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Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work. Chapter 3. Journal of Motor Behavior, MacDonald and Byblow, Does response inhibition have pre- and postdiagnostic utility in Parkinson's disease? (2015); 47(1); 29-45

Nature of contribution by PhD candidate	Responsible for writing review article
Extent of contribution by PhD candidate (%)	85

CO-AUTHORS

Name	Nature of Contribution
Prof Winston Byblow	Contributed to manuscript preparation

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The undersigned hereby certify that:

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- in cases where the PhD candidate was the lead author of the work that the candidate wrote the text.

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Nature of contribution by PhD candidate	Responsible for experimental design (ED), data collection (DC) and analysis (DA), interpretation (Int), and manuscript preparation (MSPrep)
Extent of contribution by PhD candidate (%)	85

CO-AUTHORS

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Prof Winston Byblow	Contributed to ED, Int & MSPrep

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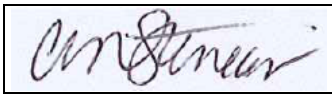
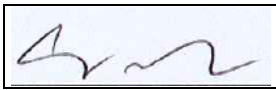
AProf Cathy Stinear		23/10/2015
Prof Winston Byblow		23/10/2015
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Nature of contribution by PhD candidate	Responsible for experimental design (ED), data collection (DC) and analysis (DA), interpretation (Int), and manuscript preparation (MSPrep)
Extent of contribution by PhD candidate (%)	85

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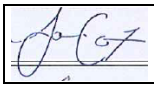
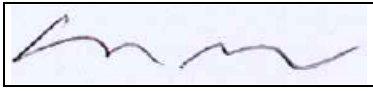
Dr James Coxon		14/10/2015
Prof Winston Byblow		23/10/2015
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Nature of contribution by PhD candidate	Responsible for model design (MD) and coding (MC), and manuscript preparation (MSPrep)
Extent of contribution by PhD candidate (%)	80

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Dr James Coxon	Contributed to MD & MSPrep
AProf Cathy Stinear	Contributed to MSPrep
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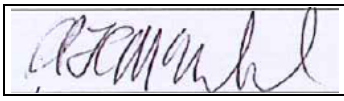
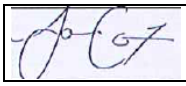
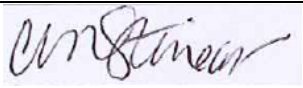
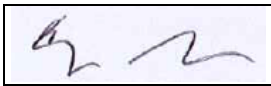
Dr Angus McMorland		27/10/2015
Dr James Coxon		14/10/2015
AProf Cathy Stinear		23/10/2015
Prof Winston Byblow		23/10/2015
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Nature of contribution by PhD candidate	Responsible for experimental design (ED), data collection (DC) and analysis (DA), interpretation (Int), and manuscript preparation (MSPrep)
Extent of contribution by PhD candidate (%)	75

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Ms April Ren	Contributed to DC & DA
Dr Barry Snow, Dr Steven Cramer	Contributed to ED; contributed to ED & MSPrep
Dr Justin Kao, Ms Lorraine Macdonald	Both contributed to DC
Prof Winston Byblow	Contributed to ED, Int & MSPrep

Certification by Co-Authors

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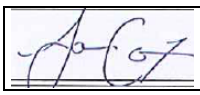
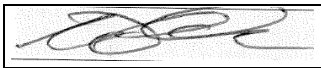
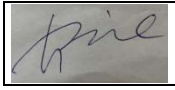
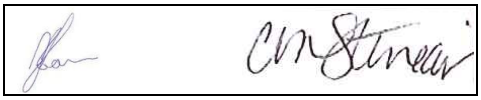
Dr James Coxon		14/10/2015
Dr Steven Cramer		1/10/2015
Ms April Ren		3/10/2015
Dr Barry Snow; AProf Cathy Stinear		23/10/2015
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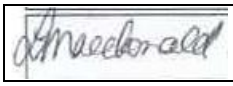
Ms Lorraine Macdonald		1/10/2015

