IMPULSIVITY IN PARKINSON'S DISEASE AND TOURETTE SYNDROME, AND HUMAN MOTOR DECISION MAKING

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This work is dedicated to my mother, who pushes me to always strive for excellence, and my father, from whom I learnt the true value of hard work.

DECLARATION

I, Vishal Rawji, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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ABSTRACT

Motor response inhibition pertains to the ability to inhibit motor actions. It is hypothesised that a breakdown in motor response inhibition might underlie impulsivity in Parkinson's disease and tics in Tourette syndrome. This thesis outlines how motor response inhibition is modulated in these clinical disorders by first characterising them in healthy subjects. We use TMS to show that one set of inputs to the motor cortex are inhibited during motor preparation whilst the other inputs reflect uncertainty about potential stopping. In the next chapter, we challenged an assumption that movement preparation during proactive inhibition always preceded movement execution and found that movement preparation and execution are two independent processes. With this in mind, we investigated features of motor response inhibition and movement preparation and execution in patients with Tourette syndrome, finding that these were remarkably similar to healthy controls, suggesting that volitional features of movement and inhibition are normal in Tourette syndrome. However, we did find a specific impairment of automatic inhibition in Tourette syndrome, which correlated with motor tic severity. As dopamine agonists are implicated as triggers for impulsivity in Parkinson's disease, we first investigated the influence of ropinirole on motor response inhibition in healthy control subjects, finding that motor response inhibition was globally impaired. This was accompanied by analyses suggesting that ropinirole impaired the ability to adjust the decision threshold when stopping might be required. However, investigation of motor inhibition in Parkinson's disease patients on dopamine agonists showed unremarkable effects compared to patients without dopamine agonist use. Our data provide a novel insight into the basic mechanisms of voluntary movement and propose a new theory for tic generation in Tourette syndrome.

IMPACT STATEMENT

We anticipate that the findings in this thesis will be relevant to a broad range of clinical and non-clinical neurosciences. Movement has long been considered in a rise-to-threshold manner, whereby neural activity during movement preparation accumulates to a decision threshold, before triggering movement initiation. Importantly in this model, movement execution is dependent on movement preparation terminating. We present evidence in this thesis that movement preparation and execution are independent processes, which deviates significantly from classical, rise-to-threshold models of movement. This finding will have implications for any experiments that use reaction times to measure underlying decision-making processes; we show that rather than representing underlying decision-making strategies, differences in reaction times may represent the time difference between triggering of movements.

In the arena of Tourette syndrome and tic disorders, we have identified a novel mechanism by which tics may arise – a failure in automatic inhibition, which correlates with clinical severity of motor scores. As well as encouraging further research into this hypothesis and an extension to other dyskinesias, the measurement of automatic inhibition via reaction times and errors may provide an objective marker of diagnosis, clinical assessment and rehabilitation of tic severity.

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CONTENTS

LIST OF TABLES

List of Figures

List of Abbreviations and Acronyms

Abbreviation	Meaning
ADHD	Attention deficit hyperactivity disorder
ANOVA	Analysis of variance
AP	Antero-posterior
CRTT	Choice reaction time task
CSE	Corticospinal excitability
CSST	Conditional stop-signal task
cTMS	Controllable transcranial magnetic stimulation
DA	Dopamine agonist
DBS	Deep brain stimulation
DDM	Drift-diffusion model
DDS	Dopamine dysregulation syndrome
DLPFC	Dorsolateral prefrontal cortex
EMG	Electromyography
FDI	First dorsal interosseous muscle
fMRI	Functional magnetic resonance imaging
ICD	Impulse control disorder
IFG	Inferior frontal gyrus
LEDD	Levodopa equivalent daily dose
LRP	Lateralised readiness potential
M1	Primary motor cortex
MEP	Motor evoked potential
NCE	Negative compatibly effect
OCD	Obsessive compulsive disorder
PA	Postero-anterior
PCE	Positive compatibility effect
PD	Parkinson's disease
QUIP	Parkinson's disease impulsive compulsive disorders questionnaire
RDE	Response delay effect
rTMS	Repetitive transcranial magnetic stimulation
SMA	Supplementary motor area
SOA	Stimulus onset asynchrony
SSD	Stop-signal delay
SSRT	Stop-signal reaction time
SST	Stop-signal task
STN	Subthalamic nucleus
TMS	Transcranial magnetic stimulation
TS	Tourette syndrome
VSP	Visuospatial priming task
YGTSS	Yale global tic severity scale

1 INTRODUCTION

1.1 An Introduction to Motor Impulsivity

1.1.1 Introduction

Impulsivity can be described as the propensity to make hasty decisions without sufficient evidence, which results in premature or erroneous actions. Whilst it is a sporadic and uncommon feature of normal human behaviour, it has gathered much attention recently due to its involvement in an array of social and psychiatric disorders such as drug addiction (1), gambling (2) and schizophrenia (3). Impulsivity is not a unitary construct; it can be divided into two broad subtypes: motor and decisional impulsivity (4). Motor impulsivity, the focus of this thesis, includes response inhibition and waiting impulsivity, which correspond to inhibition of a prepotent response and premature responding prior to reward, respectively. Response inhibition is traditionally explored under experimental conditions with the use of behavioural experiments designed to make subjects inhibit an already initiated movement with the use of a learned inhibitory cue. Impulsivity in these types of experiments can be expressed either by a failure to inhibit the prepotent response or an inability to adaptively prolong response times in anticipation of potential stopping. Waiting impulsivity can be assessed using delayed response tasks such as the delayed

choice reaction time and 5 choice serial reaction time tasks. In these tasks, the motor instruction is given, but subjects must execute the movement after a delay. Impulsive responses are ones when movements are made before the wait period has elapsed. These two examples of motor impulsivity raise an interesting question: what the role of motor preparation is in impulsivity? That is, does a heightened state of the motor system at any particular time make it more likely that a movement will be executed or less likely to stop, and is this the cause of motor impulsivity?

1.2 Motor Response Inhibition

Behavioural inhibition is a key component of normal human functioning, serving to suppress inappropriate or unwanted actions. The concept of motor inhibition therefore pertains to how motor actions are aborted or restricted. Different types of motor inhibition are employed depending on the behavioural demands, with reactive inhibition being utilised when sudden stopping of a response is required. For example, reactive inhibition is called upon when applying the brakes of a car if a person walks out into the middle of the road. It is cued by external events and requires rapid cancellation of ongoing motor activity. Proactive inhibition is a prospective and goal orientated type of behavioural inhibition. It is concerned with responding under restraint, for example, not eating cake when one is on a diet or driving slower than normal around a school in anticipation of children running out into the road. Using these examples, one can imagine that these different types of inhibition act synergistically, rather than independently, to enhance behavioural inhibition. That is, engagement of proactive inhibition enhances the efficacy of reactive inhibition (5).

The networks implicated in reactive and proactive inhibition are believed to be anatomically distinct, although they both act via the basal ganglia to exert their influences on behaviour. As such, pathologies of the basal ganglia such as Parkinson's disease (6) and Huntington's disease (7) have shown deficits in response inhibition. Reactive inhibition engages a network incorporating the hyperdirect pathway via a cortico-

subthalamic route whereas proactive inhibition is thought to employ the indirect pathway through the basal ganglia, via a cortico-striatal-thalamo-cortical loop. Evidence for the networks mediating these types of behavioural inhibition in humans has come predominantly from imaging studies (reviewed in (8,9)).

Studies in both animal and human models have supported the dysfunction of these two kinds of inhibition in the manifestation of motor impulsivity. Rats with selective subthalamic nucleus (STN) lesions exhibit impulsive and perseverative behaviour and show an inability to stop in a stop-signal reaction time task (10). Patients with STN DBS also show impaired performance on motor tasks involving inhibitory control (11).

A third type of behavioural inhibition is termed automatic inhibition. It was initially identified when a patient with a visual cortex lesion could still differentiate between two visual stimuli, despite not consciously perceiving them (12). Since then, it has been found that subliminal, sensory cues have the ability to modulate motor actions (13,14). Whilst reactive inhibition can become automatic and habitual through learning, automatic inhibition differs in that its effects are derived subliminally. Simply put, the sensory cues which evoked automatic inhibition are not perceived, whereas they are in reactive inhibition. The network implicated in automatic inhibition has proposed to involve the prefrontal cortex (medial frontal cortex) (15–17), basal ganglia (striatum) (18) and thalamus (19). However, these studies either lack statistical power (one with two patients with supplementary motor area lesions), are performed in children (20) or are performed in neurodegenerative diseases (19,21,22) (Huntington's and Parkinson's disease), where there are widespread neurological changes; hence the findings should be interpreted with caution when inferring about automatic inhibition in healthy individuals.

1.3 Investigating Response Inhibition in Humans

1.3.1 Reactive inhibition

Reactive motor inhibition describes aborting a movement in response to a sensory cue. With this in mind, two types of experiment have been used to capture the processes of reactive inhibition in the laboratory setting. These include the go/no-go task and the stop-signal task. In the go/no-go task, participants are asked to respond as quickly as possible to either a go cue (green circle) but to not go to a stop cue (red circle). Reactive inhibition is measured as the proportion of stop trials where no response is made. By changing the proportion of go:stop trials, reactive inhibition can be made more or less difficult; the greater the proportion of go trials, the greater the chance of a commission error being made – that is, subjects responding on a stop trial. The stop-signal task is a behavioural task commonly used to assess the integrity of response inhibition in both human and animal models. In essence, the task requires the subject to abort a movement, which has already been initiated by the presentation of a stop-signal on a minority of trials. In doing so, reactive inhibition can be assessed by dynamic modulation of the timing of stop signal presentation, relative to the go stimulus. The output from this behavioural experiment is the stop signal reaction time (SSRT), which gives an indication of how well a subject is at stopping reactively. The main difference between the stop-signal task and go/no-go task is that subjects are cancelling an already initiated movement in the former, but do not initiate movement in the latter.

The neural correlates of reactive inhibition have been investigated predominantly in functional human imaging studies. A large meta-analysis of functional magnetic resonance imaging (fMRI) studies in go/no-go tasks has shown that the pre-supplementary motor area (pre-SMA) is involved in response selection, and hence in the decision of when to inhibit a response. The same meta-analysis identified that activation of the putamen bilaterally and right inferior frontal gyrus (rIFG) is associated with successful inhibition of the prepared response (23). Perturbing the rIFG and pre-SMA

using repetitive transcranial magnetic stimulation (rTMS) during the stop-signal task has been shown to decrease SSRTs; fMRI in these same subjects has shown greater activation of the right striatum, implying that reactive inhibition is, in part, mediated by a cortico-striatal-cortical network (24). The STN also plays a role in reactive inhibition. Activity in the STN correlates with that in the rIFG, with their activity being negatively correlated with the SSRT, implying that they may be drivers of reactive inhibition (25). Furthermore, the strength of their activation is stronger on successful stop trials with shorter stop-signal delays; when stopping is more difficult, yet still successful, greater activation from the STN and rIFG is required (26). Patients with PD may undergo DBS of the STN. In doing so, we gain a profound insight into the role of the STN during reactive inhibition. Typically, patients with STN DBS exhibit more commission errors during the go/no-go task (27), suggesting an impairment in reactive inhibition. Patients who have undergone subthalamotomy for their PD also show an impairment in reactive inhibition during the stop-signal task (11). Interestingly, this effect is seen in those patients who have undergone a right-sided subthalamotomy only, a finding that is consistent with the right lateralisation of the stopping network. Finally, electrophysiological evidence from the STN shows an increase in beta-band power during successful stopping (28). In all, evidence suggests that reactive inhibition employs a network involving the rIFG, STN, striatum and pre-SMA.

In both the SST and go/no-go tasks, reactive inhibition is indexed as successful suppression of the response. However, this behavioural manifestation may arise as a consequence of insufficiency of motor activation as well as correct engagement of a 'stopping network', to which behavioural data is unable to disentangle. One way of reconciling these different mechanisms is to use concurrent imaging such as fMRI and perturbation of key nodes in the inhibitory network (using rTMS), as described above. Behavioural manipulations to change the difficulty of reactive inhibition have been employed to overcome the issue of an insufficiency of motor activation. These include changing the expectation of a no-go or stop trial occurring, which changes the

predictability of these trials occurring. Another method is to constrain subjects' reaction times within narrow limits, usually determines by performance in a block with no stop ot no-go trials. In doing so, experimenters ensure that subjects are engaging their motor system on as many trials as possible. In the case of the SST, a staircase method can be employed, whereby stop-signals appear at varying delays after the go cue, which track success on previous stop trials. In doing so, the predictability of when the stop trial will occur can be varied to tailor individual subjects' performance. Another way to differentiate an insufficiency to excite vs active inhibition is to probe the motor system using single pulse TMS during reactive inhibition during no-go or stop trials. Corticospinal excitability after successful no-go and stop trials has been shown to be lower than that during failed no-go and stop trials and lower than that at baseline. The fact that corticospinal excitability is lower than that at baseline suggests that an active inhibitory mechanism is employed. Indeed, paired-pulse TMS has been used to investigate cortical inhibition during this same period of successful reactive inhibition in both tasks. They show that the decrease in corticospinal excitability during successful reactive inhibition is accompanied by an increase in $GABA_A$ mediated cortical inhibition, thereby implicating an active inhibitory mechanism when reactive inhibition, as opposed to insufficient excitation of movement (29,30).

1.3.2 Proactive inhibition

In both the go/no-go and stop-signal tasks, subjects have slower reaction times on go trials compared to blocks when no stopping is required. This has been interpreted as subjects employing a degree of proactive inhibition because of the expectation of stopping. Proactive inhibition can therefore be investigated by changing the proportion of stop-signal/no-go trials or by comparing reaction times during go trials in stopping blocks with reaction times in blocks with no stop trials. Blocks with no stop trials assume that no proactive control is exerted and hence the difference in reaction time on go trials between stop-signal blocks and no stop-signal blocks gives an indication of proactive control. For the go/no-go task, a similar principle can be employed; blocks where all trials are go give

an indication of the subject's response without proactive control. Whilst proactive inhibition can be measured in this way, the reaction time difference and effects can be confounded due to the difference in attentional demands between tasks, which is an important determinant of proactive control (31–35). Furthermore, measuring proactive inhibition in this way required the addition of more blocks to an experiment, which adds time to the overall experiment.

One variant of the stop-signal task, the conditional stop-signal task (CSST), is designed to simultaneously probe reactive and proactive inhibition. Here, subjects are asked to respond to one of two choices at the go signal (right or left button press). Stop signals are again presented after the go signals in a minority of trials, but the subject is told at the beginning of each block that the stopping rule applies to one direction only (right OR left). Simply put, the subject must cancel their response if the stop signal appears after one direction but not the other. A reaction time difference is commonly seen on go trials between the effector that needs to stop vs the effector that does not need to stop (the effector that needs to stop responds slower than the one that does not). This behavioural slowing down of responding is termed the response delay effect (RDE) and represents a behavioural index of proactive inhibition; responding under restraint in anticipation of potentially needing to stop.

Functional imaging studies during task manipulations probing proactive inhibition in two separate tasks (one with stopping, one without) have shown greater activation of the striatum when a stop signal is anticipated (36) and during the period when responses are slowed, to increase the chance of stopping (37). The dorsolateral prefrontal cortex (DLPFC) has also been implicated in proactive inhibition (38–40) and hence it is proposed that a network comprising the striatum and DLPFC mediate proactive inhibition (11). Modulations of proactive inhibition have been observed in patients with PD, who have undergone a subthalamotomy. Interestingly, only surgery of the right STN resulted in deficits in proactive inhibition, in that patients were not able to slow down the responses of their left hand to an upcoming stop signal. Healthy controls, patients with

PD without surgery and those with left-sided subthalamotomy displayed retained proactive control (11). This finding supports the role of the STN in mediating proactive inhibition. In fact, activation of the STN is believed to act as a "hold-your-horses" signal, which pauses movement before conflict can be resolved (41).

1.3.3 Automatic inhibition

In everyday life, various sensory cues from the environment have the potential to trigger relevant motor actions. This activation of a movement triggered by simple external cues is an automatic mechanism, which prompts motor preparation in order to facilitate motor execution (42). On the other hand, automatic inhibition of a sensorimotor transformation is also beneficial to avoid automatic coupling of sensory cues to motor actions. Automatic inhibition has traditionally been assessed in the laboratory using the masked priming task. Subjects are asked to make responses to one of two directions (left or right). The sensory prime is presented for only a short time (approximately 17 ms), which is not perceived by the subject. This is then masked using an array of randomly orientated lines. The target stimulus is then presented for 100 ms at a varying interstimulus interval, to which the subject responds accordingly. At short interstimulus intervals (up to 100ms), if the prime is the same as the target (compatible), responses are facilitated, and reaction times are shorter than if the prime and target are different (incompatible). If this interstimulus interval increases up to 150 ms, a reversal of the priming effect is seen, such that incompatible trials now result in faster reaction times than compatible trials. These conditions are believed to represent automatic motor inhibition (13,19,43–46). If the interstimulus interval increases beyond 150 ms, then the effect of positive priming again becomes apparent, although evidence for this is scarce (47). The proposed mechanism is as follows: the subliminal prime causes an automatic, initial motor activation corresponding to the prime choice alternative, which is accompanied by inhibition of the alternative choice, that is not the prime. The mask then occludes the prime and hence evidence for the prime decreases; thereby motor activation for the prime decreases too. If the target is presented early after the prime, when motor facilitation is still active, then

responses are faster during compatible trials. If the target is presented late after the prime, when motor inhibition has now occurred, then responses on compatible trials are now slower (43). This account is reflected in the lateralised readiness potential (LRP) measured during the masked priming task. The LRP measured displays a tri-phasic waveform, which forms the excitation-then-inhibition induced by the prime-mask combination, with the final peak corresponding to motor execution (48). Central to the mechanism of subliminal inhibition is the idea that it is threshold dependent; that is, the inhibition that follows initial motor activation is present if the strength of motor activation exceeds a certain threshold. Motor activation of a specific response is triggered and dependent on stimulus (prime) strength, which can be varied by changing the prime discriminability. In a series of experiments by Eimer and Schlaghecken, they noted that prime-mask combinations presented at the periphery of the visual field failed to elicit a negative compatibility effect. Interestingly, a positive compatibility effect was still seen and LRP data showed that increase in activity for the correct response but was not followed by the expected inhibitory phase. They hypothesised that this may be due to poorer mask-prime discriminability in peripherally delivered primes and that if this was the case, increasing the stimulus discriminability would result in a negative compatibility effect and excitation-then-inhibition pattern to be seen. Indeed, diverting all stimuli (mask, prime and target) to the same location resulted in the negative compatibility effect and expected LRP pattern. Furthermore, these features were absent when the discriminability of the prime was decreased by superimposing a random dot field onto the prime. These results together suggested that there was a threshold at which inhibition would occur; that is, initial motor activation was required to be large enough to trigger this reflex inhibition (49). They proposed that this may be a sort of noise protection mechanism, whereby inhibition occurs as a result of unstained incoming perceptual information for a given effector. The inhibition seen in these experiments may therefore be a consequence of self-inhibitory circuits, which generate inhibitory feedback when perceptual evidence is no longer available. This differs from the aforementioned forms of supraliminal inhibition seen in the stop-signal task primarily due to conscious perception

of the inhibitory stimulus and engagement of an intentional, prefrontal mediated circuit to engage reactive inhibition (discussed later). Because of the reliance of motor inhibition on strength of automatic motor activation and the subliminal nature of the stimuli (they lie outside of conscious perception and hence conscious detection and volitional inhibition), the authors posed that the inhibition here may be automatic in nature (13). The automaticity of inhibition in this task is highlighted in its lack of generalisation; primes only modulate performance if they are of the same kind as targets. For example, prime-target effects are seen if the combinations are both left/rightward facing arrows, but not if the prime is an arrow and the target is a letter (L or R) denoting the effector to be used (left or right, respectively).

1.3.4 Modelling motor response inhibition

The behaviour seen in tasks of reactive and proactive inhibition have been extensively modelled. One such model is the independent race model (50), which postulates that the go and stop processes are independently coded such that evidence accumulation for each process occurs independently up to a predetermined, perceptual threshold. Whichever process reaches this hypothetical threshold first is subsequently expressed (a race between two processes). The main assumption of this model lies in the independence of the go and stop processes. Whilst the independent race model predicts the behaviour in stopping tasks, it does not explain physiological data gathered from the frontal eye fields in monkeys performing the stop-signal task (51,52). Activity in movement-related neurones decreases during successful stop trials, which is strongly correlated with the activation of fixation neurones. This suggests an interaction between populations of 'go' and 'stop' neurones in the cancellation of initiated movements.

On the other hand, the interactive race model reconciles the physiological and behavioural data (53). It postulates that go units are activated by the go signal and that stop units are activated by the stop signal. Instead of a race to a predetermined threshold between the two processes, the model predicts that the stop unit exerts a rapid and potent inhibition

upon the go unit. If activity within the go unit reaches a decision threshold before the stop unit can have its effect, then a response is made, whereas if the stop unit exerts its inhibition in time, the movement is suppressed. These models are summarised in figure 1.1.

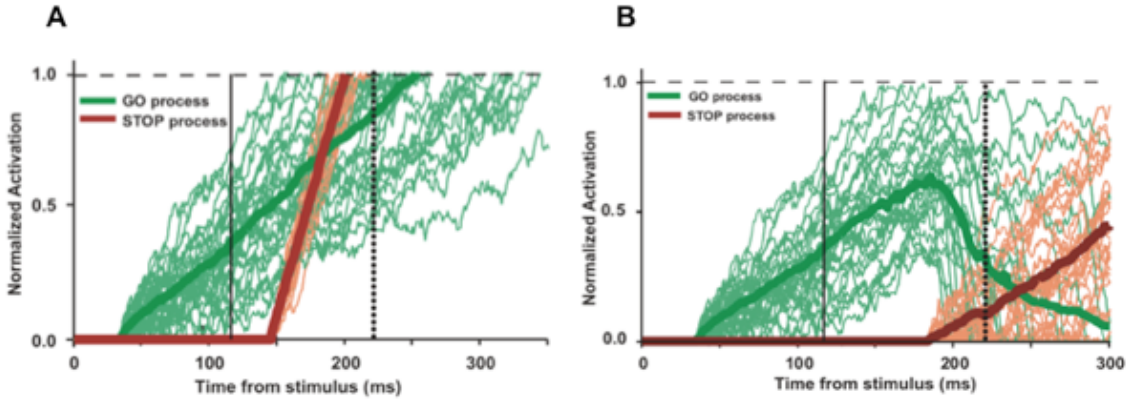


Figure 1.1: Independent and interactive race models of response inhibition.

(A) shows a model of the independent race model, whereby activity in a go unit increases towards a predefined decision threshold (dashed line). A stop unit is activated at 150 ms, which rapidly increases its own firing towards the same decision threshold. The unit whose activity reaches the decision threshold first is expressed; in this case, stopping is achieved. (B) shows the interactive race model. Go unit activity also increases towards a decision threshold. Stop unit activation occurs at around 175 ms, which exerts a powerful inhibitory effect upon the go unit, such that it does not reach the decision threshold. Stopping is again achieved. (Adapted from Boucher et al. (53))

At their cores, both models describe noisy evidence accumulation between two processes to a predetermined decision threshold, which forms the basis of drift-diffusion models (DDM) of decision making (54–56). DDMs have gained popularity due to their ability to recapture the response time and accuracy data from behavioural experiments (57–60). The model formally decomposes the parameters involved in perceptual decision making. The main parameters include the rate of evidence accumulation (drift rate), starting point

of evidence accumulation, distance from the starting point to the perceptual decision threshold (boundary separation) and time taken for visual processing of stimuli and motor execution (non-decision time). There are also parameters for the inter-trial variation in drift rate and range of the starting point and non-decision times (61). Considering perceptual decision making in this way, it is easy to see how responses are made to be more accurate but slower, for example, with increases in the boundary separation and decreases in the drift rate. The variability in drift rate to the same stimulus (due to noisy nature of evidence accumulation) and changes in drift rate and boundary separation between experimental conditions are crucial for the model to capture the reaction time distributions in two-choice reaction time tasks (62). For example, the model predicts that slower drift rates and greater boundary separations result in longer mean reaction times and wider reaction time distributions.

Modelling behavioural data from two-choice reaction time experiments in this way allows experimenters to link physiological data with stages of cognitive processing (63–66) and furthers understanding of brain-behaviour relationships. Their popularity has heightened with the development of packages for DDM fitting, which allow experimenters without the mathematical expertise required to construct the model, to still derive parameters on their experiments (67–70).

With regards to response inhibition, the DDM has also been extended to include tasks where reactive or proactive inhibition is required, such as the go/no-go task (71,72), stop-signal task (73–75) and CSST (11), by estimating the parameters that change when stopping may be required. The main conclusion from these experiments is that when stopping may be required, subjects raise their boundary separation and decrease their drift rate. In doing so, responses are made later, under caution of stopping. Whilst these models are useful for hypothesising the way in which the brain makes decisions and performs behavioural inhibition, physiological evidence remains a crucial component in deciphering these cognitive mechanisms.

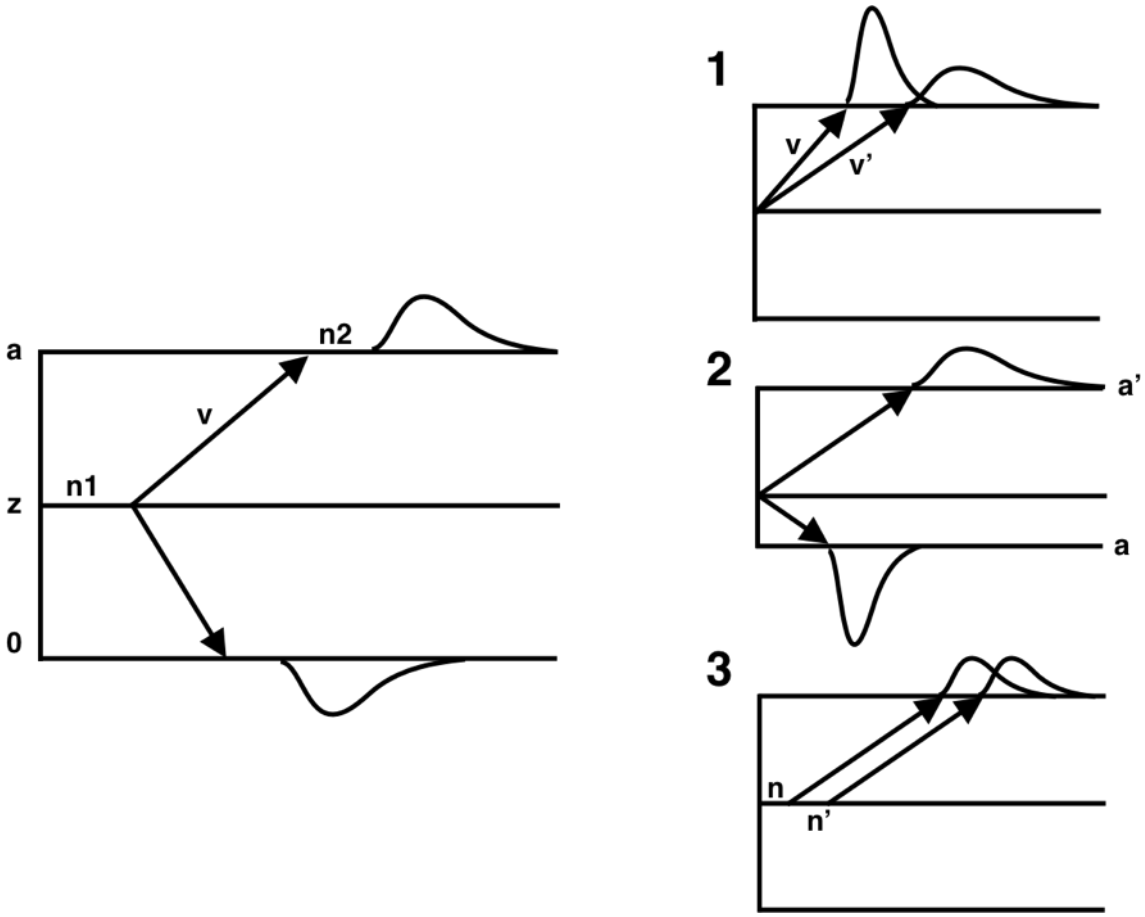


Figure 1.2: Drift-diffusion model and consequences of parameter changes on reaction times and their distributions.

Left: Schematic shows the core components of the DDM. Neural activity begins at a point between two perceptual decision thresholds (a and 0), one for each response alternative. After a delay for visual processing of the cue (n1), activity accumulates to one of the decision thresholds at a rate, v (drift rate). After reaching one of the perceptual decision thresholds and after another delay for motor execution (n2), a response is made. **Right**: Shown are predictions on reaction time distributions based on changes to each parameter. 1 shows two drift rates, v being faster than v', perhaps due to easier stimulus discriminability in condition v. Reaction times are faster and reaction time distribution narrower for drift rate v. 2 shows two boundary separations, a and a', potentially due to

an accuracy instruction in a' and speed instruction in a. Reaction times are faster and reaction time distributions narrower for a. 3 shows changes in non-decision time, where n' takes a longer time to begin evidence accumulation than n. Reaction times are longer for n' but reaction time distributions remain the same.

1.4 TMS as a Tool for Probing Response Inhibition

1.4.1 Introduction to TMS

Transcranial Magnetic Stimulation (TMS) is a noninvasive brain stimulation tool, which can specifically activate targeted brain regions. It is painless and well tolerated and allows investigators to probe the cortex in humans. If applied over the motor cortex (M1) at a suprathreshold stimulus intensity, it can result in muscular contractions in a somatotopically significant manner, which can be measured as electromyographic activity using surface electrodes over corresponding muscles. The resultant output is called the motor evoked potential (MEP). The amplitude of this MEP is believed to vary as a function of the excitability of M1 at the time of stimulation. For example, M1 excitability to a muscle is increased if there is an expectation that it is likely to be used in a forthcoming movement. Conversely, excitability can decrease if it is likely that an effector will not be called into action. The ease at which an MEP can be produced using TMS is termed corticospinal excitability (CSE), as the major output stimulated using TMS is via the corticospinal tract. It should be noted that CSE is not a pure measure of cortical excitability; the response measured at the muscle level is derived from contributions of both cortical and spinal inputs (76–80).

1.4.2 Accessing different inputs to the motor cortex using TMS

TMS is conventionally delivered by inducing a postero-anterior (PA) flowing current, approximately perpendicular to the central sulcus. Stimulating in this manner has shown to evoke responses in the contralateral limbs at the lowest stimulation intensity at a latency that is approximately 1-2 ms longer that muscular responses evoked using

electrical stimulation of corticospinal axons (81). If the direction of stimulation is changed such that current now flows in an antero-posterior (AP) direction, the threshold required to evoke an MEP is higher and latency of the MEP occurs 2-3 ms later. Increasing stimulation using PA-induced currents gradually recruits indirect waves (I-waves) (81), which are named in order of their appearance (I_1, I_2, I_3). These are believed to reflect interneurone inputs to motor cortex output neurones (82). Stimulation of M1 using AP orientated currents preferentially recruits these later inputs (I_3), suggesting that these different I-waves might represent the activity of different excitatory inputs into M1. During cervical epidural recordings in human patients, PA stimulation shows highly synchronised corticospinal activity, whereas stimulation with AP currents show less synchronised activity, which is delayed (83). Hence, the orientation of stimulation relative to M1 has been shown to evoke physiologically different responses (84,85). The conclusion from these findings has been that stimulating using these coil orientations accesses independent circuits to common motor outputs (82). In fact, these two inputs to M1 have been shown to be differentially altered in behavioural tasks (86,87), synaptic plasticity protocols (88) and measures of intracortical inhibition (89–91). Stimulating in these two different coil orientations is not totally selective for these inputs; these effects are usually seen when stimulating at low current intensities because stimulating at greater intensities tends to recruit inputs from the other direction. In doing so, increasing current stimulation intensity blurs the discriminability of the two inputs. Luckily, advancements in TMS hardware has enabled better selection of PA and AP inputs into the motor cortex. Peterchev and colleagues have recently developed a new TMS device, the controllable TMS (cTMS) device, which allows the duration of the TMS output to be altered (92). Recent work has shown that the specificity of activating these inputs can be enhanced by modulating TMS pulse width (91,93). Using the cTMS device, D'Ostillo et al. found that stimulating with briefer pulses lead to better selection of AP inputs into M1. Notably, they found that stimulation in AP orientation with a 30 μs pulse (AP_{30}) resulted in the longest latency MEPs (93). This was followed up by Hannah et al. who showed that these inputs activated by AP_{30} TMS did so more selectively that conventional TMS parameters

without recruiting earlier inputs into M1, usually evoked by PA TMS (91). They went on to exhibit the functional properties of AP inputs, showing that these AP_{30} inputs were selectively modulated by cerebellar transcranial direct current stimulation (86) and short-latency afferent inhibition (90), both of which have been previously reported to differentially modulated AP and PA M1 inputs.

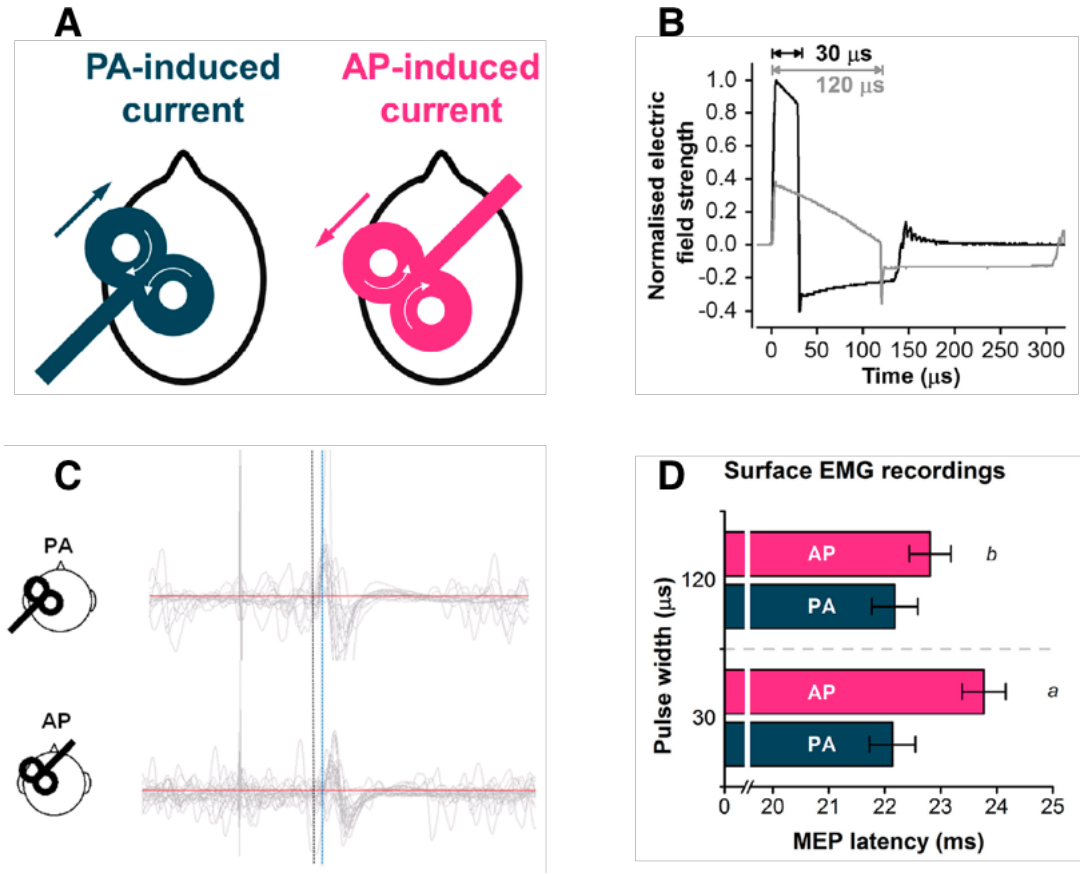


Figure 1.3: Modulation of TMS coil orientation and pulse width enable different inputs into the motor cortex to be accessed.

A: Schematic showing the orientation of TMS currents during PA and AP orientated TMS. B: Normalised electric field strength differs depending on the pulse width of stimulation used. C: MEPs evoked using PA and AP TMS are shown with PA latency indicated by the black, dashed line. AP MEP latency is indicated by the blue, dashed line.

Note that AP-evoked MEPs have longer latencies than those evoked by PA TMS. **D**: Bar chart shows the latency of MEPs evoked using TMS in PA and AP coil orientations, with 120 μs and 30 μs pulse widths. Note that latencies of AP MEPs are longer than those of PA MEPs, for both pulse widths. Also, MEPs stimulated in AP with a 30 μs pulse width give the longest latency MEPs. Diagram is produced from Hannah et al. (91) and D'Ostillo et al (93).

1.4.3 TMS studies in response inhibition

As the final common pathway for motor outputs, M1 receives inputs from other cortical areas such as the dorsal and ventral premotor cortices, prefrontal cortex, sensory cortex, posterior parietal cortex and supplementary motor area. In doing so, M1 acts as a node of integration for inputs, whose output ultimately results in motor behaviour. As such, M1 has been shown to reflect the functional output of the motor system during movement preparation in contexts such as effort (94), contextual uncertainty and surprise (95), value (96) and spatial attention (97). In these experiments, TMS is employed at times when these cognitive processes are active. By using the amplitude of the MEP during these times, inferences are made about the state of the motor system. Consequently, TMS can be employed during tasks of response inhibition to assay the state of the motor system during reactive and proactive inhibition.

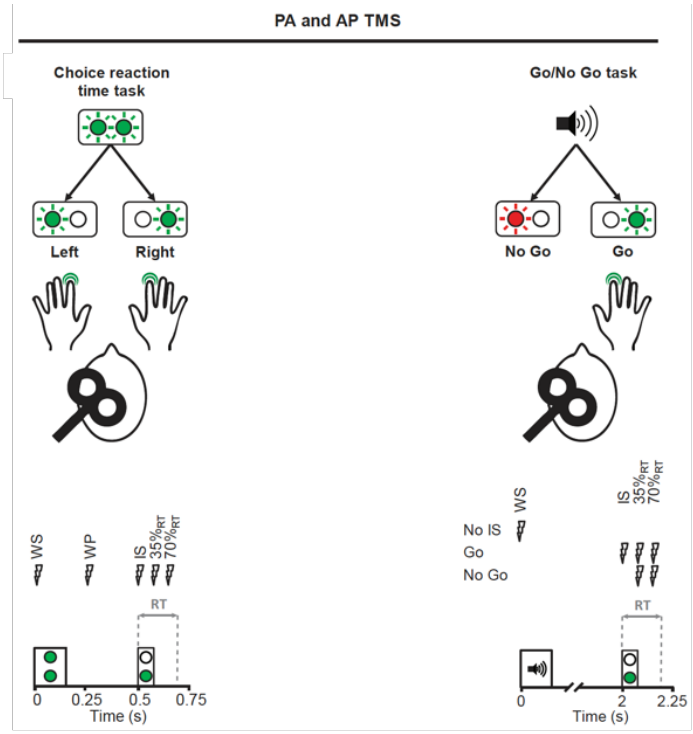
Current literature using TMS during behavioural tasks such as the stop-signal and go/no-go tasks have provided an insight into the cortical dynamics of reactive inhibition. As would be expected MEPs are suppressed in response to stop signal presentation (29,98,99). Further TMS studies have revealed that this suppression is not limited to the effector that needs to stop, but has global influences on CSE of task-irrelevant muscles; aborting a hand response decreases CSE in leg muscles, and aborting speech suddenly can decrease CSE in hand muscles (100–104). Interestingly, during successful stopping, CSE decreases to a level lower than that at baseline, which suggests that successful stopping is more than just delayed initiation and may be due to an active inhibitory

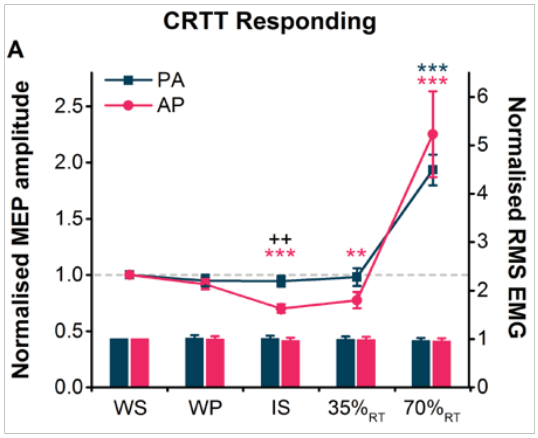
process. In fact, the intracortical dynamics of this MEP suppression have also been investigated; there seems to be an active inhibitory process mediating the reduction in CSE in the stop-signal and go/no-go tasks (29,30). The fact that the effect of reactive inhibition extends to areas other than the homologous muscle is further evidence that the stopping process is an active one (100,105).

