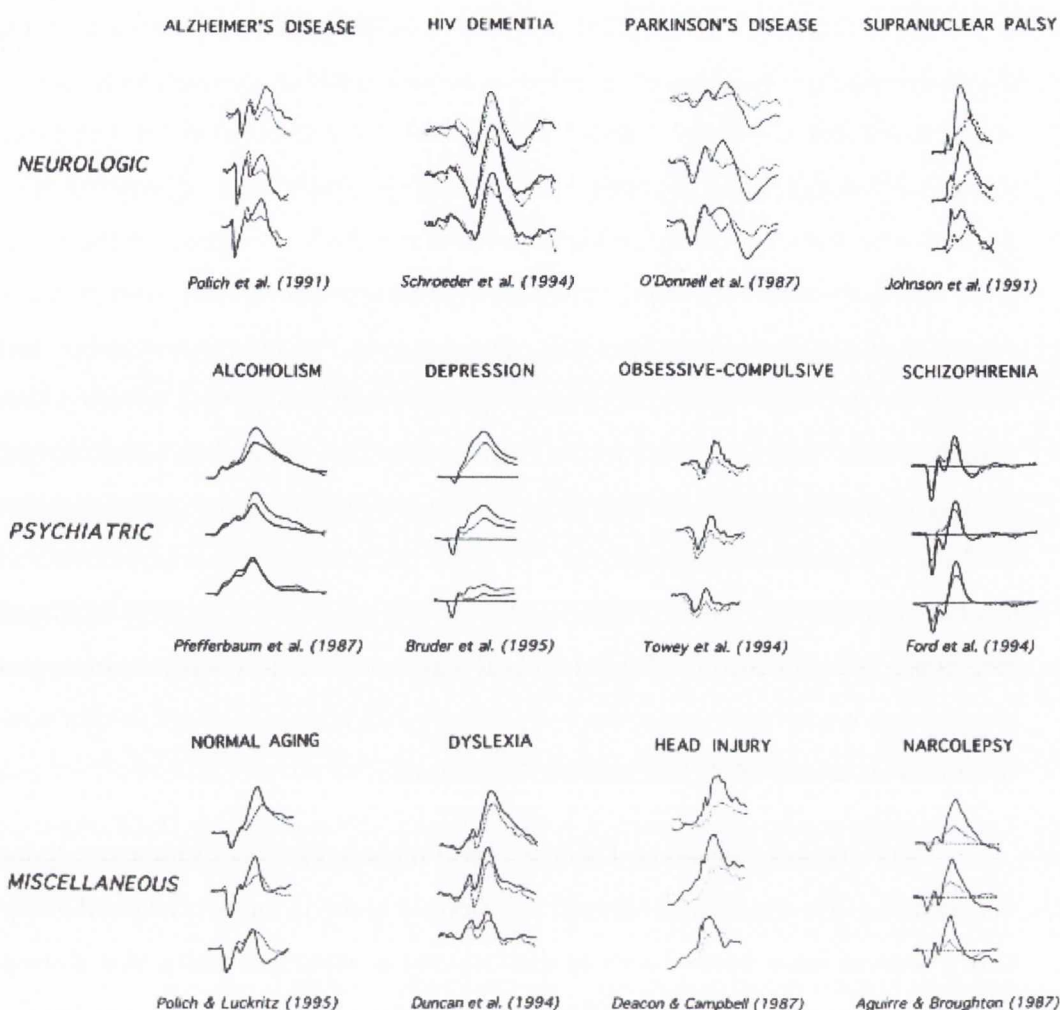


Figure 5.1: The stimulus-aligned P300 component is disrupted in a wide range of clinical disorders.

Both the peak amplitude and latency of the stimulus-aligned P300 can be affected by disease processes. The new functional interpretation of the P300 offered in Chapter 2 will provide a mechanistic framework for exploring why specific parameters of the component may be atypical in a particular clinical population. Chapter 4 of the present thesis evaluated the utility the framework as a tool for enhancing our understanding of a prevalent brain disorder – ADHD. Figure taken from Polich and Herbst (2000).