Statement of Contribution

In addition to the experiments presented in the current thesis, the candidate contributed to the following publication during the course of study:

Performed blinded neurophysiological collection sessions for two years assessing corticomotor excitability in a clinical trial testing the effects of priming upper limb physical therapy with intermittent theta burst stimulation in chronic stroke patients. Ackerley SJ, Byblow WD, Barber PA, MacDonald HJ, McIntyre-Robinson A, Stinear CM (2015) Primed Physical Therapy Enhances Recovery of Upper Limb Function in Chronic Stroke Patients. Neurorehabil Neural Repair.

Chapter 1

Introduction

The ability to control our urges and impulses is arguably one thing that sets humans apart from other species. We have the capacity to think before we act. The generally accepted principle is that higher-order brain structures (prefrontal regions) restrain primitive instincts by exerting control over lower-order brain structures. Poor impulse control is regarded as a consequence of impaired executive functioning and exhibited when an action is performed without delay, reflection, or voluntary direction (Bari and Robbins, 2013). Dopamine is necessary for effective impulse control. Dysfunctional levels of frontostriatal dopamine are particularly associated with impaired impulse control (Pattij and Vanderschuren, 2008). Impaired impulse control is observed in a laboratory setting across diverse neurological conditions such as focal dystonia (Stinear and Byblow, 2004; Stinear et al., 2006), attention deficit hyperactivity disorder (Aron and Poldrack, 2005), obsessive-compulsive disorder (Chamberlain et al., 2006), schizophrenia (Donohoe et al., 2006) and Parkinson's disease (Gauggel et al., 2004). It is intriguing that such diverse conditions can have a common behavioural deficit.

Impulse control is a multidimensional construct, too broad to be examined in its entirety in a single thesis. However it can broadly be broken down into cognitive and motor domains. Cognitive impulse control refers to the ability to evaluate the potential consequences of a decision and modify the decision accordingly. Motor impulse control refers to the ability to suppress an inappropriate movement (i.e. response inhibition). It is unclear to what extent these two domains have distinct neurophysiological influences. There is a general decrease in impulse control with ageing throughout adulthood, seen in both motor (Braver and Barch, 2002; Fisk and Sharp, 2004), and cognitive domains (Fisk and Sharp, 2004) as indexed via laboratory measures. The age-related deterioration of motor impulse control is exacerbated with basal ganglia (BG) dysfunction, as is evident in focal dystonia (Stinear and

Byblow, 2004) and Parkinson's disease (Bokura et al., 2005; Cooper et al., 1994; Gauggel et al., 2004; Obeso et al., 2011).

The current thesis focuses on motor impulse control by using a response inhibition (RI) paradigm as a means to study impulse control of an overt bimanual motor act. Investigating the inhibition of observable motor behaviour allows the objective measurement of the latency and efficiency of underlying physiological processes. The study of RI is considered a good proxy for the study of impulse control and its underlying neurophysiology (Bari and Robbins, 2013). The following chapters focus on the behavioural, neurophysiological and genetic elements of motor impulse control and consider how these elements may be affected by dopamine dysregulation.

1.1 Overview of the thesis

Chapter 2 presents a review of literature surrounding the central themes of the thesis. First, the neuroanatomy of motor, cognitive and limbic networks involved in movement control are discussed. This starting point is an acknowledgement that the behavioural manifestations of impulse control are contributed to by multiple, interrelated neural networks. Second, the brain structures participating specifically in movement inhibition are reviewed along with the behavioural and neurophysiological observations during partial inhibition of bimanual movement. Next, the pathological staging of PD is briefly reviewed along with the potential role of genetics in dopamine dysregulation.