Tasks of selective stopping combined with TMS have been used to investigate the influence of proactive inhibition. Here, subjects perform bimanual button presses on conventional go trials. At the beginning of stop trials, they are told that they may need to suppress one of the effectors, thereby employing a degree of proactive inhibition before the go signal is presented. MEP measures show suppression in the effector that may need to stop, but not in the ones that should carry on. Here, a focal, effector specific inhibition is used, which contrasts with the global inhibition of reactive stopping (106). Proactive inhibition can arise due to a delay in responding or an active inhibitory process suppressing movement execution. Whilst both are feasible, TMS studies have suggested that an active process mediates proactive inhibition; CSE measured during the intertrial period is lower than baseline CSE, only for the effector that might need to stop (106,107). A hidden assumption in these experiments is that responding to a cue occurs according to a rise-to-threshold model; activity accumulated during movement preparation triggers movement execution upon reaching a perceptual threshold. Hence prolongations in reaction time due to potential stopping arise from processes occurring during movement preparation, for example, a slower rate of rise in neural activity or a raised perceptual decision threshold, both of which result in neural activity reaching the threshold later.

Despite the wealth of TMS studies looking at the effects of proactive and reactive inhibition in tasks of stopping, there remain some outstanding questions. Firstly, there is an assumption that whilst reactive and proactive inhibition are diffuse and focal (anatomically) respectively, their inhibition upon M1 inputs is global. However, it is not made clear whether the inputs to M1 or output neurones themselves are suppressed. This is of particular interest as in models of the basal ganglia, inhibition of output is achieved

by via the cortico-subthalamic hyperdirect pathway (108–111). Activation of the STN sends diffuse excitatory projections to the globus pallidus interna (112–115), which subsequently withdraws excitation from the thalamus. In all, this decreases the excitatory drive to M1. From this model, we might expect that behavioural inhibition should not lead to a suppression of M1 output but should lead to a suppression of M1 inputs instead. In fact, recent evidence has suggested that different inputs into M1 are differentially modulated during preparatory inhibition (87). In this study, the authors investigated the role of two separate cortical inputs into M1 during phases of response preparation and execution, using PA and AP coil orientations of TMS. They employed TMS in these different coil orientations during response preparation and execution in a series of reaction time tasks. They found that only one set of inputs (AP) were suppressed during response preparation. This feature was found to be an encompassing phenomenon, being present whether the corresponding effector was called into action or not. This selective suppression was also found at the time of the imperative signal in a go/no-go task. These results counter the argument that preparatory inhibition serves to suppress motor output in order to prevent premature responding (116–120) because if that was the case, then all inputs to the motor cortex would be suppressed. Instead, the authors interpreted the selective suppression of AP inputs as a normal feature of movement preparation. Moreover, the degree of AP suppression prior to movement correlated well with the reaction time on that trial; greater preparatory suppression of AP inputs was associated with faster reaction times. Therefore, one could question whether reactive and proactive inhibition engage different inputs into M1. The authors from Hannah et al. reported that both PA and AP inputs into the motor cortex were suppressed on successfully cancelled no-go trials in the go/no-go task, implying that reactive inhibition globally suppresses motor cortex output. However, the go/no-go task assesses cancellation of the initiation of a movement. Alternative tasks, such as the SST, measure reactive inhibition as cancellation of an already initiated movement; the effect of cancelling an ongoing movement on motor cortex inputs has not been investigated.


PA and AP TMS
Choice reaction time task
Left
Right
WS
WP
IS
35%RT
70%RT
RT
0
0.25
0.5
0.75
Time (s)
Go/No Go task
No Go
Go
No IS
Go
No Go
WS
IS
35%RT
70%RT
RT
0
2
2.25
Time (s)


CRTT Responding
A
PA
AP
Normalised MEP amplitude
Normalised RMS EMG
WS
WP
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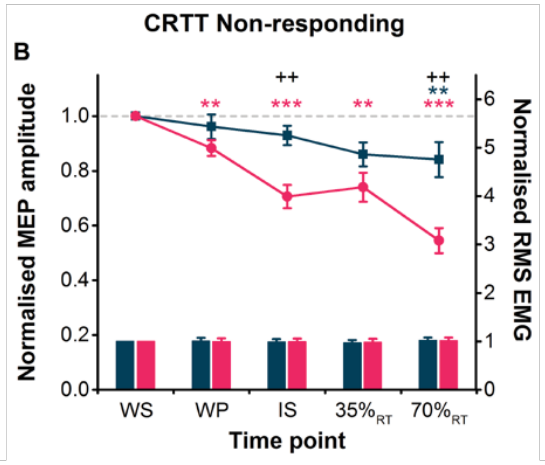
35%RT
70%RT


CRTT Non-responding
B
Normalised MEP amplitude
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70%RT
Time point

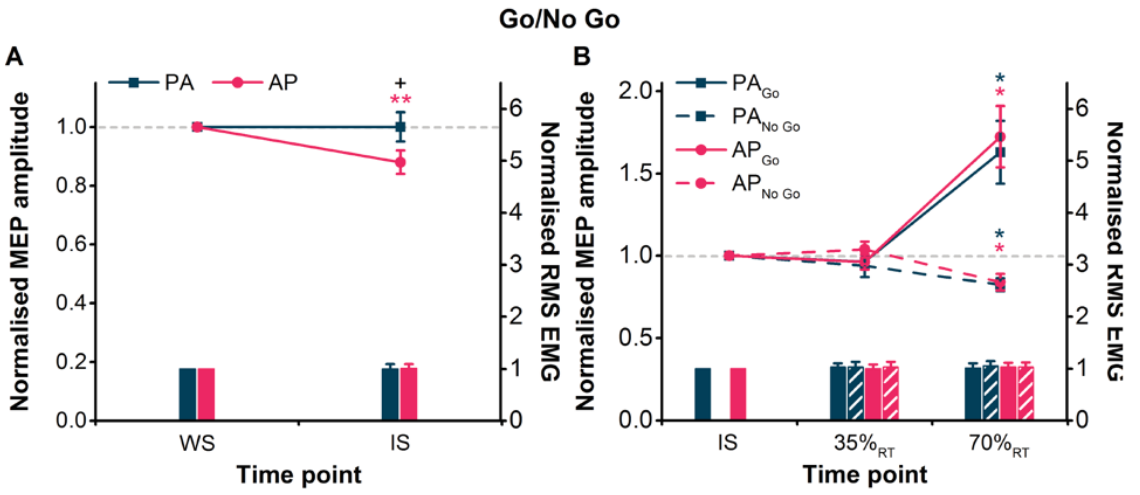
Go/No Go
A
PA
AP
Normalised MEP amplitude
Normalised RMS EMG
WS
IS
Time point
B
PAGo
PANo Go
APGo
APNo Go
Normalised MEP amplitude
Normalised RMS EMG
IS
35%RT
70%RT
Time point

Figure 1.4: Experimental design and data from the study by Hannah et al.

Top: Experimental setup showing choice reaction time task and go/no-go task used in the study with the timing of TMS delivery in each task. Normalised MEP amplitudes are shown in the plots for each task. Root-mean-squared electromyography is also shown for each condition as experiments were done on the background of a weak contraction. Suppression of AP inputs are seen at the imperative stimulus for both the choice reaction time task and go/no-go tasks. Suppression of PA and AP inputs are seen in the go/no-go task for successful no-go trials. Diagram is produced from Hannah et al. (87).

Secondly, there is an underlying assumption in previous TMS experiments that movement preparation mediates the prolongation in reaction time when stopping may be required and that movement preparation will inevitably lead to motor execution once preparation reaches the perceptual decision threshold described in rise-to-threshold models. However, a growing body of evidence has proposed that movement preparation and initiation are two independent processes, which are not inevitably coupled (121,122). A study by Haith et al. showed this independence of movement preparation and initiation by analysing reaction times and errors from a free and forced reaction time task. In the free reaction time task, subjects were asked to make a reaching movement to a target, which appeared at one of eight locations, after being cued with four auditory tones (the fourth tone was the go cue). In the forced reaction time task, subjects were instead asked to make their reaching movement *in synchrony* with the fourth tone, not after it. By adjusting when the target was revealed to the participant in the forced reaction time task, reaction time and movement preparation could be altered by the experimenters. The authors found that subjects were able to make accurate movements in the forced reaction time task approximately 80 ms earlier than their reaction times would suggest from the free reaction time task, suggesting that subjects were, for some reason, delaying their motor initiation after preparation had concluded. The authors then questioned whether there was a causal relationship between movement preparation and initiation or an independence between the two by inspecting the errors made in the free reaction time task. They predicted that

if motor initiation was triggered by motor preparation, then errors should be rare and crucially, errors should be independent of reaction time. Conversely, if movement preparation and execution were independent, then errors should occur spontaneously when either movement preparation occurred unusually late and/or movement initiation occurred unusually early. In their results, it was clear that spontaneous errors were specific to movement with low reaction times, thereby supporting the independence hypothesis. Furthermore, a model assuming the independence of motor preparation and initiation successfully predicted the frequency and characteristics of errors made in the free reaction time task (121). Despite the behavioural evidence of an independence between movement preparation and initiation, there is a lack of physiological evidence for such independence, which we can provide using TMS.

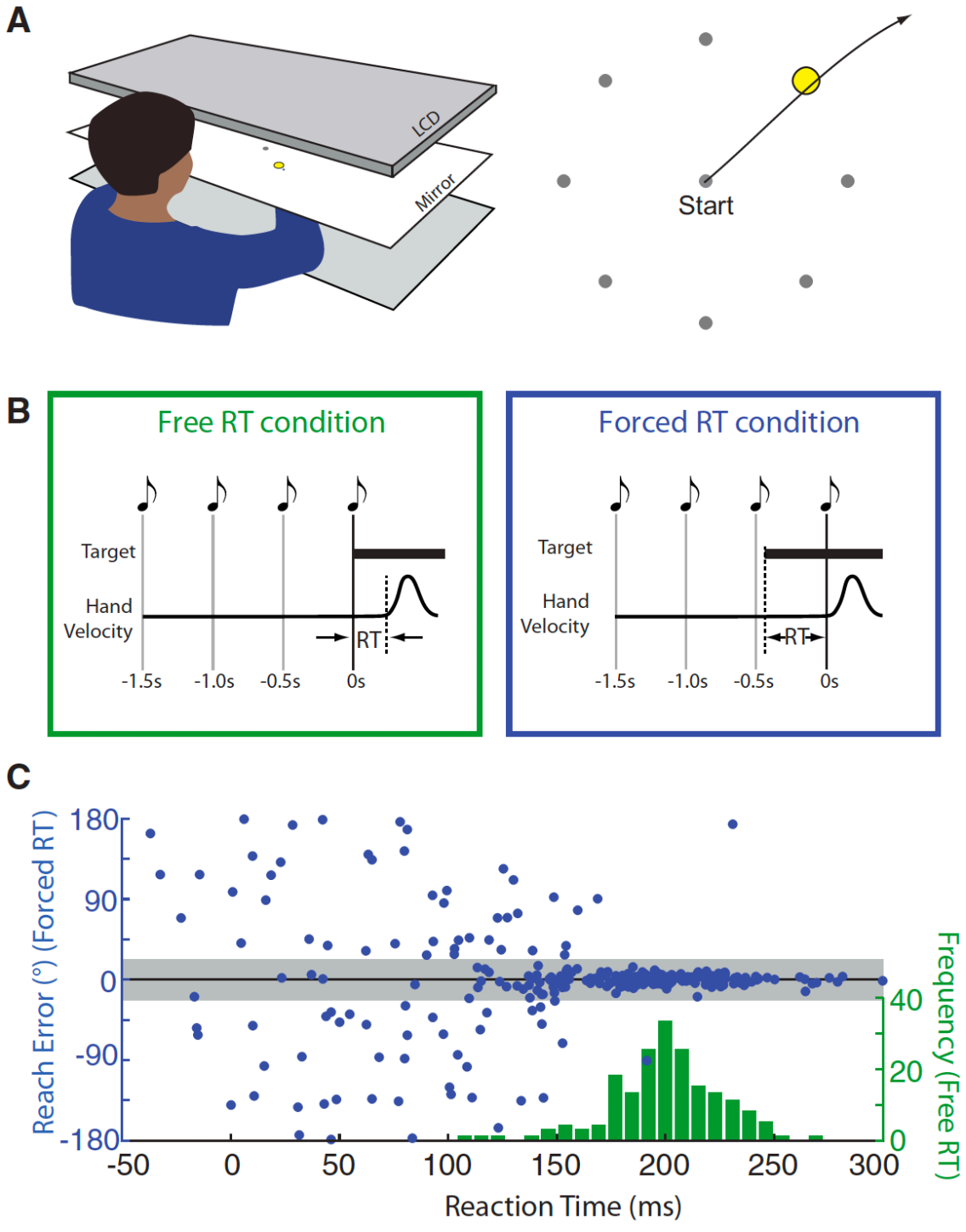

Figure 1.5: Experimental design and example data from the study by Haith et al.

A: Experimental setup showing the reaching task with eight response alternatives. **B**: In the free reaction time condition, subjects are counted in to the go cue (fourth tone), when one of the eight targets is illuminated (also at the fourth tone). Subjects are instructed to move as accurately and quickly once the target appears. In the forced reaction time condition, subjects are instructed to move with the fourth tone. The target is presented at a variable time before the fourth tone so that movement preparation and reaction times can be altered. **C**: Example data from one participant showing the reaction time distribution on the free reaction time condition in green bars. Blue dots plot the reaction time against the initial reach error in the forced reaction time task. Errors are clearly associated with shorter reaction times. Diagram is produced from Haith et al. (121).

The complexity of impulsivity can make investigating it a challenge. However, there exist clinical populations where impulsivity can be a common feature. By investigating clinical samples, groups of patients with presumably common pathophysiological mechanisms of impulsivity can help reduce the heterogeneity that comes from investigating impulsivity in disparate cohorts. In essence, specific disease pathophysiology can 'normalise' population studies to reduce noise.

1.4.4 Clinical models of impulsivity

As aforementioned, impulsivity can be divided into decisional and motor subtypes. In addition to impulsivity as a consequence of brain injury to a key inhibitory node (traumatic brain injury to the right inferior frontal gyrus (123)), there exist idiopathic disorders, where impulsivity is a feature. Here, we discuss how decisional and motor impulsivity are exemplified in two clinical models.

Parkinson's disease (PD) is a neurodegenerative disease affecting 1 in every 500 people in the United Kingdom (Parkinson's UK). It is primarily characterised by degeneration of dopaminergic neurones of the substantia nigra pars compacta, giving rise to characteristic motor symptoms such as bradykinesia, resting tremor, rigidity and postural instability. Since its description in 1817 by James Parkinson (124), the motor symptoms

have been highlighted as the most debilitating from the patient perspective. Over time, advancements in medicine and engineering have enabled these motor symptoms to be well addressed with pharmacotherapy and deep brain stimulation (DBS) leading clinical practice.

Unfortunately, these therapies have given rise to an array of cognitive behavioural problems, impulse control disorders (ICD) being one example. Patients on dopaminergic medication can exhibit compulsive gambling, shopping, sexual behaviour and eating (4,125–127), with incidence reported to be approximately 17% (126). Interestingly, the association between ICD generation and dopaminergic medication is much stronger for agonist medication that for levodopa (128,129), although. Given that, in principle, levodopa eventually activates post-synaptic dopaminergic terminals, this disparity seems strange. A reason for the dissociation may be that as levodopa is taken up by pre-synaptic dopaminergic neurones, their release into the synaptic cleft is physiological, and hence tightly regulated. Dopamine agonists on the other hand 'flood' the system with dopamine and cause excessive, non-physiological activation of post-synaptic dopaminergic receptors, irrespective of where they are necessarily needed. This 'spillover' may potentially be why dopamine agonists cause more off-target effects than levodopa. Furthermore, it is known that dopamine agonists differ in their propensity to cause ICDs. The reason for this has been postulated to lie in the relative affinity of dopaminergic agonist medication to D3 receptors (4,130). Indeed, ropinirole and pramipexole have a relatively high affinity for D3 receptors compared to other dopamine agonists and subsequently confer the greatest risk of developing ICDs (131). Conversely, bromocriptine and apomorphine have a relatively low affinity for D3 receptors and it follows that they confer a significantly smaller ICD risk. Moreover, D3 receptors localise to structures contained in the limbic nuclei of the basal ganglia, supporting D3 receptors' role in ICD generation. ICDs are not only selective for dopaminergic agonist therapy; they have also been implicated in cases of patients with DBS (132), although this

relationship can be bidirectional; DBS reduced dopaminergic medication load but can itself cause behavioural changes.

The incidence of ICDs may be considered small, but the clinical impact can be devastating. Reports of patients gambling away their life savings or exhibiting unsociable behaviour and breakdown of relationships, highlights this problem (128). Furthermore, the incidence of ICDs is probably underestimated; ICDs are only recorded once an event, such as those described, has occurred. In fact, there are probably more patients exhibiting ICD-like behaviour on dopaminergic therapy, but who have not yet committed an act worthy of reporting. In essence, these patients may be considered as ticking time-bombs. To this end, understanding the mechanisms of ICD generation, particularly signatures that might be predictive of their occurrence, is an important field of study.

Tourette syndrome (TS) is a neurological condition, which affects approximately one in 100 children, with over 300,000 children and adults currently living with the condition in the United Kingdom (Tourettes Action). The most prominent feature is a tic disorder but up to 85% of patients will experience co-occurring conditions such as attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD) and anxiety. Tics are fast, repetitive, involuntary movements and sounds, which can be difficult to control.

Hypotheses regarding tic generation can be made if we consider tics as movements generated in a rise-to-threshold manner. It separates out motor preparation as the cognitive process involving the build-up of activity to a threshold and motor execution as the compulsory process which occurs when the threshold is met. One hypothesis is that the motor system in patients with tics is in a constantly heightened state. According to the model, this heightened state could arise due to faster rates of build-up of activity or lower perceptual thresholds. Indeed, there is evidence from TMS experiments suggesting alterations in the motor system of TS patients. Motor input-output curves at rest in TS are less steep (133) and TMS measures of intracortical inhibition are greater (134) than in healthy, age-matched controls. These findings both point towards compensatory mechanisms to control tics. Although these findings seem contradictory to the hypothesis,

one must note that these measurements were taken at rest, not during a movement. An alternative hypothesis is that motor noise is greater in TS than in healthy, age-matched controls (135) and that this excess is what causes tics. Motor noise refers to the spontaneous changes in brain activity in the motor system, which is not related to experimental conditions or stimuli (136), akin to the noisy evidence accumulation/variations in drift rate in DDMs. If the noise is large enough, as may be the case in TS, then the perceptual threshold in rise-to-threshold accounts of movement may be erroneously reached more frequently and movement executed, thereby generating tics.

Despite the differences in manifestations of uncontrolled behaviours in PD and TS, it seems apparent that in both clinical contexts of decisional and motor impulsivity, there exists some deficit in behavioural inhibition. That is, an inability to appropriately inhibit one's thoughts and actions.

1.5 Motor Response Inhibition in Parkinson's disease

Individuals with PD exhibit a breakdown in response inhibition and generally perform poorly in tasks designed to engage behavioural inhibition, such as the stop-signal and Stroop tasks (137). These deficits are even present in the absence of an overt ICD (4). These patients have prolonged SSRTs, which are independent of their slower speed on go trials, indicating impaired reactive inhibition (138). A battery of inhibitory tests including the CSST, Stroop, Hayling sentence completion test and random number generation performed by Obeso et al. showed significant deficits in a variety of inhibitory functions, and concluded that PD is a generalised disorder of inhibition as well as activation (6). Whilst response inhibition is impaired in PD, recent work has shown that impulsivity is not a unitary construct with a unifying mechanism. Factor analysis of the performance on a number of objective behavioural measures, self-reported questionnaires about impulsivity and a neuropsychological battery revealed four principal components. Each of these four components was associated with different elements of clinical and

demographic variables, indicating different mechanisms contributing to impulsivity (139).

PD is not solely a disease of dopamine deficiency but also of noradrenergic (140) and serotoninergic (141) neurones. There is a growing body of evidence that these neurotransmitters can mediate features of response inhibition (142,143). In fact, replenishment of noradrenaline using the noradrenaline reuptake inhibitor, atomoxetine, has been shown to improve laboratory measures of response inhibition (144). As such, it is clear that impulsivity in PD is not solely due to modulations in dopaminergic transmission but represents a complex interplay between different neurotransmitter systems. That being said, the dopamine agonist use still dominates as the causative agent for ICD generation (126,131,145) and their withdrawal remains the mainstay of resolving ICDs (146). Furthermore, a recent meta-analysis from 42 response inhibition in PD was conducted to assess the interaction between dopaminergic medication and disease duration on measures of response inhibition (147). This was prompted by the finding that dopaminergic therapies improve response inhibition in early-stage PD patients (148,149). The authors found deficits in inhibitory control for PD patients who were both "on" and "off" medications. Moreover, their analysis revealed a differential effect of dopamine depending on disease duration. The role of dopamine agonists therapy in ICD generation is complicated, however, in view of the findings that that PD patients on levodopa can also exhibit these (126).

PD patients with ICDs have also been investigated for a deficit in inhibitory function, albeit it to a lesser degree. One study found a lack of motor impulsivity in PD patients with a history of ICDs, with SSRTs in fact faster than those of age-matched healthy controls (150). In another looking at performance on the Stroop test between PD patients with ICDs vs those without, no differences were seen on inhibitory performance between groups (151). Another found no difference on the Simon task between PD patients who were on dopamine agonist monotherapy vs levodopa medication monotherapy (149). These studies all speak against the role of response inhibition being implicated in

impulsivity, although one important caveat from these studies is that proactive inhibition is not studied, the main type of behavioural inhibition believed to underlie ICD generation in PD (8); they all assess reactive inhibition.

A handful of studies have assessed automatic inhibition in PD using a masked priming approach. They all show that automatic inhibition is impaired in PD, with an attenuation of the negative compatibility effect: the measure of automatic inhibition (21,22,152). The impact of dopaminergic medication, however, has not been investigated. Considering the link between dopamine agonists and ICDs, it may be interesting to explore this.

1.6 Motor Response Inhibition in Tourette Syndrome

Motor response inhibition in TS has been extensively studied albeit with mixed results. Whilst some studies report a deficit in inhibitory control (153–155), others show no change (156–159) and some enhanced (160–162), relative to age-matched, healthy controls. There are numerous reasons for the heterogeneity in these findings. Firstly, TS is known to co-exist with other disorders such as OCD, ADHD and anxiety, each of which can confound results from behavioural experiments (157). For example, where attention is required in tasks of response inhibition, patients with concomitant ADHD may perform poorly not due to a deficit in behavioural inhibition, but rather a deficit in attention. Failure to account for these differences undoubtedly adds noise to the dataset. Studies reporting abnormalities in response inhibition in TS often sample from adults with tics or with mixed samples of children and adults. This is an issue, as there is an emerging view that adult TS is not representative of the typical presentation (163). Moreover compensatory reorganisation that takes place in patients with TS when tic control improves as a function of disease duration (160) may further add variance to the data. Positron emission tomography imaging in TS patients shows widespread abnormalities of the GABA-ergic system, with decreased binding of $GABA_A$ receptors in the ventral striatum, globus pallidus, thalamus, amygdala and right insula. Increased binding, however, is found on the substantia nigra (164). Physiological interrogation of $GABA_A$

concentrations as measured by short-interval intracortical inhibition in the motor cortex of TS patients generally shows corticospinal hyperexcitability (133,134,165–167). Furthermore, the rise in CSE with increasing TMS intensities at rest (134) and during movement preparation (168) are attenuated relative to healthy, controls. Interestingly, magnetic resonance spectroscopy has found increased GABA concentrations within the supplementary area, which is inversely correlated with corticospinal excitability (134). This is believed to reflect compensatory associated with increasing control of tics, which may confound results from tests of behavioural inhibition if patients are tested at different times during this compensatory period. If this was the case, this could feasibly give rise to the conflicting results seen. Inherent differences in the behavioural tasks used (Stroop, SST, Eriksen flanker, go/no-go) will also contribute to the differences in results seen between studies, as each behavioural experiment differs in their cognitive demands.

As in PD, the majority of studies assessing response inhibition in TS have focused on reactive inhibition. Seeing as how tics can arise from a premonitory urge and can be voluntarily suppressed for a period of time, it seems proactive inhibition should be investigated instead. On the other hand, in cases where the premonitory urge is absent, and tics occur without warning, it seems that a failure in automatic inhibition could be a candidate mechanism by which tics arise. Only one study has looked specifically at proactive inhibition in TS. The investigators assessed proactive inhibition by comparing reaction times on go trials during the stop-signal task, when stopping was required, against go reaction times in a simple reaction time task, when no stopping was required. As TS can co-exist with OCD, the investigators categorised groups by whether they had pure TS, pure OCD or both. In doing so, they found that impairments in proactive and reactive inhibition were found, but specifically for patients with OCD, compared to healthy, age-matched controls. Furthermore, the severity of symptoms scaled with the deficits in behavioural inhibition (169). No studies have assessed automatic inhibition in TS.

1.7 Excessive Motor Noise as a Cause of Tics in Tourette Syndrome

An alternative hypothesis to tic generation has been the motor noise hypothesis (135). In this hypothesis, the putative noise (136) displayed in the motor system is exacerbated in TS. If overlain onto the rise-to-threshold accounts of movement, then this noise is akin to noisy evidence accumulation and variations in drift rate. Increasing noise in the system therefore increases the chances of activity crossing a perceptual boundary and movement being executed, this movement being the tic.

1.8 Aims of the Current Thesis

The title of this thesis is: “Impulsivity in Parkinson’s Disease and Tourette Syndrome, and Human Motor Decision Making”. I aim to explore the mechanisms by which impulsivity arise in these clinical disorders, pursuing two main hypotheses: a failure in response inhibition and alterations in motor preparation, by focusing on the role of motor decision making and response inhibition TS and PD.

To investigate whether there are any deficits in motor inhibition in TS, it is important to first establish the characteristics and mechanisms of putative motor response inhibition in healthy individuals. It is also unclear whether proactive or automatic inhibition are altered in TS. To address this, I will employ tasks of reactive, proactive and automatic inhibition on populations of patients with TS and tic disorders, using healthy, age-matched individuals as controls. As aforementioned, models of response inhibition posit a competition between two processes to a predefined decision threshold, following DDM architecture. Using TMS, it is possible to test whether there is a physiological reflection of this rise-to-threshold model within M1 during decision making. The model predicts that CSE would rise after the go signal, as evidence is accumulated for the cued effector. I will test with TMS whether the gradient of excitability increase (akin to drift rate in the DDM) or the threshold for activation changes in the context of a stopping task. Hence, by using DDM analyses to explain strategic processes underlying adaptive decision making

when stopping may be required, a cognitive framework for the mechanism of proactive inhibition will be formed. I will compliment this framework with physiological recordings from M1 using TMS, to inform of the role of M1 during response execution and inhibition, specifically during proactive and reactive inhibition. Indeed, basal ganglia models of response inhibition predict that during stopping the basal ganglia exerts its effects on the inputs to M1 rather than the outputs. Using intricate TMS manipulations such as altering coil orientation and pulse width, these different M1 inputs will be accessed during tasks of proactive and reactive inhibition. Having established these normal mechanisms of response execution and inhibition in healthy subjects, I would look to assess whether they are the same in patients with TS. There is a hypothesis that increased motor noise causes tic generation in TS. With this in mind, there are specific hypotheses that can be tested regarding motor noise and its effects on motor responding.

It is clear that dopamine agonists are causative agents in inducing impulsivity in PD. However, studies investigating the role of dopamine use in response inhibition suffer from two core limitations: firstly, these studies rarely distinguish dopamine agonists from levodopa when assessing response inhibition. Seeing as how the incidence of ICDs in PD is more common with dopamine agonists than levodopa, this seems erroneous. Secondly, reactive inhibition is predominantly investigated in tasks of response inhibition; there are a paucity of studies assessing dopamine agonist use in proactive or automatic response inhibition. I will firstly look at how dopamine agonists specifically modulate response inhibition in healthy control subjects, before assessing the role of these drugs in PD. Again, I will aim to use DDM analyses to investigate the underlying cognitive processes that mediate response inhibition and that change under the influence of dopamine agonist medication.

2 METHODS

2.1 Participants

Healthy subjects were recruited from a database of healthy volunteers at the Institute of Neurology, University College London. Patients with a diagnosis of Tourette syndrome or any tic disorder were recruited from clinics at The National Hospital of Neurology and Neurosurgery, by Professor Eileen Joyce and Professor Kailash Bhatia, and from a patient database organised by Tourettes Action. Patients with Parkinson's disease were recruited from outpatient clinics at The National Hospital for Neurology and Neurosurgery, by Professor Thomas Foltynie and Professor Kailash Bhatia. Individual chapters outline the inclusion and exclusion criteria.

2.2 Institutional and Ethical Approval

All experiments performed at the Institute of Neurology (London) were approved by the University College London Research Ethics Committee. Studies performed on patients with Tourette syndrome and tic disorders were performed with an amendment to an existing ethical application, approved by the Health Research Authority of University College London Hospitals. Studies performed on patients with Parkinson's disease were performed with ethical approval from the Research Ethics Committee of University College London Hospitals. All studies were performed in accordance with the Declaration of Helsinki.

2.3 Transcranial Magnetic Stimulation (TMS)

2.3.1 TMS Coils and magnetic stimulators

All experiments used monophasic, single pulse TMS delivered via a figure-of-eight shaped coil with 70 mm internal wing diameter. We used two magnetic stimulators to deliver stimuli: the Magstim 200 (The Magstim Company, Dyfed, UK) and controllable TMS device (cTMS3, Rogue Research Inc., Canada). The methods of individual chapters specify which stimulator was used. For all TMS experiments, subjects were seated comfortably in an armchair, whilst the investigator stood behind them holding the stimulating coil.

2.3.2 Hotspot location and test stimulus threshold measurement

The primary motor cortex corresponding to the first dorsal interosseous (FDI) muscle was targeted in all experiments. The hotspot was identified as the area on the scalp where the largest and most stable motor evoked potentials (MEPs) could be obtained for the right FDI muscle, using a given suprathreshold intensity. We employed TMS in two ways: i) with the coil held approximately perpendicular to the presumed central sulcus and tangentially to the skull, TMS was given either with the coil handle pointing backwards for postero-anterior (PA) stimulation or ii) with the coil handle pointing forwards for antero-posterior (AP) stimulation. Where the cTMS device was used, we gave TMS at a pulse width of 120 μs for PA stimulations and 30 μs for AP stimulation; stimulation with these parameters has shown to recruit early and late inputs into the motor cortex for PA and AP stimulation, respectively (91). Accordingly, the hotspot was found for each coil orientation. For each coil parameter, the stimulation intensity was set to one whereby resting peak-to-peak MEP amplitude was 0.5 mV. Coil parameters are specified in the methods section of each chapter, where appropriate.

2.3.3 Recording of evoked responses

Surface electromyography (EMG) was obtained from the FDI muscle using a belly-tendon montage using 19 mm x 38 mm surface electrodes (Ambu WhiteSensor 40713). The raw signals were amplified, and a bandpass filter was also applied (20 Hz to 2 kHz (Digitimer, Welwyn Garden City, United Kingdom)). Signals were digitised at 5 kHz (CED Power 1401; Cambridge Electronic Design, Cambridge, United Kingdom) and data were stored on a computer for offline analysis (Spike2 version 8.10, Cambridge Electronic Design, United Kingdom).

2.4 Administration of Medication

Experiments with healthy subjects employed ropinirole 1 mg and placebo. Each participant received Ropinirole and placebo in two different sessions, the order of which was determined by a random number generator. The placebo used was a sugar pill, which looked similar to ropinirole. Ropinirole and placebo pills were separately placed into two pill bottles and taped using opaque tape. These were then labelled ‘1’ and ‘2’ by an independent investigator, who knew and recorded the identity of the Ropinirole and placebo, thereby blinding the original investigator. During the experiment using ropinirole and placebo, the chosen pill was given to the subject from the corresponding bottle. The subject closed their eyes, put the pill in their mouth and swallowed with water. It was made sure that a clinician was on-site in the case of any adverse effects from the ropinirole or placebo.

2.5 Clinical Parameters

2.5.1 Screening for the presence of Impulse Control Disorders in Parkinson’s Disease

The Parkinson’s Disease Impulsive-Compulsive Disorders Questionnaire (QUIP) was used to screen for impulse control disorders in patients with PD. The QUIP is a binary, yes/no questionnaire assessing symptoms of impulsivity (gambling, sexual behaviour,

buying and eating), dopamine dysregulation syndrome and other compulsive behaviours, such as punding (170). Patients self-completed the questionnaire in private.

2.5.2 Drug history

A patient's medication history was ascertained on reporting for their testing session. If patients were known to the hospital and clinical records could be accessed, a drug history was compiled and checked. For patients with Parkinson's disease, we made particular note of Parkinson's disease-specific medication, including levodopa, dopamine agonists, dopa decarboxylase inhibitors and monoamine oxidase inhibitors, and their respective doses. Moreover, we calculated the levodopa equivalent daily dose (LEDD) for each patient using a levodopa equivalent daily dose calculator.

2.5.3 Disease duration

The onset of disease for all patients was made by asking the patient when they were formally diagnosed by a clinician with either a tic disorder, Tourette syndrome or Parkinson's disease. Where possible, this was confirmed by looking at patient records. Although disease duration is strictly time from symptom onset to date of testing, we were unable to ascertain this some patients. Furthermore, the subjective experience of when symptoms pertaining to their specific disease started might not be accurate. To this end, the duration of disease was therefore the time between formal diagnosis and time of testing.

2.5.4 Measuring tic severity and co-morbidities

Tic severity was measured in patients with Tourette syndrome and tic disorders using the Yale Global Tic Severity Scale (YGTSS). The YGTSS is a validated scale for assessment of tic severity in Tourette syndrome (171,172), which marks tic severity by motor and phonic subtypes (/25 each), with a score for impairment (/50) on daily living. It is known that TS can co-exist with ADHD and OCD, which may confound measurements of

response inhibition. With this in mind, patients were asked if they had a formal diagnosis of either disorder.

2.6 Behavioural Paradigms

2.6.1 Choice reaction time task

As this was a validation study of previously published results, the methodology is outlined in the original paper (87). Subjects were asked to maintain contraction in each FDI to 10% of their maximum voluntary contraction. An auditory cue signalled the beginning of the trial. 500 ms later, a warning cue (left AND right light-emitting diodes) flashed, signalling the beginning of the preparatory period. 500 ms after the warning cue, the imperative stimulus (left OR right) diode flashed, to which the subject had to respond by pressing the dynamometer as fast as possible with the corresponding index finger. The reaction time was defined as the time difference between the imperative stimulus and EMG onset.

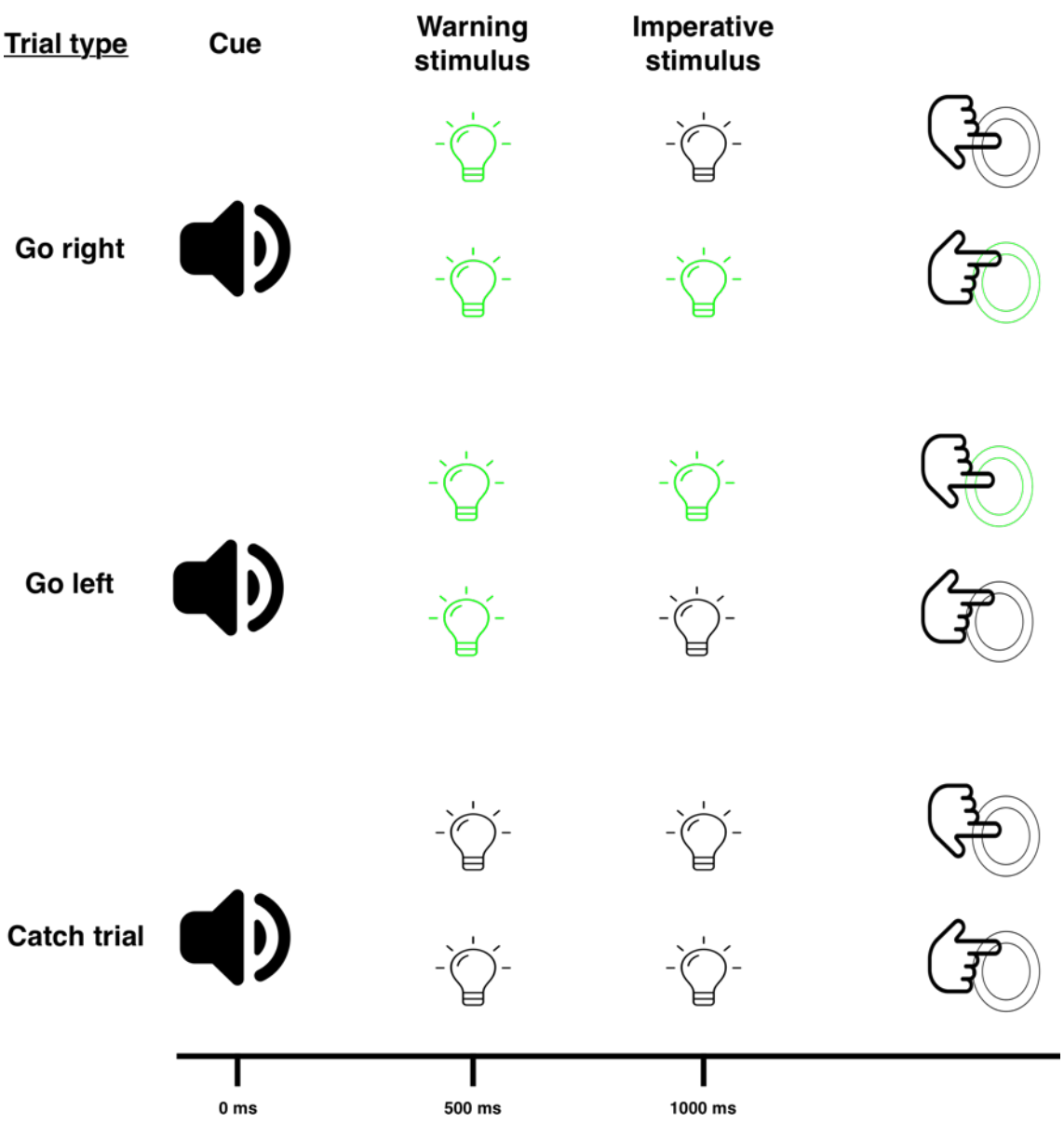

Figure 2.1: The Choice reaction time task.

Schematic shows the different trial types in the CRTT and the appropriate response. Each trial begins with an auditory cue. After 500 ms, two light emitting diodes flash indicating the beginning of the warning period. After 500 ms, one of the light emitting diodes flashes, which prompts the subject to press on the dynamometer with the appropriate effector. Catch trials are given where a cue is given, but no diodes light up.

2.6.2 Go-only reaction time task

The go-only reaction time task was driven by custom-made MATLAB (MathWorks) scripts using Psychtoolbox. Subjects are presented with a white fixation cross on a black background. After 500 ms, an imperative stimulus is presented (right arrow), to which subjects respond by pressing the 'M' key on the keyboard as fast as possible with their right index finger. Catch trials, where a fixation cross is presented, without imperative stimuli, were also used.

2.6.3 Stop-signal task

The stop-signal task (173) (SST) was driven by custom-made MATLAB (MathWorks) scripts using Psychtoolbox. For the SST, subjects are first presented with a white fixation cross on a black background. After 500 ms, an imperative stimulus (right arrow) is presented, which instructs the subject to press the 'M' key on the keyboard as fast as possible with their right index finger (go trials). On 25% of trials, a stop signal (red cross) appears above the imperative stimulus at a variable delay after the imperative stimulus, which instructs subjects to abort their ongoing movement (stop trials). This delay, known as the stop signal delay (SSD), is controlled by a dynamic tracking algorithm, whereby the SSD changes depending on the outcome of the previous stop trial. The starting SSD is set to 150 ms. If the subject successfully aborts their button press on a stop trial, the next stop trial has its SSD set 50 ms later, whereas if the subject fails to stop, the next stop trial has its SSD set 50 ms earlier. This dynamic tracking algorithm has been shown to reliably induce a convergence onto 50% successful inhibition across subjects (174). The SSDs ranges from 100-250 ms (100, 150, 200 and 250 ms). There are also catch trials, where no signals were given. The order of trials is pseudorandomised, such that one in every four trials contains a stop trial. One advantage of designing the experiment in this way is that the probability of a stop trial occurring can dynamically change between zero or seven sequential go trials. In doing so, we can modulate the uncertainty around potential stopping, and hence reactive and proactive inhibition. Consequently, we can

assess the effect of expectancy of potential stopping on behaviour and motor cortex physiology.