The primary aim of Chapter 3 was to shed light on the functional characteristics of neural decision signals during delayed perceptual reports. Two distinct classes of decision variable signal coexist in the human brain: motor-selective decision signals that convert a decision directly into a motor plan and abstract decision-signals that do not play any role in action preparation (O'Connell et al., 2012). The functional dissociations

between the two types of decision signal have only begun to be determined and their dynamics during decisions with deferred actions with or without foreknowledge of stimulus-effector mapping - a commonly studied task scenario in single-unit and functional imaging investigations - have not been established. Chapter 3 traced the dynamics of distinct abstract and effector-selective decision signals in the form of the CPP and limb-selective β -band activity, respectively, during delayed-reported motion direction decisions with and without foreknowledge of direction-response mapping. Chapter 3 showed that with foreknowledge, the CPP and β -band signals exhibited a similar gradual build-up following evidence onset, but while choice-predictive β -band activity persisted up until the delayed response, the CPP dropped toward baseline after peaking. Without foreknowledge, the CPP exhibited identical dynamics, whereas choice-selective β -band activity was eliminated. Thus, Chapter 3 successfully highlighted the functional independence of abstract and effector-selective decision variable signals and showed that we cannot assume that two classes of decision signal will exhibit equivalent dynamics across different experimental conditions.

More broadly speaking, Chapter 3 also underlines a very important dissociation between decision signals in the human and monkey brain. In monkeys, lateral intraparietal (LIP) neurons have been shown to demonstrate a pattern of firing that distinguishes between categorical alternatives (Freedman and Assad, 2006; Bennur and Gold, 2011). Interestingly, when the stimulus-response contingency is unknown, such that the emerging decision cannot be converting directly into a motor plan, both the CPP and the firing rate of category-selective neurons in LIP descend towards baseline levels following the decision (Bennur and Gold, 2011). However, when the stimulus-response contingency is known in advance, LIP neurons demonstrate a pattern of firing that sustains right up until response execution. Chapter 3 shows that the CPP returns to baseline levels under the same conditions. The findings in Chapter 3 suggest that the CPP's complete autonomy from motor preparation is a unique aspect of the signal, such that it is functionally different from category-selective single-unit decision variable signals.

The findings in Chapter 3 are also highly relevant to neuroimaging studies of perceptual decision-making. As noted in Chapters 1 and 3, fMRI studies often invoke assumptions about the expected pattern of activation that decision regions should exhibit. One of the most frequently employed criteria for isolating a candidate decision region is

that the amplitude of the BOLD response in that region should scale with the strength of sensory evidence across trials (Heekeren et al., 2004; Heekeren et al., 2006; Pleger et al., 2006; Tosoni et al., 2008; Ho et al., 2009; Liu and Pleskac, 2011). Using a delayed-response paradigm that closely resembles those used in functional imaging studies, Chapter 3 reveals that the integrated activity of the CPP across trial duration was insensitive to sensory evidence strength (Heekeren et al., 2004; Heekeren et al., 2006; Pleger et al., 2006; Liu and Pleskac, 2011). Although one-to-one correspondence cannot be assumed between ERPs and the BOLD response, the findings highlight that contrasts based on evidence-scaling predictions may not result in differential activation of abstract evidence accumulation regions under delayed response conditions.

5.2.2 Limitations and Future Directions

The interpretation of the work presented within this thesis is heavily contingent on the assumption that the CPP reflects a build-to-threshold decision variable signal. A number of studies have provided clear empirical evidence to support this assumption (O'Connell et al., 2012; Kelly and O'Connell, 2013; Loughnane et al., 2016). However, as briefly discussed in Chapter 1, there are other possible functional interpretations of the signal that merit consideration. One aspect of the CPP that undermines its interpretability as a decision variable signal is that although it can predict the timing of the perceptual report, it does not exhibit choice-selective activity. For example, on a random dot motion task, it cannot predict whether the participant will select leftward or rightward motion. This aspect of CPP differentiates it from the motor-selective decision variable signals in the human (Donner et al., 2009; O'Connell et al., 2012) and monkey brain (Shadlen and Kiani, 2013). As a confidence signal would not be expected to exhibit choice-predictive activity, it has been suggested that rather than directly encoding the decision, the CPP may encode decision confidence which builds in parallel to the accumulated evidence (Shadlen and Kiani, 2013; Urai and Pfeffer, 2014). Urai and Pfeffer (2014) also suggest that the CPP may not demonstrate choice-predictive activity due to the macroscopic scale of EEG activity, such that it may reflect the summed activity of two overlapping neuronal populations that are coding for two separate motion directions. However, existing empirical data are not entirely consistent with an interpretation of the CPP as a confidence signal. The CPP reaches a fixed amplitude immediately prior to response execution irrespective of sensory evidence strength and reaction time and these factors are known