Chapter 3 builds on the background from the previous chapter to discuss impulse control in PD and how objective measures of impulse control could be used clinically pre- and postdiagnosis. First, the functional changes in frontostriatal and BG-thalamocortical networks in PD are reviewed and summarized, along with their effect on impulse control, specifically RI. Second, the potential of standardized RI paradigms are introduced as a means to provide useful measures to identify insidious motor changes during the prediagnostic phase. Third, the idea is introduced to combine information obtained from RI tasks with genetic analysis in the postdiagnostic phase of PD. The aim of which is to better identify mechanisms which predispose individuals to impulse control disorders with dopaminergic treatment.

Chapter 4 provides an overview of the main techniques used in the experimental Chapters 5 to 8.

Chapter 5 is a behavioural and electromyography experiment characterizing how bimanual movement components are integrated during response preparation and how this influences RI of a subset of the prepared response (partial RI).

Chapter 6 presents two experiments investigating primary motor cortex (M1) function during RI and presents a model to encapsulate the empirical data. The first experiment investigates the temporal modulation of M1 preceding and during partial RI using single-pulse transcranial magnetic stimulation (TMS). The second experiment examines the role of intracortical inhibitory circuits during partial RI by applying paired-pulse TMS.

Chapter 7 validates and extends the model from the previous chapter to develop a conceptual framework for neural mechanisms of RI.

Chapter 8 utilizes a RI task in conjunction with cognitive impulse control measures to examine how dopamine agonist drugs interact with dopamine gene polymorphisms to influence impulse control.

Chapter 9 concludes the body of experimental work with a brief summary of the main results, limitations of the research and possible future directions.

Chapter 2

Review of Literature

Movement is fundamentally the only way to interact with our environment. An essential role of the brain is therefore to control our movements and generate ones appropriate for the surroundings. Movements can be classed as either voluntary or reflexive, each of which are controlled by different neural networks. Voluntary actions are those executed under conscious cognitive control and most commonly organized around a goal-directed task e.g. swinging a squash racquet to hit a ball. They are executed in the context of several decisions including: when to act, which action to execute and whether or not to proceed with the action. The decision about whether to inhibit or proceed with an action is a necessary part of daily behaviour and is particularly important to enable adaptation to novel and challenging situations. Another essential function of the brain is therefore to prevent unwanted or inappropriate movements.

Without time restrictions, movements are entirely self-driven and under 'free will'. Or are they? Studies which have investigated neural activity prior to the conscious perception of the decision to move (Fried et al., 2011; Libet et al., 1983; Matsuhashi and Hallett, 2008), reveal increases in medial prefrontal brain activity that precede the awareness of the decision to move, by at least a few hundred milliseconds. Fried et al. (2011) even used single neuron recordings to demonstrate that the activity of neuron populations within medial prefrontal regions have the potential to predict volition and the time it will occur on a single trial basis. However participants report when they 'feel the urge' to move which is subjective and potentially inaccurate. Nonetheless, this is an interesting area of research questioning how much control we really have over our actions.

Another aspect of 'free will' is 'free won't'. Research into 'free won't' examines our control over stopping voluntary actions. The inhibition of voluntary movements when they are no longer appropriate is termed response inhibition (RI). Studies designed to investigate the

control of movement commonly peg the execution and/or inhibition of voluntary movement to a stimulus rather than movement remaining entirely self-driven. The cortical organization of stimulus-driven versus self-driven movements may be fundamentally distinct (Dum and Strick, 2002). However a certain extent of neural overlap is also evident, as all voluntary movements can be internally generated.

The current thesis focuses on RI of voluntary stimulus-driven movement. Although the neurophysiological experiments probe voluntary movement control at the level of the primary motor cortex (M1), network components upstream of M1 also contribute to results at a behavioural level. The next two sections therefore discuss firstly the neuroanatomy of the networks involved in movement control, and then more specifically inhibition of movement.

2.1 Neurophysiological control of voluntary movement

Voluntary movement begins with the general outline of a desired behaviour, which is then translated into concrete motor responses through processing within movement-related networks. Individual neurons are not hard-wired for specific motor responses, but instead may fire during a range of related motor behaviours. It is the pattern of neuronal firing within large neural networks that dictates the expression of simple or complex motor behaviours.