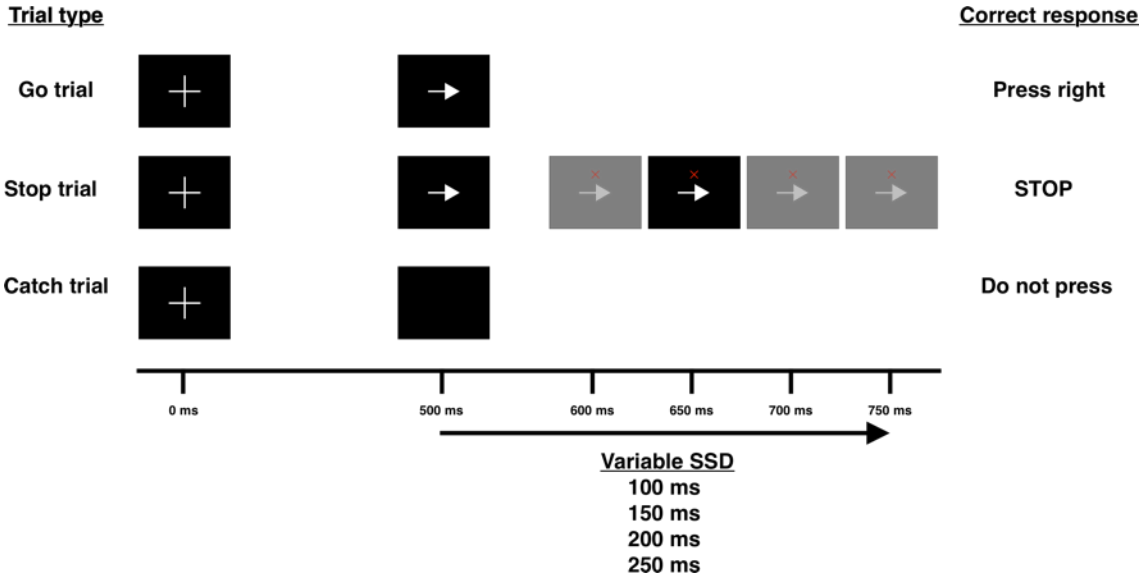

Figure 2.2: The Stop-signal and Go-only task.

Schematic shows the different trial types in the SST with their appropriate responses (critical direction is right). All stimuli stay on the screen until the next stimulus appears. SSD changes between one of four stop signal delays depending on the performance of the previous critical stop trial. The Go-only task consisted of go and catch trials only.

2.6.4 Conditional stop-signal task

The conditional stop-signal task (6,11,40) (CSST) was driven by a custom-made MATLAB (MathWorks) script using Psychtoolbox. The CSST begins with a white fixation cross, which is replaced 500 ms later by one of two imperative stimuli (right or left arrow). The occurrence of these arrows is random, and each occurs at 50% probability. The subject is asked to respond as quickly as possible to the right or left imperative stimulus by pressing the 'M' or 'Z' key on the keyboard with their right or left index fingers, respectively. On 25% of the trials, a stop signal is presented after the go signal, which instructs subjects to abort their ongoing movement (stop trial). The timing

of this delay between go and stop signals is called the stop signal delay (SSD). The SSD can occur at one of four time points (100, 150, 200 and 250 ms) and was adjusted using a staircase procedure. The SSD for a particular trial was altered based on the outcome of the previous trial; successfully stopping in the previous stop trial would increase SSD by 50 ms (to make the next trial harder to inhibit on). Failure to stop on a stop trial would decrease SSD by 50 ms in the next trial (thereby making stopping easier on the next trial). SSD was set to 150 ms at the beginning of each block. Catch trials, where no signals were given, were also presented.

At the beginning of each block, subjects were told that they would have to follow the stopping rule if the stop signal was presented for one direction (critical direction) but to ignore the stop signal if it appeared after the other imperative signal (non-critical direction). Hence responses between the critical and non-critical hand could be compared to look at the effect of proactive control. The structure of the block is pseudorandomised, such that one stop trial appears in every four trials.

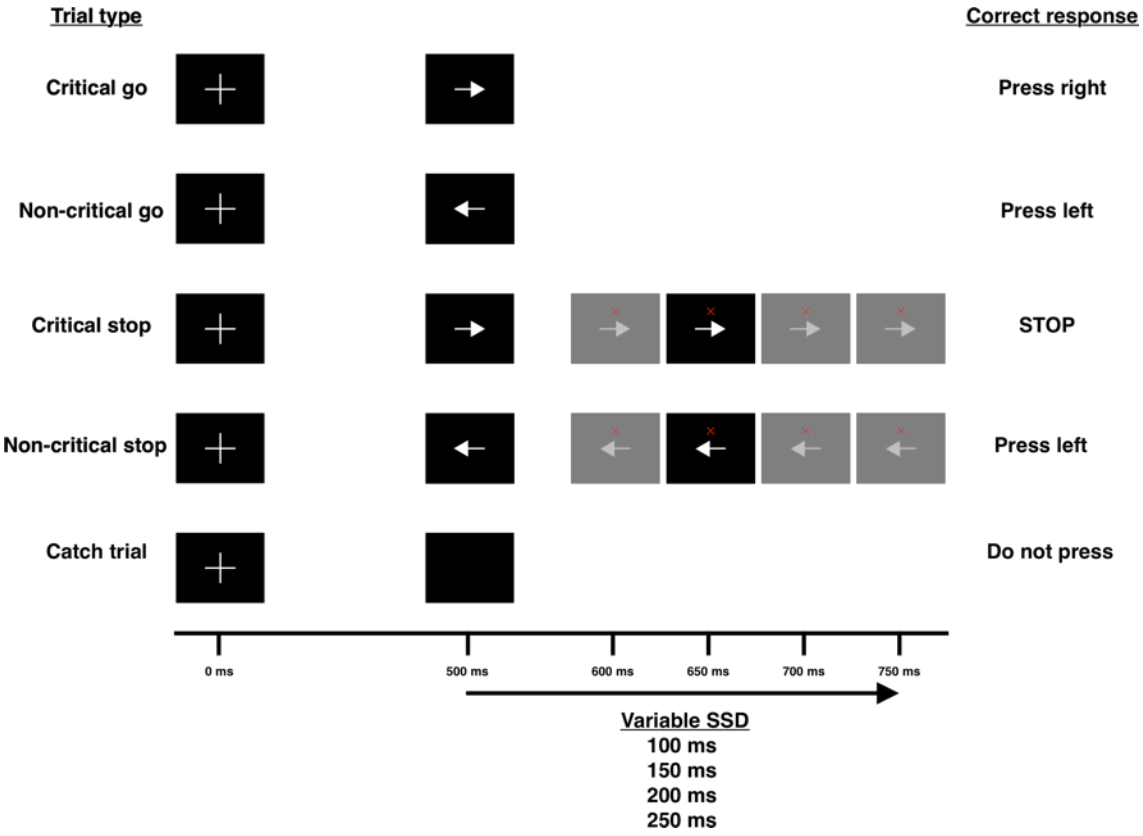

Figure 2.3: The Conditional stop-signal task.

Schematic shows the different trial types in the CSST with their appropriate responses (critical direction is right). All stimuli stay on the screen until the next stimulus appears. SSD changes between one of four stop signal delays depending on the performance of the previous critical stop trial.

2.6.5 Masked priming task

The masked priming task was delivered using the Masked Priming Toolbox (44), made available as an open-source collection of functions, using MATLAB (MathWorks) and Psychtoolbox. Each trial begins with a black fixation dot on a white background. After 100 ms, the prime (<< or >>) is presented for 17 ms, after which the mask (a rectangular array of randomly orientated line) is presented for 100 ms. After a variable delay (0,16,32.48,100,150,200,250 ms), the target stimulus is presented (<< or >>), to which

the subject must respond by pressing the ‘A’ or ‘L’ key on the keyboard for left and right responses, respectively. The variable delay is known as stimulus-onset asynchrony (SOA). As well as the variable delay between the mask and the target, the congruency of the prime and target is also altered; if prime and target are the same stimulus (<</<< or >>/>>) they are deemed as compatible whereas if the prime and target stimuli are pointing in different directions (<</>> or >>/<<), the trial is deemed incompatible. Note that the timing of stimuli are dictated by the refresh rate of a 60 Hz monitor. Consequently, the variable SOAs are determined by increasing numbers of frames rather than coded as absolute timings. For example, 48 ms SOA is produced by three frames of the screen refreshing.

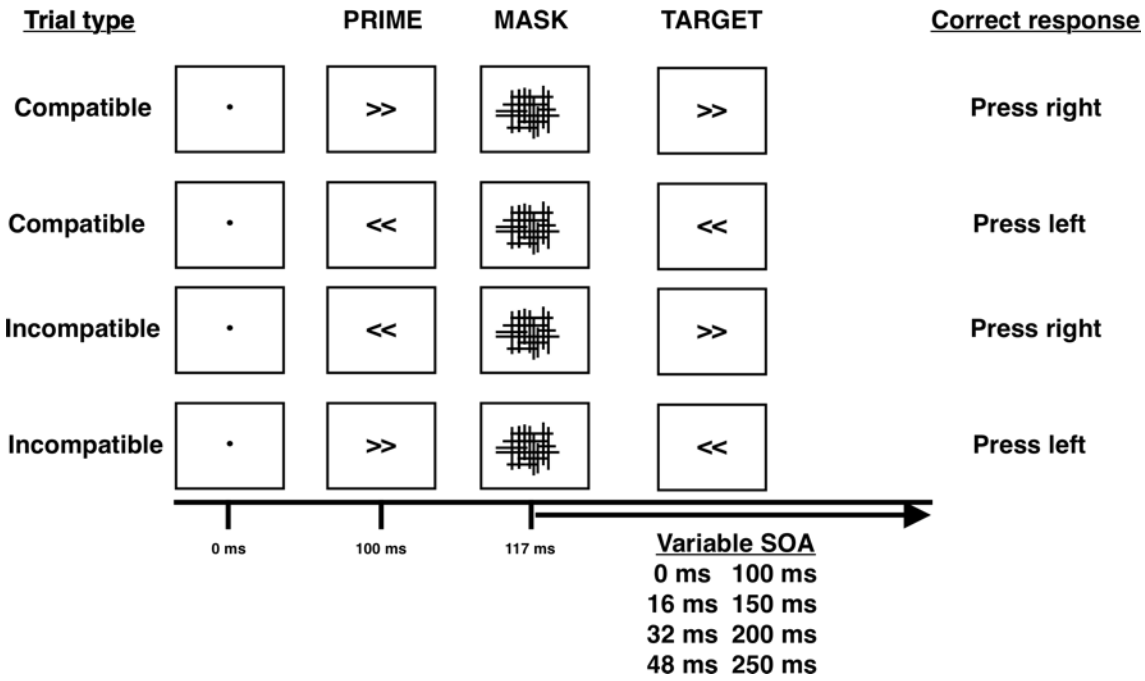

Figure 2.4: The masked priming task.

Schematic shows the four compatibility types in the masked priming task and their appropriate responses. Fixation dot is shown for 100 ms, primes for 17 ms, masks for 100 ms and targets for 100 ms. The onset of the target relative to the mask changes between one of eight interstimulus intervals – stimulus onset asynchrony (SOA).

2.7 Integration of TMS and Behavioural Tasks

In some experiments, TMS was delivered during the behavioural task to assay corticospinal excitability during different periods of response execution and inhibition. TMS was delivered via a BNC connector from the computer running the behavioural experiment to the TMS stimulator and 1401 device, to align TMS pulses to the MEP in Spike software for offline analysis. As such, the timing of TMS delivery was embedded in the script controlling the behavioural experiment. Specific chapters outline the way in which TMS was delivered during each behavioural task.

2.8 Data Analysis

2.8.1 TMS parameters

EMG recordings were stored within Spike software (Cambridge Electronic Design, Cambridge, UK). Custom made scripts were used to extract peak-to-peak amplitudes of TMS evoked MEPs. These amplitudes were exported to MATLAB and combined with behavioural data for further analysis. Individual chapters outline the nature of these further analyses.

2.8.2 Go-only reaction time task

Reaction times were measured by the time difference between the imperative stimulus (right arrow) onset and button press, stored as an output variable in MATLAB. The number of omitted trials were also recorded – omitted trials were ones where no button press was made.

2.8.3 Stop-signal task

Reaction times were measured by the time difference between the imperative stimulus (right arrow) onset and button press, stored as an output variable in MATLAB. The go reaction time was the reaction measured on go trials i.e. trials where a fixation cross and imperative stimulus were presented only. The proportion of successful stop trials (stop

trials where the button press was aborted) was also calculated (p(inhibit)). The reaction time on failed stop trials (stop trials where the subject failed to stop and hence pressed a button) was also calculated (Stop respond reaction time). If the proportion of successfully inhibited trials was approximately 50%, the stop-signal reaction time (SSRT) was calculated using the mean method – that is, the mean stop signal delay (SSD) subtracted from the mean go reaction time. For deviations from this, we appropriately used the integration method to calculate the SSRT – we ranked the go reaction times and found the *nth* reaction time, where *n* represents the p(inhibit) multiplied the number of go trials (the finishing time of the stop process). This is then subtracted from the average SSD to give the SSRT. The number of omitted trials were also recorded – omitted trials were ones where no button press was made.

2.8.4 Conditional stop-signal task

Reaction times were measured by the time difference between the imperative stimulus (right arrow) onset and button press, stored as an output variable in MATLAB. Trials were first organised into whether they were to the critical or non-critical direction; for ease, the remainder of this section will refer to 'right' as the critical direction and left as the non-critical direction. The critical go reaction time was the reaction time measured on critical (right arrow) go trials and the non-critical go reaction time was the reaction time measured during non-critical (left arrow) go trials. (p(inhibit)) was calculated as the proportion of successful stop trials (where the subject correctly aborted their response) to the critical (right) direction. The reaction time on failed stop trials (stop trials where the subject failed to stop and hence pressed a button) was also calculated (Stop respond reaction time). The stop-signal reaction time (SSRT) was calculated as described above. The number of omitted trials were also recorded – omitted trials were ones where no button press was made. As a measure of proactive inhibition, the response delay effect (RDE) was also measured by subtracting the non-critical (left) go reaction time from the critical (right) go reaction time.

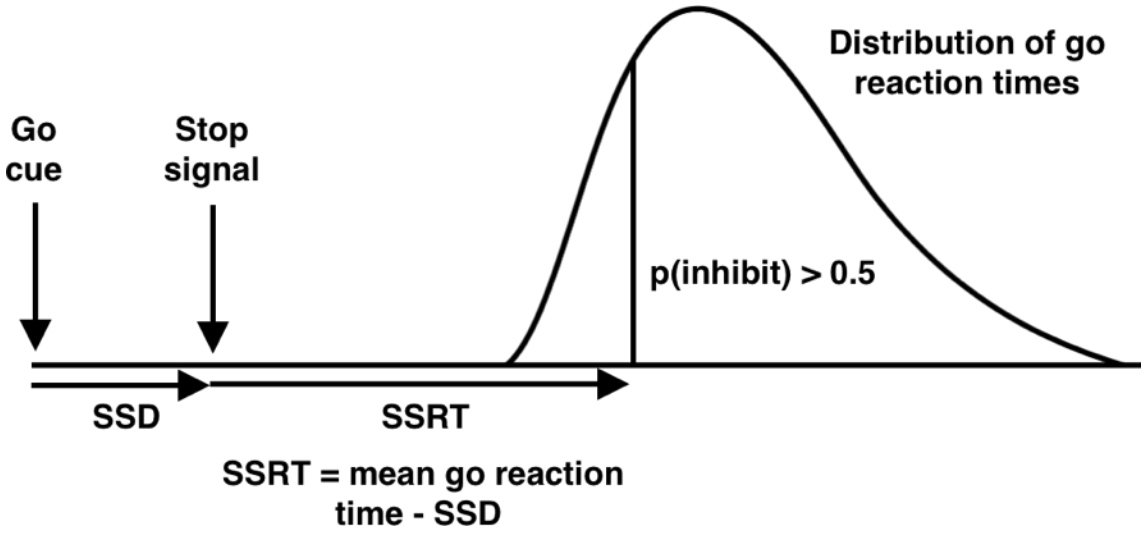

Figure 2.5: Principles of stop-signal reaction time calculation.

Reactive inhibition is indexed by the stop-signal reaction time (SSRT). As it cannot be measured with an overt response, it is inferred by calculating the reaction time at which the probability of successful inhibition is 50%. The average stop-signal delay (SSD) is then subtracted from this mean value. The same calculation is made to measure reactive inhibition in the CSST.

2.8.5 Masked priming task

Reaction times from the masked priming task were given as an output variable in MATLAB and exported for offline analysis. The reaction time pertains to the time difference between target presentation and button press. As there were eight different SOAs and prime-target could be compatible or incompatible, this gave rise to 16 different trial combinations. As such, reaction times were sorted into one of these 16 trial types. Between each SOA, we calculated the reaction time difference between incompatible and compatible trials – that is, assessing the influence of the prime on the target reaction time. If the resultant reaction time difference is positive (subjects are slower on incompatible prime-target sets than on compatible prime-target sets), this is deemed the positive compatibility effect (PCE). If the reaction time is negative, it is deemed the negative

compatibility effect (NCE). The number of errors for each participant was also recorded. Errors could come in three forms: omissions (where the response was longer than one second), commissions (the wrong button was pressed) and responses which were too fast (response was made before the target was presented). These fast responses were classified as either 'fast' or premature; premature responses were those made before target presentation whereas 'fast' responses were those made <150 ms. Commission errors were further divided into whether they were compatible or incompatible commission errors, depending on whether the prime and target were pointing in the same direction or not. Finally, the reaction time for commission error trials was also calculated.

2.8.6 Drift-diffusion model

The drift-diffusion model (61) (DDM) was used to investigate the strategic effects on task performance in the CSST. For each participant, we used the DMAT toolbox to estimate DDM parameters. We allowed the drift rate, boundary separation and non-decision time to vary between context (critical vs non-critical). Starting point was set to half of the boundary separation seeing as left/right go cues could appear with equal probability.

For experiment where TMS was used we only used go trials derived from the right hand in this analysis; hence right-hand responses when the right hand was critical in one block and right-hand responses when the right hand was non-critical in the other block (the critical rule was changed between blocks). We did this so that we could make comparisons between the TMS derived measures for the right hand and behaviour from the same hand. Furthermore, TMS has been known to modulate reaction time, so we wanted a comparison, which controlled for this.

For chapters where no TMS was used we separated trials out into whether they were critical or non-critical, regardless of the hand used. In doing so, we made comparisons of the DDM parameters between critical and non-critical trials – that is, comparisons when stopping was required vs when it was not, regardless of the effector used.

2.8.7 Statistics

Statistical analyses were performed using the SPSS package (IBM Corporation). Where more than three groups or variables were included for statistical analysis, a repeated measures analysis of variance (ANOVA) was used to explore the statistical significance of any interactions. Where statistically significant interactions existed, a t-test was used to probe the interaction further, with reports of effect size measured by Cohen's d. When testing the variances of reaction time distributions, Levene's test for equality of variances was used. Individual chapters contain details for any additional statistical tests.

3 Modulation of Different Interneurone Inputs During Response preparation and Execution

3.1 Introduction

As noted in the Introduction, movement execution is often viewed as a rise-to-threshold phenomenon in which movement occurs when a given level of excitation in the motor cortex (M1) exceeds a certain threshold (51,55,175–177). Proactive inhibition of movement in this model involves suppression of M1 excitability in order to delay/prevent the rise to threshold. Reactive inhibition involves abrupt suppression of excitability in circumstances where the initial rise to threshold has already been triggered.

However, recent experiments have begun to re-examine this model (121,122,178). For example, the physiological finding that MEPs are reduced at the time of the imperative stimulus in a warned reaction time task has traditionally been interpreted as a proactive inhibition that reduced M1 excitability to avoid premature responding (116,179,180). Recent work from our laboratory questions this by showing that the inhibition only affects one class of inputs to the M1 output neurones (the ones activated by AP directed TMS pulses). Furthermore, the degree of suppression correlates with reaction time on any one trial: the greater the suppression of these AP inputs, the faster the reaction time. The

suggestion was that the suppression of some inputs to M1 was part of the putative preparation to move and not a reflection of proactive inhibition (87).

Interestingly the authors also found that the same preparatory suppression of AP inputs occurred prior to the imperative stimulus in a go/no-go task, but that following a no-go instruction there was a rapid reduction in excitability of all inputs to M1, which was assumed to be due to a blanket inhibition of the corticospinal output neurones. The model was therefore that movement preparation, at least as tested in M1, progressed in the same way in a simple warned reaction time task as an in go/no-go task; there was no direct proactive suppression in M1. In contrast, after the no-go instruction the motor cortex received an inhibitory input (reactive inhibition) that prevented any output from occurring. Thus, reactive inhibition involves acute suppression of M1, whilst it is unclear whether proactive inhibition has any influence on M1.

The present thesis makes extensive use of stop-signal reaction tasks (SST). Although these are similar to the go/no-go task, in that preparation for movement includes the possibility that no movement will be required, in the SST, movement is always cued, but then interrupted later by the stop signal. In later chapters I will spend some time examining the rise in M1 excitability that precedes movement execution in circumstances where stopping may be required. Here I address whether this process is reflected equally in AP and PA inputs to M1. The experiments suggest that both are affected equally and therefore in all the later chapters I employ only one current direction (PA) to probe M1 excitability.

Experiment 1 first confirmed the difference in behaviour of AP and PA inputs in the warned choice reaction time task described by Hannah et al. Following this, experiment 2 asked whether these different inputs into M1 were equally modulated during preparation to respond in an SST.

3.2 Methods

3.2.1 Experiment 1: Choice reaction time task

3.2.1.1 Participants

Given that there is no previous data on the relative variability of MEP responses to different coil orientation, except in the study by Hannah et al., we decided to use the same number of participants as in their study. 15 healthy volunteers (12 male, 13 right handed) aged 20-31 (mean age 23.67, SD 3.58) participated in this experiment. The study was approved by UCL Ethics Committee and none of the participants had contraindications to TMS, which was assessed using a TMS safety screening questionnaire.

3.2.1.2 Electromyography and force recordings

Subjects were seated comfortably in a non-reclining chair, with their right and left arms pronated and their index fingers rested over the centre of two dynamometers, to measure force. Electromyographic (EMG) activity was recorded from the right and left, first dorsal interosseous (FDI) muscles using 19 mm x 38 mm surface electrodes (Ambu WhiteSensor 40713) arranged in a belly-tendon montage. The raw signals were amplified, and a bandpass filter was also applied (20 Hz to 2 kHz (Digitimer, Welwyn Garden City, United Kingdom)). Signals were digitised at 5 kHz (CED Power 1401; Cambridge Electronic Design, Cambridge, United Kingdom) and data were stored on a computer for offline analysis (Signal version 5.10, Cambridge Electronic Design, United Kingdom).

3.2.1.3 Transcranial magnetic stimulation

MEPs in the right FDI were evoked using the controllable TMS (cTMS) device (cTMS3, Rogue Research Inc., Canada), connected to a standard figure-of-eight coil (wing diameter 70 mm, Magstim, United Kingdom). The hotspot was identified as the area on the scalp where the largest and most stable MEPs could be obtained for the right FDI muscle, using a given suprathreshold intensity. Modulation of current parameters, such as coil direction and pulse width, have been shown to selectively recruit different M1

interneurone inputs (91). To this end, we decided to employ TMS in two ways. With the coil held approximately perpendicular to the presumed central sulcus and tangentially to the skull, TMS was given either with the coil handle pointing backwards for postero-anterior stimulation at 120 μs pulse width (PA_{120}) or with the coil handle pointing forwards for antero-posterior stimulation at 30 μs pulse width (AP_{30}). For each coil parameter, the stimulation intensity was set to one whereby peak-to-peak MEP amplitude was 1 mV, when subjects were contracting their right FDI to 10% of their maximum voluntary contraction. This was done for three reasons: 1) a smaller test pulse could be used, which overcomes the technical difficulties of using AP_{30} pulses, which are of low power, 2) smaller test pulses were less likely to interfere with task performance and 3) latency of the MEPs is generally calculated under active rather than resting conditions.

3.2.1.4 Choice reaction time task

As this was a validation study of previously published results, the methodology is outlined in the original paper (87). Subjects were asked to maintain contraction in each FDI to 10% of their maximum voluntary contraction. A cue signalled the beginning of the trial. 500 ms later, a warning cue (left AND right light-emitting diodes) flashed, signalling the beginning of the preparatory period. 500 ms after the warning cue, the imperative stimulus (left OR right) diode flashed, to which the subject had to respond by pressing the dynamometer as fast as possible with the corresponding index finger. The reaction time was defined as the time difference between the imperative stimulus and EMG onset.

3.2.1.5 Integration of TMS with the choice reaction time task

The aim of using TMS was to investigate how movement preparation and selection affected different inputs into M1, by measuring the amplitude of MEPs evoked by TMS. To this end, we employed TMS using the two different stimulus parameters outlined above: PA_{120} and AP_{30}, whilst subjects performed the CRTT. To assay during movement preparation, we gave TMS 250 ms after the warning cue (in the preparatory period) and at the imperative stimulus. To assay during movement selection, we tailored the timing

of TMS pulses to the subject's reaction time without TMS. To do this, the beginning of the experiment consisted of a preliminary block of the CRTT. This consisted of 30 randomised trials, to ascertain reaction times to each effector. Using these reaction times, we calculated 35% and 70% of the reaction time to each effector and delivered TMS at these times during the remaining blocks. We also gave catch trials, where no stimuli were given, but TMS was given 500 ms into the block, to ascertain a degree of baseline corticospinal excitability (CSE). Each block, therefore, consisted of five different conditions, in which five TMS pulses were given for each. As well as measuring CSE, we validated that these were indeed different M1 inputs by measuring the latency of MEPs evoked during catch trials by PA_{120} and AP_{30} TMS. Subjects performed four blocks for each coil orientation, resulting in eight TMS blocks of the CRTT, summarised in figure 3.1.

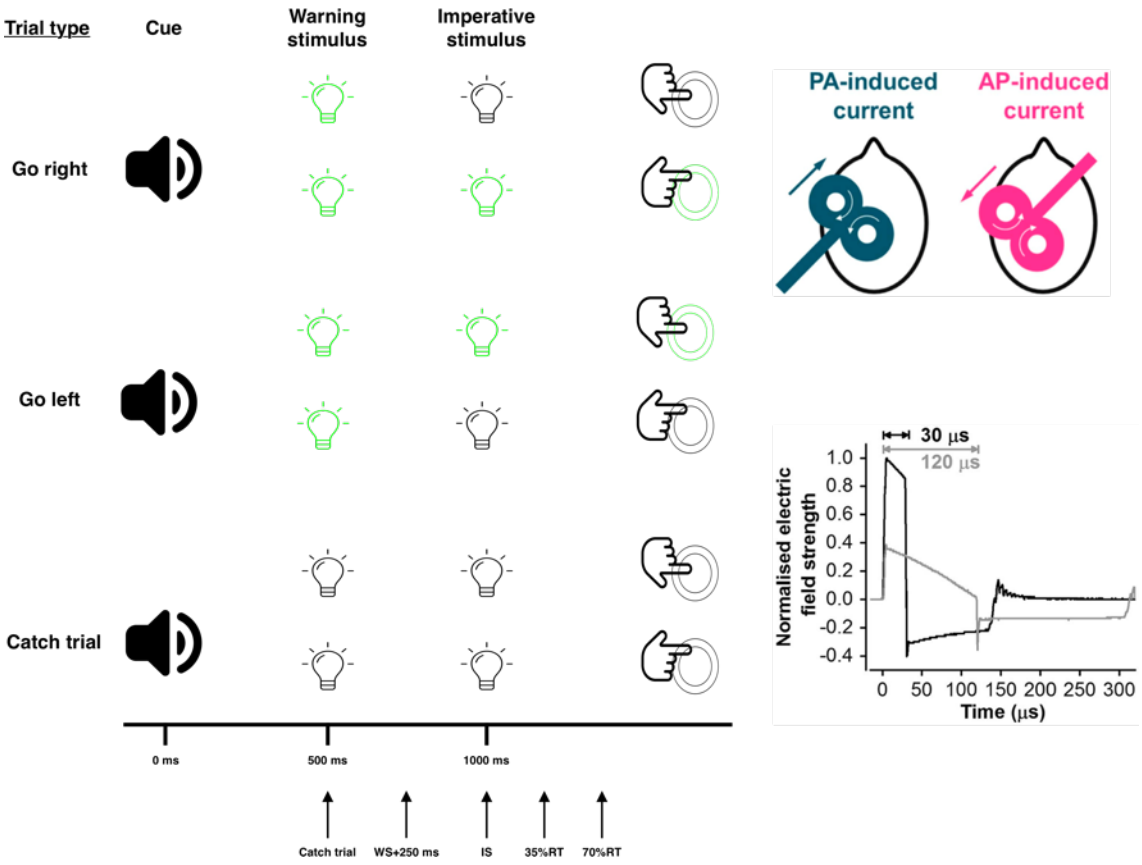

Figure 3.1: Integration of PA_{120} and AP_{30} TMS in the Choice reaction time task.

Schematic shows the different trial types in the CRTT and the appropriate response. Each trial begins with an auditory cue. After 500 ms, two light emitting diodes flash indicating the beginning of the warning period. After 500 ms, one of the light emitting diodes flashes, which prompts the subject to press on the dynamometer with the appropriate effector. Catch trials are given where a cue is given, but no diodes light up. Arrows show the time points at which TMS are delivered. TMS is delivered in one of two ways: PA orientated current at 120 μs pulse width or AP orientated current at 30 μs pulse width. The electric field strength generated by these two pulse widths is shown from Hannah et al. (91).

3.2.1.6 Data analysis

MEPs were normalised to the baseline MEP value. A two-way repeated measures ANOVA was performed with main factors: COIL ORIENTATION (PA_{120}/AP_{30}) and TIME POINT (baseline, warning cue+250 ms, imperative stimulus, 35% of reaction time and 70% of reaction time). If any statistically significant interactions were present, we interrogated these further using paired t-tests.

We also compared the latency of PA_{120} and AP_{30} TMS inputs using a paired t-test.

3.2.2 Experiment 2: Stop-signal and Go-only task

3.2.2.1 Participants

13 healthy volunteers (9 male, 13 right handed) aged 19-33 (mean age 24.65, SD 4.13) participated in this experiment. The study was approved by UCL Ethics Committee and none had contraindications to TMS, which was assessed by a TMS screening questionnaire.

3.2.2.2 Electromyography recordings

Throughout the experiment, subjects were seated comfortably in a non-reclining chair, with their right index finger rested over the 'M' key on the keyboard. Their forearms were supported using a cushion. EMG activity was recorded and processed in the same way as described in experiment 1.

3.2.2.3 Transcranial magnetic stimulation

TMS was delivered in the same way as in experiment 1 with PA_{120} and AP_{30} pulses.

3.2.2.4 Stop-signal task and Go-only

Participants were asked to perform both two blocks of the SST and two blocks of a simple reaction time (Go-only) task, which were driven by custom-made MATLAB (MathWorks) scripts using Psychtoolbox. For the SST, subjects were first presented with a white fixation cross on a black background. After 500 ms, an imperative stimulus (right arrow) was presented, which instructed the subject to press the 'M' key on the keyboard as fast as possible with their right index finger (go trials, n=105). On 25% of trials, a stop signal (red cross) appeared above the imperative stimulus at a variable delay after the imperative stimulus (stop trial, n=35). This delay, known as the stop signal delay (SSD) was controlled by a dynamic tracking algorithm, whereby the SSD would change depending on the outcome of the previous stop trial. The starting SSD was always set at 150 ms. If the subject successfully prevented their button press on a stop trial, the next stop trial would have its SSD set 50 ms later, whereas if the subject failed to stop, the next stop trial would have its SSD set 50 ms earlier. This dynamic tracking algorithm has been shown to reliably induce a convergence onto 50% successful inhibition across subjects. The SSDs ranged from 100-250 ms (100, 150, 200 and 250 ms). There were also 15 baseline trials, where no signals were given, but TMS was given to give a representation of baseline corticospinal excitability. These trials also served as catch trials. The order of trials was pseudorandomised, such that one in every four trials contained a stop signal.

The Go-only task was similar to the SST, except no stop signals appeared in the block. Hence, this was a block where no proactive control would be required. 105 go trials were given, with 15 trials with no imperative signals to act as baseline. This has been summarised in figure 3.2.

Behavioural measures taken included Go reaction time (reaction time on go trials), Stop Respond reaction time (reaction time on failed stop trials), average SSD and p(inhibit) (proportion of correct stop trials in the SST). We also calculated the SSRT using the mean method (mean go reaction time – mean SSD).

3.2.2.5 Integration of TMS with the stop-signal and Go-only tasks

TMS was given in all trials, in all blocks to the M1 representation for the right FDI muscle, at an intensity required to produce a test MEP of 0.5 mV peak-to-peak amplitude. During go trials, one TMS pulse was given randomly at one of seven time points (at the imperative signal and 50, 100, 150, 200, 250 and 300 ms after the go signal). 15 MEPs were taken at each time point. In the 15 baseline trials, TMS was given 1000 ms into the beginning of the trial to assess CSE at rest. This has been summarised in figure 3.2.

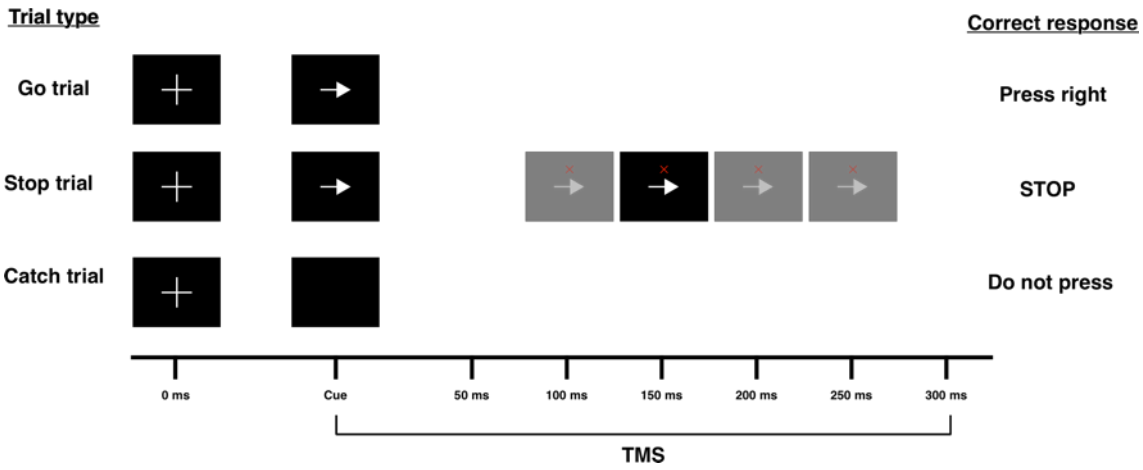

Figure 3.2: The Stop-signal and Go-only task.

SST: Go trials consist of a presentation of a fixation cross, followed by an imperative stimulus (right arrow) 500 ms later. In 25% of trials, the right arrow is followed by a stop

signal (red cross) at one of four SSDs (100, 150, 200 or 250 ms after the arrow). Subjects must attempt to abort their button press on presentation of a stop signal. Failure to do so will result in the next stop signal having a shorter SSD (-50 ms) whereas success will lead to the next SSD becoming longer (+50 ms). PA_{120} or AP_{30} TMS is delivered on go trials at one of seven time points (counterbalanced and randomised), or 1000 ms into a trial where no signals are shown (baseline trial). The Go-only task comprised of go and catch trials only; TMS was delivered at the same timepoints described above.

Behavioural measures taken included Go reaction time (reaction time on go trials), Stop Respond reaction time (reaction time on failed stop trials), average SSD and p(inhibit) (proportion of correct stop trials in the SST). We also calculated the SSRT using the mean method (174) (mean go reaction time – mean SSD).

3.2.2.6 Data analysis

To track the progression of CSE from different M1 inputs under different stopping conditions a three-way repeated measures ANOVA with conditions COIL ORIENTATION, BLOCK TYPE and TIME was performed using peak-to-peak MEP amplitude as the dependent variable. Based on the outcome of this analysis, post-hoc paired t-tests were performed between MEPs at each time point against that at baseline. We also represented CSE between stopping conditions and inputs from the viewpoint of movement execution. To do this, we calculated the time between TMS delivery and response, then binned MEPs according to 50 ms time bins from the response. A three-way repeated measures ANOVA with conditions COIL ORIENTATION, BLOCK TYPE and TIME BIN was performed using the peak-to-peak MEPs as the dependent variable. As statistically significant interactions were further interrogated using post-hoc paired t-tests.

3.3 Results

3.3.1 Experiment 1: Choice reaction time task

The aim of experiment 1 was to confirm the findings found in Hannah et al. that early and late inputs into M1 could be accessed via PA_{120} and AP_{30} TMS, respectively (91). As there is a putative suppression of AP inputs during movement preparation (87), we also sought to confirm whether this was present.

3.3.1.1 Physiological and behavioural measurements

Mean baseline MEPs recorded for each coil orientation (PA_{120}: 1.35 mV SD: 0.35, AP_{30}: 1.41 mV SD: 0.37) during catch trials did not differ to a statistically significant level ($p = 0.091$, $t = -1.81$, $d = -0.184$). The intensity of stimulation was greater for AP_{30} stimulation than PA_{120} stimulation, which was expected. Mean reaction time for right and left hands (right: 178.7 ms, SD 23.2, left: 181.3 ms, SD 16.7) were also not significantly different ($p = 0.637$, $t = -0.482$, $d = -0.128$).

3.3.1.2 Corticospinal excitability decreases during movement preparation and increases during movement execution

MEPs were taken from the right hand at different times during a warned, choice reaction time task, during response preparation and execution. The result from the two-way repeated measures ANOVA showed a statistically significant effect of TIME ($p < 0.001$, $F(4,56) = 22.29$, $\eta^2 = 0.614$) but not COIL ($p = 0.946$, $F(1,14) = 0.005$, $\eta^2 < 0.001$), and a borderline COIL*TIME interaction ($p = 0.069$, $F(4,56) = 0.079$, $\eta^2 = 0.142$). Further interrogation of which time points were significantly modulated with respect to baseline revealed that for all time points, the MEP had deviated significantly from baseline. A graphical representation of these results is shown in figure 3.3.

3.3.1.3 Movement preparation differentially affects PA_{120} and AP_{30} inputs

As the ANOVA above showed a statistical trend for COIL and due to previously published literature, we decided to perform paired t-tests to explore whether movement

preparation or execution differentially modulated CSE. Before performing these t-tests, we normalised MEPs to their respective baseline to account for any differences in baseline CSE. The only statistically significant difference in CSE between coil orientations was when TMS was delivered at the imperative stimulus ($p = 0.017$, $t = 2.701$, $d = 0.788$). This was in keeping with previously published data (87). We did not compute a power calculation prior to beginning this experiment and performed the experiment in the same number of participants as reported in the study by Hannah et al. A post-hoc power calculation was performed based on the decrease in CSE at the imperative stimulus in our study and the previously published one. At an alpha of 0.05, this power calculation showed a post-hoc power of 98.9%.

3.3.1.4 PA_{120} and AP_{30} TMS activate physiologically different inputs

One line of evidence that PA and AP inputs into M1 are physiologically distinct is that their MEPs have different latencies, with AP MEP latencies being longer than PA MEPs (82,85,86). We therefore measured the latency of the MEPs evoked by PA_{120} and AP_{30} TMS. As expected, the latency of AP_{30} MEPs was greater than PA_{120} MEPs ($p < 0.001$, $t = 8.054$, $d = 2.87$), shown in figure 3.3.