to have a rather systematic effect on decision confidence (Kiani and Shadlen, 2009; Yeung and Summerfield, 2012). Future research should investigate the possibility that the CPP indexes decision confidence. This could be achieved by probing the observer's confidence using either subjective report measures such as the Likert scale or post-decisional wagering (Shadlen and Kiani, 2013) and subsequently linking decision confidence to the distinct parameters of the CPP (Urai and Pfeffer, 2014).

As discussed in Chapter 1, Philiastides et al. (2014) also questioned the interpretation of the CPP as a neural decision variable signal as they could not replicate the boundary-crossing effect observed in Kelly and O'Connell (2013). More specifically, a machine learning approach was used to obtain a spatiotemporal of activity that discriminated decision-related stimulus- and response-aligned signals. Here, a response-aligned decision component continued to co-vary positively with the strength of sensory evidence and did not reach a stereotyped zenith at choice commitment (Philiastides et al., 2014). To mirror the analysis approach taken by Kelly and O'Connell (2013), they also converted the data to current source density and still found no convergence at a common threshold. A regression analysis with the impact of sensory evidence factored out revealed that although single-trial component amplitude was only weakly correlated with the rate of evidence accumulation it reliably and independently predicted choice-accuracy. Therefore, the authors concluded that component amplitude at choice commitment may represent the impact of post-sensory decision signals such as those related to decision confidence (Philiastides et al., 2014).

It is noteworthy that a number of factors may have contributed to the lack of boundary-crossing effect observed in Philiastides et al. (2014). Firstly, the data were high-pass filtered using a 0.5 Hz high-pass filter which may have attenuated the signal amplitude and obscured the boundary-crossing effect in their data. Secondly, as a machine-learning approach was used to isolate the decision component, it is likely that this component also captured decision-correlated signals other than the CPP. Alternatively, the lack of boundary-crossing effect may have been driven by the fact that discrete trials with a relatively short deadline for responding were used which may have promoted a 'collapsing bound' effect. The Philiastides et al. (2014) work provides further impetus for new studies that can conclusively address the issues raised. Firstly, it is imperative that future investigations probe the extent to which the discrepancies between

the findings of Philiastides et al. (2014) and those reported in other EEG studies (O'Connell et al., 2012; Kelly and O'Connell, 2013) are in fact driven by differences in either the stimuli or the tasks used across studies. Additionally, it should be a priority for future empirical investigations to determine whether the population-level responses recorded by EEG can be accurately equated with the build-to-threshold dynamics observed at the single-cell level in primates (Philiastides et al., 2014).

Chapter 2 offered critical new insights into a longstanding neural phenomenon and has opened up a number of important avenues for future research. Firstly, although this chapter made a significant contribution to resolving the long standing debate in the literature regarding the functional significance of the P300, the picture is still incomplete. In particular, we still do not have a good understanding of which brain regions actually generate the P300 (see Linden, 2005 for a review). Despite the inconsistencies in both the definitions and methodologies used, a consistent pattern of generators has emerged in the literature with target-related P3b responses observed over parietal cortex and the cingulate and novelty-related P3a activations recorded over the inferior parietal and prefrontal regions (Linden, 2005). A high volume of scalp-recorded EEG, intracranial EEG, brain lesion and neuroimaging studies have invoked imprecise functional definitions of the P300 which has resulted in P300-like components being identified in a multitude of brain regions many of which may not actually play a role in decision-making (see Linden, 2005 for a review). The findings in Chapter 2 provide a more precise set of criteria for isolating a P300-generator that may help resolve the confusion in the literature. Invoking this new definition of the P300 and demonstrating that the component emanates from a decision-related region such as parietal cortex would add considerable weight to the interpretation of the P300 as an evidence accumulation signal offered in Chapter 2. This particular goal may be better achieved using a method such as electrocorticography, which has a superior spatial resolution than EEG, as it involves recording electrical activity directly from the surface of the brain (Ritaccio et al., 2010). Determining the cortical origins of the P300 is a critical issue for cognitive neuroscience, first because it holds the key to achieving a fuller understanding of the brain's decision-making machinery, and secondly because it is of direct relevance to the question of why certain clinical conditions impact on decision-making behaviour (Linden, 2005).