The motor system recruits several interrelated networks to successfully achieve movement control. All networks involved in voluntary movement converge onto M1 located in the precentral gyrus. M1 is principally responsible for executing voluntary movement by transmitting neural signals down pyramidal neurons to the spinal cord. These signals are then conveyed trans-synaptically to alpha motor neurons and control muscle contraction. Inputs to M1 come from several cortical and subcortical regions. Direct somatotopically organized cortical inputs to M1 come from the primary somatosensory cortex (S1), premotor cortex (PMC), supplementary motor area (SMA), and posterior parietal area 5. M1 also receives input from subcortical basal ganglia (BG) nuclei and the cerebellum via different populations of nuclei in the thalamus. There is a unique pattern of cortical and subcortical input for each motor area. For example, M1 receives a large number of cerebellar projections (Asanuma et al., 1983), while PMC is primarily the target of pallidal output via the thalamus (Schell and Strick, 1984). Consequently, there are several cortico-subcortico-cortical network loops with varying contributions to motor behaviour. A discussion of the exhaustive list is beyond the scope of this doctoral work. The following section focuses on the motor,

cognitive and limbic cortico-BG-thalamcocortical networks that influence the control of movement.

2.1.1 Basal ganglia - thalamocortical networks

Motor, cognitive and limbic networks are maintained through distinct nuclei within BG-thalamocortical circuitry (Alexander and Crutcher, 1990a; Redgrave et al., 2010). Despite their naming, all of the networks are important for movement control. The exact degree of separation and integration between the three networks is still unclear. It is important to consider the locations where there might be anatomical and functional overlap. Acknowledging the possibility of substantial integration between networks helps understand the diverse symptoms arising from BG disorders such as Parkinson's disease. Network integration might also explain why treatments aimed at improving function in one network (e.g. boosting nigrostriatal dopamine or deep brain stimulation within the motor network) might produce side effects relating to the other networks. Although each network projects from and outputs to different cortical regions (Alexander and Crutcher, 1990a; Alexander et al., 1986; Haynes and Haber, 2013; Lanciego et al., 2004; Romanelli et al., 2005), there are a few basic properties common to each which influences voluntary movement.

Each network originates within the cortex and contains a 'direct pathway' to its associated BG output nuclei (Figure 2.1A). The direct pathway is comprised of excitatory glutamatergic projections to the striatum, which is functionally divided into the caudate nucleus, posterior and anterior putamen and ventral striatum. The striatum is the main input nuclei of the BG, receiving projections from the cerebral cortex, midbrain and thalamus. The direct pathway involves monosynaptic GABAergic projections from the striatum to the pallidum and substantia nigra. The pallidum is functionally separated into ventral and dorsal regions. The dorsal pallidum is known commonly as the globus pallidus (GP) and is divided into internal (GPi) and external (GPe) segments. The substantia nigra (SN) consists of the pars reculata (SNpr) and pars compacta (SNpc). The SNpr, GPi and ventral pallidum are the specific output nuclei of these BG structures. The BG output nuclei maintain inhibitory GABAergic projections onto thalamocortical neurons. Suppression of these nuclei via any network's direct pathway results in disinhibition and a net increase in thalamocortical drive.