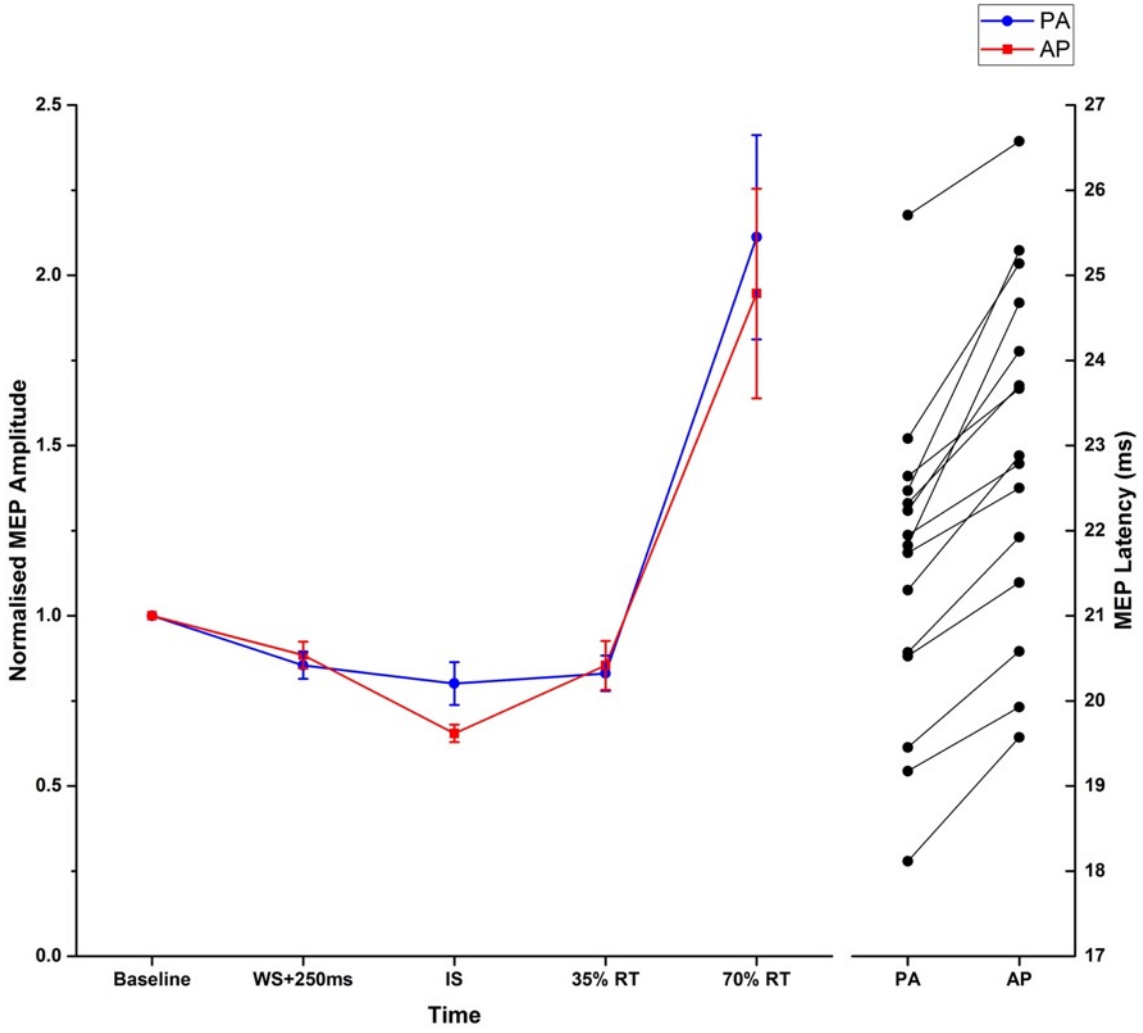

Figure 3.3: Corticospinal excitability of PA_{120} and AP_{30} inputs during the choice reaction time task and their MEP latencies

Left: Normalised to baseline MEPs in the right hand are plotted against the time they were assayed during the choice reaction time task, for PA_{120} and AP_{30} inputs. **Right**: MEP latencies collected at the imperative stimulus are shown for individual subjects. Error bars represent SEM, blue circles are PA_{120} inputs, red squares are AP_{30} inputs.

3.3.2 Experiment 2: Stop-signal task vs Go-only task

This experiment tests how CSE changes with respect to time under different stopping conditions, for each M1 input. Interestingly, in the SST, the probability of stopping changes on a trial-to-trial basis and as such, we expected that subjects internally update this stopping probability, so that we could test how this might be reflected in M1 excitability.

3.3.2.1 Physiological measurements

No significant differences were found between the amplitudes of the test MEPs across sessions. As expected AP_{30} TMS test intensities were higher than those for PA_{120} stimulation. Consequently, 16 subjects provided data for PA_{120} TMS, 13 for AP_{30} TMS.

3.3.2.2 Behavioural measures

Behavioural measurements are shown in table 3.1. There was an expected go reaction time difference between the SST and Go-only blocks (103.24 ms) due to the anticipation to stopping in the former ($t = 7.583$, $p < 0.001$, $d = 3.07$). The dynamic tracking algorithm correctly resulted in a convergence of successful inhibition to 50%.

Measure	Measure description	SST		Go-only	
Critical direction		PA	AP	PA	AP
Go	RT to go stimulus in the critical direction	391.55 (35.01)	402.36 (44.42)	288.31 (32.12)	324.15 (52.28)
p(inhibit)	% correct inhibition	50.54 (7.36)	56.70 (11.30)		
Stop Respond	RT on failure to stop trials	287.84 (33.13)	319.69 (47.90)		
Go omission	% of omissions	0.36 (0.68)	0.44 (0.84)	0.36 (0.84)	0.66 (0.98)
Stop signal delay	Delay between go and stop signals	167.05 (25.42)	185.29 (31.52)		
SSRT	Calculated time taken to abort response	224.50 (27.75)	216.98 (32.59)		

Table 3.1: Behavioural measurements from the SST and Go-only task.

The table shows the behavioural measures from the SST, Go-only task. Measures are accompanied by SD in brackets. Reaction times are given in ms.

3.3.2.3 Evolution of corticospinal excitability in stop-signal and Go-only tasks.

The SST was used to probe the temporal dynamics of CSE changes during which proactive inhibition is implemented. This was compared to the same TMS timings in a

task where no proactive inhibition should be employed: the Go-only task. We first assessed how CSE changed with respect to time by performing a stimulus-locked analysis. A three-way repeated measures ANOVA with conditions (COIL ORIENTATION, BLOCK TYPE and TIME) revealed significant effects for COIL ORIENTATION ($p = 0.002$, $F(1,12) = 15.863$, $\eta^2 = 0.569$), BLOCK TYPE ($p = 0.002$, $F(1,12) = 15.733$, $\eta^2 = 0.567$), TIME ($p < 0.001$, $F(7,84) = 32.51$, $\eta^2 = 0.730$) and a COIL ORIENTATION*BLOCK TYPE*TIME interaction ($p = 0.027$, $F(7,84) = 2.411$, $\eta^2 = 0.167$). There were no other significant findings from the ANOVA.

In subsequent analyses, data for AP and PA stimulation were treated separately. Baseline MEP sizes between go and stop blocks did not differ for PA_{120} or AP_{30} TMS, indicated by a two-way repeated measure ANOVA with factors COIL and BLOCK TYPE, which revealed no statistically significant interactions.

In go trials within the SST, the main rise in excitability, indexed by the timepoint at which CSE became significantly greater than CSE at the cue, occurred later than in Go-only trials for both PA (Go-only: 100 ms, $p = 0.048$, $t = 2.151$, $d = 0.39$; SST: 200 ms, $p = 0.002$, $t = 3.699$, $d = 0.91$) and AP inputs (Go-only: 150 ms, $p = 0.008$, $t = 3.057$, $d = 1.05$; SST: 200 ms, $p = 0.008$, $t = 3.037$, $d = 0.984$). In addition, excitability at the time of the cue and shortly afterwards was lower in SST trials than in Go-only trials for both PA and AP stimulation. As argued in the analysis in the next section this may reflect the lower probability of responding in the SST, affecting both sets of inputs.

As there was a reaction time difference between go trials in the SST and Go-only task of 103.24 ms we realigned the data to the time of the response onset (see next chapter for more details of this), thereby performing a response-locked analysis. The data show that the rate of rise in excitability preceding movement was the same during go trials in both the SST and Go-only blocks. Furthermore, the time courses of the rise of excitability were the same for PA and AP stimulation. Interestingly, there were statistical trends for CSE to be lower at timepoints for go trials in the SST than Go-only task far from movement

execution (300-350 ms), presumably early after the cue had been presented for PA (p = 0.056, t = 2.059, d = 0.640) and AP (p = 0.067, t = 2.030, d = 0.729) inputs.

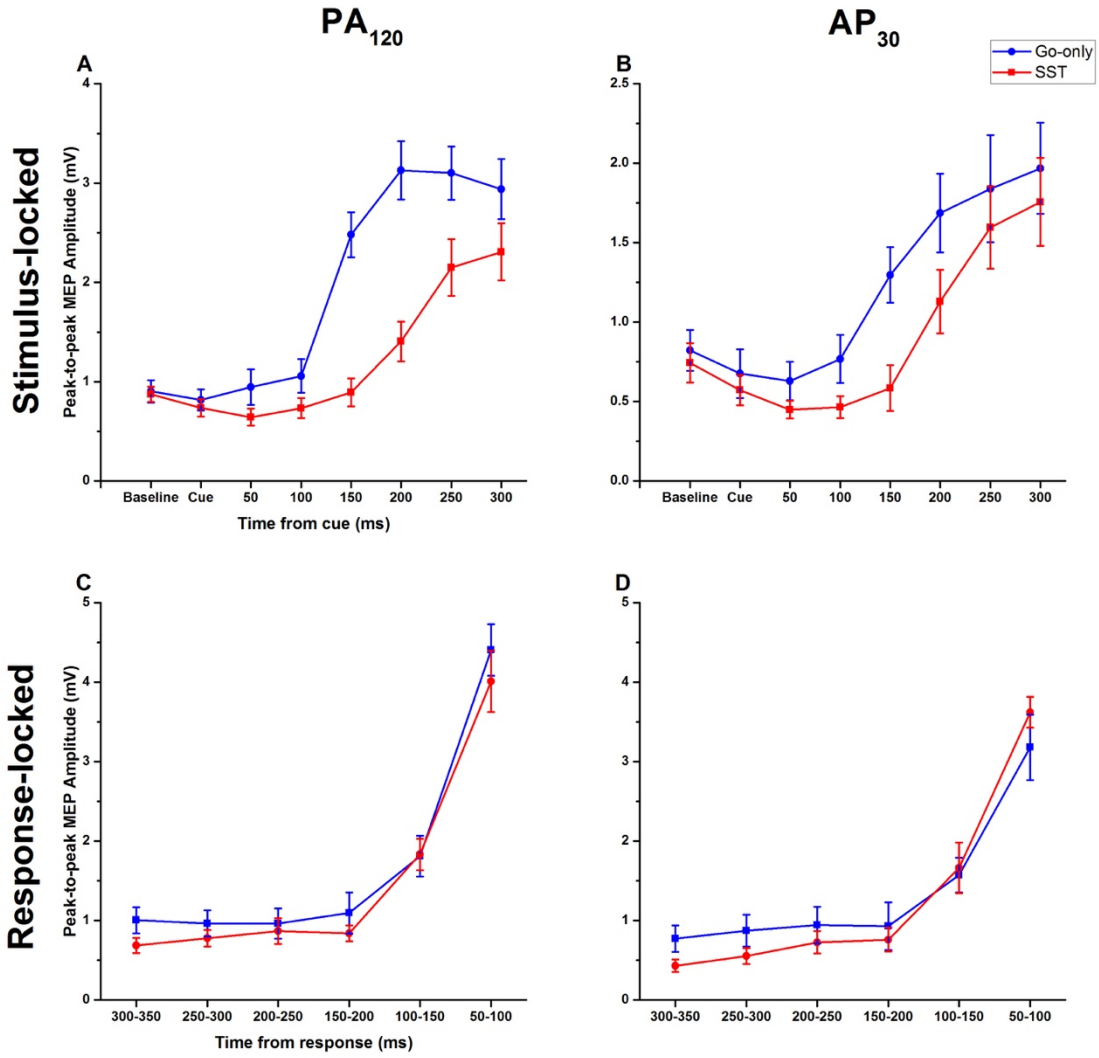

Figure 3.4: Corticospinal excitability changes during the SST and Go-only task for AP_{30} and PA_{120} TMS.

MEPs are taken on go trials during baseline and various times after the go cue has been presented, for the Go-only task and SST. Graphs represent responses evoked using PA_{120}

TMS (left column) and AP_{30} TMS (right column) TMS for stimulus-locked (top row) and response-locked (bottom row) analyses. Error bars represent ±SEM.

3.3.2.4 Motor cortex excitability reflects the trial by trial expectation of stopping

Due to the pseudorandom design of the experiment, the probability of a stop trial occurring changed as a function of consecutive go trials. In doing so, we predicted that this would change a participant's expectation of stopping, which would manifest behaviourally and physiologically within M1. In order to test this hypothesis, we performed a detailed analysis of the SST data.

Because the task was designed pseudorandomly, such that one stop trial arose in every four trials, this meant that the probability of stopping on a particular trial dynamically changed throughout the task. Consequently, the more consecutive go trials that arose, the greater the probability the next trial would be a stop trial. Conversely, the probability of a stop trial occurring straight after another stop trial, was lowest of all trial combinations. We compared this with behavioural data of the probability of successful inhibition on a particular stop trial, p(inhibit), based on the number of preceding go trials. The behavioural data showed that the number of go trials preceding a stop trial significantly modulated the probability of successfully stopping on the next trial ($p = 0.001$, $F(3,36) = 7.344$, $\eta^2 = 0.380$). That is, the probability of successfully stopping was lowest when a stop trial occurred after 0 (STOP-STOP) or 1 (STOP-GO-STOP) go trials. The reaction time on a particular go trial, however, was not related to when it occurred after a stop trial ($p = 0.143$, $F(3,36) = 1.922$, $\eta^2 = 0.138$).

PA_{120} MEPs were modulated depending on which go trial they were evoked on after a stop signal; MEP size was greatest the trial straight after a stop trial and decreased with increasing go trials ($p = 0.045$, $F(3,36) = 3.643$, $\eta^2 = 0.185$). Interestingly, there was no such relationship present for AP_{30} MEPs ($p = 0.399$, $F(3,36) = 1.099$, $\eta^2 = 0.072$), shown in figure 3.5. To assess whether this was a true suppression in the light of potential stopping, we compared the CSE from PA_{120} MEPs with those collected at equivalent

times during a Go-only task, where no stop signals were shown; consequently, these MEPs reflect early time point CSE when no proactive control is expressed. Paired t-tests showed statistically significant suppression of PA_{120} MEPs, which were taken on the 2nd ($p = 0.031$, $t = -2.379$, $d = 0.629$), 3rd ($p = 0.046$, $t = -2.179$, $d = 0.600$) and 4th ($p = 0.019$, $t = -2.624$, $d = 0.727$) go trials after a stop trial.

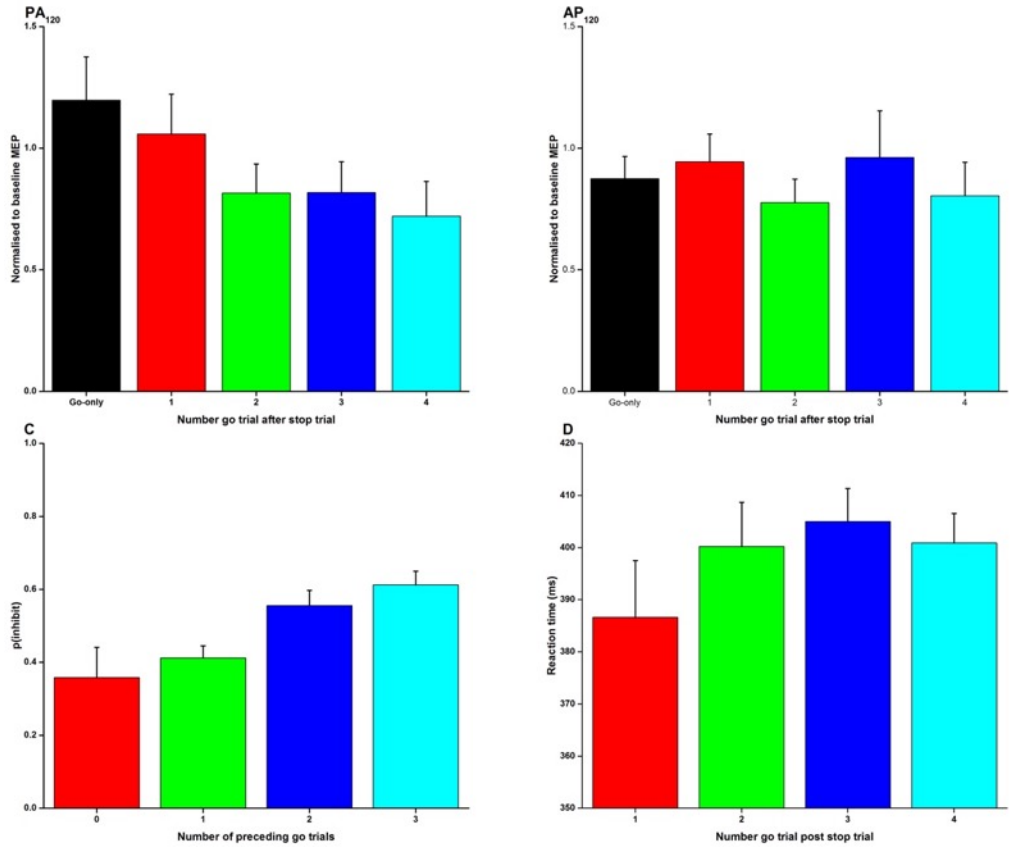

Figure 3.5: Changes in corticospinal excitability of PA_{120} inputs reflected in the probability of successful inhibition and reaction times of go trials post stop trials.

MEP: Top row displays mean (±SEM) normalised to baseline MEPs taken during go trials in the SST using PA_{120} and AP_{30} TMS. MEPs were taken at one of three time points taken and used as the grand average (cue, 50 ms and 100 ms). This is plotted against the number trial that TMS was given after a stop trial. Also shown in the collective,

normalised to baseline MEP from equivalent time points during the Go-only task (black bars), when no stopping was required.

Behaviour: (C) shows the number of preceding go trials (relative to a stop trial) against the probability of successfully inhibiting the response. (D) shows the reaction time on a particular go trial, depending on when it occurred after a stop trial. Bars are colour coded such that MEP measures and behaviours correspond if they are the same colour. Error bars represent SEM.

3.4 Discussion

The aims of this experiment were primarily to confirm whether or not physiologically distinct M1 inputs could be accessed with different TMS pulse parameters and whether these inputs were indeed differentially modulated during the SST when proactive inhibition was active.

3.4.1 Validation that physiologically distinct motor cortex inputs can be accessed and their modulation during response preparation

According to Hannah et al. movement preparation differentially modulated inputs into the motor cortex (87). As we wanted to examine whether these inputs were modulated during response initiation and inhibition, we first sought out to validate their results. To this end, we performed the same experiment reported in their original paper. We found that different motor cortex inputs were indeed modulated differentially by movement preparation; AP_{30} inputs were significantly modulated at time of the imperative stimulus compared to PA_{120} inputs. This differential modulation supports the notion that they access different inputs into the motor cortex. As another line of evidence to support this, we assessed the latencies of TMS evoked MEPs during this the time of the imperative stimulus. It is well known that AP inputs into the motor cortex display longer latencies than PA inputs when stimulated with monophasic TMS (85,91). It has also recently been found that by modulating the pulse width of TMS, these inputs can be better selected (91).

We confirmed that this was also true in our experiment, as all participants had MEPs with longer latencies when evoked with AP_{30} TMS. Our results from this study validated the use of AP_{30} and PA_{120} TMS to access physiologically distinct motor cortex inputs.

3.4.2 Corticospinal outputs when stopping might be required

Assessing CSE during the SST and Go-only tasks, it is clear that CSE rises later when stopping might be required, presumably due to the influence of proactive inhibition. However, the response-locked analysis showed that most of this difference was due to the difference in reaction times between the two tasks. Indeed, the rise in excitability prior to movement onset was the same for PA and AP inputs. Because of this, the remaining chapters use only one direction of TMS pulse. More detailed analysis of this data is continued in the next chapter.

Interestingly, we noticed that PA inputs were suppressed during early time points when stopping might be required in the SST relative to their counterparts in the Go-only task. We interpreted this as suppression as a reflection of the requirement to stop, something we confirmed in the next analysis. Because the task was designed pseudorandomly, such that one stop trial was presented in every four trials (one stop, three go), which were then randomised themselves and concatenated, the probability of stopping on a particular trial dynamically changed. With this in mind, we predicted that subjects also dynamically change their 'stopping expectation'. Figure 3.5C shows the probability of successfully stopping on a stop trial, depending on when it came after a stop trial. Hence, 0 refers to STOP-STOP, 1 refers to STOP-GO-STOP, 2 refers to STOP-GO-GO-STOP and so on. It shows that the probability of successfully inhibiting increases with more go trials after a stop trial, presumably because the expectation of a stop trial occurring increases. However, the reaction time on subsequent go trials after a stop trial does not significantly change in line with this change in 'stopping expectancy'. One caveat of designing the experiment in this way was that the stopping expectancy could be learnt, which could potentially confound measures of response inhibition. However, we observed that

subjects successfully inhibited their responses on approximately 50% of stop trials, showing that the staircase procedure was correctly followed.

Different M1 inputs are accessed (PA_{120} or AP_{30} TMS), at one of three time points: at the cue, 50 ms or 100 ms after the cue. If we assume that any changes in expectation of stopping and decision making are reflected early on in these time-points, then we can use these MEPs to investigate M1 inputs during this period, which may reflect the upcoming probability of a stop trial occurring. Indeed, CSE significantly differs with that at baseline from 200 ms in the SST and reaction times are 103.24 ms slower when stopping may be required between the SST and Go-only task. This suggests that preparatory steps, including decision making of a movement, occur over 100 ms after the go cue has been presented. Figure 3.5A shows the excitability probed with PA_{120} TMS on go trials as a function of when they occurred after stop trials. Here, the numbers correspond to the number of the go trial after stop trial: 1 = STOP-GO, 2 = STOP-GO-GO and so forth. It shows that CSE is largest on the go trial straight after a stop trial, presumably because the expectation of stopping is lowest on the trial after a stop trial. Consequently, CSE may be higher to set the motor state in a heightened one, primed to make a fast response. This lies in agreement with lower probability of stopping on the corresponding trial. As the number of go trials increases, the probability of successful stopping increases, whilst CSE decreases. However, this relationship exists for PA_{120} MEPs only; this pattern is not exhibited in AP_{30} MEPs. A relationship between CSE and reaction times has previously been shown to be under the influence of cognitive preprocessing pertaining to uncertainty and surprise (95). In the SST, it is possible that what we have measured is a manifestation of the uncertainty of a stop signal occurring, which manifests as proactive inhibition.

Many authors have shown that the expectation of movement is reflected in M1 excitability in the preparatory period prior to movement (116,118–120). By analogy we suggest that the SST-Go-only difference observed here reflects a similar phenomenon (94–96,181–183). In this task, the effector being called into action is always the right index finger. Therefore, one can assume that motor preparation, from an effector selection perspective,

is equal in the Go-only and SST. Interestingly, we see that AP inputs are suppressed with respect to baseline in both tasks and regardless of the go trial they occurred on. These results support earlier findings that AP suppression is a necessary component of movement preparation, irrespective of stopping requirements and does not reflect proactive inhibition. Hence what is probably being assayed in these early time points, in AP_{30} MEPs, is probably movement preparation. PA inputs, on the other hand, seem to track behaviour regarding reaction times and stopping probability; they are suppressed when stopping might be required, in a dose-dependent fashion. In all, these results seem to point to two simultaneous processes occurring: AP suppression reflecting putative movement preparation, which is overlain by suppression of PA inputs regarding the possibility of stopping.

Despite being differentially modulated during response preparation and inhibition, we do not believe that these are the exclusive pathways mediating these processes. Our interpretation is more conservative, that response preparation and inhibition can act via different inputs (response inhibition is not merely less response initiation) and that our data strengthen the hypothesis that PA and AP inputs into M1 are physiologically and behaviourally distinct (86,87,90,184).

3.5 Conclusions

From this chapter, we have validated that different M1 inputs can be accessed via previously reported TMS manipulations. We confirm that AP inputs are preferentially suppressed at the time of the cue-signal the choice reaction time task (experiment 1). However, PA and AP inputs are affected in the same way by increases in excitability prior to movement execution which means that this feature can be explored in subsequent chapters by use of one direction (PA) only. We also provide confirmation that expectation of movement can also affect M1 excitability as reported previously by many other authors. However, we have not addressed how response times are prolonged when stopping may be required. In rise-to-threshold models, this prolongation is presumably

mediated by a slower build-up of activity or increase in the boundary separation. Recent work has suggested that the major determinant of the reaction time is not in motor preparation, but in the motor execution; more specifically, in the command that executes motor execution (121). The next chapter will aim to answer whether these processes of movement preparation are reflected during movement execution within M1.

4 Movement Preparation and Execution are Independent Processes

4.1 Introduction

In the previous chapter, we showed how different inputs into the motor cortex (M1) can be differentially modulated during periods of response preparation and inhibition. We did not, however, address how reaction times are prolonged in the face of potential stopping. Reaction times have long been considered to reflect the time taken to prepare a movement after which the movement is executed. This idea is captured in rise-to-threshold models, where activity during movement preparation builds up to a perceptual threshold, after which movement is triggered; thereby coupling processes of motor preparation and execution. Evidence for an integrative process of sensory accumulation originated from the discovery that movement was initiated if activity in frontal eye field neurones exceeded a fixed threshold (175). Over the years, evidence for this idea has encompassed other cortical areas (56,60,185) and come from both human (177,186–188) and primate neurophysiology (175,185,189). The slope and variation of activity during preparation and height of the threshold are believed to mediate differences in reaction times. However, recent evidence has suggested that these preparation and execution of a movement are independent, and that movement execution is the same irrespective of reaction time (121,122). In doing so, they suggest that the trigger for movement execution is the key determinant of the reaction time, rather than movement preparation. Whilst

behavioural data speaks to the independence of movement preparation and execution, there is surprisingly a lack of human physiological data to support this.

We aim to resolve these competing models of motor responding. In this chapter, we make use of two tasks, the stop-signal task (SST) and conditional stop-signal task (CSST), which required subjects to exhibit the same behaviour but prepare this behaviour in different ways. The hypothesis is that movement preparation will differ between these two tasks. We simultaneously employ TMS at different time points during go trials and analyse corticospinal excitability (CSE) from the viewpoints of both motor preparation and motor execution. In doing so, we can answer whether motor preparation and motor execution are coupled, as predicted by the rise-to-threshold model, or independent of one another.

Experiment 1 presents data from healthy human volunteers performing a simple reaction time task (Go-only task) and the SST. We noted that participants prolonged their reaction time on go trials during the SST compared to the Go-only, presumably because stopping may be required in the stop-signal task. Comparing the reaction time distributions during go trials between these tasks, we showed that the most likely mode of prolonging reaction times is due to a delay in movement execution. CSE measured during movement preparation shows that this differs between the Go-only task and SST, such that rise in CSE occurs later when stopping may be required, consistent with proactive inhibition. However, CSE analysed from a motor execution perspective showed no differences according to stopping requirements. These results suggested that proactive inhibition was medicated by a real-time delay, which was incorporated between movement preparation and execution. In a second experiment using the CSST, we showed that for the same behavioural manifestation (slowing down when stopping may be required), a different strategy was used. Interrogating this strategy using reaction time distribution and drift-diffusion model analyses, we found that drift rate was decreased, and boundary separation was increased when stopping might be required, showing that movement preparation was different from that in experiment 1. However, CSE measured could not differentiate

between stopping conditions. Our data therefore favours the model that movement preparation and execution are two independent processes, rather than a rise-to-threshold model.

4.2 Methods

4.2.1 Experiment 1: Stop-signal Task vs Go-only

4.2.1.1 Participants

16 healthy volunteers (13 male, 16 right handed) aged 19-33 (mean age 23.13, SD 3.84) participated in these experiments. We did not conduct a prior power calculation to determine the sample size for this study. Instead, we decided to recruit a similar number of participants as in Chapter 3. Since collection of the data, a paper by Brown et al. has shown the predicted sample sizes required in TMS experiments for particular ICC(2,1) values, for different effect sizes (190). The numbers in the paper are calculated taking into account the day-to-day reliability of MEP measures within an individual. If we assume that the ICC(2,1) for the MEP amplitude at rest is 0.8, then we are adequately powered (approximately 80%) to see a paired t-test with an effect size of 0.8 or more with around 15 subjects. This makes the analyses of the paired t-test analyses of MEPs prior to movement and during movement preparation, adequately powered. However, to see a significant effect in a two-way ANOVA (i.e. different time courses of MEPs in two different conditions), we would need slightly larger numbers (approximately 20 subjects). The study was approved by UCL Ethics Committee and none had contraindications to TMS, which was assessed by a TMS screening questionnaire.

4.2.1.2 Transcranial Magnetic Stimulation and Electromyography Recordings

TMS was delivered in the same fashion described in Chapter 3, experiment 1, with PA_{120} pulses only. EMG was collected as described in Chapter 3, experiment 1.

4.2.1.3 Stop-signal task and Go-only task

Participants were asked to perform both two blocks of the SST and two blocks of a simple reaction time (Go-only) task, which were driven by custom-made MATLAB (MathWorks) scripts using Psychtoolbox. For the SST, subjects were first presented with a white fixation cross on a black background. After 500 ms, an imperative stimulus (right arrow) was presented, which instructed the subject to press the 'M' key on the keyboard as fast as possible with their right index finger (go trials, n=105). On 25% of trials, a stop signal (red cross) appeared above the imperative stimulus at a variable delay after the imperative stimulus (stop trial, n=35). This delay, known as the stop signal delay (SSD) was controlled by a dynamic tracking algorithm, whereby the SSD would change depending on the outcome of the previous stop trial. The starting SSD was always set at 150 ms. If the subject successfully prevented their button press on a stop trial, the next stop trial would have its SSD set 50 ms later, whereas if the subject failed to stop, the next stop trial would have its SSD set 50 ms earlier. This dynamic tracking algorithm has been shown to reliably induce a convergence onto 50% successful inhibition across subjects. The SSDs ranged from 100-250 ms (100, 150, 200 and 250 ms). There were also 15 baseline trials, where no signals were given, but TMS was given to give a representation of baseline corticospinal excitability. These trials also served as catch trials. The order of trials was pseudorandomised, such that one in every four trials contained a stop signal.

The Go-only task was similar to the SST, except no stop signals appeared in the block. Hence, this was a block where no proactive control would be required. 105 go trials were given, with 15 trials without imperative stimuli to act as baseline.

To measure CSE during response preparation and execution, TMS was given in all trials, in all blocks to the M1 representation for the right FDI muscle, at an intensity required to produce a test MEP of 0.5 mV peak-to-peak amplitude. During go trials, one TMS pulse was given randomly at one of seven time points (at the imperative signal and 50, 100, 150, 200, 250 and 300 ms after the go signal). As such, 15 MEPs were taken at each time point. During stop trials, TMS was given 50 ms after the stop signal. In the 15 baseline

trials, TMS was given 1000 ms into the beginning of the trial to assess corticospinal excitability at rest. This has been summarised in figure 4.1.

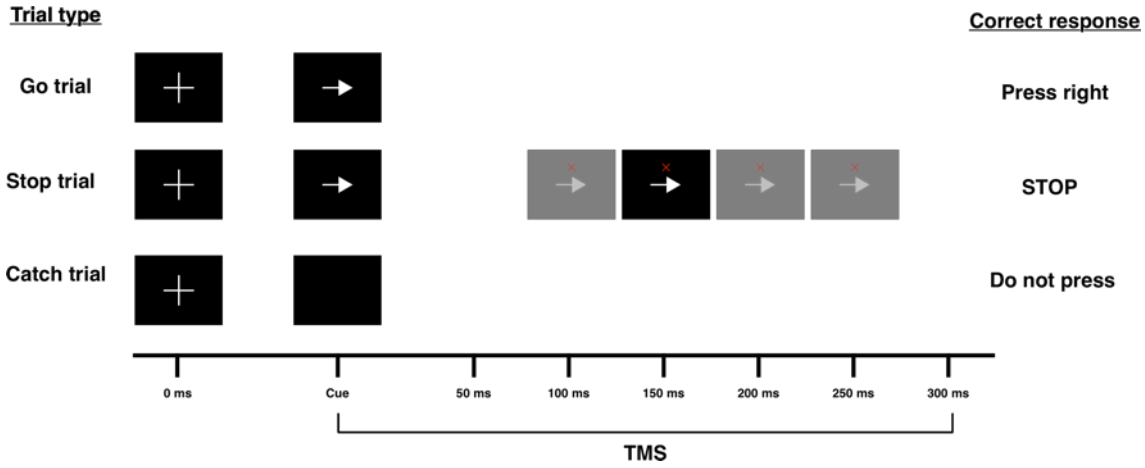

Figure 4.1: TMS delivery in the Stop-signal and Go-only tasks.

SST: Go trials consist of a presentation of a fixation cross, followed by an imperative stimulus (right arrow) 500 ms later. In 25% of trials, the right arrow is followed by a stop signal (red cross) at one of four SSDs (100, 150, 200 or 250 ms after the arrow). Subjects must attempt to abort their button press on presentation of a stop signal. Failure to do so will result in the next stop signal having a shorter SSD (-50 ms) whereas success will lead to the next SSD becoming longer (+50 ms). TMS is delivered on go trials at one of seven time points (counterbalanced and randomised) or 1000 ms into a trial where no signals are shown (baseline trial). The Go-only task comprised of go and catch trials only; TMS was delivered at the same timepoints described above.

Behavioural measures taken included Go reaction time (reaction time on go trials), Stop Respond reaction time (reaction time on failed stop trials), average SSD and p(inhibit) (proportion of correct stop trials in the SST). We also calculated the SSRT using the mean method (mean go reaction time – mean SSD).

4.2.1.4 Data analyses

To investigate motor preparation used between the tasks, we plotted log normalised Go reaction time distribution histograms for each condition (Go-only and SST), for each participant. In rise-to-threshold models, if drift rate, boundary separation or non-decision time differs between conditions, this gives rise to different reaction time distributions (62). To assess whether these distributions were statistically different, we computed Levene's test of equality of variances. As we were testing a null hypothesis in experiment 1, the variance of reaction distributions during go and stop blocks were equal, we computed a Bayesian paired t-test on standard deviations from each participant, using JASP (JASP Team (2018). JASP (Version 0.9.2)).

MEPs at each time point were collapsed into a grand average and then expressed as a fraction of the MEP at the go cue. A two-way repeated measures ANOVA with conditions BLOCK TYPE and TIME was performed. Based on the outcome of this analysis, post-hoc paired t-tests were performed between MEPs at each time point until they differed significantly from the go cue MEP, to assess if a delay had occurred in the rise of CSE.

To assess CSE during movement execution between blocks of potentially stopping in the SST compared to never stopping in the Go-only task, we controlled for reaction time differences (response-locked analysis). To this end, we calculated the time difference between TMS delivery and reaction time for each trial. MEPs were then categorised into 50ms time bins and a two-way repeated measures ANOVA was performed with main factors TIME BIN and BLOCK TYPE. Post-hoc paired t-tests were then performed to compare which were significant interactions.

4.2.2 Experiment 2: Conditional stop-signal task

4.2.2.1 Participants

15 healthy volunteers (13 male, 15 right handed) aged 19-29 (mean age 21.27, SD 2.96) participated in these experiments. We chose this sample size because we observed significant changes during movement preparation in the previous chapter using a similar

number of subjects, during the SST. The study was approved by UCL Ethics Committee and none had contraindications to TMS, which was assessed by a TMS screening questionnaire.

4.2.2.2 Transcranial Magnetic Stimulation and Electromyography Recordings

Single pulse, monophasic TMS was employed using a Magstim 200^2 stimulator (The Magstim Co. Ltd) connected via a figure-of-eight coil with an internal wing diameter of 70 mm. The hotspot was identified as the area on the scalp where the largest and most stable MEPs could be obtained for the right FDI muscle, using a given suprathreshold intensity. The coil was held approximately perpendicular to the presumed central sulcus and tangentially to the skull, with the coil handle pointing backwards for postero-anterior (PA) stimulation. Stimulation intensity was set to one whereby resting peak-to-peak MEP amplitude was 0.5 mV. EMG was recorded as in experiment 1.

4.2.2.3 Conditional Stop-signal task

Participants were asked to perform both two blocks of the CSST, which were driven by custom-made MATLAB (MathWorks) scripts using Psychtoolbox. The CSST is similar to the SST, with some important differences. Firstly, subjects now have two response alternatives, a right or left arrow, to which the subject responds with their right or left index finger. Stop signals are pseudorandomly presented after the go cue in 25% of trials. The main difference is that subjects are told at the beginning of the block that they must follow the stopping rule for one direction (critical) and ignore it to the other direction (non-critical). In this way, subjects still employ proactive control (slowing down in the face of potential stopping), but for one effector only. The behavioural index of proactive control is therefore the reaction time difference when stopping might be required (critical go trial) vs reaction time when stopping is not required (non-critical go trial). By sampling the left motor cortex and changing the rule of the right hand between blocks (critical vs non-critical), corticospinal excitability can be compared when proactive control is employed (right hand critical) vs when it is not required (right hand non-critical).

Dynamic tracking of the stop signal was the same as the SST. There were also 15 baseline trials, where no signals were given, but TMS was given to give a representation of baseline corticospinal excitability. These trials served as catch trials. The order of trials was pseudorandomised, such that one in every four trials contained a stop signal. Each block consisted of 120 go trials (60 critical, 60 non-critical) and 40 stop trials (20 critical and 20 non-critical).

TMS was given in all trials, in all blocks to the M1 representation for the right FDI muscle, at an intensity required to produce a test MEP of 0.5 mV peak-to-peak amplitude. During go trials, one TMS pulse was given randomly at one of five time points (200, 250, 300, 350 and 400 ms after the go signal). As such, 12 MEPs were taken at each time point. During stop trials, TMS was given 50 ms after the stop signal. In the 15 baseline trials, TMS was given 1000 ms into the beginning of the trial to assess corticospinal excitability at rest. This has been summarised in figure 4.2.

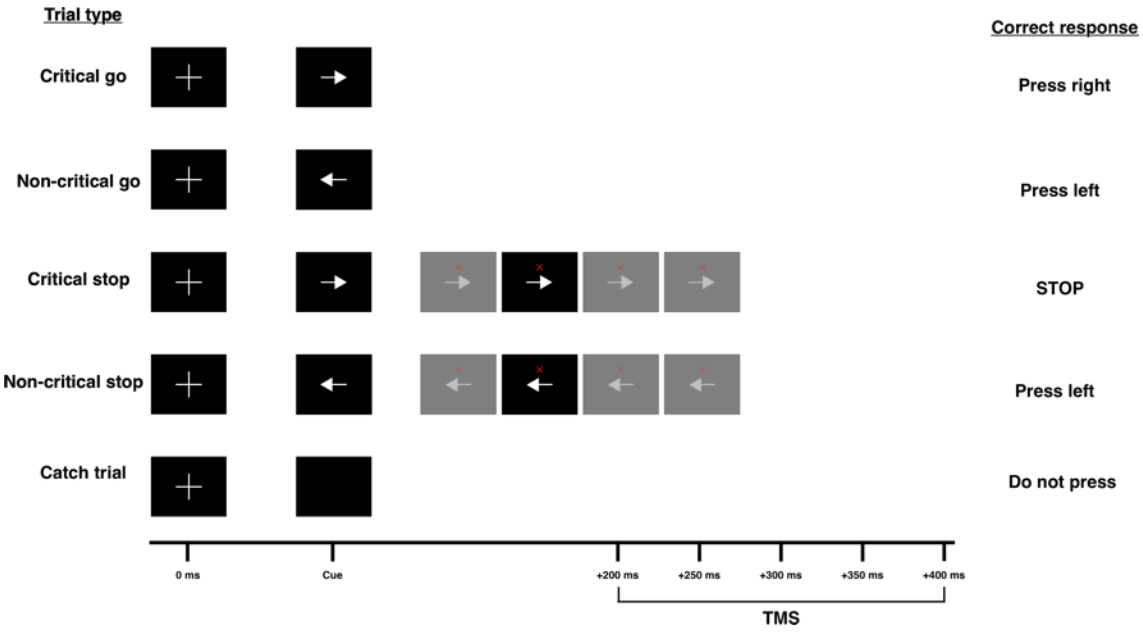

Figure 4.2: TMS delivery in the Conditional stop-signal task.