Chapter 2 succeeds in linking the P300 to a well-validated computational framework for understanding perceptual decision-making. However, further investigation is required to determine whether the build-to-threshold interpretation of the component can account for all the instances in which the P300 is observed, including those in which the decision is not associated with a motor response (Summerfield and Tickle, 2015). The findings also raise the interesting possibility that other late ERPs may reflect accumulation-to-bound processes (Summerfield and Tickle, 2015). For example, a large, gradually-building, N400 response maximal over parietal scalp is typically elicited by semantically incongruent or unexpected information (Kutas and Federmeier, 2011). Future work could explore the possibility that the N400 component indexes a semantic decision-making process in which evidence is accumulated as to whether the information presented is congruent or incongruent.

Chapter 3 demonstrated that important differences exist in the dynamics of abstract and motor-selective decision variable signals during decisions with deferred actions with or without foreknowledge of stimulus-effector mapping. The chapter also highlighted a number of issues that merit further investigation. Firstly, in marked contrast with the existing literature (e.g. de Lange et al., 2013), the data presented in Chapter 3 revealed that under delayed-response conditions, β -band lateralisation was insensitive to sensory evidence strength. The findings may be driven by the minute differences in the levels of motion coherence used in this study (20% and 30%). However, the result is interesting given that other studies have shown that when a delay is introduced between choice commitment and response execution, that the association between coherence and the build-up rate of lateral intraparietal area responses is diminished (Roitman and Shadlen, 2002) or even absent (Rao et al., 2012). A challenge for future work is to determine whether delayed response conditions serve to reduce the relationship between the evidence integration and action preparation processes in the human brain such that β -band lateralisation is no longer modulated by sensory evidence strength. A dedicated empirical investigation should address this question by determining whether the build-up rate of β -band lateralisation is modulated by sensory evidence strength under delayed-response conditions in which there are greater differences between the levels of motion coherence (e.g. 10%, 20%, 30% and 40%). In this case, if the slope of β -band lateralisation does not vary as a function of sensory evidence strength, it would highlight

another critical functional dissociation between the CPP and motor-selective decision signals in both the human and monkey brain.

Of relevance to the broader field of cognitive neuroscience, Chapter 3 also raises a very important question about how a choice representation is maintained during the interval between the decision and the response when the perceptual report is deferred. The present thesis is the first to demonstrate that the motor-selective decision signal carries out this role when the stimulus-effector mapping is known in advance. However, interestingly, neither the abstract nor the motor-selective decision variable signal carried out the role during the delay period when the emerging decision could not be directly translated into a specific motor plan. Future dedicated empirical investigations should explore how choice representations are maintained in delayed-response scenarios (Shadlen and Kiani, 2013; Tsetsos et al., 2015).

To acquire a better understanding of the decision-making machinery in the human brain, additional investigation is required to determine whether further possible functional dissociations exist between the abstract and motor-selective decision variable signals. This could be achieved by exploring the signal dynamics under different experimental conditions such as those in which either the speed or accuracy of the decision is emphasised. The prevalent view drawn from mathematical psychology is that a speed-emphasis in decision-making tasks results in a strategic boundary adjustment such that the decision-threshold is decreased and less evidence is accepted for the decision. However, recent monkey neurophysiology studies indicate that these models do not offer a good account of the neural adaptations underpinning speed-accuracy trade-off (Heitz and Schall, 2012; Hanks et al., 2014). An important finding from these studies is that, contrary to model predictions, speed pressure leads to changes in the firing rates of the decision variable signals (Heitz and Schall, 2012; Hanks et al., 2014). It has yet to be determined if similar dynamics are observed when humans are placed under varying speed-accuracy emphasis conditions. Addressing this question would not only indicate the level(s) of the decision-making architecture on which the speed-accuracy trade-off is implemented, but may reveal further functional distinctions between the two classes of decision variable signal in humans. That is to ask, would speed pressure increase the gain of the neural decision process, resulting in a steeper rate of rise and a higher amplitude at