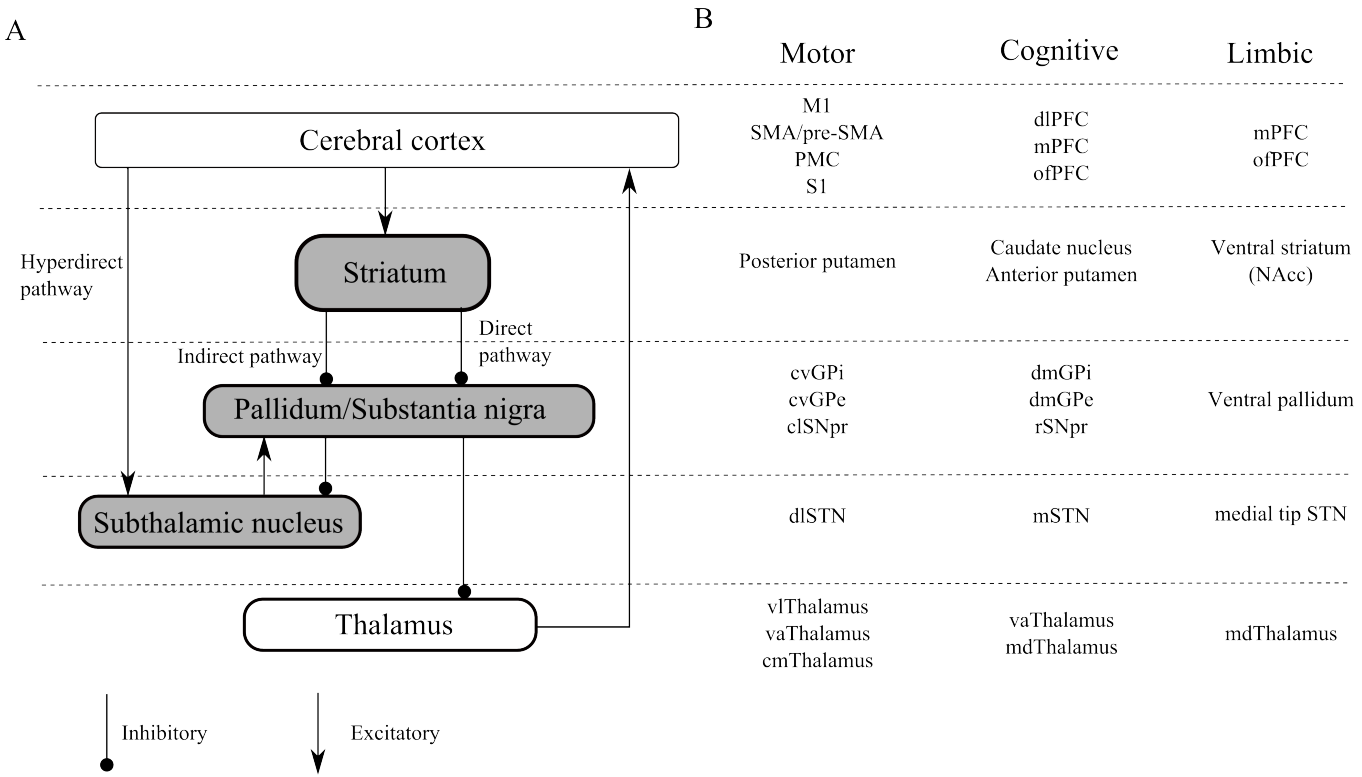


Figure 2.1 Motor, cognitive and limbic networks. The motor, cognitive and limbic basal ganglia-thalamocortical networks that contribute to voluntary movement control share common structures (A). All three networks contain direct, indirect and hyperdirect pathways that follow the same basic architecture with the same pattern of excitatory and inhibitory connections. However the three networks project to relatively segregated subdivisions within each of the common structures (B), suggesting some degree of segregation between the networks. M1: primary motor cortex; SMA: supplementary motor area; PMC: premotor cortex; S1: primary sensory cortex; PFC: prefrontal cortex; NAcc: nucleus accumbens; GPi: globus pallidus internus; GPe: globus pallidus externus; SNpr: substantia nigra pars reticulata; STN: subthalamic nucleus; of: orbitofrontal; cv: caudoventral; cl: caudolateral; dm: dorsomedial; r: rostral; dl:dorsolateral; m:medial; vl: ventrolateral; va: ventroanterior; cm: caudomedial; md: mediodorsal.