Subjects are told that one direction is critical and the other is non-critical. Go trials consist of a fixation cross, followed by one of two imperative stimuli (right or left arrow) 500 ms

later. In 25% of trials, the go cue is followed by a stop signal (red cross) at one of four SSDs (100, 150, 200 or 250 ms after the arrow). Subjects must attempt to abort their button press on presentation of a stop signal if after a critical go cue. If the stop signal appears after the non-critical go cue, subjects must ignore is and continue pressing the correct button. Failure to successfully stop will result in the next stop signal having a shorter SSD (-50 ms) whereas success will lead to the next SSD becoming longer (+50 ms). TMS is delivered on go trials at one of five time points (counterbalanced and randomised), or 1000 ms into a trial where no signals are shown (baseline trial).

Behavioural measures taken included Critical Go reaction time, Non-critical Go reaction time, Stop Respond reaction time (reaction time on failed stop trials), average SSD, p(inhibit) (proportion of correct stop trials in the CSST) and response delay effect (reaction time difference between critical go and non-critical go trials). The response delay effect is the behavioural index of proactive control, as stopping is required during critical go trials, but no in non-critical go trials. We also calculated the SSRT using the integration method, as described in the Methods.

4.2.2.4 Drift-diffusion modelling

The rise-to-threshold model has been captured and quantified by the drift-diffusion model (DDM) (54,191). The model (54) is used to quantify the variables, that give rise to the reaction time distributions in two-choice reaction time tasks, by assuming that responses are made when noisy evidence accumulation for a particular choice reaches a perceptual decision threshold. The main parameters of interest are the drift rate, boundary separation and non-decision time. Drift rate refers to the rate of evidence accumulation for a particular choice. Larger drift rates mean that evidence reaches the decision threshold earlier, leading to faster responses, but with lower accuracy. Boundary separation refers to the distance between the two perceptual decision thresholds (one for each response alternative). A lower boundary separation means that evidence reaches the threshold earlier and with less evidence, resulting in faster responses, with lower accuracy. Finally, non-decision time encodes the time taken for stimulus processing and motor execution.

DDM analysis was therefore used to investigate the strategic effects on task performance in the CSST when stopping may be required, akin to quantifying movement preparation. For each participant, we used the DMAT toolbox (67) to estimate DDM parameters. We allowed the drift rate, boundary separation and non-decision time to vary between context (critical vs non-critical). Starting point was set to half of the boundary separation seeing as left/right go cues could appear with equal probability. We only used go trials derived from the right hand in this analysis; hence right-hand responses when the right hand was critical in one block and right-hand responses when the right hand was non-critical in the other block (the critical rule was changed between blocks). We did this so that we could make comparisons between the TMS derived measures for the right hand and behaviour from the same hand. Furthermore, TMS has been known to modulate reaction time, so we wanted a comparison, which controlled for this.

4.2.2.5 Data analyses

For each participant, we plotted log normalised Go reaction time distribution histograms for each condition (critical and non-critical). If drift rate, boundary separation or non-decision time differed between conditions, this would give rise to different reaction time distributions; larger drift rates and boundary separations lead to wider reaction time distributions. To assess whether these distributions were different, we computed Levene's test of equality of variances. Again, a Bayesian paired t-test was performed on standard deviations of go reaction distributions during critical and non-critical blocks, for each participant, using JASP (JASP Team (2018). JASP (Version 0.9.2)).

A two-way repeated measures ANOVA with conditions CONDITION and TIME was performed. To assess differences in CSE during motor preparation between critical and non-critical trials, post-hoc paired t-tests were performed between MEPs at each time point until they differed significantly from the go cue MEP.

As in experiment 1, we performed a response-locked analysis to control for differences in reaction time between conditions, which allowed us to assess motor execution.

Paired t-tests were between critical and non-critical DDM parameters to assess whether there were any differences in strategy between contexts.

4.3 Results

4.3.1 Experiment 1: Stop-signal task vs Go-only task

4.3.1.1 Behavioural measures

Behavioural measurements are shown in table 4.1. There was an expected go reaction time difference between the SST and Go-only blocks (103.24ms) due to the anticipation to stopping in the former ($t = 7.583$, $p < 0.001$, $d = 3.07$, 95% CI [1.99 – 4.00]). The dynamic tracking algorithm correctly resulted in a convergence of successful inhibition to 50%.

Measure	Measure description	SST	Go-only
Go	RT to go stimulus in the critical direction	391.55 (35.01)	288.31 (32.12)
p(inhibit)	% correct inhibition	50.54 (7.36)	
Stop Respond	RT on failure to stop trials	287.84 (33.13)	
Go omission	% of omissions	0.36 (0.68)	0.36 (0.84)
Stop signal delay	Delay between go and stop signals	167.05 (25.42)	
SSRT	Calculated time taken to abort response	224.50 (27.75)	

Table 4.1: Behavioural measurements from the Stop-signal task and Go-only task.

The table shows the behavioural measures from the SST and Go-only task. Measures are accompanied by SD in brackets. Reaction times are given in ms.

4.3.1.2 Responses are made later when stopping may be required

The DDM predicts that prolongations in reaction time in the face of potential stopping can occur via: 1) decreases in drift rate, 2) increase in boundary separation or 3) increase in non-decision time. As such, each of these hypotheses predicts that the variances of reaction time distributions between conditions would be different for changes in drift rate and boundary separation, but the same for changes in non-decision time (62). To investigate this, we plotted log-transformed reaction time distributions for go trials in the

SST and Go-only task, for each participant, shown in figure 3. To compare the variances, we performed Levene's test of equality of variances on each subject's data. All 16 subjects showed a prolongation of reaction time during go trials in the SST compared to the Go-only task. 12 of these showed no difference in the reaction time distribution variance when measured using Levene's test of equality of variances. A Bayesian paired t-test between the standard deviations of each condition resulted in a Bayes Factor of 0.602, which is interpreted as anecdotal evidence that the reaction time distributions were not different between the SST and Go-only tasks. This pattern of this reaction time prolongation is consistent with an increase in non-decision time when stopping may be required.

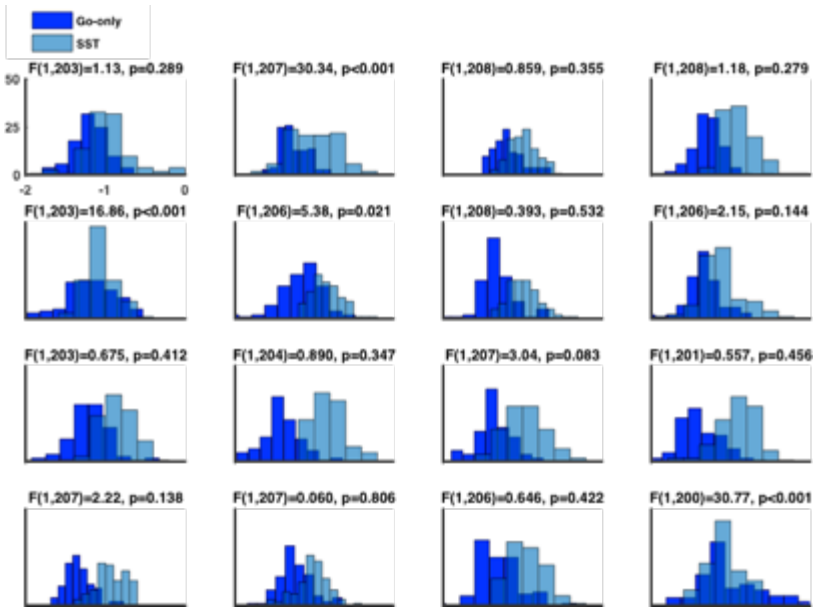

Figure 4.3: Reaction time distributions are shifted to the right when stopping may be required during the Stop-signal task.

Each reaction time distribution histogram plots the log reaction time for go trials in the Go-only task (blue bars) and SST (light blue bars). Levene's test of equal variances is calculated between responses for the Stop-signal task and Go-only task. Levene's test statistics are given for each participant, with significance set at $p < 0.05$, representing a

significant difference in variances. Each plot represents a different participant and axes are the same for each participant.

4.3.1.3 Corticospinal excitability rises later during go trials when stopping may be required

We employed TMS to the left motor cortex during go trials to track the evolution of CSE when subjects respond to a go cue unabated (Go-only task) and under a context when they may need to stop (SST). We found that CSE increased later when stopping may be required, shown in figure 4.4. A two-way repeated measures ANOVA with main factors CONDITION and TIME revealed significant effects of CONDITION ($F(1, 15) = 22.476$; $p < 0.001$, $\eta^2 = 0.600$), TIME ($F(6, 90) = 53.89$; $p < 0.001$, $\eta^2 = 0.782$) and a CONDITION*TIME interaction ($F(6, 90) = 8.241$; $p < 0.001$, $\eta^2 = 0.355$). We used paired t-tests to determine the time point at which CSE first significantly differed from that at the cue. During the Go-only task, this occurred at 100 ms ($p = 0.048$, $t = 2.151$, $d = 0.39$, 95% CI [-0.31 – 1.08]) and at 200 ms during the SST ($p = 0.002$, $t = 3.699$, $d = 0.91$, 95% CI [0.16 – 1.62]). The rise difference in CSE rise time (100 ms) is consistent with the behavioural difference in reaction time (103.24 ms).

4.3.1.4 .... but output from the motor cortex is the same, regardless of stopping requirements

The later rise time of CSE and shift in reaction time distribution to the right, without a change in distribution variance, suggest that non-decision time is increased when stopping may be required. To confirm this, we performed a response-locked analysis of CSE before a response was made in go trials, for the two contexts. The response-locked analysis views activity from the perspective of movement execution rather than preparation, as in the cue-locked analysis. Crucially, if according to a rise-to-threshold model of movement, boundary separation or drift rate mediated the differences in reaction time, this would be reflected between contexts during motor execution. We found, in fact, that CSE was not significantly different between conditions when the reaction time was controlled for. This was confirmed by a two-way repeated measures ANOVA: CONDITION ($F(1,$

15) = 2.338; p = 0.149, η^2 = 0.142), TIME (F (5, 75) = 81.143; p < 0.001, η^2 = 0.853) and a CONDITION*TIME interaction (F (5, 75) = 0.365; p = 0.871, η^2 = 0.025).

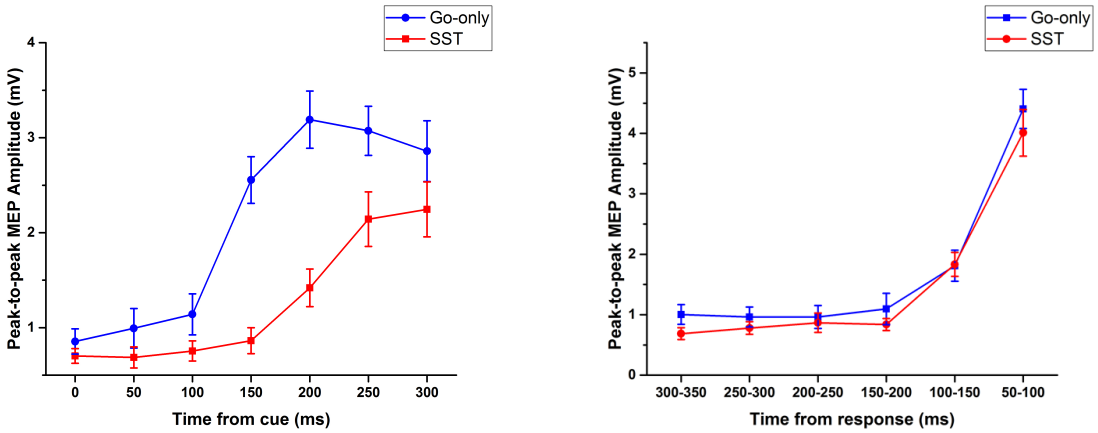

Figure 4.4: Evolution of corticospinal excitability in the Go-only and Stop-signal task.

Left: Normalised to cue MEPs are plotted against the time from cue presentation for go trials in the Go-only task (blue circles) and SST (red squares). **Right**: Corticospinal excitability is plotted in 50 ms time bins determined by the time between TMS and response, such that smaller values represent data points closer to responses. Error bars represent mean±SEM.

From experiment 1, we deduced that prolongation of reaction time in the face of potential stopping was mediated by an increase in the non-decision time, rather than changes in the drift rate or boundary separation. We next sought to change movement preparation in a task requiring the same behavioural output and measure whether CSE differed from the perspectives of movement preparation and execution. We hypothesised that if movement is made via a rise-to-threshold account, then changing movement preparation would change measures of movement execution. If these processes were independent however, then no changes in movement execution should be detected if movement preparation is changed.

4.3.2 Experiment 2: Conditional stop-signal task

4.3.2.1 Behavioural measures

Behavioural measurements are shown in table 4.2. As in the SST, there was an expected go reaction time difference between critical and non-critical trials due to the anticipation to stopping in critical trials (right hand critical: $t = 6.374$, $p < 0.001$, $d = 1.42$, 95% CI [0.59 – 2.18], right hand non-critical: $t = 4.701$, $p < 0.001$, $d = 0.88$, 95% CI [0.10 – 1.60]). This is indexed by the response delay effect.

Measure	Measure description	Right hand rule	
Critical direction		**Critical**	**Non-critical**
Go	RT to go stimulus in the critical direction	410.01 (56.40)	397.10 (53.93)
p(inhibit)	% correct inhibition	45.90 (14.97)	46.82 (16.62)
Stop Respond	RT on failure to stop trials	375.89 (41.10)	352.38 (46.72)
Go error	% of go discrimination errors	0.67 (1.10)	0.39 (0.88)
Stop signal delay	Delay between go and stop signals	149.50 (41.49)	150.67 (44.00)
SSRT	Calculated time taken to abort response	229.76 (43.12)	223.90 (46.67)
Non-critical direction			
Go	RT to go stimulus in the non-critical direction	340.86 (39.37)	355.88 (39.08)
Other variables			
Response delay effect	(Critical go) - (Non-critical go) RT	69.15 (42.02)	41.22 (33.96)

Table 4.2: Behavioural measurements from the Conditional stop-signal task.

The table shows the behavioural measures from the CSST. As two blocks were performed, each block's results are presented. Measures are accompanied by SD in brackets. Reaction times are given in milliseconds.

4.3.2.2 A different decision-making strategy mediates prolonged reaction times when stopping may be required in the CSST

As in experiment 1, we plotted log-transformed reaction time distributions for critical and non-critical go trials. Levene's test was also performed and reported for each subject, shown in figure 4.5. Of the 15 subjects tested, all showed increases in go reaction times for critical trials (when stopping may be required) compared to non-critical trials (when stopping was not required). Contrary to experiment 1, 11 of the 15 subjects showed

significant differences in the variances of their critical and non-critical reaction time distributions. A Bayesian paired t-test between the standard deviations of each condition resulted in a Bayes Factor of 692.6, which is interpreted as extremely strong evidence that the reaction time distributions differed between the critical and non-critical conditions. This suggested that a different mechanism was mediating the prolongation in reaction time. To this end, we used a drift-diffusion model to investigate this further.

The DMAT Toolbox was used to estimate DDM parameters for critical and non-critical trial reaction times. Because the critical direction changed between blocks, we grouped trials by whether they were critical or non-critical, irrespective of the hand used to respond. The parameters estimated were: boundary separation, drift rate and non-decision time, all others were held fixed and starting point was set at half of boundary separation. Figure 4.5 shows individualised parameter estimation for each parameter. We found that boundary separation was greater ($t = 2.746$, $p = 0.017$, $d = 0.79$, 95% CI [0.00 – 1.53]) and drift rate was lower ($t = -3.279$, $p = 0.006$, $d = -1.05$, 95% CI [-1.81 – -0.23]) during critical trials, when stopping was required. Non-decision time ($t = 1.308$, $p = 0.214$, $d = 0.38$, 95% CI [-0.38 – 1.12]) was not significantly modulated between conditions. One subject's data was removed due to a drift rate, that was more than two standard deviations greater than the mean. The results from the reaction time distribution and DDM analyses together show that motor preparation differed from that in experiment 1, where non-decision time mediated the prolongation in reaction time, in response to potential stopping.

4.3.2.3 Motor cortex output is the same, regardless of decision-making strategy

We once again found that CSE became significantly different later under conditions when stopping was required (critical) than when stopping was not (non-critical), between critical and non-critical trials. This was confirmed with a two-way repeated measures ANOVA: CONDITION ($F(1, 14) = 6.822$; $p = 0.021$, $\eta^2 = 0.328$), TIME ($F(5, 70) = 11.962$; $p < 0.001$, $\eta^2 = 0.461$) and a CONDITION*TIME interaction ($F(5, 70) = 4.284$; $p = 0.002$, $\eta^2 = 0.234$). To assess motor execution, we controlled for reaction

time and performed a similar response-locked analysis as in experiment 1. Despite a change in motor preparation (change in boundary separation) to slow down in the face of potential stopping, motor cortex output remained the same: CONDITION ($F(1, 13) < 0.001$; $p = 0.985$, $\eta^2 < 0.01$), TIME ($F(3, 39) = 18.234$; $p < 0.001$, $\eta^2 = 0.584$) and a CONDITION*TIME ($F(3, 39) = 3.440$; $p = 0.039$, $\eta^2 = 0.209$). Note that one subject had missing data for one data point. These findings are illustrated in figure 4.5.

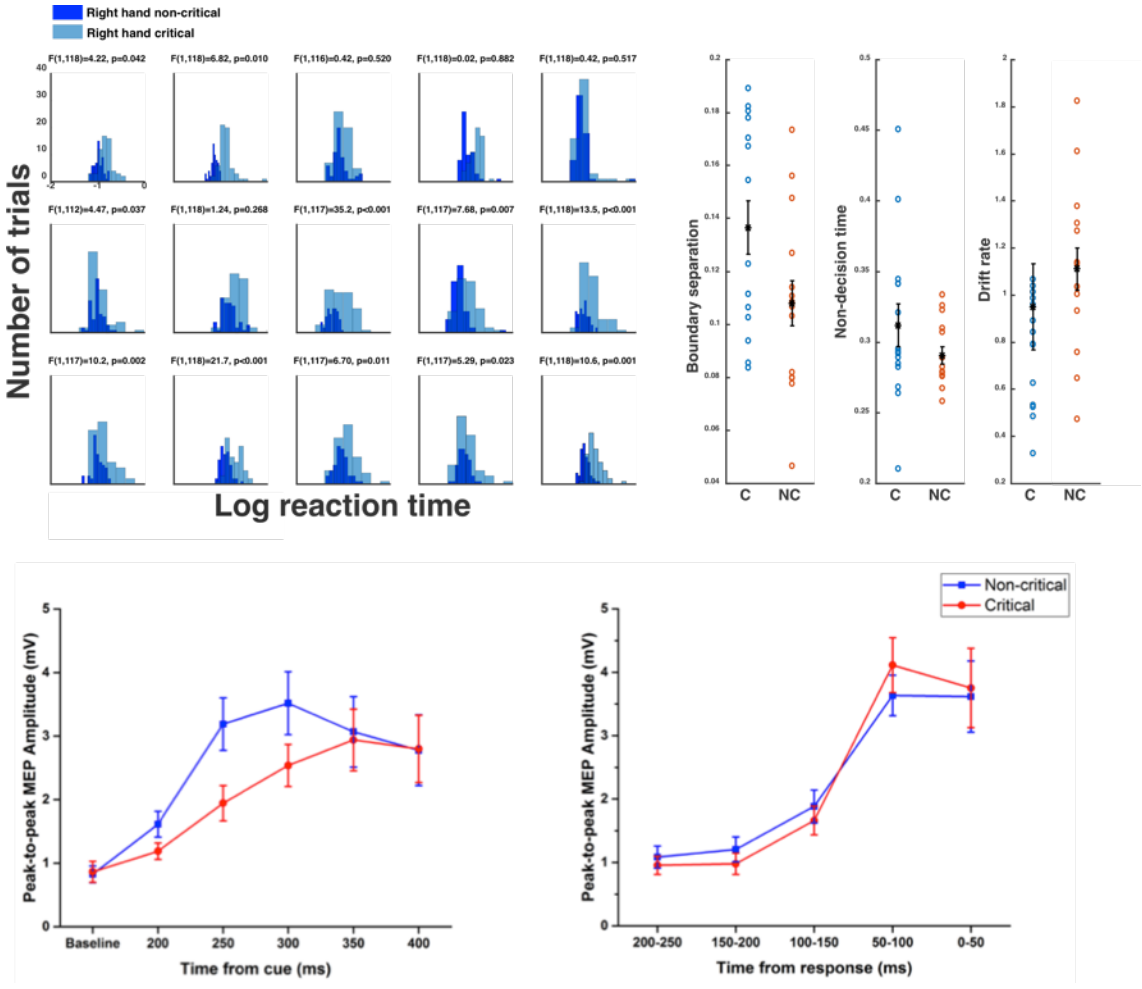

Figure 4.5: Decision making strategy differs between critical and non-critical go trials, yet movement execution remains the same

Top left: Plots are similar to those in experiment 1, with log-transformed go reaction times for critical trials (blue bars) and non-critical trials (light blue bars). Levene's test of equal variances is calculated between critical and non-critical responses. Levene's test statistic for variance is shown above each subject's plot. Significance is set at $p < 0.05$. Each plot represents a different participant and axes are the same for each participant. **Top right**: Estimated DDM parameters are shown for individual subjects, for boundary separation, non-decision time and drift rate, for right-handed, critical and non-critical go trials. Black stars represent mean parameter estimation, whilst error bars reflect SEM. **Bottom**: Left panel shows MEPs plotted against the time from cue presentation for go trials in the non-critical direction (blue circles) and critical trials (red squares). Right panel shows corticospinal excitability plotted in 50 ms time bins determined by the time between TMS and response, such that smaller values represent data points closer to responses. Error bars represent mean±SEM.

4.4 Discussion

4.4.1 Validation of the conditional stop-signal task

We wanted to probe proactive and reactive inhibition, both in this experiment and future ones. Hence, we assessed whether the CSST could exhibit these behavioural features as reported in previous literature (6,11,40,106). We found that the CSST reliably probed aspects of response inhibition reported in the literature. Of note, we show the expected slowing down in go trials for the critical direction compared to the non-critical direction (the response delay effect). This was reported as a mean of 69.15 ms and 41.22 ms when the right hand was critical and non-critical, respectively, and shows that the CSST can indeed probe proactive inhibition. Next, we looked at the ability of the task to converge upon a probability of inhibiting of approximately 50%, especially in the light of concurrent TMS. This was proven true, as the task resulted in an average p(inhibit) of 45.90% and 46.82%. Stopping efficacy was also assessed via the SSRT (229.76 ms and 223.90 ms), which was again in line with reports in the literature (192,193). Finally, we

assessed whether there were any violations of the calculation of the SSRT (174). An assumption of SSRT calculation is that failed stop (stop-respond) reaction times are faster than the mean go reaction time; the stop-respond trials arise from the fastest part of the reaction time distribution and are too fast for the stop process to intervene. We saw that the stop-respond trials had faster reaction times (375.89 ms and 352.38 ms) than the go reaction times (410.01 ms and 397.10 ms). This had thus provided validation of the use of the CSST as a technique to probe proactive and reactive inhibition in humans.

4.4.2 Motor preparation can be altered by changing task demands

We show that different decision-making strategies, akin to motor preparation, can be employed to achieve the same behavioural manifestation i.e. slowing down in anticipation of potential stopping. As DDM analyses are specific for two-choice reaction time tasks, and experiment 1 was a once-choice task, we looked at the reaction time distribution patterns to make inferences on decision making strategy. We observed that subjects increased their non-decision time in the face of potential stopping. This was indexed by a reaction time distribution, that was shifted to the right when stopping was required and with an unchanged variance. If drift rate or boundary separation mediated the increase in reaction time, this would change variance in reaction time distribution (62). To confirm these results, we recorded motor cortex output during this task. From the cue-locked analysis, we observed that CSE increased later when stopping may be required, consistent with an increase in the non-decision time. If drift rate or boundary separation were mediating this increase in reaction time, as per a rise-to-threshold model, we would also expect changes in CSE when the reaction time was controlled for. To this end, we performed a response-locked analysis, looking at response execution, but observed no changes in CSE between the SST and Go-only task. This provides further evidence that a real-time delay is incorporated into the response process to increase reaction time in response to potential stopping.

In the CSST the reaction time difference between critical go and non-critical go trials gave an index of slowing down in the face of stopping. The decision-making strategy employed in experiment 2 was different for several reasons. Firstly, the magnitude of the slowing down effects was smaller than in experiment 1. The reaction time distributions also differed between experiments; rather than shifting the distribution to the right when stopping may be required, this effect was less clear, with different variances between critical and non-critical trials. These differences suggest that a different mechanism of decision-making was used to prolong responding in the face of potential stopping. To investigate this further, we fit our reaction time data to a DDM, which showed that boundary separation was greater and drift rate was smaller in critical go trials than in non-critical go trials. These changes in DDM parameters are in keeping with the changes in the variance of the reaction time distributions (62).

The behaviour exhibited during proactive inhibition, when subjects might need to stop, is an example of the speed-accuracy tradeoff. Traditionally, changes in boundary separation have been implicated in mediating this tradeoff. It is reassuring that in the context of the CSST, we also find that boundary separation is increased when more cautious responding is required, during critical go trials. Interestingly, we also find that non-decision time, in the form of a real-time delay, is used to mediate caution when stopping might be required during go trials in the SST. The neural correlate of the speed-accuracy tradeoff has been proposed to lie within either cortical or subcortical basal ganglia structures (194). The cortical theory proposes that when speed is prioritised, cortical integrators receive additional excitatory input, which increases their baseline activity. As a consequence, this perceptual threshold is reached earlier, and decisions are made quicker. Evidence for this hypothesis comes from stimulation studies, which show that a common input to cortical areas can control the speed-accuracy tradeoff (195,196). Our data speak against this hypothesis; we would expect changes in corticospinal excitability during response execution if the increase in boundary separation was indeed expressed in the cortex. Why strategy is changed to mediate the same behavioural effect is unknown. It is known that

subjects can change their decision-making strategy based on task demands (23,64,197,198); whilst the task remains the same, task instructions differ. For example, in the random dots task, instructions to respond quickly or accurately exert their effects by modulating drift rate and boundary separation, respectively. In our experiment, however, the task differs but the behavioural manifestation remains the same i.e. slowing down in the face of potential stopping.

4.4.3 Motor preparation and execution are independent processes

Behavioural analysis from experiments 1 and 2 showed that the decision-making strategy used to slow down in the face of stopping can change depending on task demands. In experiment 1, motor preparation was the same between the SST and Go-only task, as only one response needed to be prepared. Hence, the reaction time differences between tasks represent a difference in motor initiation, as motor preparation is equal between tasks. This observation shows that motor preparation and initiation are not inevitably coupled, as a real-time delay can be incorporated into the response. We noticed that the rise in CSE was either delayed (SST) or slower (critical go trials) when stopping might be expected compared to when it is not. Since non-decision time mediates the slowing down in the SST, it is no surprise that no differences are observed in the response-locked analysis, when the reaction times are controlled, between SST and Go-only go trials. That is, the decision to respond is made at the same time in both conditions, but the point at which that movement is initiated and executed by M1, is different. This difference in movement initiation is what mediates the reaction time difference between conditions. A delay in the initiation of saccades has been shown to be present in neurones recorded in the frontal eye fields and superior colliculus of macaque monkeys performing the stop-signal task (199). Our results extend this notion that movement generation under apprehension can occur via a method of delayed initiation, outside of the ocular system.

In contrast, reaction time distribution and DDM analysis of CSST behavioural data revealed that the slowing down during critical go trials was mediated by an increase in

the boundary separation and decrease in drift rate. Consequently, we expected there to be differences in CSE between critical and non-critical go trials during movement execution in the response-locked analysis. However, as in experiment 1, there was no difference in M1 activity during response execution, between stopping conditions.

These results together show that M1 executes the same process, regardless of differences in movement preparation and hence favour a model whereby movement preparation and execution are independent; motor execution does not necessarily occur when the perceptual decision threshold has been reached. The independence between movement preparation and movement initiation has recently been reported using free and forced reaction time paradigms, showing that accurate responses can be made when movement preparation has not been completed (121). Evidence for a physiological distinction between the decision-related component of an action and the execution is sparse, although it has been reported that variations in evidence accumulation impact parietal delta oscillations and lateralised beta-band power integrate the sensory evidence as a response preparation signal (186). In monkeys, changes in decision-related neural activity rather than changes in threshold can mediate reaction time during the speed-accuracy tradeoff (200).

It is likely that once the decision to move is resolved, a signal is sent to M1 to execute the necessary action. The neural correlate of this signal is currently unknown, although a candidate could be dorsal premotor cortex (201,202); variability of activity in the dorsal premotor cortex has been shown to correlate with motor execution, and has been proposed to be a signature of motor preparation (203). Alternatively, the supplementary motor area is a region that has long been implicated in the triggering of volitional movements (202,204–207). The subthalamic nucleus may also be implicated in the delay period between the command to move and the execution of the motor command; lesion studies and deep brain stimulation in patients with Parkinson's disease of the subthalamic nucleus have shown deficits in the ability to pause when stopping may be required (11,41,208).

It is known that M1 excitability can vary as a function of the functional state of the motor system, reflecting inputs to the motor system regarding decision-making or processes involving action selection. For example, effort (94), contextual uncertainty and surprise (95), value (96) and spatial attention (97) are reflected in changes in CSE before movements are executed. In fact, Klein-Flugge and Bestmann have shown that the MEP amplitude before action execution can differentiate between the selected and unselected effectors (181). Furthermore, the subjective value of such choices was also reflected in motor cortex excitability before the choice was expressed thereby reflecting incoming evidence for one option over another (96). Thus, it is tempting to assume that the rate of accumulation of evidence or change in boundary separation in the drift-diffusion model will also be reflected as a rise in CSE. However, the response-locked analyses in our experiment could not differentiate between go trials when stopping may be required, despite a difference in DDM parameters. Although seemingly contradictory, this finding speaks to the role of the M1 as a binary executor of motor commands; here we assayed during movement execution and found no differences between critical and non-critical go trials, whereas in previous TMS studies reflecting higher order cognitive processes as aforementioned, TMS was delivered in the preparatory phase. Perhaps functional states are expressed in the preparatory phase, which are not expressed during movement execution. However, there is evidence from Chapter 3 of this thesis that CSE can reflect elements of expectancy of stopping. To reconcile this, we propose that on receipt of the go signal, a “decision centre” detects the signal and queries whether it is correct or not. If it is correct, the decision centre queries M1 and the state of motor preparation – that is, it asks whether the appropriate movement plan is in place. If it is, then movement is triggered and M1 executes the corresponding movement. In this scenario, M1 excitability is a marker of how ready M1 is to receive the motor command from the decision variable to execute the movement. Hence, it can be understood that in Chapter 3 when CSE reflected the probability of subsequent stopping, that M1 in these cases was not ready to receive the motor command.

4.5 Conclusions

In this chapter, we questioned whether voluntary movements to a stimulus are made in accordance with a rise-to-threshold model or if, according to recent findings, the processes of movement preparation and execution are independent. Our data show that whilst movement preparation can be altered between different stopping tasks, the execution of the motor command is the same, regardless of stopping requirements. This suggests that movement preparation and execution are two independent processes and that response to a cue does not always occur in a rise-to-threshold manner. Having investigated this in healthy controls, we next sought to investigate this independence was retained in a disorder where movement is generated spontaneously, sometimes without preparation – Tourette syndrome.

5 Response Inhibition in Tourette Syndrome and Tic Disorders

5.1 Introduction

Tourette syndrome (TS) is characterised by rapid, repetitive, stereotyped movements that result in sudden jerks that are difficult to control, called tics. These tics can be preceded by premonitory urges, whereby the patient knows that a tic is ensuing and can, to a degree, be inhibited. In others, however, a premonitory urge is not identifiable, and tics occur spontaneously (209). Therefore, the relationship between the urge and tic is not clear at present.

One theory of tic generation is in a failure in behavioural inhibition, which at its core, postulates that the premonitory urge represents a growing urgency signal (210,211), which cannot be inhibited by putative inhibitory mechanisms. This principle is applied to habit reversal therapy for tics, which teaches patients to become aware of sensations that precede their tics and to initiate competing movements to the tic (212). Using this model, patients may use reactive inhibition to detect and suppress the premonitory urge to avoid the tic from manifesting; a failure in reactive inhibition may be a cause of tics. Reactive inhibition may therefore be called upon rapidly to cancel the internal stimulus that drives the tic. An alternative hypothesis for tic generation is that patients with tic disorders have greater neural noise in their motor system, called motor noise (135). Motor noise refers to spontaneous, neural activity that is task unrelated and is a normal phenomenon (136). In rise-to-threshold models of movement, neural activity accumulates towards a

perceptual decision threshold, after which movement is executed. Inherent in these models is the concept of noise in the accumulation process. Overlaying these two concepts, one might predict that greater motor noise may lead to responses being prematurely executed in tasks of two-choice decision making. This theory also allows for independence between urges and tics, although it does not demand it. This motor noise hypothesis of tic generation also posits that control over tics can be gained via tonic inhibition of the motor system, akin to proactive inhibition. Proactive inhibition is a goal-derived, long-term form of behavioural inhibition, that would act to suppress the urgency signal from developing or from triggering movement. Hence, failure in proactive inhibition may release tonic inhibition of the motor system and result in tics. A third possibility is that there may be automatic inhibition of a nascent movement, failure of which would cause tics. Importantly, this third hypothesis does not need an overt stimulus to be perceived and responded to, which makes it an encompassing hypothesis, seeing as premonitory urges can or cannot precede tics.

Each of these hypotheses can be tested: reactive and proactive inhibition can be tested using the conditional stop-signal task (CSST), whereas automatic inhibition can be assessed using the masked priming task. In the CSST, failures in proactive and reactive inhibition would be indicated by smaller response delay effects (RDE) and larger stop-signal reaction times (SSRT), respectively. In the masked prime task, a failure in automatic inhibition can be measured in several ways. The conventional reaction time measure for automatic inhibition is the negative compatibility effect (NCE), outlined in the Introduction. In tic disorders, we might predict that this is lost relative to healthy controls. Furthermore, a failure in automatic inhibition predicts that more errors may be made by patients with tic disorders. Indeed, if there is a failure in inhibiting a nascent movement (which is evoked by the prime) then we might expect that patients will inappropriately respond to the prime rather than the target. This would lead to responses being made before the presentation of the target or very fast reaction times that could not be attributed to recognition and response to the target. Furthermore, if subjects are failing

to inhibit the prime, then it follows that commission errors (the wrong imperative stimulus selected) should be more prevalent for incompatible (prime and target different) than compatible (prime and target the same) trials.

As primarily a motor disorder, tics have garnered the attention of investigations into the motor system. Having previously characterised the independence of motor preparation and execution, we decided to test whether this held true in patients with tics. We hypothesised that any modulations in proactive inhibition may be reflected in the end output structure of response execution – the motor cortex. Specifically, the distinction between motor preparation and its expression in M1 may be erroneously coupled in tic patients. This may result in 'leakage' of motor preparation into M1, which would cause significant changes in corticospinal excitability (CSE) during response preparation and execution. Indeed, electroencephalographic recordings from patients with tics show that normal pre-movement activity is absent during tics, which suggests that tics and voluntary movements have separate origins (213).

5.2 Methods

5.2.1 Measurement of tic severity using the Yale Global Tic Severity Score

Tic severity was measured using the Yale Global Tic Severity Score, which has been outlined in the Methods.

5.2.2 Experiment 1: Measuring reactive and proactive inhibition in Tourette syndrome and tic disorders using the conditional stop-signal task

5.2.2.1 Participants

19 patients (14 male, mean age 35.05, SD 11.96) participated in this experiment. All had either a diagnosis of Tourette syndrome or a tic disorder. As this study was exploratory, we did not conduct a power calculation to determine our sample size; we attempted to simply maximise the number of patients that we could recruit for the study. The study

was approved by University College London Hospitals Ethics Committee and none had contraindications to TMS, which was assessed by a TMS screening questionnaire.

5.2.2.2 Protocol

The CSST was used to probe behavioural measures of proactive and reactive inhibition, which were further interrogated using reaction time distribution and DDM modelling to assess strategic decision making, pertaining to movement preparation. TMS was integrated into the CSST and analysed in cue-locked and response-locked manners to assess movement preparation and execution, respectively. The protocol analysis pipeline for this experiment is the same as that described in Chapter 4, experiment 2.

5.2.2.3 Data analysis

Handling of behavioural and physiological data within the patient group was the same as described in Chapter 4, experiment 2.

5.2.3 Experiment 2: Measuring reactive and proactive inhibition using the conditional stop-signal task. Tourette vs non-Tourette individuals

We wanted to investigate whether there were any deficits in proactive or reactive inhibition in our population of patients. To do this, we performed unpaired t-tests between measures of proactive (response delay effect) and reactive inhibition (SSRT) between this patient population and the equivalent data from healthy control subjects in Chapter 4, experiment 2.

It has been shown in previous literature that the rise in CSE during motor preparation and execution differ in patients with TS than healthy controls (168), although this was in the context of a go/no-go task, where action cancellation rather than inhibition of an already initiated movement (as in the CSST) is required. We therefore performed a mixed ANOVA to assess whether physiological measures of movement preparation or execution differed during go trials between patients and healthy controls. This was then further interrogated using unpaired t-tests.

5.2.4 Experiment 3: Automatic inhibition measured by the masked priming task

5.2.4.1 Participants

The masked priming task was performed on the same patients used in experiment 1, except one for whom data were missing. It was also performed on a group of 29 control participants (14 male, mean age 27.70, SD 7.43), who did not have a diagnosis of TS or a tic disorder.

5.2.4.2 The masked priming task

The masked priming task was delivered using the Masked Priming Toolbox, made available as an open-source collection of functions, using MATLAB (MathWorks) and Psychtoolbox. Each trial begins with a black fixation dot on a white background. After 100 ms, the prime (<< or >>) is presented for 17 ms (one frame at 60 Hz), after which the mask (a rectangular array of randomly orientated line) is presented for 100 ms. After a variable delay determined by increasing frame numbers on a 60 Hz monitor (0,16,32,48,100,150,200,250 ms), the target stimulus is presented (<< or >>), to which the participant must respond by pressing the 'A' or 'L' key on the keyboard for left and right responses, respectively. The variable delay between the mask and the target presentation is known as stimulus-onset asynchrony (SOA). As well as the variable delay between the mask and the target, the congruency of the prime and target is also changed; if prime and target are the same stimulus (<</<< or >>/>>) they are deemed as compatible; whereas if the prime and target stimuli are pointing in different directions (<</>> or >>/<<), the trial is deemed incompatible. Each block consisted of 16 different SOA-compatibility combinations, with five repetitions per condition. Participants performed three blocks of the masked priming task. This is summarised in figure 5.1.

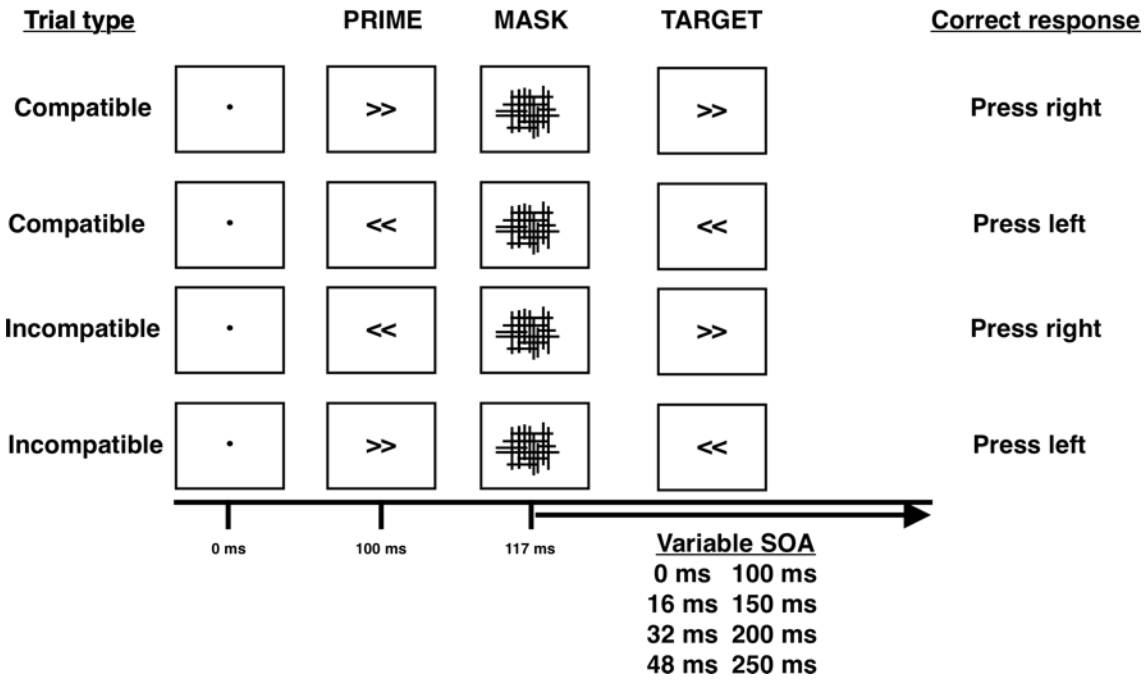

Figure 5.1: The masked priming task.