response in both the abstract and motor-selective decision signals, or would the gain only occur at the abstract level and be communicated to the motor level?

Recent neurophysiological recordings in rodents have demonstrated that under variable stimulus durations, the posterior parietal cortex and the frontal orienting fields in prefrontal cortex exhibited distinct relationships to evidence accumulation for a simple perceptual decision (Hanks et al., 2015). More specifically, rodents were trained to complete a task in which they kept their nose in a central port during the presentation of two simultaneous trains of randomly timed auditory clicks, one played from a speaker to their left and another from a speaker to their right. Following a variable stimulus duration which varied on a trial-to-trial basis, a response cue or Go-signal would appear which indicated that the rat needed to decide which side had played a greater number of clicks. Under these conditions, the posterior parietal cortex encoded a graded value of the accumulated evidence for the decision, while the neuronal firing in the frontal orienting fields categorically encoded which of the two alternatives was favoured by the available evidence (i.e. the evidence accumulated so far). It was surmised that evidence accumulation occurs upstream to the frontal orienting fields and that it may instead reflect the final step in the decision process; the translation of the graded accumulated evidence into a categorical or binary choice (Hanks et al., 2015).

The data presented in Chapter 3 reveal that under certain conditions (varied stimulus-effector mapping conditions), β -band activity does not compute the choice, but converts it into action. Thus, the findings fit well with the Hanks et al. (2015) suggestion that at least under certain experimental conditions, the evidence accumulation process is housed in higher-order, more parietal regions of the brain while activity in the motor regions reflects the translation of the decision into a categorical motor plan (left versus right press). However, future work should interrogate the signal dynamics of the CPP and β -band activity under variable stimulus durations to determine whether this is the case. Based on the observations of Hanks et al. (2015), it is hypothesised that under variable stimulus durations the CPP would continue to index the temporal integration of the sensory evidence for the decision, while β -band activity would exhibit a more rapid build-to-threshold in favour of one alternative. Such a study would not only be informative about how the human decision-making architecture contends with temporal uncertainty, but would offer additional insight into the functional characteristics of abstract and motor-selective decision variable signals.

5.3 Perceptual Decision-Making in Emerging Adults with ADHD

5.3.1 Contributions

A handful of recent studies hint that the perceptual decision-making process may not be fully intact in adults with ADHD (Mulder et al., 2010; Cross-Villasana et al., 2015). Owing to a paucity of empirical investigations, the electrophysiological basis of compromised perceptual decision-making capacities in ADHD remains poorly understood. In Chapter 4 it was shown that emerging adults with ADHD were significantly less accurate than controls on a novel task of perceptual decision-making, and a visual inspection of the neural data also suggested that important group differences may exist in attentional engagement, sensory encoding, abstract decision formation, and motor preparation. However, the pronounced inter-subject variability in the EEG responses meant that no statistically significant differences were observed in the neural measures of the two groups (see error bars Fig. 4.7). It follows that the reduced accuracy could not be directly linked to a specific abnormality in the electrophysiological indices of information processing or in pre-stimulus state. Supporting the idea that sensorimotor transformations may be impaired in ADHD, individuals with ADHD exhibited deficits across multiple cognitive domains that are of relevance to the perceptual decision-making process. It is noteworthy that the reduced accuracy for the ADHD group was associated with poorer performance on psychometric test measures of sensory-motor integration and processing speed, prior to correcting for multiple comparisons.