Schematic shows the four compatibility types in the masked priming task and their appropriate responses. Fixation dot is shown for 100 ms, primes for 17 ms, masks for 100 ms and targets for 100 ms. The onset of the target relative to the mask changes between one of eight interstimulus intervals – stimulus onset asynchrony (SOA).

From the masked priming task, we measured the go reaction time on each trial, indicated by the time between the target presentation and pressing of the button. This was averaged per SOA-compatibility condition. For reaction time analyses, trials with responses <150 ms and >1000 ms were excluded, and only correct trials were included. The reaction time difference between compatibility conditions for each SOA was calculated to give the compatibility effect. This was deemed the positive compatibility effect (PCE) if reaction times were longer on incompatible trials and the negative compatibility effect (NCE) if the reaction times on incompatible trials were shorter. The NCE has shown to be a manifestation of automatic motoric inhibition. The mean reaction time for all correct trials was also calculated.

We also calculated the number of errors, which could take shape in one of four ways: 1) commission errors (the wrong button was pressed in response to the target), 2) omission errors (responses that were greater than one second long or no button was pressed, 3) fast errors (the subject responded before the target had been presented), and 4) premature errors (subject responded <150 ms after the target, believed to be the subject responding to the prime instead). We also calculated the mean reaction time of the commission errors and whether they occurred on trials which were compatible (prime and target the same) or incompatible (prime and target different).

5.2.4.3 Data analyses

We predicted that there may be a failure in automatic inhibition in our patient populations relative to healthy controls. To this end, a three-way ANOVA with variables: COMPATIBILITY (compatible/incompatible), SOA (0,16,32,48,100,150,200,250 ms) and SUBJECT (patient/healthy) was used to probe any statistically significant interactions. Another ANOVA with variables: COMPATIBILITY EFFECT and SUBJECT (patient/healthy control) was performed to investigate differences in priming effects between patients and healthy controls. Compatibility effect was calculated as the mean reaction time on incompatible trials – mean reaction on compatible trials, for each SOA, regardless of the imperative direction. We were particularly interested in compatibility effects for SOAs of 100 ms and 150 ms, where automatic inhibition is believed to operate. Unpaired t-tests were then used to further interrogate any interactions indicated by the ANOVA.

Another manifestation of failing to automatically inhibit could be responding to the prime rather than the target. If this were true, we would expect three types of error to be more prevalent in our patient group: 1) commission errors, 2) premature errors and 3) fast errors. An ANOVA with all types of error was computed according to whether subjects were patients or healthy controls and then further interrogated using unpaired t-tests to check specifically which types of error were more or less common in our patient group.

After our findings regarding the errors made by patients with TS and tic disorders, we decided to investigate whether the incidence of these errors correlated with clinical measures of tic severity. Hence, we calculated Spearman's rank correlation coefficient between errors made (total errors, commission, fast, premature, omission and total fast) and motor tic severity as measured by the YGTSS. We also extended this correlation to the NCE at an SOA of 100 ms and 150 ms as we hypothesised that motor tic severity may be correlated with the reaction time measure of automatic inhibition.

5.3 Results

5.3.1 Clinical characteristics of patients with Tourette syndrome and tic disorders

Table 5.1 shows the clinical characteristics of our patient population. All had their tic scores assessed by the YGTSS and were asked whether they had any co-morbid neuropsychiatric conditions – specifically OCD or ADHD. Mean motor score was 13.05 with an SD of 4.62. Mean total score was 46.40 with an SD of 15.40.

		YGTSS Score							
Patient	Age	Motor	Vocal	Severity	Impairment	Total	OCD	ADHD	Medication
1	26	24	24	48	0	48	No	Yes	Sertraline
2	43	10	8	18	10	28	Yes	Yes	Clonazepam
3	59	9	0	9	40	49	Yes	No	None
4	38	9	0	9	10	19	Yes	No	Melatonin
5	23	18	18	36	30	66	No	Yes	Sertraline
6	46	18	13	31	30	61	No	Yes	Paroxetine
7	32	5	5	10	30	40	No	No	Iron
8	30	16	16	32	30	62	No	No	None
9	44	15	13	28	30	58	Yes	Yes	None
10	48	9	9	18	20	38	Yes	No	Citalopram, Clonazepam
11	29	8	17	25	20	45	No	No	None
12	20	17	10	27	30	57	No	Yes	None
13	20	12	22	34	40	74	Yes	Yes	None
14	19	15	15	30	20	50	Yes	No	None
15	36	17	15	32	10	42	No	No	Pimozide
16	28	14	6	20	10	30	No	No	None
17	26	14	8	22	20	42	No	No	None
18	49	16	16	32	30	62	No	No	None
19	50	9	0	9	10	19	No	No	None

Table 5.1: Clinical characteristics of patients with Tourette syndrome and tic disorders involved in this study.

The table shows the clinical characteristics of our patient population. Patients were asked to complete the YGTSS. As such, the breakdown of their scores is displayed. As TS can exist with other neuropsychiatric conditions, we asked patients about a diagnosis of OCD or ADHD. YGTSS motor and vocal scores are marked out of 25, severity is a sum of these two and impairment is scored out of 50. Total score is therefore out of 100. Medications are noted for each patient.

5.3.2 Experiment 1: Measuring proactive and reactive inhibition using the conditional stop-signal task

5.3.2.1 Behavioural measures

Behavioural measurements are shown in table 5.2. As in previous stopping experiments, there was an expected go reaction time difference between critical and non-critical trials due to the anticipation to stopping in critical trials (right hand critical: $t = 5.361$, $p < 0.001$, $d = 1.01$, right hand non-critical: $t = 2.097$, $p < 0.001$, $d = 0.407$). This is indexed by the response delay effect. Participants unexpectedly achieved a greater than expected probability of successful inhibition. These results show that volitional inhibition is intact in patients with TS and tic disorders.

As OCD and ADHD can both modulate performance on tasks of stopping, we conducted a mixed ANOVA with each of the parameters as dependent variables and OCD and ADHD status as main factors. This mixed ANOVA found a significant effect of OCD status ($F(1, 15) = 5.745$; $p = 0.030$, $\eta^2 = 0.277$) but not ADHD status ($F(1, 15) = 0.717$; $p = 0.410$, $\eta^2 = 0.046$). Further interrogation of which parameter was significantly modulated by OCD status using a one-way ANOVA showed that only non-critical stop reaction time was statistically significantly altered ($F(1, 17) = 4.859$; $p = 0.042$, $\eta^2 = 0.011$).

Measure	Measure description	Right hand rule	
Critical direction		**Critical**	**Non-critical**
Go	RT to go stimulus in the critical direction	501.64 (77.31)	494.65 (76.48)
p(inhibit)	% correct inhibition	62.39 (18.20)	61.32 (19.64)
Stop Respond	RT on failure to stop trials	419.00 (77.14)	461.22 (95.44)
Go error	% of go discrimination errors	1.14 (1.94)	1.18 (1.85)
Stop signal delay	Delay between go and stop signals	190.26 (38.59)	185.00 (41.51)
SSRT	Calculated time taken to abort response	334.98 (89.63)	332.30 (87.00)
Non-critical direction			
Go	RT to go stimulus in the non-critical direction	429.72 (64.95)	457.60 (103.73)
Other variables			
Response delay effect	(Critical go) - (Non-critical go) RT	71.93 (58.48)	37.05 (17.67)

Table 5.2: Behavioural measurements from the Conditional stop-signal task performed in patients with Tourette syndrome and tic disorders.

The table shows the behavioural measures from the CSST. As two blocks were performed, each block's results are presented. Measures are accompanied by SD in brackets. Reaction times are given in milliseconds.

5.3.2.2 Patients employ a similar decision-making strategy to healthy controls when stopping might be required

The DMAT toolbox was again used to quantify the variables changed during stopping between critical and non-critical go trials. We found that patients increased their decision boundary ($t = 4.393$, $p < 0.001$, $d = 1.40$) and decreased their non-decision time ($t = 2.695$, $p = 0.015$, $d = -0.92$) in the face of potential stopping. Drift rates were not significantly modulated between stopping conditions ($t = 0.606$, $p = 0.552$, $d = 0.162$). Note that both healthy control subjects and patients were shown to heighten their boundary separation when stopping might be required. However, control subjects were shown to decrease their drift rate when stopping might be required, although this finding should be interpreted with caution due to reasons outlined in Chapter 4. Curiously, non-decision time was significantly reduced in patients, which may be a mathematical compensation for the higher drift rate during critical than non-critical go trials; it has been shown that fixing or changing in one parameter can lead to changes in another, yielding similar behavioural predictions (214–216).

As OCD and ADHD might influence the strategy used to slow down, we performed a mixed ANOVA using the DDM parameter as the dependent variable and OCD and ADHD statuses as main factors. We found no significant effects of OCD ($F(1, 15) = 0.169$; $p = 0.687$, $\eta^2 = 0.011$) or ADHD ($F(1, 15) = 0.007$; $p = 0.933$, $\eta^2 = 0.275$) status on the DDM parameter used during the CSST.

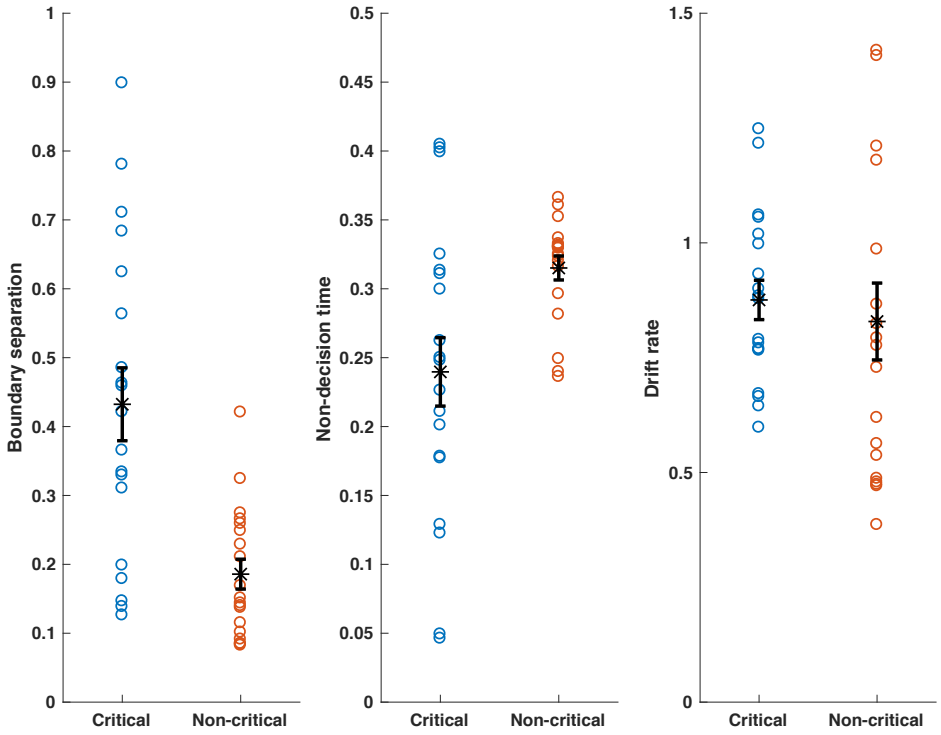

Figure 5.2: Drift-diffusion model parameters for the Conditional stop-signal task.

Estimated DDM parameters are shown for individual subjects, for boundary separation, non-decision time and drift rate, for right-handed, critical and non-critical go trials. Black stars represent mean parameter estimation, whilst error bars reflect SEM.

5.3.2.3 Evolution of corticospinal excitability in the conditional stop-signal task in patients with Tourette syndrome and tic disorders

We assessed how CSE would evolve between trials when stopping might be required (critical trials) against those where stopping was not (non-critical trials) by plotting CSE in a stimulus-locked manner. Baseline CSE as measured by MEP amplitude was the same for critical and non-critical go trials ($t = 1.047$, $p = 0.309$, $d = 0.244$). We found that CSE became statistically significantly greater than that at baseline later for critical go trials (300ms: $t = 2.941$, $p = 0.009$, $d = 0.992$) than non-critical go trials (250 ms: $t = 2.931$, $p = 0.009$, $d = 0.881$). These results appeared to show a slower rise to threshold when stopping might be required. If this was the case, then this should also be observed when

the reaction times are controlled for between conditions. We therefore performed a response-locked analysis. A two-way repeated measures ANOVA with main factors CONDITION and TIME showed that motor execution was equivocal between stopping conditions: CONDITION ($F(1, 14) = 1.335$; $p = 0.267$, $\eta^2 = 0.087$), TIME ($F(3, 42) = 46.31$; $p < 0.001$, $\eta^2 = 0.768$), CONDITION*TIME interaction ($F(3, 42) = 0.944$; $p = 0.428$, $\eta^2 = 0.063$). This showed that movement execution occurs the same, regardless of the stopping requirements of the go trial. We therefore concluded that movement did not occur in these patients due to a slower rise to threshold and that the findings from the stimulus-locked analysis were solely due to differences in the reaction time difference between conditions.

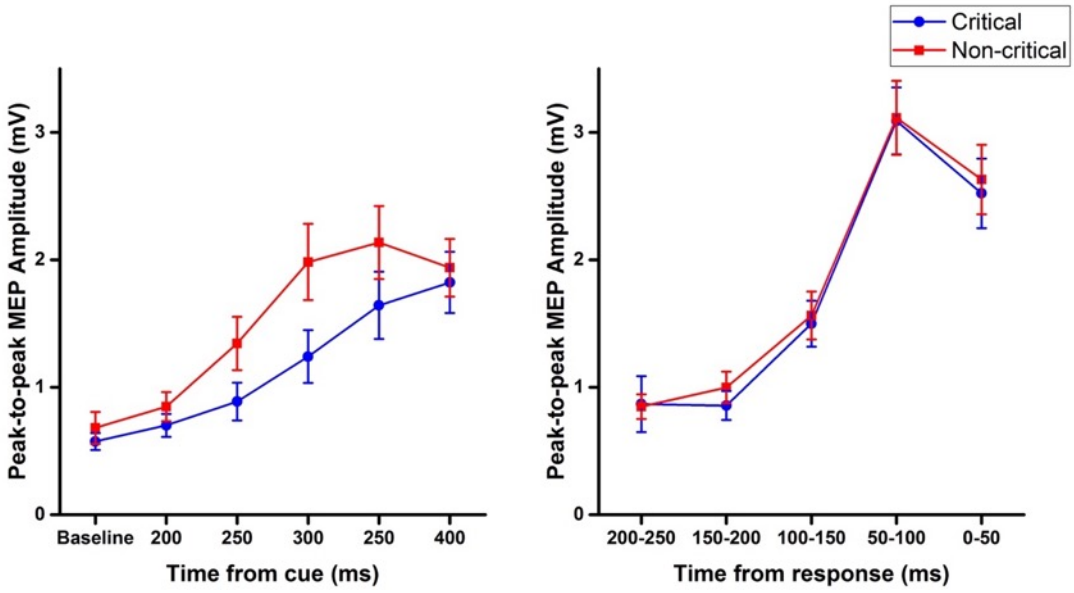

Figure 5.3: Evolution of corticospinal excitability in the Conditional stop-signal task.

Left: MEPs are plotted against the time from cue presentation for go trials in the non-critical direction (blue circles) and critical trials (red squares). **Right**: Corticospinal excitability is plotted in 50 ms time bins determined by the time between TMS and

response, such that smaller values represent data points closer to responses. Error bars represent mean±SEM.

These results together show that the putative mechanisms of response preparation and response execution are retained within patients with TS and tic disorders, and that these processes are still independent. We next aimed to assess whether motor preparation and execution were significantly altered relative to a population of healthy control subjects, without tics or TS. To do this, we compared data from this patient group with that outlined in Chapter 4.

5.3.3 Experiment 2: Measuring proactive and reactive inhibition using the conditional stop-signal task. Tourette versus non-Tourette individuals

5.3.3.1 Rise in corticospinal excitability in Tourette syndrome and tic disorders relative to healthy controls: stimulus-locked comparison

Baseline MEPs were not statically different between patients and controls for critical ($t = 1.764$, $p = 0.087$, $d = 0.583$) and non-critical ($t = 0.784$, $p = 0.439$, $d = 0.271$) go trials. A mixed ANOVA with main factors PATIENT and TIME and dependent variable CSE was used to compare the effects of movement preparation between patients and healthy controls, for critical and non-critical go trials. For critical go trials, there were significant effects of TIME ($F(4, 128) = 14.503$; $p < 0.001$, $\eta^2 = 0.312$) and PATIENT ($F(1, 32) = 11.879$; $p = 0.002$, $\eta^2 = 0.271$) but no interaction between the two ($F(4, 128) = 1.149$; $p = 0.336$, $\eta^2 = 0.035$). For non-critical go trials, there was a significant effect of TIME ($F(4, 128) = 13.009$; $p < 0.001$, $\eta^2 = 0.290$) and PATIENT ($F(1, 32) = 9.204$; $p = 0.005$, $\eta^2 = 0.223$) but no interaction between the two ($F(4, 128) = 2.114$; $p = 0.083$, $\eta^2 = 0.062$). However, these results can be wholly explained by the reaction time differences on go trials being greater in our patient population by 91.63ms for critical trials and 97.55ms for non-critical trials.

5.3.3.2 Rise in corticospinal excitability in Tourette syndrome and tic disorders relative to healthy controls: response-locked comparison

A mixed ANOVA with main factors TIME and PATIENT as a covariate, and dependent variable CSE was used to compare the effects of movement execution between patients and healthy controls, for critical and non-critical go trials. The MEP amplitudes were derived from the response-locked analysis. For critical go trials, there was a significant effect of TIME ($F(4, 104) = 44.870$; $p < 0.001$, $\eta^2 = 0.633$) but not PATIENT ($F(1, 26) = 2.717$; $p = 0.111$, $\eta^2 = 0.095$) nor an interaction between the two ($F(4, 104) = 1.631$; $p = 0.172$, $\eta^2 = 0.059$). For non-critical go trials, there was a significant effect of TIME ($F(4, 96) = 52.736$; $p < 0.001$, $\eta^2 = 0.687$) but not PATIENT ($F(1, 24) = 0.655$; $p = 0.426$, $\eta^2 = 0.027$) nor an interaction between the two ($F(4, 96) = 0.240$; $p = 0.915$, $\eta^2 = 0.010$). There were therefore no differences in response execution between our patients and healthy control subjects. This differs from previous data in a go/no-go task where a slower rate of excitability was found prior to movement onset in Tourette patients (168).

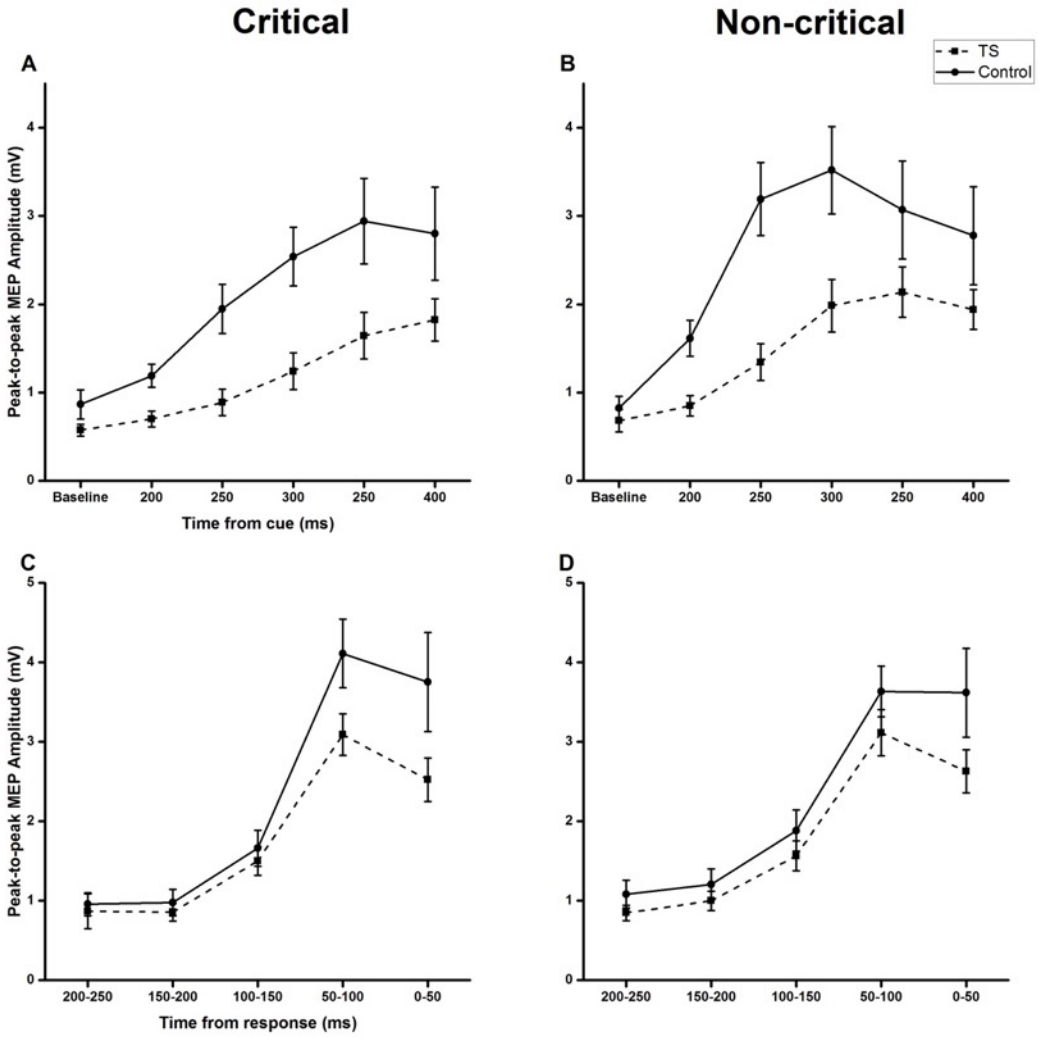

Figure 5.4: Cue and response-locked MEPs for patients and healthy control subjects during critical and non-critical go trials in the conditional stop-signal task.

Cue-locked: MEP amplitudes are plotted against the time at baseline and from cue presentation for go trials in the critical direction (A) and non-critical trials (B).

Response-locked: MEP amplitudes are plotted in 50 ms time bins determined by the time between TMS and response, such that smaller values represent data points closer to responses. Plots on each graph represent CSE from patients and control subjects. These

are plotted for critical (C) and non-critical (D) go trials, for patients and healthy controls. Error bars represent mean±SEM.

Our data indicate that there is no evidence for any major differences in the rise of CSE prior to movement onset in our patient population. This suggests that patients with TS or tic disorders do not have an abnormally excitable motor output.

5.3.4 Experiment 3: Measuring automatic inhibition using the masked priming task

5.3.4.1 The positive compatibility effect, but not negative compatibility effect is present in patients with Tourette syndrome and tic disorders

We investigated positive and negative priming in patients with TS and tic disorders with the specific hypothesis that there may be a failure in automatic inhibition, which can be indexed by the NCE in the masked priming task. A two-way repeated measures ANOVA with main factors TIME and COMPATIBILITY showed significant effects of TIME ($F(7, 119) = 52.28$; $p < 0.001$, $\eta^2 = 0.758$), COMPATIBILITY ($F(1, 17) = 18.06$; $p = 0.001$, $\eta^2 = 0.515$) and an interaction between the two ($F(7, 119) = 2.717$; $p = 0.012$, $\eta^2 = 0.138$). We found that positive compatibility effects were seen in our patient population with reaction times longer on incompatible trials than compatible trials for 0 ms ($t = 3.688$, $p = 0.002$, $d = 0.399$), 16 ms ($t = 3.596$, $p = 0.002$, $d = 0.374$), 32 ms ($t = 1.929$, $p = 0.071$, $d = 0.210$), 48 ms ($t = 2.600$, $p = 0.019$, $d = 0.317$), 200 ms ($t = 3.203$, $p = 0.005$, $d = 0.391$) and 250 ms ($t = 4.268$, $p = 0.001$, $d = 0.450$). Negative compatibility effects, however, were not observed in our patient population at 100 ms ($t = 0.664$, $p = 0.515$, $d = 0.059$) or 150 ms ($t = 0.138$, $p = 0.892$, $d = 0.017$). Where NCEs represent automatic motor inhibition, a lack of an effect here suggests that automatic inhibition is impaired in patients with TS and tic disorders.

5.3.4.2 … but priming effects are not seen in healthy control subjects

As we performed the masked prime task in healthy control subjects, we calculated PCE and NCEs for this population too. A two-way repeated measures ANOVA with main

factors TIME and COMPATIBILITY showed significant effects of TIME ($F(7, 196) = 74.79$; $p < 0.001$, $\eta^2 = 0.728$) and an interaction between the two main factors ($F(7, 196) = 3.603$; $p = 0.001$, $\eta^2 = 0.114$) but no effect of COMPATIBILITY ($F(1, 28) = 1.993$; $p = 0.169$, $\eta^2 = 0.066$). Post-hoc testing found no statistically significant priming effects at any time point ($p > 0.05$) except at a SOA of 250 ms ($t = 2.666$, $p = 0.013$, $d = 0.303$) and a statistical trend at SOA of 200 ms ($t = 1.927$, $p = 0.064$, $d = 0.192$). These results therefore make interpretation of those found in our patient population, problematic.

5.3.4.3 Patients with Tourette syndrome and tic disorders make more errors than healthy controls. These are consistent with a failure of automatic inhibition

A mixed ANOVA with main factor ERROR and covariates PATIENT and AGE revealed a significant effect of ERROR ($F(5, 195) = 4.049$; $p = 0.002$, $\eta^2 = 0.094$) and PATIENT ($F(1, 39) = 5.389$; $p = 0.026$, $\eta^2 = 0.066$) but not AGE ($F(1, 39) = 0.420$; $p = 0.521$, $\eta^2 = 0.066$). There was also a significant ERROR*PATIENT interaction ($F(5, 195) = 4.840$; $p < 0.001$, $\eta^2 = 0.110$) but not ERROR*AGE ($F(5, 195) = 0.820$; $p = 0.537$, $\eta^2 = 0.021$). Unpaired t-tests showed that patients made globally more errors than healthy control subjects in the masked priming task ($t = 2.669$, $p = 0.011$, $d = 0.708$). Errors in the masked priming task can take shape in one of four ways: 1) commission errors (the wrong button was pressed in response to the target), 2) omission errors (responses that were greater than one second long or no button was pressed, 3) fast errors (the subject responded before the target had been presented), and 4) premature errors (subject responded <150 ms after the target, believed to be the subject responding to the prime instead). With this in mind, we identified the specific types of error that were made in the masked priming task. It was found that patients made more commission ($t = 2.601$, $p = 0.013$, $d = 0.702$), fast ($t = 2.349$, $p = 0.023$, $d = 0.614$) and premature ($t = 2.253$, $p = 0.029$, $d = 0.590$) errors than healthy control subjects. Seeing as how fast and premature errors are active arise due to the same consequence, we combined these errors between groups, which showed that they were more prevalent in patients than controls ($t = 2.324$,

p = 0.025, d = 0.608). Patients and controls did not significantly differ in the number of omission errors made (t = 0.530, p = 0.598, d = 0.168).

Looking at individual data points, we observed that there was substantial variation in the number of errors made. To this end, we repeated the comparisons of errors made between patients and healthy controls with outliers removed. Outliers were identified as subjects who made more errors than two times the standard deviation of the group. Consequently, one patient's and one healthy control's data were removed. Patients made more total (t = 2.487, p = 0.017, d = 0.77), commission (t = 2.595, p = 0.013, d = 0.80), fast (t = 2.014, p = 0.048, d = 0.62) and total fast errors (t = 2.010, p = 0.049, d = 0.62). Premature (t = 1.929, p = 0.061, d = 0.60) and omission (t = 0.462, p = 0.646, d = 0.14) errors did not achieve statistical significance.

We hypothesised from the above results that patients were failing to inhibit the prime. If this was true, then it should follow that more commission errors would be made to incompatible prime-target combinations that compatible combinations; if our hypothesis was not true, then commission errors should be equally distributed between incompatible and compatible trials. We found that more commission errors were indeed made on incompatible trials that compatible trials in patients (t = 2.751, p = 0.014, d = 0.551), a relationship not present in control subjects (t = 1.344, p = 0.193, d = 0.295).

One possibility to explain these results is that patients prioritised speed over accuracy, despite being told to aim for both. However, mean reaction times between patients and controls were not statistically different (t = 0.204, p = 0.839, d = 0.064), nor was a one-way ANOVA assessing reaction time differences across all conditions types (all p values > 0.05, smallest being 0.086 at compatible SOA 200 ms).

As OCD and ADHD might confound our results, we performed two separate one-way ANOVAs on the errors made by our subjects, using OCD and ADHD status as between-subjects factors. For OCD, we found that there were no statistically significant differences

for any of the types of errors made between patients with and without OCD (smallest p value = 0.338). Analysis using ADHD yielded similar findings (smallest p value = 0.178).

These results suggest that patients with TS and tic disorders exhibit a failure to inhibit the prime in the masked prime taking – a manifestation of an impairment in automatic inhibition.

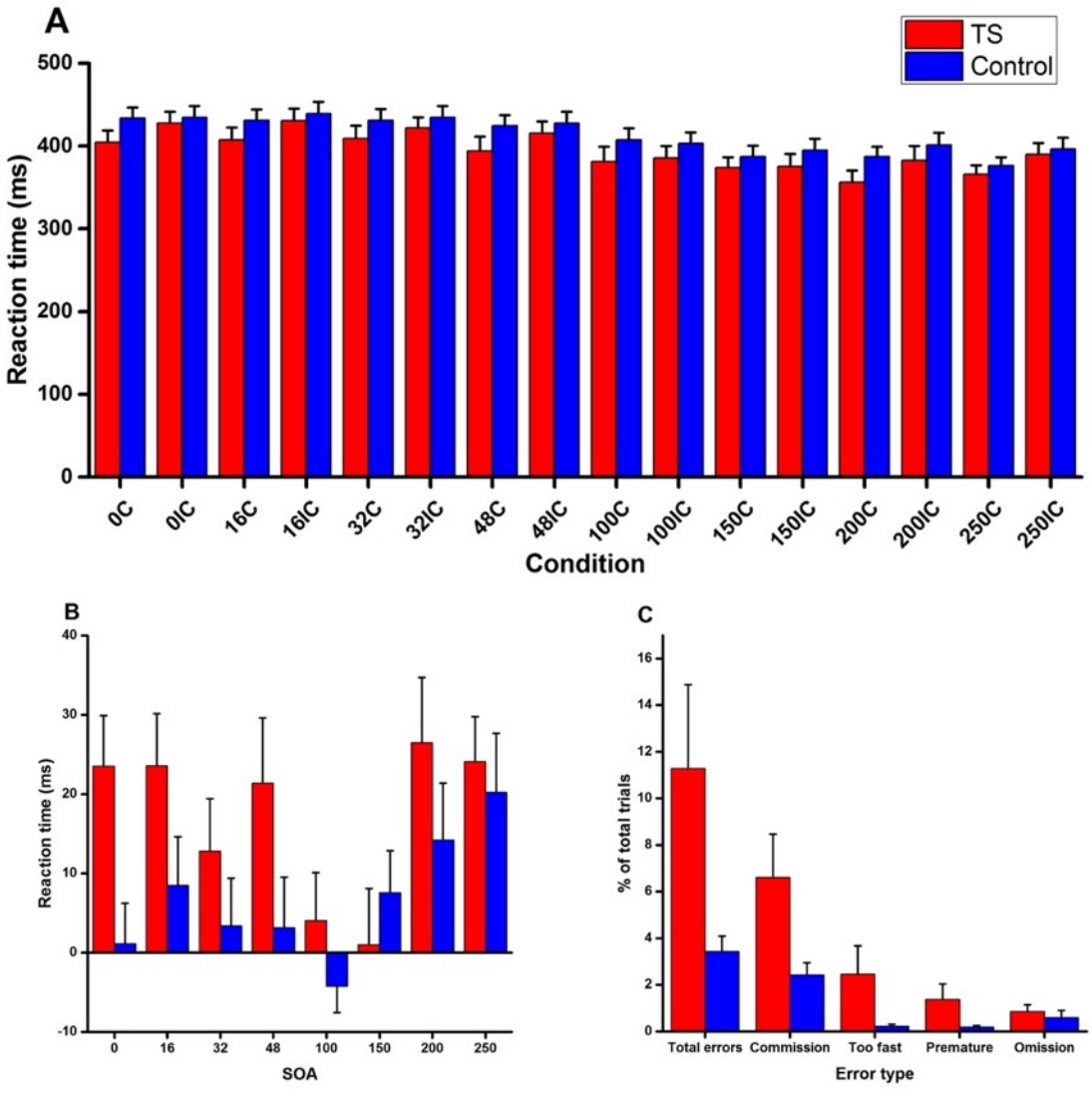

Figure 5.5: Priming effects and errors from the masked priming task.

A: Reaction times are plotted for each condition with numbers denoting the SOA (time difference between the mask and target) and letter denoting the compatibility of the prime-target set (C = compatible, IC = incompatible). **B**: The compatibility effects are shown for each SOA, with values lying above 0 meaning positive compatibility effects and those below 0 meaning negative compatibility effects. **C**: Bar plot shows the errors made on the masked priming task as a proportion of the total number of trials. Error bars represent mean±SEM.

5.3.4.4 Errors consistent with a failure of automatic inhibition are positively correlated with motor tic severity

After finding that patients with TS and tic disorders made more errors consistent with a failure of automatic inhibition, we decided to investigate whether any of these measures correlated with the clinical severity of motor tics. We therefore calculated Spearman's rank correlation coefficient between each of the errors made in the masked priming task and the motor tic severity scores as measured by the YGTSS. We found that motor tic severity correlated with total ($r_s = 0.530$, $p = 0.024$), commission ($r_s = 0.530$, $p = 0.024$), too fast ($r_s = 0.579$, $p = 0.012$), premature ($r_s = 0.502$, $p = 0.034$) and total fast errors ($r_s = 0.605$, $p = 0.008$) but not omission errors ($r_s = 0.331$, $p = 0.180$). The Spearman's rho value of each of the statistically significant errors indicates that each error is moderately, positively correlated with the severity of motor tics. We next investigated whether this correlation was present for the reaction time measure of automatic inhibition – the NCE. We performed Spearman's rank correlation coefficient for motor tic severity scores and the compatibility effect (incompatible trial – compatible trial reaction time) at an SOA of 100 ms and 150 ms. We found no significant correlation between motor tic severity and compatibility effect at 100 ($r_s = -0.099$, $p = 0.697$) or 150 ms ($r_s = 0.251$, $p = 0.315$).

As aforementioned, there was substantial variance in the number of errors made in our study groups. We repeated the correlations with motor tic severity with the one subject, who committed more total errors than the mean + two times the standard deviation. Again, we found statistically significant correlations between the motor tic severity and total (r_s

= 0.601, p = 0.011), commission (r_s = 0.580, p = 0.015), too fast (r_s = 0.661, p = 0.004), premature (r_s = 0.562, p = 0.019) and total fast errors (r_s = 0.679, p = 0.003) but not omission errors (r_s = 0.375, p = 0.139).

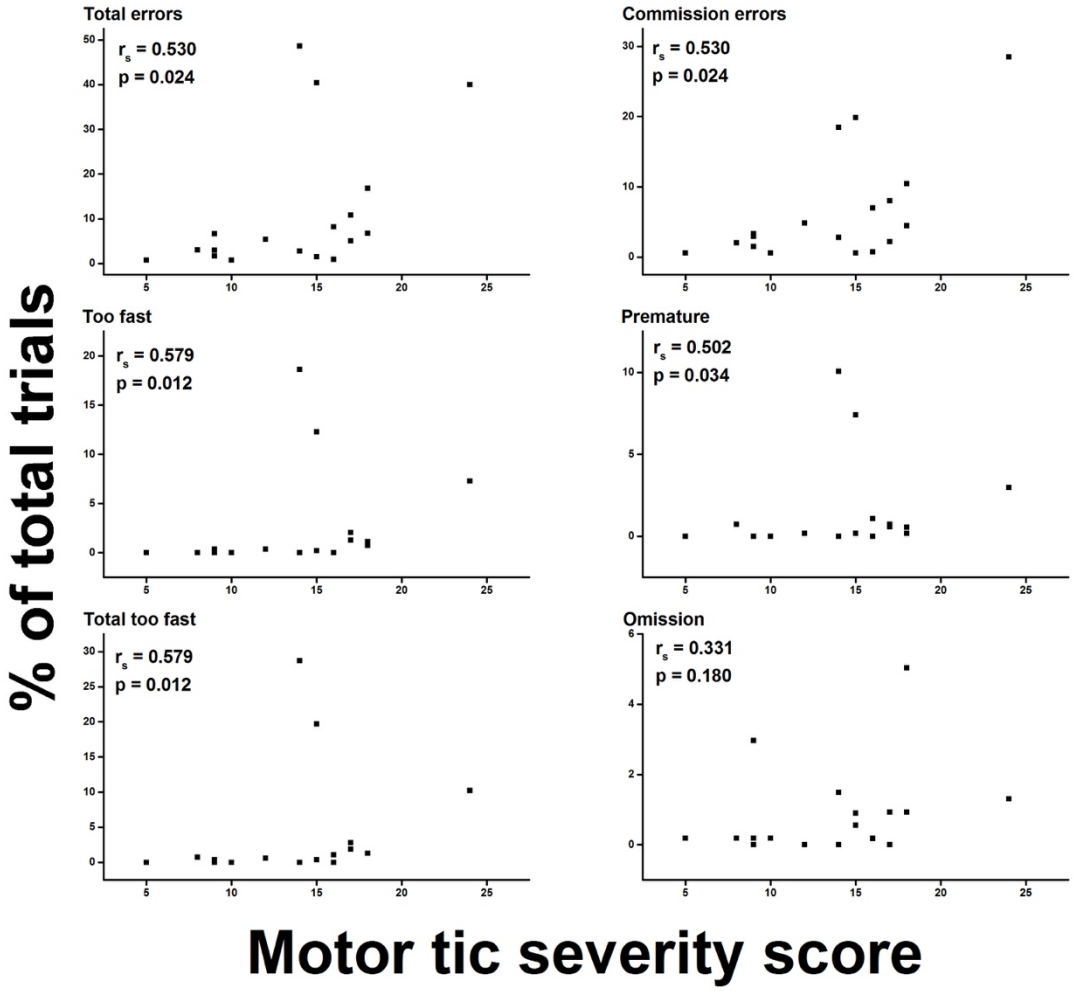

Figure 5.6: Spearman's rank correlation coefficients between error types in the masked priming task and motor tic severity score measured by the Yale Global Tic Severity Scale.

Each subplot plots the number of errors as a percentage of the total trials (y-axis) against motor tic severity score (x-axis), for each error type. Spearman's rank correlation coefficient is shown for each comparison and p values are reported for each correlation.

5.4 Discussion

5.4.1 Proactive inhibition is retained in Tourette syndrome and patients with tic disorders

In this chapter, we sought to establish whether there were any behavioural deficits in patients with TS or a tic disorder by employing the CSST to probe proactive and reactive inhibition. Our patient population displayed intact proactive and reactive inhibition, indexed by the RDE and SSRT, respectively. The pattern of the RDE follows similarly to that found in healthy controls; the magnitudes were comparable to those found in Chapter 4. Although SSRT was greater than our patient population compared to our healthy controls, patients successfully inhibited their responses on significantly more than 50% of stop trials and hence the results must be interpreted with caution. As the dynamic tracking algorithm is supposed to converge upon 50% successful inhibition, the finding suggests that patients did not perform the task properly, perhaps waiting too long on critical trials. However, the magnitude of the RDE is comparable to that in Chapter 4, suggesting that this is not the case. Instead, it may be the case that patients were generally slower than healthy controls alltogether; their non-critical go trials were also slower than that of control subjects. Due to longer go reaction times in our patient population, it may be the case that the SSDs used in this experiment were not appropriate at probing reactive inhibition. An improvement would be to use SSDs that were tailored to the go reaction times of each subject – that is, have SSDs that are proportions of the go reaction time. From these results, we can conclude that proactive inhibition in our clinical population is unaffected, due to the presence of an RDE, that is of similar magnitude to healthy control subjects. However, due to errors in experimental design, we cannot make any confident conclusions regarding how reactive inhibition is modulated in patients. The finding of

intact proactive inhibition is unsurprising seeing as tics are considered by some to be different from voluntary movements (210,211,213) and voluntary movement control.

5.4.2 Normal principles of movement preparation and execution when stopping might be required are retained in Tourette syndrome and tic disorders

In Chapter 4, we saw that movement preparation occurs slower when stopping might be required. In contrast, movement execution is equivocal regardless of the stopping requirements. Due to the observation that pre-movement activity is absent during tics and because of the hypothesised breakdown in proactive and reactive inhibition, we predicted that these putative signatures of movement preparation and execution may be altered in TS and tic disorders.

We found that movement preparation and execution evolved in the same way as in healthy controls. That is, movement preparation increased later when stopping was required but movement execution was the same between critical and non-critical go trials. Indeed, interrogation of the strategy used during movement preparation with DDM analyses revealed that boundary separation was raised when stopping might be required, a feature seen in the healthy control data in Chapter 4. We also noted that non-decision time decreased when stopping might be required, which should result in faster reaction times. Although this seems counterintuitive, we anticipate that this is a mathematical consequence of the DDM to explain the observed data (61,214); non-decision time varies as a consequence of drift rate to compensate for tails of the reaction time distribution (217). In the Introduction, we hypothesised that tics may be a consequence of heightened motor preparation, which decreases the amount of activity required to reach the perceptual threshold and trigger movement. However, this hypothesis seems implausible in the light of the independence of movement preparation and execution – reaching the perceptual threshold does not necessarily trigger movement. A caveat to this hypothesis to explain tics would be if the processes of movement preparation and execution were indeed coupled in TS and tic disorders. If this was the case, then we might expect processes of

movement preparation, such as changes in boundary separation, to be reflected within M1 during both cue-locked and response-locked analyses. However, no such relationship was seen. In fact, the pattern of movement preparation and execution during potential stopping was the same as that seen in healthy controls, thereby indicating that the processes of movement preparation and execution were still independent in TS and tic disorders.

5.4.3 Movement preparation and execution are very similar in patients relative to controls

After finding that these signatures of movement preparation and execution behaved in the same way as in healthy controls, and that they were still independent, we next investigated whether these processes differed relative to healthy control subjects.

We used the stimulus-locked analysis to compare the rise in CSE during trials when stopping might be required between our patient population and healthy control subjects. We observed that this rise in excitability increased at a slower rate in patients than controls, which suggested that there was a slower rise to threshold in patients than controls. If this was a true suppression, then we expected to see an effect when the reaction times were controlled for. Consequently, we performed a response-locked comparison of CSE prior to movement for our patients and controls. This analysis showed that that the rise of excitability prior to movement was remarkably similar between our two groups. We therefore concluded that movement did not occur as a slower rise to threshold in TS and tic disorders. Indeed, the reaction time differences between groups for both critical and non-critical go trials was approximately 90 ms, which we hypothesise solely accounted for the difference in CSE rise time.

It has been reported by Draper et al. (168) that M1 excitability prior to movement reaches a lower level than healthy control subjects. However, we found no difference between pre-movement M1 excitability between patients and controls. It has been suggested that impairment of basal ganglia-thalamic-cortical circuits in TS gives rise to cortical hyperexcitability (133,218), which normalises as tic control is improved with age. The

study performed by Draper et al. was done so in a group of adolescents with TS. As previously mentioned, tic control generally improves with age (219–221) and so the results of the cited study (168) may not be directly applicable to our adult population; it may be the case that our older, adult population has had more time for corticospinal excitability to normalise. It may be the case that successful CSE suppression determines the extent of tic control.

5.4.4 Automatic inhibition is impaired in patients with Tourette syndrome and tic disorders

We hypothesised that tics in TS and tic disorders may arise as a consequence of failed automatic inhibition – an inability to suppress stimuli, which evokes motor activity. Using the masked priming task, we explored both positive and negative priming in TS and tic disorders. Patients exhibited normal positive priming indexed by the PCE at all reported timepoints in the literature. However, the NCE, a marker of automatic inhibition, was absent in our population of patients. However, data from our control subjects failed to show any significant compatibility effects, making interpretation of the findings in patients, difficult. To resolve this, we turned to analysis of the errors made, finding that patients made more errors than control subjects. On further inspection of these errors, patients made more commission, fast and premature errors, all of which point towards patients failing to inhibit the prime. If this was the case, we expected commission errors to be more likely for incompatible prime-target combinations than compatible ones. Indeed, we showed that commission errors were more prevalent on incompatible trials, consistent with the hypothesis that the prime was not inhibited in our patient group. Of course, these effects could be observed if patients and controls prioritised speed or accuracy due to the speed-accuracy trade-off. To investigate whether this was the case, we showed that the reaction times between patients and control subjects were equivocal, thereby ruling out that errors arose due to the patient group prioritising speed over accuracy. To our knowledge, this is the first study showing an impairment of automatic inhibition in TS and tic disorders.

The neural correlates of subliminal positive and negative priming are of interest here. As mentioned in the Introduction, the prime-mask combination induces a biphasic, positive-then-negative deflection in the lateralised readiness potential (LRP) measured by electroencephalography (43,48). The NCE in the masked priming task is associated with target stimuli, which arrive during the negative phase of the biphasic LRP. Although we did not measure the LRP in this study, it would be interesting to see whether the negative phase still existed in patients with TS and tic disorders. We would predict the lack of any substantial negative or positive LRP, as a constant positive LRP, which does not decay, would expect to show positive priming effects across all SOAs. In fact, it is surprising that our patients show positive priming effects either side of the time period implicated in the NCE (100-150 ms). This observation provides a strong case for implicating a specific failure of automatic inhibition in TS and tic disorders.

As mentioned in the Introduction, the inhibitory phase seen during the masked priming task is viewed as a consequence of motor activation exceeding a specific threshold; motor activation not reaching this threshold will not trigger inhibition. This raises an interesting point, that the absence of the NCE in our patients could be due to impaired inhibitory mechanisms following sufficient motor activation, insufficient motor activation to trigger inhibition or a higher threshold to trigger motor inhibition. As we observed strong positive priming effects, the possibility that motor activation was not sufficiently strong enough, becomes unlikely. From our data, we are unable to disentangle whether the absence of the NCE is due to impaired putative inhibitory mechanisms or a raising of the threshold required to trigger automatic inhibition. However, this threshold-dependent inhibition has been thought to prevent obligatory responding to sensory cues and is therefore considered a form a noise protection. Overlaying this idea onto the motor noise hypothesis, which poses that patients with TD have excessive neural noise in their motor system, suggests that this excess noise might be due to an inability to implement this form of noise protection (due to failed automatic inhibition).

Priming responses in TS have been explored before using a visuospatial priming task (VSP). The task contains two trials, a prime and a probe. In the prime trial, two stimuli (a distractor and target) at two different locations. In the probe trial subjects are presented with the target stimulus. If the target in the probe trial occurs in the same place as the distractor in the prime trial, then a negative effect on performance is observed i.e. reaction times are longer. Conversely, if the target appears in the probe trial appears in the same place as the target in the prime trial, then a positive effect on performance is seen i.e. reaction times are shorter. These two effects are believed to reflect negative and positive priming, respectively. In the context of TS, it has been shown that negative priming is impaired whereas positive priming is enhanced (222,223). Whilst these results may seem similar to ours, there is a crucial difference. The prime in the VSP is displayed for 400 ms and hence the prime is consciously perceived and processed by the subject. On the other hand, primes in the masked priming task are only shown for 17 ms and are hence subliminal – they are not consciously perceived by the subject yet still have influences on behaviour. Considering this, the masked priming task and hence its findings, are more consistent with reflecting automatic inhibition than the volitional, inhibitory control and processing of the prime in the VSP (224,225). It may be the case that automatic (as opposed to volitional) selection and inhibition of a movement accesses different neural mechanisms, akin to a reflex. Indeed, reactive (207,226,227) and volitional (226,228,229) movements are highly dependent on circumstance. Furthermore, the finding of impaired automatic inhibition in the masked priming task is an encompassing hypothesis to explain tic generation, that does not rely on premonitory urges being present. This is also concordant with the finding that premonitory urges do not correlate with tic severity or inhibitory control and may be independent processes (230). Nevertheless, these findings of absent negative priming in the VSP are complementary to our own in that there seems to be an aberrancy in inhibitory sensory processing.

Perhaps our most compelling finding to implicate an impairment of automatic inhibition as a mechanism of tic generation is the positive correlation between those errors

associated with impaired automatic inhibition and clinical measures of motor tic severity. Importantly, this association was specific for automatic inhibition errors; omission errors were not correlated with motor tic severity. The neural substrate for this failure in automatic inhibition is currently unknown, although the putative network implicated in masked priming tasks has been shown to involve a cortico-subcortical network, including the medial prefrontal cortex and striatum (17,18). Our findings support a role for a deficit in automatic inhibition when this putative network is mapped onto the neurological deficits in TS of the frontal lobes and basal ganglia (striatum) (168,231).

5.4.5 Limitations

It is widely known that TS can coexist with comorbid conditions such as OCD and ADHD. However, not all patients exhibit OCD or ADHD. As such, the presence of these conditions might confound our results. To account for this, our analyses accounted for the OCD and ADHD status of our subjects. However, subjects were only asked whether they had a formal diagnosis of OCD or ADHD. This could prove problematic as undiagnosed OCD or ADHD could go unrecognised and hence exacerbate unmeasured confounders into our study. Furthermore, our approach of assessing OCD and ADHD was binary – patients either had the condition or did not. Perhaps a better approach would have been to use severity scales for each disorder, such as the Yale-Brown Obsessive-Compulsive Scale or ADHD rating scale. Doing so would enable us to treat each co-morbidity as a continuous measure of differing severities.

5.5 Conclusions

In this chapter, we sought to answer why patients with TS and tic disorders, tic. We hypothesised tics may be due to failures in proactive, reactive or automatic inhibition. Having previously established the independence of motor preparation and execution, we also hypothesised that this might be erroneously coupled in TS and tic disorders, such that motor preparation was more likely to lead to overt movement. Our experiments showed that proactive inhibition was retained within our patient population. Furthermore,

patients displayed normal independence of motor preparation and execution. Compared to healthy controls, our patients exhibited remarkably similar profiles of pre-movement CSE, indicating that patients with TS or tic disorders do not have an abnormally excitable motor output. The findings from the DDM analyses, M1 TMS and CSST all point toward a conclusion that voluntary aspects of movement generation and inhibition are normal in patients with TS and tic disorders. Conversely, automatic inhibition was impaired in patients with TS and tic disorders. This was indexed by multiple lines of evidence, such as the absence of an NCE and errors, which were consistent with a failure to inhibit the subliminal prime. Interestingly, these errors associated with impaired automatic inhibition were all positively and significantly correlated with clinical measures of motor tic severity and hence provides a compelling case for impaired automatic inhibition as a mechanism for tic generation.

6 Effect of Ropinirole on Motor Response Inhibition

6.1 Introduction

In some pathological scenarios such as schizophrenia (232), addiction (233) and attention deficit hyperactivity disorder (234), there is a breakdown in response inhibition, which has encouraged a drive to further understand the neurochemistry mediating response inhibition. Interestingly, use of dopamine agonist medication in Parkinson's disease (PD) has been shown to predispose to impulse control disorders (ICD) in some patients, manifesting as excessive shopping, gambling and hypersexuality. Consequently, a role for dopamine as a mediator of behavioural inhibition may therefore be indicated. A network involving the basal ganglia, right inferior frontal gyrus and pre-supplementary motor area has been implicated in mediating stopping in behavioural tasks employed to probe reactive and proactive inhibition. Seeing as dopamine is a key player in modulating activity in these regions, it seems plausible to study dopamine as a candidate neurotransmitter in response inhibition (235,236). Positron emission tomography of D2 and D3 receptors in humans has shown that their activity is negatively correlated with the speed of response inhibition and positively correlated with inhibition related functional magnetic resonance imaging activation in the fronto-striatal stopping network (237). Furthermore, infusions of a selective D1 receptor antagonist into rat striatum improves indexes of reactive motor inhibition, whereas infusions of a D2 receptor antagonist impairs it (238). In humans, administration of the dopamine and noradrenaline reuptake

inhibitor, amphetamine, increases D2 receptor expression and improves measures of reactive inhibition (239).

In spite of the link between D1/D2 receptors, response inhibition and impulsivity (240), an association between D3 receptor activity of dopamine agonists and ICD generation in PD has been found, with pramipexole and ropinirole being two agents both with relatively high D3 affinity compared to other dopamine agonists and greatest risk of ICD generation in clinical practice (128,131). The link between use of dopamine agonists with relatively high D3 affinity and response inhibition remains limited and only reactive inhibition has been explored (241,242). Proactive inhibition, on the other hand, has not been investigated under the influence of these agents. As we wanted to investigate the specific role of dopamine agonists in motor response inhibition in a future experiment, we first wanted to understand what the role of dopamine agonists was in response inhibition, in a population of healthy subjects.

To this end, we devised a randomised, double-blind, placebo-controlled trial to investigate both reactive and proactive inhibition under the influence of a dopamine agonist with relatively high D3 affinity, in healthy human subjects. Importantly, we used a variation of the stop-signal task, the conditional stop-signal task (CSST), to specifically investigate proactive inhibition. We chose the dopamine agonist, ropinirole, which was commonly used clinically and implicated in the generation of ICDs. Ropinirole directly activates dopamine receptors with a relatively high affinity for D3 receptors (243,244) and hence is a suitable candidate to explore the effect of dopamine agonists on motor response inhibition.

6.2 Methods

6.2.1 Participants

30 healthy volunteers (20 male) aged 19-30 (mean age 23.63, SD 3.64) participated in this experiment. A power calculation showed that 30 subjects would be needed to show

a 20% reduction of the RDE under ropinirole, assuming an intraclass correlation coefficient of 0.655 with 80% power at an alpha level of 0.05. study was approved by University College London Ethics Committee and subjects were recruited from University College London. Subjects were screened beforehand for any contraindications to ropinirole and were excluded if they had any.

6.2.2 Conditional Stop-signal task

Participants were asked to perform both four blocks of the CSST, which has already been outlined in the Methods. Each block consisted of 102 go trials (51 critical, 51 non-critical) and 34 stop trials (17 critical and 17 non-critical).

Behavioural measures taken included Critical Go reaction time, Non-critical Go reaction time, Stop Respond reaction time (reaction time on failed stop trials), average SSD, p(inhibit) (proportion of correct stop trials) and response delay effect (reaction time difference between critical go and non-critical go trials). The response delay effect is the behavioural index of proactive control, as stopping is required during critical go trials, but no in non-critical go trials. We also calculated the SSRT using the integration method.

6.2.3 Protocol

Informed consent was obtained using an information sheet and verbal communication to take part in the study. Importantly, subjects were excluded if they had any contraindications to ropinirole or fell outside of the age limits (18-30). They were brought into the laboratories and asked to perform one block of the CSST, acting as a practice block. Subjects were then given one of two pills (ropinirole 1mg or placebo), which were blinded to both the subject and experimenter by concealed bottles (a third-party investigator, not part of the experiment, knew the identity of the pills). The pill given was selected using a random number generator. The subject stayed in the room for one hour, a time period consistent for ropinirole to reach an appropriate blood level to have CNS effects (245,246). Following this, the subject performed four blocks of the conditional

stop signal task: two in the critical direction in the right direction and two in the critical direction in the left direction. The order of these blocks was also randomised. After at least 48 hours, the subject returned to the laboratories and underwent the same protocol as session one, except with the other pill.

6.2.4 Drift-diffusion modelling

The drift-diffusion model (DDM) was used to investigate the strategic effects on task performance in the CSST, when stopping may be required. We also used the DDM to investigate how ropinirole modulated decision-making parameters during the CSST.

For each participant, we used the DMAT toolbox (67) to estimate DDM parameters. We allowed the drift rate, boundary separation and non-decision time to vary between context (critical vs non-critical). Starting point was set to half of the boundary separation seeing as left/right go cues could appear with equal probability. To maximise available data for the model, we combined all four blocks per drug condition by labelling trials as critical and non-critical, independent of whether they were right or left-handed responses.

6.2.5 Data analyses

A two-way repeated measures ANOVA with factors DRUG and BEHAVIOURAL MEASURE was performed to investigate whether there was any effect of ropinirole on the recorded behavioural measures. Following this, paired t-tests were performed to further investigate any significant interactions. In particular, we compared the response delay effect and go discriminations errors between ropinirole and placebo to investigate the effect of dopamine agonist modulation on proactive inhibition.

After performing the DDM analyses, we performed a three-way repeated measures ANOVA with factors: DRUG (ropinirole or placebo), RULE (critical or non-critical) and PARAMETER (drift rate, boundary separation and non-decision time). Paired t-tests were between critical and non-critical DDM parameters to assess whether there were any differences in strategy between contexts. To investigate how ropinirole was exerting its

effects on decision-making strategy we compared the critical DDM parameters between ropinirole and placebo, using paired t-tests.

6.3 Results

6.3.1 Behavioural measures

Behavioural measurements are shown in table 6.1. There was an expected go reaction time difference between critical and non-critical trials (response delay effect) due to the anticipation to stopping in critical trials (placebo: $t = 10.995$, $p < 0.001$, $d = 0.99$, 95% CI [0.44 – 1.51]; ropinirole: $t = 3.781$, $p = 0.001$, $d = 0.87$, 95% CI [0.33 – 1.39]).

Measure	Measure description	Drug	
Critical direction		**Placebo**	**Ropinirole**
Go	RT to go stimulus in the critical direction	456.94 (73.97)	460.53 (76.30)
p(inhibit)	% correct inhibition	58.08 (15.57)	53.92 (14.47)
Stop Respond	RT on failure to stop trials	406.00 (65.76)	428.65 (71.70)
Go error	% of discrimination errors	0.60 (0.72)	1.06 (1.19)
Stop signal delay	Delay between go and stop signals	188.82 (33.32)	176.34 (32.25)
SSRT	Calculated time taken to abort response	276.29 (83.68)	279.81 (75.65)
Non-critical direction			
Go	RT to go stimulus in the non-critical direction	386.62 (75.35)	402.00 (75.64)
Other variables			
Response delay effect	(Critical go) - (Non-critical go) RT	70.32 (35.00)	58.53 (30.78)

Table 6.1: Behavioural measurements from the Conditional Stop-signal task performed in subjects on placebo and ropinirole.

The table shows the behavioural measures from the CSST. Measures are accompanied by SD in brackets. Reaction times are given in milliseconds.

6.3.2 Boundary separation is increased, and non-decision time decreased when stopping may be required

The DMAT toolbox (67) was used to investigate the mechanisms of decision making between drug conditions, by estimating drift-diffusion model parameters for critical and non-critical trial reaction times. Because the critical direction changed between blocks, we grouped trials by whether they were critical or non-critical, irrespective of the hand used to respond. The parameters estimated were: boundary separation, drift rate and non-decision time, all others were held fixed and starting point was set at half of boundary separation. Figure 6.1 shows individualised parameter estimation for each parameter.

A three-way repeated measures ANOVA revealed a significant effect of DRUG ($F(1, 29) = 5.271$; $p = 0.029$, $\eta^2 = 0.154$) and PARAMETER ($F(2, 58) = 119.83$; $p < 0.001$, $\eta^2 = 0.805$) but not RULE ($F(1, 29) = 0.742$; $p = 0.396$, $\eta^2 = 0.025$). We also found a trending DRUG*PARAMETER ($F(2, 58) = 3.727$; $p = 0.051$, $\eta^2 = 0.114$) and significant RULE*PARAMETER ($F(2, 58) = 14.994$; $p < 0.001$, $\eta^2 = 0.341$) interaction. There was no significant three-way interaction ($F(2, 58) = 1.605$; $p = 0.216$, $\eta^2 = 0.052$).

We showed that boundary separation was greater (placebo: $t = 7.389$, $p < 0.001$, $d = 1.71$, 95% CI [1.10 – 2.27]; ropinirole: $t = 4.076$, $p < 0.001$, $d = 1.08$, 95% CI [0.53 – 1.61]) and non-decision time was lower (placebo: $t = -6.063$, $p < 0.001$, $d = 1.49$, 95% CI [0.90 – 2.04]; ropinirole: $t = -3.522$, $p < 0.001$, $d = 0.92$, 95% CI [0.37 – 1.44]) during critical trials, when stopping was required. Drift rate (placebo: $t = -0.879$, $p = 0.387$, $d = 0.21$, 95% CI [-0.30 – 0.72]; ropinirole: $t = -0.903$, $p = 0.374$, $d = 0.21$, 95% CI [-0.30 – 0.72]) was not significantly modulated between conditions.

6.3.3 Ropinirole impairs proactive inhibition and induces more commission errors

We performed a two-way repeated measures ANOVA to explore whether there were any significant interaction of drug and variable. We found a significant effect of BEHAVIOURAL MEASURE ($F(7, 203) = 499.59$; $p < 0.001$, $\eta^2 = 0.945$), but not

DRUG ($F(1, 29) = 2.708$; $p = 0.111$, $\eta^2 = 0.085$), nor a DRUG*BEHAVIOURAL MEASURE interaction ($F(7, 203) = 3.325$; $p = 0.083$, $\eta^2 = 0.100$). Although there was no significant effect of drug or an interaction, our prior hypothesis led us to conduct an exploratory analysis to measure the effect of ropinirole on proactive and reactive inhibition. To this end, we performed a paired t-test between the response delay effect for placebo and ropinirole. We found that ropinirole reduced the magnitude of this stopping adaptation ($t = 2.249$, $p = 0.032$, $d = 0.36$, 95% CI [-0.16 – 0.86]). The SSRT is a measure of reactive inhibition; it is the hypothesised time taken for stopping to occur. A paired t-test between the SSRTs between drug conditions showed that reactive inhibition was unchanged on ropinirole ($t = 0.294$, $p = 0.770$, $d = 0.04$, 95% CI [-0.55 – 0.46]). We also found that under the influence of ropinirole, subjects made more go discrimination errors than when on placebo ($t = 2.291$, $p = 0.029$, $d = 0.47$, 95% CI [-0.05 – 0.98]).

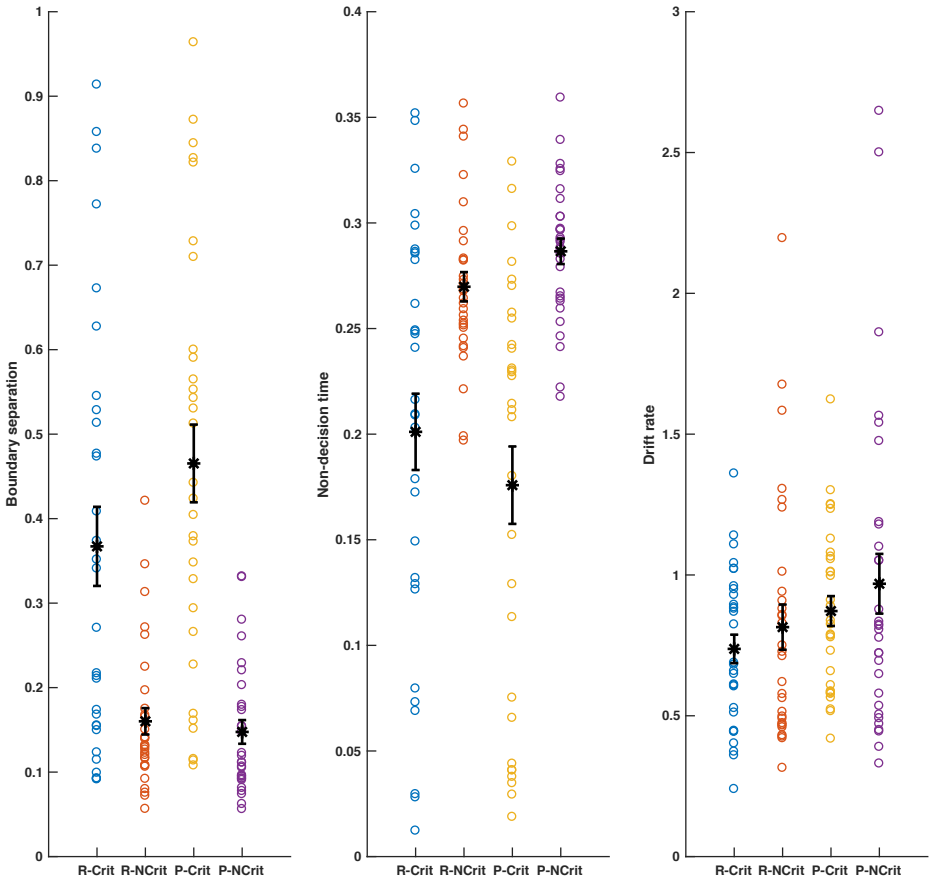

Figure 6.1: Drift-diffusion model parameters for the Conditional Stop-signal task between critical and non-critical trials.

Estimated DDM parameters are shown for individual subjects, for boundary separation, non-decision time and drift rate, for critical and non-critical go trials. X-axis labels refer to drug x condition combinations such that R- refers to ropinirole and P- to placebo. Black stars represent mean parameter estimation, whilst error bars reflect SEM.

6.3.4 Change in boundary separation is smaller under the influence of ropinirole

We next compared how response strategies were modulated by ropinirole. We calculated the change in each DDM parameter between critical and non-critical conditions for both ropinirole and placebo conditions. This difference in DDM parameters represents the adaptation made when stopping may be required. Paired t-tests revealed that the change in boundary separation between non-critical and critical go trials was less under the influence of ropinirole ($t = -2.202$, $p = 0.036$, $d = -0.43$, 95% CI [-0.94 – 0.09]). Drift rate ($t = 0.186$, $p = 0.854$, $d = 0.04$, 95% CI [-0.47 – 0.54]) and non-decision time were not statistically significantly modulated under the influence of ropinirole ($t = 1.811$, $p = 0.080$, $d = 0.41$, 95% CI [-0.11 – 0.91]).

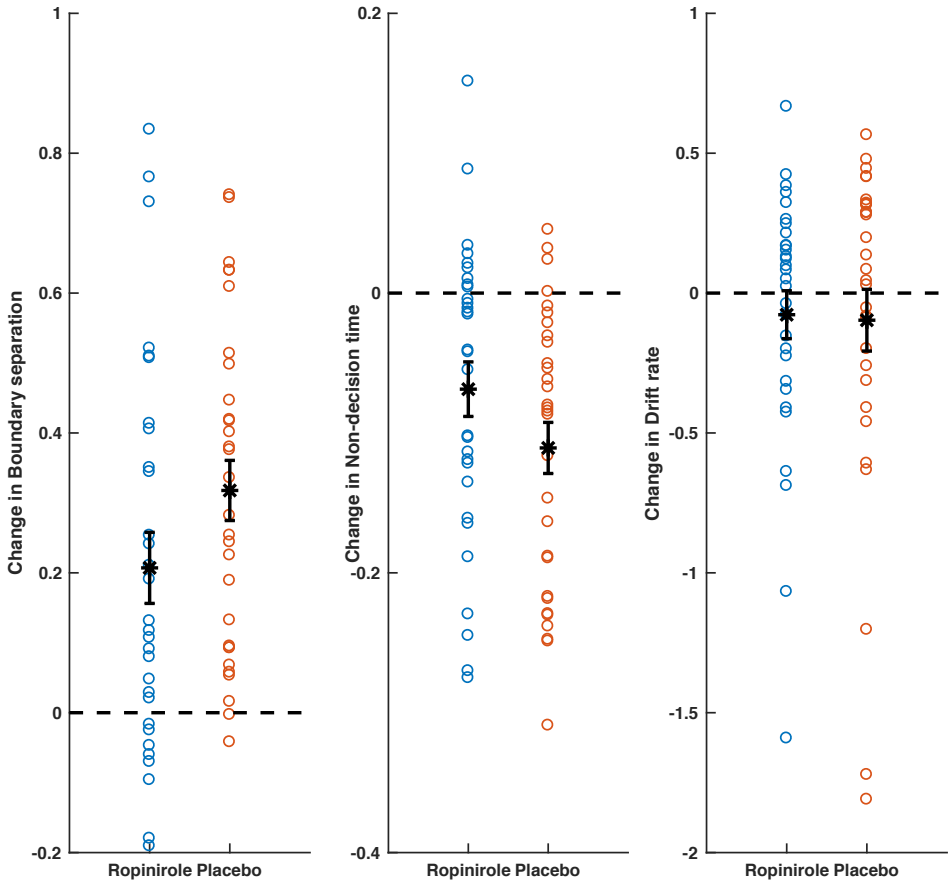

Figure 6.2: Adaptation in Drift-diffusion model parameters between non-critical and critical go trials, for ropinirole and placebo.

Difference between non-critical and critical DDM parameters are shown for individual subjects, for boundary separation, non-decision time and drift rate. Change represents the adaptation made when stopping may be required. Black stars represent mean parameter estimation, whilst error bars reflect SEM. Dashed lines represent no change in parameter estimation between non-critical and critical go trials.

6.4 Discussion

6.4.1 A single dose of ropinirole may impair motor response inhibition in healthy subjects

Here we present data showing how proactive and reactive inhibition are modulated during administration of ropinirole, a dopamine agonist with relatively high D3 activity. The data show that proactive inhibition is impaired with administration of ropinirole, indexed by a significant decrease in the RDE. Reactive inhibition, on the other hand, is unaffected by ropinirole administration. This was accompanied by an increase in the number of commission errors made when on ropinirole – a rather surprising finding seeing as the imperative stimuli are unambiguous, although it has been reported that dopamine replacement in PD results in more commission errors on a random moving dots task (247). A role of ropinirole in response inhibition has been previously explored in healthy adults of typical PD onset age. In this study, subjects were randomised to receive a placebo, 0.5 mg or 1 mg of ropinirole and asked to perform tasks of response inhibition, the SST being one. Interestingly, this group also genotyped their subjects to form a dopamine genetic risk score, which indexed basal dopamine neurotransmission. They found that ropinirole modulated response inhibition dependent on their genetic risk score, such that ropinirole improved reactive inhibition in those with a low genetic risk score but impaired it in those with a high genetic risk score. The group concluded that, as others have (248,249), dopamine follows an inverted-U shape with impulse control (242). Whilst we did not measure our subjects' dopamine genetic risk score, our results reinforce the idea that dopamine agonists can modulate motor response inhibition.

6.4.2 Ropinirole impairs increasing of boundary separation when stopping might be required

We next investigated the strategy that subjects employed when stopping might be required. Under both ropinirole and placebo, our subjects decreased their non-decision time and increased their boundary separation when stopping might be required, the latter

a feature seen both in previous chapters in this thesis and reported in previous literature (11). We then asked what specific effects ropinirole administration had on changes in strategy when stopping might be required. We found that ropinirole impaired the ability to adjust boundary separation when stopping was potentially required. This finding was in keeping with the behavioural results, where a smaller RDE and a greater number of commission errors were observed. The effect of dopamine on strategic decision making has predominantly been investigated in the context of dopaminergic replacement in PD. In that case, it seems that dopamine administration induces more errors on tasks of perceptual decision making in the random moving dots task, but only when asked to prioritise accuracy over speed. Although this finding is similar to our own, the DDM analysis in the study showed a *decrease* in drift rate on medication, which they proposed reflected impaired sensory evidence accumulation (247). This finding is counterintuitive seeing as how a decrease in drift rate is more likely to result in fewer errors. Whilst the mechanism for errors is different from the one outlined in this chapter, there are key differences. For example, the study by Huang et al. used patients with PD, which may very well differ from healthy subjects off medication. Furthermore, the random moving dots task inherently varies its difficulty via coherence such that drift rate is varied across trials; in the CSST, the stimulus is unambiguous and hence drift rate can be considered rather constant. As we have repeatedly shown, boundary separation and non-decision time seem to be the predominant parameters modulated in the CSST. Lastly, the study performed in PD patients used levodopa equivalent daily doses as their measure of dopaminergic medication, rather than isolating the dopamine agonist, as we did. Perhaps a more applicable study to compare is the one by Beste et al. who used methylphenidate (MPH), a dopamine/noradrenaline reuptake inhibitor, to study perceptual decision making in healthy individuals using the random moving dots task. They found that administration of MPH significantly increased drift rates compared to placebo and showed that modulation of the dopaminergic system can selectively modulate sensory accumulation (250). These results seem to contradict those found in the study by Huang et al. but it must be noted that the effect of dopaminergic therapy in PD patients is likely

to be different to that in healthy controls. Furthermore, MPH is not selective for dopamine; it is well known that noradrenaline is a key regulator of response inhibition (10,143,144,236) and as such, the study by Beste et al. may be confounded by not accounting for this.

The speed-accuracy tradeoff is a feature of decision-making, whereby decisions that are made faster from experimental instructions suffer from decreased accuracy, whereas those that are more accurate are generally slower. The mechanisms by which this tradeoff occurs has been explained using DDMs, with increases in boundary separation results in greater accuracy and slower reaction times. Winkel et al. have investigated the role of a dopamine agonist, bromocriptine, on the speed-accuracy tradeoff using the random motion dots task. They failed to find an effect of bromocriptine on boundary separation in mediating the tradeoff (251). Crucially, the dopamine receptor affinity profile of bromocriptine differs from that of ropinirole; whilst both agents have a high affinity for D2 receptors, ropinirole has a relatively higher affinity for D3 receptors than bromocriptine. Interestingly, therefore, it may be the case that dopamine does indeed have the potential to mediate the speed-accuracy tradeoff via D3 receptors. These studies and our own highlight that the role of dopamine in perceptual decision making is complex, with interactions between pathological and healthy individuals, neurotransmitter specificity and design of behavioural tasks.

6.5 Conclusions

Our results provide evidence that an acute dose of ropinirole selectively impairs proactive motor response inhibition in a population of healthy subjects. The results of the DDM support that strategic decision making under conditions where stopping might be required, may underlie the deficits observed in the behavioural data. Considering that an acute dose of ropinirole can impair motor response inhibition, one naturally questions what the effects of larger, chronic doses are. To that end, we next sought to investigate

the specific effects of dopamine agonists in a population of patients with Parkinson's disease.

7 THE SPECIFIC EFFECT OF DOPAMINE AGONISTS ON BEHAVIOURAL INHIBITION IN PARKINSON'S DISEASE

7.1 Introduction

In Chapter 6, we found that an acute dose of ropinirole, a dopamine agonist, impaired proactive inhibition in a group of healthy subjects. We also noted that ropinirole impaired the putative increase in boundary separation that comes when stopping might be required. Consequently, we were next interested in what larger, chronic doses of a dopamine agonist could have on motor response inhibition. As this is not feasible in healthy subjects, we made use of a clinical population with such practices.

Patients on dopaminergic agonist medication, such as those with Parkinson's disease (PD), can exhibit impulse control disorders (ICD) (4,126). These include compulsive gambling, shopping, sexual behaviour and eating, with the incidence reported to be approximately 17% (126). ICD incidence may be considered small, but the clinical impact can be devastating. Reports of patients gambling away their life savings or exhibiting unsociable behaviour and breakdown of relationships, highlights this problem. Furthermore, the incidence of ICDs is probably underestimated; ICDs are only recorded once an event, such as those described, has occurred. In fact, there are probably more patients exhibiting ICD-like behaviour on dopaminergic therapy, but who have not yet committed an act worthy of reporting. With the role of dopamine agonists extending

beyond PD, such as for the treatment of restless leg syndrome, an understanding of how dopamine agonists predispose to ICDs is key.

It is known that ICDs in PD are more likely on dopamine agonist medication than on levodopa therapy, despite both acting to increase available dopamine in the basal ganglia. Interestingly, it is becoming apparent that dopamine agonists are not born equal in their ability in inducing ICDs – some confer a greater risk than others. Explanations for this heterogeneity have proposed that ICD generation depends on the specific dopamine receptor subtype that the drug acts on (131).

Current theories of ICD generation in PD revolve around failures in behavioural inhibition (8). Behavioural inhibition is a key component of normal human functioning, serving to suppress inappropriate or unwanted actions. Different types of behavioural inhibition are employed depending on the contextual demands. For example, reactive inhibition is called upon when applying the brakes of a car if a person walks out into the middle of the road. It is cued by external events and requires rapid cancellation of ongoing motor activity. Proactive inhibition is a prospective and goal orientated type of behavioural inhibition. It is concerned with responding under restraint, for example, driving slower than normal around a school in anticipation of children running out into the road. Using these examples, one can imagine that these different types of inhibition act synergistically, rather than independently, to enhance behavioural inhibition. That is, engagement of proactive inhibition enhances efficacy of reactive inhibition. In fact, a deficit in proactive inhibition has been proposed to underlie impulsivity seen in PD (8).

Studies exploring the breakdown in behavioural inhibition hypothesis have shown a generalised failure in response inhibition (6,21,26,139,150,252,253) in PD. However, a crucial caveat to these studies is that they do not make a distinction between levodopa and dopamine agonist medication. Bearing in mind that ICD generation is much more likely with dopamine agonist medication, rather than levodopa administration, treating these two drugs as equal in studies of behavioural inhibition, seems erroneous. Furthermore, most studies assessing motor response inhibition use the stop-signal task to

do so, which measures reactive inhibition only. As such, the influence of dopamine agonists on proactive inhibition PD has not been assessed.

As we found in Chapter 5, patients with Tourette syndrome and tic disorders display a failure in automatic inhibition. Indeed, it has been shown that patients with PD also exhibit a breakdown in automatic inhibition (21,22,152), but like proactive and reactive inhibition, a dissociation between the effect of levodopa and dopamine agonists on automatic inhibition has not been made.

To this end, we designed a cohort study to investigate behavioural inhibition in PD patients on dopamine agonists vs those without dopamine agonist use. Primarily, this was performed as a pilot study, testing feasibility of further examining the effect of dopamine agonist use on motor response inhibition. Based on the results from Chapter 6 where an acute dose of a dopamine agonist could impair behavioural inhibition, we hypothesised that patients on a dopamine agonist would be similarly impaired, both in behaviour and in their ability to adjust strategy when stopping might be required. Furthermore, we hypothesised that patients on dopamine agonists would display impairments in automatic inhibition, indexed by more errors and an absence of the negative compatibility effect. We measured reactive and proactive inhibition using the conditional stop-signal task (CSST) and to measure automatic inhibition, we used the masked priming task.

7.2 Methods

7.2.1 Participants

14 patients diagnosed with PD (10 male) aged 55-78 (mean age 62.64, SD 5.93) participated in this experiment. The study was approved by University College London Hospitals Ethics Committee and subjects were recruited from clinics at The National Hospital for Neurology and Neurosurgery.

7.2.2 Protocol

The CSST was administered to patients in the same manner as described in Chapter 6. Informed consent was obtained using an information sheet and verbal communication to take part in the study. They were brought into the laboratories and asked to perform one block of the conditional stop-signal task, acting as a practice block. Following this, the subject performed four blocks of the conditional stop signal task: two in the critical direction in the right direction and two in the critical direction in the left direction. The order of these blocks was also randomised. Patients were also asked to complete three blocks of the masked priming task as outlined in Chapter 5 in order to assess automatic inhibition. Importantly, the end of the experiment required patients to complete the Questionnaire for Impulsive-Compulsive Disorders (QUIP) and they were asked to note down their PD specific medications. The levodopa equivalent daily dose (LEDD) was also calculated for each patient. We performed this at the end of the experiment to not bias ourselves at the beginning of the experiment.

7.2.3 Data analyses

We were mainly interested in the effect of dopamine agonists on behavioural inhibition in PD. To this end, we first divided out total patient cohort into two categories: those on a dopamine agonist and those without. An ANOVA between the behavioural measures collected during the CSST and group was conducted to assess whether there were any significant effects of dopamine agonist administration. After the results from Chapter 6, finding that an acute dose of ropinirole could affect proactive and reactive inhibition, we compared the response delay effect, SSRT and go discriminations errors between groups to investigate the effect of dopamine agonist medication on behavioural inhibition.