The study offers important, albeit limited, support to a slowly emerging body of evidence which suggests that individuals with ADHD may not only show deficits in higher order cognitive processes (Mulder et al., 2010; Cross-Villasana et al., 2015). The difficulty that individuals with ADHD experience in modulating their behaviour to meet social and environmental demands may not be driven solely by deficits in higher-order cognitive processes such as response inhibition, but may actually stem from a more basic inability to adequately compute a decision about the environment or social situation (Mulder et al., 2010).

The findings presented in Chapter 4 also reveal that the perceptual decision-making framework is a promising tool for parsing out impairments in the constituent components of the decision-making process in brain disorders. Although not statistically

significant due to the substantial variability in the EEG responses, group differences were evident in the neural correlates of the decision-making process. If an analysis technique could be developed to contend with the variability in the electrophysiological responses, the new EEG metrics of the decision process would be well placed to parse out specific abnormalities in the information processing stream and in pre-stimulus state in ADHD. While further investigation is required to establish whether real differences exist in how perceptual decisions are implemented in ADHD, the findings presented here are interesting as the perceptual decision-making process is key to normal social and physiological functioning in the world. If we can precisely probe the perceptual decision-making architecture in clinical populations to shed light on the exact neural computations that are impacted by a given pathology, research can begin to focus on developing more targeted behavioural and pharmacological interventions to ameliorate the impact of the disorder on that process.

The study presented in Chapter 4 also highlighted pivotal methodological issues that merit consideration when using the neural metrics of the perceptual decision-making process to investigate the neurophysiology of clinical disorders. This point will be discussed in greater detail in the section that follows.

5.3.2 Limitations and Future Directions

There were a number of key factors that may have contributed to the lack of significant group differences observed in both the behavioural and neural data presented in Chapter 4 which are of great relevance to future studies in this area. The lack of significant differences observed in the behavioural data, combined with the high rates of accuracy, strongly suggest that the task was not taxing enough to tap into possible deficits in sensorimotor transformations in ADHD. As discussed in Chapter 4, the existing literature highlights that deficits in this cognitive operation can only be teased apart in behavioural tasks that are taxing on multiple processing stages or in those that include both target and distractor stimuli or that use more complex stimulus-effector mapping (Schoechlin and Engel, 2005; Cross-Villasana et al., 2015). Future work employing the contrast discrimination task, or indeed any other perceptual decision-making task, should bear this in mind. Indeed, future studies adopting the contrast discrimination task used in Chapter 4 should also ensure that the target detection is more challenging so as to produce greater

differences in behavioural performance and therefore, greater measurable neurophysiological effects.

Critically, in Chapter 4 an examination of the EEG signals measured in the grand-average strongly suggested that there were differences between the two groups in the EEG components that indexed sensory encoding, abstract decision formation, motor preparation and attentional engagement. However, as has already been noted in Chapter 4 and in the sections above, there was substantial variability in the EEG responses measured across subjects which was at least partly responsible for the lack of statistical significance observed in the study (see Fig 4.7). The variability in the EEG responses may in part be driven by differences in the size, shape, and folding of the cortex across participants as well as being possible general features of the neuropathology of the disorder (Gonen-Yaacovi et al., 2016). Firstly, anatomical differences in cortex will cause inter-individual differences in the EEG (da Silva, 2009). While a number of other studies of perceptual decision-making have successfully used the EEG metrics to study cognition in within-subject designs (see O'Connell et al., 2012; Kelly and O'Connell, 2013; Loughnane et al., 2016), Chapter 4 is the first empirical investigation to use them not only to probe decision-making in a clinical population, but to compare cognitive processing in two distinct groups of participants. The study makes an important contribution to the existing literature by demonstrating that variability in the EEG responses represents a much more significant challenge when using the electrophysiological metrics to compare across subjects as opposed to within-subjects, especially when studying a clinical population. Future work in this area will need to develop more complex analysis techniques that can be used to capture within-subjects effects, thus circumventing the necessity to use a between-subjects design. One possible solution might be to collect a high volume of single-trial data for each subject and employ regression-based analyses in which the resultant β coefficients could be used for group comparisons.