After performing the DDM analyses, we performed a three-way mixed repeated measures ANOVA with factors: GROUP (agonist or no agonist), RULE (critical or non-critical) and PARAMETER (drift rate, boundary separation and non-decision time). Paired t-tests between critical and non-critical DDM parameters were performed for each group to

assess whether patients were adjusting their decision making when stopping was potentially required. To investigate whether there were any differences in the strategy used to slow down in the face of potential stopping between groups, we conducted unpaired t-tests between groups and parameters.

After finding in Chapter 5 that patients with Tourette syndrome and tic disorders displayed a failure of automatic inhibition, we predicted that there may be a failure in automatic inhibition in our patient patients who were on dopamine agonists. Also, it has previously been reported that patients with PD display a failure in automatic inhibition as assayed by the masked priming task (21,22,152). To this end, we performed the same data analysis steps for the masked priming task described in Chapter 5, except we compared patients on a dopamine agonist vs those without dopamine agonist use. We also extended the time period for omissions from 1 s to 1.5 s to account for bradykinesia that patients may have.

7.3 Results

7.3.1 Clinical characteristics of patients with Parkinson's disease

Of the 14 patients who took part in this study, 7 were on a dopamine agonist. A one-way ANOVA showed no significant effects between patients on a dopamine agonist and those not, for age ($p = 0.171$, $F(1,13) = 2.120$), total QUIP score ($p = 0.571$, $F(1,13) = 0.339$) or LEDD ($p = 0.321$, $F(1,13) = 1.072$).

		QUIP Score						
Patient	Age	ICD	DDS	Other	Total	Specific ICD	Medication	LEDD
No Dopamine agonist								
1	59	2	0	0	2	Sexual behaviour	Rasagiline, sinemet	200
2	62	4	1	1	6	None	Sinemet, amantadine, rasagiline, opicapone, mirapexin	1350
3	68	0	0	1	1	Sexual behaviour	Sinemet	300
8	55	0	0	0	0	None	Rasagiline, sinemet	138
12	60	0	0	0	0	None	Sinemet	300
13	57	0	0	1	1	None	Madopar, rasagiline	500
14	62	0	0	1	1	None	Sinemet	150
Dopamine agonist								
4	63	5	0	2	7	Sexual behaviour, buying	Co-careledopa, ropinirole, rasagiline	860
5	78	0	0	0	0	None	Pramipexole, rasagiline, sinemet	715
6	65	1	1	2	4	Sexual behaviour	Sinemet, rasagiline, pramipexole	615
7	69	0	0	0	0	None	Ropinirole	240
9	58	0	0	2	2	None	Madopar, ropinirole, rasagiline, amantadine	915
10	62	1	0	0	1	Sexual behaviour	Pramipexole, sinement, rasagiline	750
11	59	2	0	0	2	Sexual behaviour	Ropinirole	240

Table 7.1: Clinical characteristics of patients with Parkinson's disease involved in this study.

Patients are categorised into whether they were on a dopamine agonist or not. Scores from the QUIP and subsections are shown, with specific ICD if patients had any. Scores are broken down by category as specified in the QUIP: ICD = Impulse control disorder, DDS = Dopamine dysregulation syndrome, Other = Other compulsive behaviour. Medications and the corresponding levodopa equivalent daily dose are given for each patient.

7.3.2 Experiment 1: Measuring proactive and reactive inhibition in patients with Parkinson's disease

7.3.2.1 Behavioural measures

Behavioural measurements are shown in table 7.2. There was an expected go reaction time difference between critical and non-critical trials (response delay effect) due to the anticipation to stopping in critical trials (no dopamine agonist: $t = 4.524$, $p = 0.004$, $d = 1.23$; dopamine agonist: $t = 2.723$, $p = 0.035$, $d = 0.38$). A one-way ANOVA between the two groups showed a statistically significant difference between the non-critical go reaction time only ($p = 0.047$, $F(1,13) = 4.915$). As we were specifically interested in the differences in behavioural inhibition between the two groups, we also report the statistics for behavioural measures of proactive and reactive inhibition. We found that there were

no differences between the groups in the RDE ($p = 0.153$, $F(1,13) = 2.333$) and SSRT ($p = 0.250$, $F(1,13) = 0.659$). Patients on a dopamine agonist also made more discrimination errors than those without agonist use., although this difference was not statistically significant ($t = 1.595$, $p = 0.137$, $d = 0.853$). Despite the lack of differences between our two groups, we hypothesised that dopamine agonist use might change the way patients were responding when stopping might be required. To investigate this, we conducted a DDM analysis on strategic decision-making.

Measure	Measure description	Group	
Critical direction		**No Dopamine Agonist**	**Dopamine Agonist**
Go	RT to go stimulus in the critical direction	612.18 (24.38)	687.61 (40.90)
p(inhibit)	% correct inhibition	58.74 (11.39)	58.07 (9.63)
Stop Respond	RT on failure to stop trials	600.83 (41.89)	604.24 (53.31)
Go error	% of discrimination errors	1.93 (0.63)	5.95 (2.44)
Stop signal delay	Delay between go and stop signals	189.39 (20.88)	195.28 (18.37)
SSRT	Calculated time taken to abort response	479.58 (155.59)	558.09 (202.10)
Non-critical direction			
Go	RT to go stimulus in the non-critical direction	534.57 (23.22)	645.34 (44.23)
Other variables			
Response delay effect	(Critical go) - (Non-critical go) RT	77.61 (17.15)	42.27 (15.52)

Table 7.2: Behavioural measurements from the Conditional Stop-signal task performed in patients with Parkinson's disease.

The table shows the behavioural measures from the CSST. Measures are accompanied by SD in brackets. Reaction times are given in milliseconds.

7.3.2.2 Drift-diffusion parameter estimation between patients on a dopamine agonist vs those without agonist use

We next sought to investigate whether there were any differences in decision making strategy between our two patient populations to assess the effect of dopamine agonist use in PD. We performed a mixed ANOVA with main factors GROUP, CONDITION and PARAMETER. This revealed a significant effect for PARAMETER only ($F(2, 24) = 8.287$, $p = 0.002$, $\eta^2 = 0.408$). Crucially, there were no significant interactions between GROUP and CONDITION ($F(1, 12) = 0.765$, $p = 0.399$, $\eta^2 = 0.060$) or

PARAMETER ($F(2, 24) = 0.628$, $p = 0.429$, $\eta^2 = 0.068$). We did notice that non-decision time seemed to be shorter in the group without agonist use and boundary separation tended to be greater. Curiously, these two findings would have opposite effects on the reaction time. We then decided to ask whether the change in parameters when stopping might be required was different on a dopaminergic agonist.

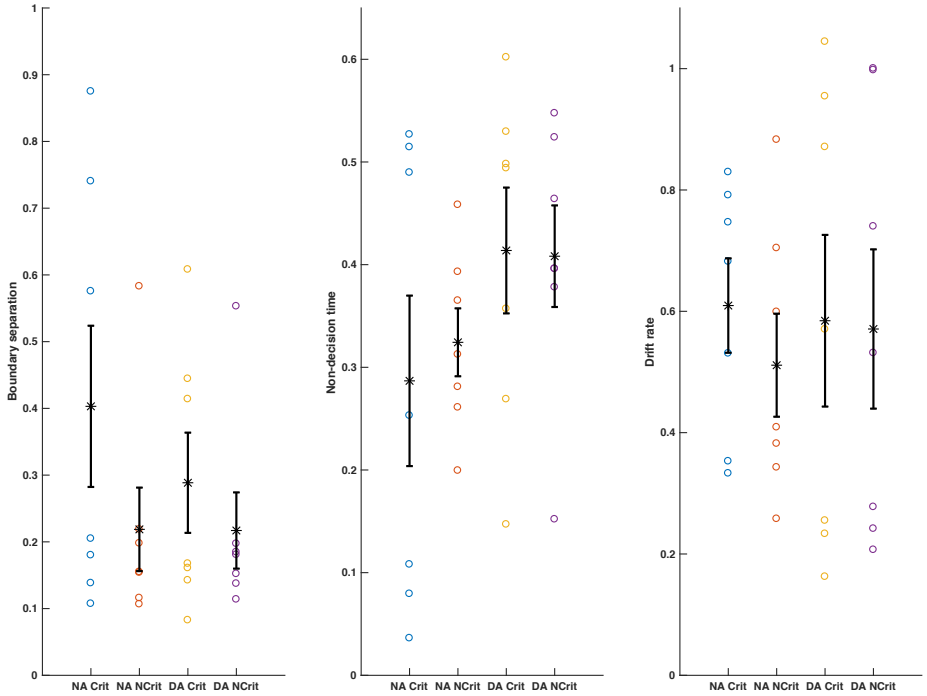

Figure 7.1: Drift-diffusion model parameters for the Conditional Stop-signal task.

Estimated DDM parameters are shown for individual subjects, for boundary separation, non-decision time and drift rate, for critical and non-critical go trials. X-axis labels refer to patient group x condition combinations such that NA refers to no dopamine agonist and DA to dopamine agonist. Black stars represent mean parameter estimation, whilst error bars reflect SEM.

7.3.2.3 Change in decision making parameters between patients on a dopamine agonist and those without, when stopping might be required

In Chapter 6, we found that ropinirole impaired the ability of subjects to increase their boundary separation when stopping might be required. To this end, we hypothesised that use of dopamine agonists in patients with PD may also impair adjustments in these parameters when stopping might be required. We calculated the change in each DDM parameter between critical and non-critical conditions for patients who were on a dopamine agonist and those who were not. This difference in DDM parameters represents the adaptation made when stopping may be required. A one-way ANOVA revealed no statistically significant differences between the change in boundary separation ($p = 0.559$, $F(1,13) = 0.362$), non-decision time ($p = 0.715$, $F(1,13) = 0.139$) or drift rate ($p = 0.395$, $F(1,13) = 0.779$) between groups, when stopping might be required.

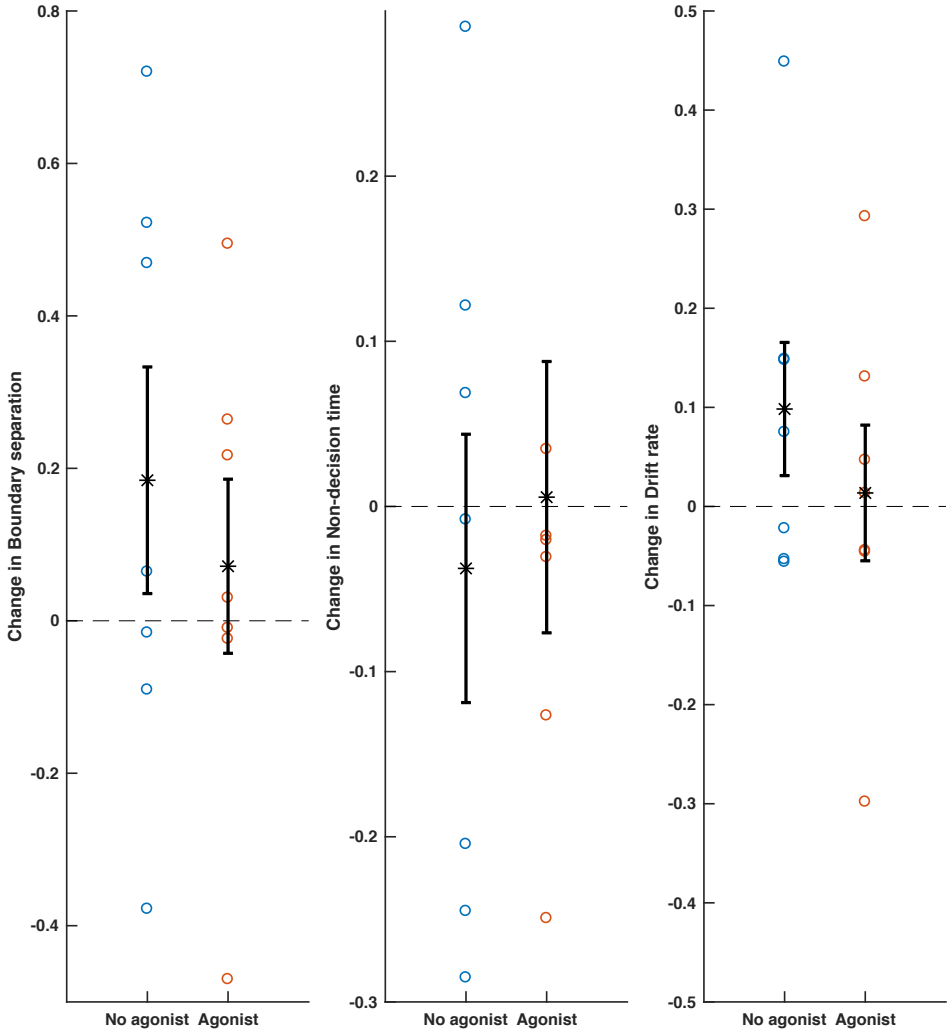

Figure 7.2: Adaptation in Drift-diffusion model parameters between non-critical and critical go trials, for patients with Parkinson's disease without dopamine agonist use and those with.

Difference between non-critical and critical DDM parameters are shown for individual subjects, for boundary separation, non-decision time and drift rate. Change represents the

adaptation made when stopping may be required. Black stars represent mean parameter estimation, whilst error bars reflect SEM. Dashed lines represent no change in parameter estimation between non-critical and critical go trials.

7.3.3 Experiment 2: Measuring automatic inhibition using the masked priming task

7.3.3.1 Reaction times for patients on a dopamine agonist are longer than those for patients not on an agonist

We performed a one-way ANOVA on the reaction times between the two groups for all 16 of the compatibility x SOA combinations. We found that reaction times for all combinations were significantly longer for patients on a dopamine agonist than those without (largest p-value of 0.009).

7.3.3.2 Compatibility effects for patients with Parkinson's disease

We next investigated whether positive and negative priming effects were present in patients with PD. For patients without dopamine agonist use a two-way repeated measures ANOVA with main factors TIME and COMPATIBILITY showed significant effects of TIME ($F(7, 42) = 28.61$; $p < 0.001$, $\eta^2 = 0.827$) but not COMPATIBILITY ($F(1, 6) = 1.590$; $p = 0.254$, $\eta^2 = 0.209$) or an interaction between the two ($F(7, 42) = 1.058$; $p = 0.407$, $\eta^2 = 0.150$). In patients with dopamine agonist use, we found similar effects: TIME ($F(7, 42) = 6.924$; $p < 0.001$, $\eta^2 = 0.536$) but not COMPATIBILITY ($F(1, 6) = 0.253$; $p = 0.633$, $\eta^2 = 0.040$) or an interaction between the two ($F(7, 42) = 1.387$; $p = 0.236$, $\eta^2 = 0.188$). We concluded that no significant priming effects, positive or negative, were seen in patients with PD.

7.3.3.3 Patients with Parkinson's disease on a dopamine agonist make more errors than those patients without dopamine agonist use

As in Chapter 5, we compared the errors made on the masked priming task. A one-way ANOVA showed that patients on dopamine agonists made more errors in total ($p = 0.050$, $F(1,13) = 4.749$). On further inspection of the type of errors committed by each group, it

was found that patients on a dopamine agonist made more omission errors ($p = 0.033$, $F(1,13) = 5.817$), with a statistical trend for making more commission errors ($p = 0.055$, $F(1,13) = 4.509$). Fast ($p = 0.195$, $F(1,13) = 1.884$) and premature ($p = 0.597$, $F(1,13) = 0.294$) errors were made equally by the two groups. In Chapter 5, we implicated the commission errors as a marker of failed automatic inhibition and validated this with the finding that more commission errors were made on incompatible than compatible prime-target sets. However, errors were equally as likely on compatible as in incompatible trials in patients on an agonist ($t = 1.448$, $p = 0.198$, $d = 0.254$).

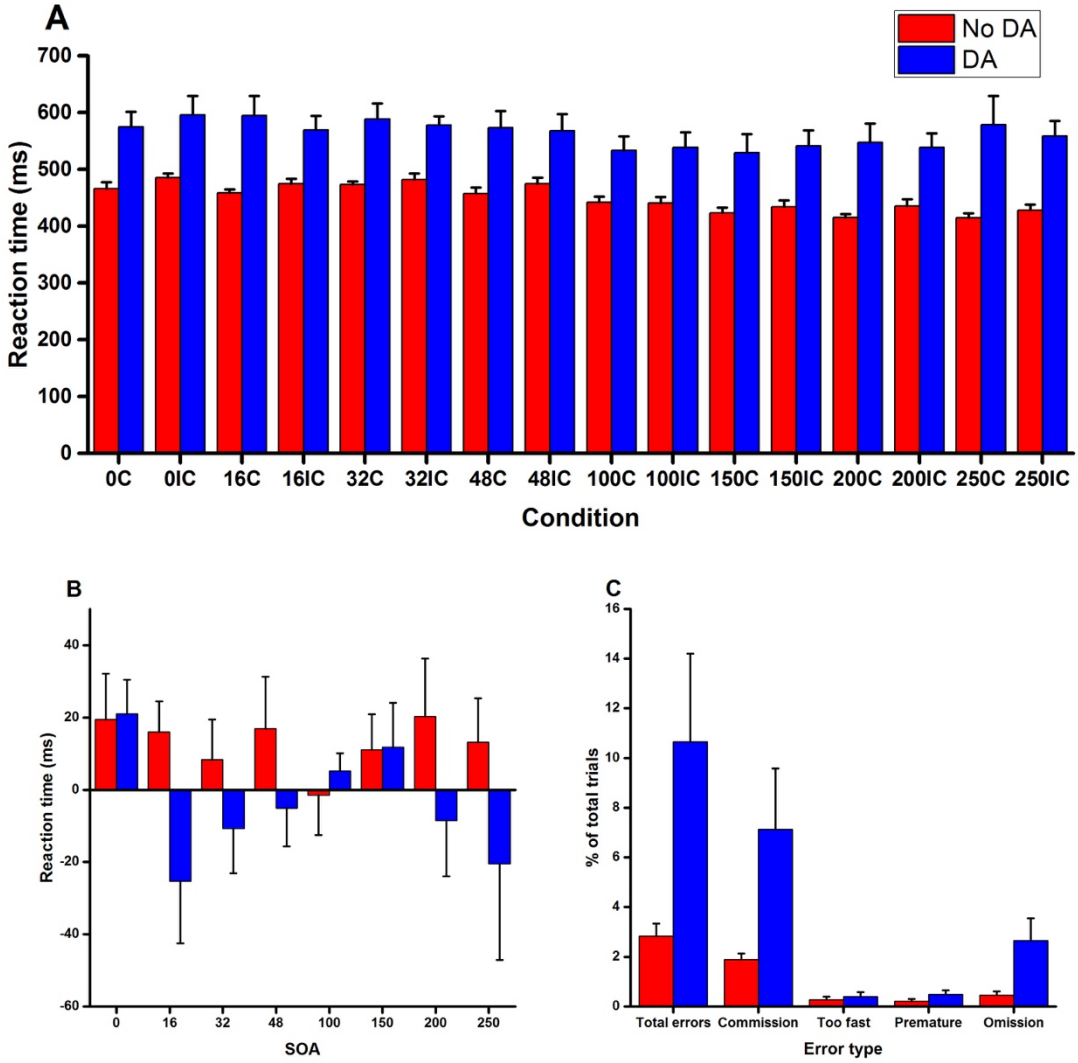

Figure 7.3: Priming effects and errors from the masked priming task between patients on a dopamine agonist and those not.

A: Reaction times are plotted for each condition with numbers denoting the SOA (time difference between the mask and target) and letter denoting the compatibility of the prime-target set (C = compatible, IC = incompatible). **B**: The compatibility effects are shown for each SOA, with values lying above 0 meaning positive compatibility effects and those below 0 meaning negative compatibility effects. **C**: Bar plot shows the errors

made on the masked priming task as a proportion of the total number of trials. Error bars represent mean±SEM. DA = patients on a dopamine agonist, No DA = patients not on a dopamine agonist.

7.4 Discussion

7.4.1 Motor response inhibition and decision-making strategies in Parkinson's disease

In this chapter, we wanted to investigate the specific effect of dopamine agonists on motor response inhibition in PD with the specific hypothesis that there may be a failure in proactive inhibition in patients on a dopamine agonist. We did this by asking patients to complete a behavioural task to probe proactive and reactive inhibition, then splitting them into groups according to their dopamine agonist use. We noted that patients with PD, both with and without dopamine agonist use, had retained reactive and proactive inhibition, indexed by successful inhibition on stop trials and the ability to slow down when stopping might be required. However, the proportion of successfully stopped trials deviated from 50%, indicating that the staircases that we used were not appropriate in proving reactive inhibition. Further experiments of motor response inhibition in PD should, therefore, employ longer SSDs to compensate for the bradykinesia in PD. For example, this could be derived using a proportion of the subject's go reaction time, instead of arbitrary SSDs. Comparing the index of proactive inhibition between groups, we found that patients on dopamine agonists had a lower RDE than those without. Although this did not reach statistical significance, there was a slight trend, indicating that further research in a larger sample size is warranted. Indeed, our findings from Chapter 6 suggest that dopamine agonists may impair motor response inhibition. Of course, the biggest weakness of this study is the lack of power and more patients should be tested to investigate whether there truly is a deficit or not in motor behavioural inhibition in PD patients with dopamine agonists. We could have chosen to conduct a within-subjects design, whereby patients on a dopamine agonist were tested on and off their agonist medication. Whilst this would

increase statistical power for the same number of participants, we wanted an answer to the long-term effects of dopaminergic agonists on motor response inhibition. A within-subjects trial design where patients would be asked to omit a dose, would instead give us an answer to the acute effects of a dopamine agonist in PD; due to the half-life of dopamine agonist medication, it is plausible that even if one dose was omitted (akin to the "off" medication condition), we would still be testing during a state where dopamine agonists were present.

To investigate the decision-making strategy made by patients, we performed DDM analyses. We found that patients in both cohorts could adapt their decision-making strategies in the face of potential of stopping, although these findings did not reach statistical significance, an issue that again we put down to the lack of statistical power. However, this statistical insignificance may in fact be a true effect that patients with PD cannot modulate their decision-making strategies in the face of potential stopping. Indeed, the CSST has previously been performed on a group of unoperated PD patients, with DDM analyses showing no change in any DDM parameter between critical and non-critical go trials (11). The lack in change of DDM parameters between critical and non-critical trials is unsurprising considering that the basal ganglia are thought to be involved in setting the height of the decision threshold, which determines the amount of evidence that needs to be accumulated prior to decision making (64,254). Even adjustments in the starting point of evidence accumulation are mediated by the basal ganglia and fronto-parietal cortical networks (255,256), both of which are affected in PD (257).

One caveat to our approach is that impairments in motor response inhibition may not be the main vector by which ICDs are generated. Instead, there is evidence that decisional impulsivity is linked to ICD generation (126,258,259). However, alterations of motor response inhibition may still be applicable to an altered risk in ICD generation. Indeed, it has been shown that sensorimotor as well as affective striatal networks have been associated with alterations in ICD risk in patients with Parkinson's disease (258). Specifically, weaker connectivity in frontal-striatal networks may lead to an impaired

assessment of reward value and stronger sensorimotor basal ganglia-cortical networks may increase the propensity to act upon that erroneously evaluated reward information. Consequently, further experiments should aim to investigate the effect of dopamine agonist therapy on decisional impulsivity as well as motor impulsivity, perhaps focusing on the interaction between the two components of impulsivity.

7.4.2 Priming effects and automatic inhibition in Parkinson's disease

After the findings in Chapter 5 of an impairment of automatic inhibition in patients with Tourette syndrome and tic disorders, we asked whether this impairment might also be implicated in those patients on a dopamine agonist. In line with previous literature (21,22,152), we noticed that patient with PD exhibited positive priming effects, without a negative priming effect at SOA 100 ms. However, this relationship was not statistically significant and only present in PD patients without dopamine agonist use. On inspection of the errors made during the task, we found that patients on an agonist made more errors than those without agonist use. Curiously, the specific errors which were made included commission and omission errors, which seem contradictory. Indeed, in Chapter 5, we implicated commission errors as a failure of automatic inhibition, indexed by a greater proportion being made on incompatible than compatible trials. This was not the case in PD patients on a dopamine agonist and hence we believe that these errors do not reflect impaired automatic inhibition. Further evidence to support this is the lack of other errors associated with impaired automatic inhibition, such as fast and premature errors. The greater incidence of omissions in patients on agonists can be explained by assessing the mean reaction times. It was found that mean reaction time for patients on an agonist were significantly greater than those on no agonist patients, suggesting a motor deficit. Seeing as dopamine agonists are usually prescribed to patients further into the disease course, it may be the case that patients on dopamine agonists had greater motor impairment than those not on agonists. Despite an effort being made to account for these presumed motor deficits by increasing the threshold of omission errors to 1.5 seconds, this may not have fully sufficed.

7.5 Conclusions

In this feasibility study, we attempted to dissociate the effect of dopamine agonists on motor response inhibition in PD. We did not find any substantial effects implicating dopamine agonists in causing deficits in motor response inhibition, although there was a statistical trend for proactive inhibition to be less under the influence of an agonist. Consistent with previous reports on strategic decision-making in two-choice reaction time tasks, PD patients in either cohort did not make any significant adaptations in their response strategy when stopping might be required, which may reflect deficits in the basal ganglia in PD. Underscoring these results is an acknowledgement that statistical power is low. However, our results are encouraging that there may be an effect of dopamine agonists on motor behavioural inhibition in PD, which should be borne out in a larger sample.

8 General Discussion

This final chapter will bring together the evidence laid out in this thesis in order to present a clear account of human motor decision-making pertaining to tics in Tourette syndrome and impulsivity in Parkinson's disease.

8.1 On the independence of movement preparation and movement execution

The beginning of the thesis outlined that movement in perceptual decision-making has been considered to occur in a rise-to-threshold manner, whereby neural activity accumulates for a response alternative towards a perceptual threshold. After this threshold has been reached, movement is triggered. This model therefore posits that movement preparation precedes movement execution and that the two processes are coupled. Even in cases of pressured choice decision making, it has been proposed that an urgency signal decreases boundary separation such that movement preparation and hence movement execution occur earlier (260). However, we outlined that recent evidence has suggested that movement preparation and initiation are independent processes (121), which was a significant deviation from the classical model of movement (261–263). Consequently, we decided to reconcile this debate by providing physiological data using TMS.

Firstly, we aimed to validate established TMS signatures of movement preparation and extend this to movement inhibition and execution. In Chapter 3, we confirmed that different inputs to the motor cortex could be accessed using different TMS parameters. It was unknown how these different inputs were influenced by proactive inhibition, that is, the processing of slowing down responses in anticipation of future stopping. We extended that putative AP suppression was present in a cued reaction time task and during times

when stopping might be required. Proactive inhibition can be viewed as two separate effects: a delay in the rise to movement threshold of a fully prepared response or reduced preparation of an expected response. The latter can be considered as a form of preparatory inhibition of CSE prior to onset of the go cue. These two processes could be the same or separate. If they were the same, then we would expect that the lower the level of preparation, the longer the rise-to-threshold would take, resulting in longer reaction times. Alternatively, these two types of proactive inhibition could be uncoupled; data from Chapter 3 suggest that they are different processes, seeing as the effect on PA and AP inputs is different. That is, we noticed that only PA inputs reflected some degree of uncertainty or prediction about upcoming stopping, displaying proportional inhibition when stopping was more likely. It was in this chapter that we also noticed that motor execution was equal between conditions when stopping was or was not required.

In Chapter 4, we directly aimed to resolve the debate between rise-to-threshold accounts of movement and the independence of motor preparation and execution hypothesis. Using two different stopping tasks, we showed that we altered movement preparation. In Experiment 1, reaction time distribution data suggested that movement when stopping was potentially required occurred due to a delay in movement initiation. In this case, movement execution was the same regardless of stopping requirements. In Experiment 2, we made use of drift-diffusion modelling in two-choice reaction time tasks to show that changes in boundary separation and drift rate mediated the slowing down when stopping was required. Hence, we changed movement preparation in a different way between trials when stopping was required and when it was not. According to rise-to-threshold models, these changes should be reflected in movement execution but according to an independence of movement preparation and execution, movement execution should be the same. Again, we found that corticospinal excitability rise time before movement was the same regardless of stopping requirements, thereby providing physiological evidence of the independence of movement preparation and execution.

But why are movement preparation and execution independent processes? Indeed, coupling movement preparation and execution would mean that movements would be executed with maximal accuracy. However, this also means that movements made under urgent situations would be inefficient if preparation would always need to be fully completed prior to movement execution. In these instances, an independence of movement preparation and execution is both advantageous and necessary. Take the instance of a batsman facing an unexpected bouncer in cricket. The batsman has approximately 500 ms to readjust their motor plan, prepare the appropriate shot and execute it; failure to do so could injure the batsman. If movement preparation had to finish for movement execution to occur, this would probably be too slow to account for the urgent readjustment in shot selection. Having an independent trigger for movement initiation allows for movements to be executed, even if they are not fully prepared. Even being partially prepared, movements can still be advantageous. On the other side of the coin, what is the advantage of delaying a movement once it has been prepared? As we have seen throughout this thesis, especially Chapter 3, Experiment 1, delaying a prepared action increases the chance of successfully stopping in response to a stop signal; this is the basic function of proactive inhibition. Effectively, delaying execution buys more time until enough evidence has been accumulated regarding the correct choice (264) or for late changes of mind (188). It also means that the response is always fully prepared, whereas it might not be if the rise to threshold was slower in order to implement a delay in responding. In essence, the independence of movement preparation and execution represents a form of "freedom of immediacy" – our actions are not always dictated by stimuli from our environment (265,266).

8.2 Heightened motor preparation does not cause tics

The Introduction to the thesis outlined that heightened motor preparation may be a cause of the tics seen in Tourette syndrome. When overlain onto rise-to-threshold models of movement, heightened motor preparation would result in spontaneous neural activity

reaching the perceptual decision threshold more frequently, thereby triggering movements i.e. the tics. Having found that movement preparation and execution were independent in Chapter 4, we revised this hypothesis such that in Tourette syndrome, movement preparation and execution may be erroneously coupled rather than independent. We therefore reproduced the experiment from Chapter 4 in a population of patients with Tourette syndrome and tics. Whilst we drew a distinction between Tourette syndrome and tic disorders due to the clinical diagnosis, it should be noted that all patients had experienced tics for over one year and hence fall under the category of Tourette syndrome. We found multiple lines of evidence suggesting that behavioural inhibition and motor preparation were remarkably normal in our patients; behavioural measures of proactive and reactive inhibition were retained in patients. They also changed their decision-making strategy when stopping was potentially required, in a similar manner to healthy control subjects. The independence of movement preparation and execution were also present in patients, with similar profiles in the rise of excitability prior to movement as in healthy controls. These findings all pointed away from a hypothesis that heightened movement preparation could cause tics. If anything, there was a suggestion of suppressed motor preparation in patients; the response-locked analysis showed that corticospinal excitability reached a lower plateau than that in healthy subjects, potentially because of tonic proactive control used to inhibit tics.

8.3 Impaired automatic inhibition and excessive motor noise as a cause of tics

After finding that volitional control over movement was normal in Tourette syndrome, we turned our attention to assessing automatic inhibition in these patients. Analysis of the reaction times in the task showed strong positive priming effects at the timepoints consistent with positive priming. We also found that the negative priming effects usually seen at 100 ms were not found, thereby implicating a selective impairment of automatic inhibition in Tourette syndrome. However, we did not notice any significant negative priming effects, in our control subjects, making the interpretation of our findings in

patients, difficult. Analysis of the errors made in the task revealed that patients were much more likely to make errors than controls. Furthermore, these errors were specific for ones that would be consistent with a failure to inhibit the prime. Finally, we found that these automatic inhibition associated errors were significantly correlated with clinical, motor scores of tic severity.

This theory of tic generation is appealing because, unlike the heightened movement preparation hypothesis, the impaired automatic inhibition hypothesis allows for an independence of premonitory urges and tics. This is in keeping with findings that premonitory urges are not indicative of tic severity (230). Interestingly, the impaired automatic inhibition hypothesis lines up with the motor noise hypothesis of tic generation. The motor noise hypothesis of tic generation (135) states that excessive neural noise (267) in the motor system in Tourette syndrome leads to movement being spontaneously generated, thereby giving the tic. These two hypotheses are complimentary with each other, such that motor activation by the prime is accentuated by the excessive motor noise in patients with Tourette syndrome. This excessive motor noise combined with the impaired inhibition of the prime may therefore increase the strength of prime associated motor activation and cause overt movements to be generated. Recent evidence using continuous force measurement, instead of button presses, has shown that prime induced motor activation may not be sub-threshold and actually causes overt motor activity to be generated (268). Interestingly, no such effects of excessive motor noise were found in patients with Tourette syndrome during the CSST. To reconcile this, we suggest that voluntary mechanisms of inhibition, such as proactive inhibition in the CSST, can suppress motor noise and reduce tic frequency. This contrasts with impaired automatic inhibition in the masked priming task where errors are derived from stimuli that subconsciously perceived and not under volitional control. Furthermore, the CSST involved distraction away from tics; it has been found that attention away from tics can reduce their frequency (135). In all, our data suggest that generation of tics does not occur

due to aberrancy of voluntary streams of movement but rather via involuntary, automatic circuits instead.

We suggest that future experiments should aim to prove this hypothesis using positive physiological data. For an impairment in automatic inhibition, inspiration could come from the study by McBride et al. who showed that masked primes resulted in overt motor activity, specifically in the effector that the prime pertained to. Importantly, these small releases of motor activity were only detected when measured with continuous EMG measurements (268), which are usually missed by button presses, which are binary. We would predict that this would be greater or more likely in patients with Tourette syndrome. Furthermore, TMS could be used to investigate what the physiological consequences of the prime was on motor cortex excitability, something that has not been explored in healthy controls. We would predict in healthy subjects that positive priming at short SOAs would lead to an increase in CSE, whereas negative priming effects at an SOA of 100-150 ms would lead to corticospinal suppression. In patients with Tourette syndrome, we would predict that these priming effects and physiological consequences would be absent, such that there would be no corticospinal suppression at SOAs of 100-150 ms. This could be complemented with measurements of the LRP, which putatively show a triphasic waveform. As mentioned in Chapter 5, we would predict that the negative phase of this waveform would be isoelectric.

8.4 Excessive motor noise and the independence of motor execution as a combined hypothesis for tic generation

We propose an alternative account of tic generation by combining the motor noise and movement preparation and execution independence hypotheses. We found that movement preparation and execution are independent processes, such that the trigger for movement does not necessarily occur after movement preparation has completed. This suggests that the trigger for movement can be initiated spontaneously and erroneously. The motor noise hypothesis posits that motor noise is excessive in patients with Tourette syndrome. Hence,

the excessive motor noise could apply to the trigger for movement as opposed to movement preparation. In fact, the phenomenology of tics is such that they are not purposeful movements – they do not look like they are fully prepared movements. Hence, we propose that excessive motor noise might prematurely activate the trigger for movement, which incorporates the presumably low level of motor preparation to give a seemingly incompletely prepared movement – the tic. In fact, the cortico-striatal pathway determines the timing of movement (269,270); seeing as there is an imbalance between striatal and globus pallidus internal segment inhibitory neurone distribution in Tourette syndrome, an impairment in the timing of movement execution seems plausible (271). This hypothesis might be extended to other dyskinesias such as those induced by levodopa, where it is found that excessive striato-cortical connectivity in response to levodopa produces an abnormal reinforcement signal, which may produce involuntary movements (272). In the case of the masked priming task, it could be that the prime prepares a movement for the corresponding effector. Therefore, when the trigger to move comes in, which we predict would be earlier in patients with Tourette syndrome, what we see is movement to the prime instead of the target.

8.5 Dopamine agonists and motor response inhibition

Based on the clinical observation that ICDs in PD are more likely when dopamine agonist medications are used, we sought to investigate the specific effect of dopamine agonists on motor response inhibition. We predicted that motor response inhibition may be impaired under the influence of a dopamine agonist and that this effect might implicated as a marker for ICDs in PD. As the effect of dopamine agonists on response inhibition is scarcely investigated in healthy humans, we performed a cohort study to address this. Chapter 6 showed that an acute dose of ropinirole, a D3 receptor agonist, proactive inhibition, indexed by a lower RDE compared to placebo. On investigating decision-making strategy in the face of potential stopping, we found that ropinirole impaired the ability to increase boundary separation when stopping might be required. These results

together provided a scientific (rather than clinical) rationale to study the specific role of dopamine agonists on motor response inhibition in PD. In Chapter 7, we compared motor response inhibition in PD patients on a dopamine agonist and those without dopamine agonist use. We found no significant differences in motor response inhibition between the two groups, although there were statistical trends for an impairment in proactive and reactive inhibition. Due to the small sample sizes in each group, the results are encouraging but inconclusive. Results from the masked priming task showed that patients on an agonist made more errors than those without agonist use, although this was made up predominantly of omission errors, which we attribute to the slower reaction times in the agonist group. It is no surprise that the dopamine agonist group did not reveal any significant effects in proactive in reactive inhibition considering the small effect sizes found in Chapter 6.

The Introduction to the thesis alluded to different forms of impulsivity, which may reflect impairments in specific forms of decision-making. For example, delay-discounting refers to delaying responses to small, immediate rewards in order to attain a larger reward, over a longer period of time; this is centred on accumulation and valuation of evidence in decision-making. Conversely, motor-decision making pertains to the processes of movement planning and execution. It may be the case the dopamine agonists affect different aspects of decision-making and have a minimal effect on motor decision-making. Indeed, PD patients on dopamine agonists have shown deficits in tasks assessing cognitive impulsivity (273) where delay discounting tasks are used. That is, PD patients on an agonist collect less information before a decision is made than patients not on an agonist. According to rise-to-threshold models of decision-making, this can be achieved by lowering of boundary separation such that evidence accumulation terminates earlier. This is consistent with our finding in Chapter 6, although the effect was seen in motor decision-making. Perhaps this suggests that dopamine agonists have a global effect to impair adaptation of boundary separation, but this manifests differently depending on the type of impulsivity probed i.e. motor vs cognitive (274). In fact, evidence from DBS

shows that ICDs can increase or decrease post-surgery (275–277). The hypothesis for this differential effect is based on where stimulation in the STN occurs; stimulation of motor loops ameliorates the motor symptoms and reduced dopaminergic therapy load, whereas stimulation of cognitive loops may induce behavioural deficits, impulsivity being one manifestation of this (278). In addition, studies of response inhibition in patients with STN DBS show deficits in motor proactive and reactive inhibition (11,279) but not delay discounting (280).

There is a hypothesis that ICDs mediated by D2/D3 receptor activity are a manifestation of a disrupted mesocorticolimbic reward pathway (281), with evidence that reward and risk processing is altered in PD patients with a history of ICDs (282–284). The tasks performed in Chapter 7 did not have any clear features of risk or reward. Consequently, effects of dopamine agonists on these processes may have been missed.

8.6 Concluding remarks

This thesis has explored the mechanisms of motor preparation, execution and inhibition and the differential contribution of inputs to the motor cortex in each of these stages. It was then shown that preparing a movement and executing it are two, independent processes, which deviates from the conventional viewpoint of perceptual decision-making that movement execution occurs after neural activity during movement preparation reaches a perceptual threshold.

Having classified this independence, we showed that this was retained in patients with Tourette syndrome and tic disorders, thereby showing that enhanced motor preparation is not likely causes of tics. Instead, we propose that an impairment of automatic inhibition and excessive motor noise are encompassing hypotheses that explain tics in the presence and absence of premonitory urges.

In the next section, we investigated the role of dopamine agonists on motor response inhibition, after the observation that dopamine agonists are highly implicated in impulse control disorders in Parkinson's disease. We firstly provided evidence that a small, acute

dose of a dopamine agonist had the potential to impair both reactive and proactive forms of motor behavioural inhibition in healthy subjects. We then investigated the role of dopamine agonists on motor inhibition in the context of Parkinson's disease, with evidence suggesting that dopamine agonists may impair some aspects of motor response inhibition.

We anticipate that the findings in this thesis will impact a broad range of clinical and non-clinical neurosciences. The independence of movement preparation and execution deviates significantly from classical models of movement. This finding will have implications for any experiments that use reaction times as a measure of underlying decision-making processes; we show that rather than differences in reaction times representing underlying decision-making strategies, they in fact may represent the time difference between when movements are triggered. In the arena of Tourette syndrome and tic disorders, we have identified a novel mechanism by which tics may arise – a failure in automatic inhibition, which correlates with clinical severity of motor scores. As well as encouraging further research into this hypothesis and an extension to other dyskinesias, the measurement of automatic inhibition via reaction times and errors may provide an objective marker of diagnosis. clinical assessment and rehabilitation of tic severity.

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