As briefly discussed in Chapter 4, recent work has shown that individuals with ADHD exhibit increased trial-by-trial variability in EEG responses related to specific cognitive processes (Luu et al., 2004; Saville et al., 2015), and indeed in the ongoing neural activity that is not directly tied to any specific cognitive process (Gonen-Yaacovi et al., 2016). While Chapter 4 did not explicitly test the neural variability in each group, future work should explore the extent to which the neuropathology of ADHD is associated with mechanisms that govern the stability of the ongoing neural activity (Gonen-Yaacovi et al., 2016). It follows that future analysis of the present data should aim to establish

whether emerging adults with ADHD exhibited elevated trial-by-trial variability in their EEG responses, and whether elevated variability in EEG metrics of decision-making can be directly linked to the performance deficits observed in ADHD.

Chapter 4 represents the first effort to use novel EEG metrics that can be directly linked to perceptual performance to identify a disease-specific aetiological pathway in a brain disorder. The data reveal that it is by no means a foregone conclusion that this basic cognitive function is fully intact in all clinical populations. It is imperative that future clinical research uses a similarly mechanistic approach to examine the integrity of sensorimotor transformations in other clinical disorders, such as obsessive compulsive disorder, that appear to be characterised by higher-order deficits.

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Appendices

Appendix A

Table A.1: Partial correlations between accuracy on the contrast discrimination task and the selected metrics EEG metrics of the perceptual decision-making process with group, partialled out.

	Accuracy – Contrast Discrimination Task
1. R-aligned CPP peak amplitude	
Partial <i>r</i>	0.249
P value	0.095
2. R-aligned CPP slope	
Partial <i>r</i>	0.181
P value	0.228
3. Pre-target α-band amplitude	
Partial <i>r</i>	-0.067
P value	0.660
4. Post-target α-band amplitude	
Partial <i>r</i>	-0.068
P value	0.653
5. Post Target S-aligned contralateral β-band amplitude	-0.202
Partial <i>r</i>	0.178
P value	
6. Post Target S-aligned ipsilateral β-band amplitude	
Partial <i>r</i>	-0.216
P value	0.149
7. S-aligned SSVEP amplitude	
Partial <i>r</i>	-0.008
P value	0.958

*Denotes the level of statistical significance: * $p < 0.05$, ** $p < 0.0071$.

Appendix B

Table A.2: Partial correlations between accuracy on the contrast discrimination task and selected cognitive capacities relevant to the perceptual decision-making process with group, partialled out.

	Accuracy – Contrast Discrimination Task
1. SART Omission errors (%)	
Partial <i>r</i>	−0.092
P value	0.544
2. SART Commission errors (%)	
Partial <i>r</i>	0.049
P value	0.747
3. SART Coefficient of Variation	
Partial <i>r</i>	−0.105
P value	0.487
4. SART Mean Go RT (ms)	
Partial <i>r</i>	0.095
P value	0.529
5. Stroop Interference (T)	
Partial <i>r</i>	0.283
P value	0.057
6. Trail Making A (s)	
Partial <i>r</i>	−0.298
P value	0.044*
7. Trail Making B (s)	
Partial <i>r</i>	−0.466
P value	0.001*
8. Processing Speed Index of WAIS-IV^{UK}	
Partial <i>r</i>	0.304
P value	0.040*

*Denotes the level of statistical significance: **p* < 0.05, ** *p* < 0.00625.

Appendix C

Table A.3: Partial correlations between Inattentive symptom severity and selected metrics EEG metrics of the perceptual decision-making process with group, partialled out.

	Inattentive symptom severity
1. R-aligned CPP Peak Amplitude	
Partial r	0.088
P value	0.561
2. R-aligned CPP Slope	
Partial r	0.134
P value	0.374
3. Pre-target α-band Amplitude	
Partial r	0.052
P value	0.731
4. Post-target α-band Amplitude	
Partial r	0.066
P value	0.665
5. Post-target S-aligned contralateral β-band Amplitude	
Partial r	0.151
P value	0.316
6. Post-target S-aligned ipsilateral β-band Amplitude	
Partial r	0.174
P value	0.248
7. S-aligned SSVEP Amplitude	
Partial r	0.102
P value	0.498

*Denotes the level of statistical significance: * $p < 0.05$, ** $p < 0.0071$.