Each network also contains an 'indirect' pathway from the striatum to the BG output nuclei, which has the opposite effect on the output nuclei compared to the direct pathway. The indirect pathway also starts with excitatory glutamatergic corticostriatal projections. However the indirect pathway is oligosynaptic, projecting from the GPe to the subthalamic nucleus (STN) before projecting back to the output nuclei of the SN and/or GPi (Figure 2.1A). Output from the pallidum is always GABAergic but STN output is glutamatergic. This means activation of the excitatory projections from STN to the output nuclei result in greater inhibition of thalamic neurons and a net decrease in thalamocortical drive. Recruiting the direct versus indirect BG pathway therefore have opposite effects on thalamocortical drive according to the classic model from Alexander et al. (1986).

A third, 'hyperdirect' pathway is also present in each network. The hyperdirect pathway is comprised of excitatory projections directly from the cortex to STN, bypassing the striatum (Figure 2.1A). The remainder of the pathway connections are the same as the indirect pathway so the hyperdirect pathway has the same net effect of decreasing thalamocortical drive. Importantly, the hyperdirect pathway achieves the shortest conduction time of all BG pathways by eliminating striatal projections. The effects of the hyperdirect pathway would therefore be observed first during simultaneous activation of all three pathways. The hyperdirect pathway is of potential importance in the context of sudden, time constrained changes to behaviour.

Precise spatial and temporal recruitment of all three pathways within each network (motor, cognitive, limbic) gives rise to complex functions. The role of dopamine in modulating the neuronal output from the three pathways is discussed in the following chapter. The main neuroanatomical features of each BG network and their role in voluntary movement control are discussed in turn below.

The motor network

In primates, the motor network originates from precentral motor fields (i.e. M1, SMA and PMC) and postcentral somatosensory areas (Jones et al., 1977; Kunzle, 1978; Selemon and Goldman-Rakic, 1985) (Figure 2.1B). The posterior putamen receives projections from both cortical regions and integrates movement related signals with sensory feedback. Topographical projections in the direct pathway connect the motor regions of the putamen to the caudoventral portions of GPi and caudolateral regions of SNpr (Parent et al., 1984). The indirect pathway synapses from the posterior putamen to the caudoventral GPe, then the dorsolateral motor region of STN (Haynes and Haber, 2013) and subsequently the motor regions of GPi and SNpr. The motor portions of GPi and SNpr send topographical projections

to specific thalamic nuclei: the ventrolateral nucleus (pars oralis), ventroanterior nuclei (pars parvocellularis and pars magnocellularis), and centromedial nucleus (DeVito and Anderson, 1982; Ilinsky et al., 1985). The network loop is then completed by projections from thalamic nuclei back to the motor cortical regions from which the network originated. The SMA, PMC and M1 all receive a common input from the ventrolateral nucleus. However, the pars magnocellularis projects specifically to SMA, pars parvocellularis to PMC, and the centromedian nucleus to M1 (Nakano et al., 2000; Schell and Strick, 1984; Strick, 1976; Wiesendanger and Wiesendanger, 1985). Physiological and anatomical evidence indicate somatotopically organized subchannels through the motor network (Crutcher and DeLong, 1984; Hoover and Strick, 1993; Romanelli et al., 2005; Strick, 1976).

The default state of the motor system is analogous to driving with the brakes on. The braking occurs via BG inhibition of thalamocortical neurons (Ballanger et al., 2009). Movement initiation through recruitment of the direct pathway is therefore an active process requiring a phasic pause in the tonic inhibition of the thalamus. The traditional view of opposing direct and indirect pathways has, however, recently been challenged (Cui et al., 2013). Cui and colleagues used a mouse model to illustrate that neural activity increases in both direct and indirect pathways during movement initiation and decreases in both pathways during inactivity. There is further evidence of bridging collaterals between the two pathways in the rodent GP (Cazorla et al., 2014) and within the striatum (for a review see Calabresi et al. 2014). This co-activity and presence of bridging connections between the two seemingly opposing pathways would suggest that the interaction during movement is more complex. Indeed, evidence of more intrinsic and extrinsic BG connections adds further complexity to the classical model of BG function (for a review see Redgrave et al. 2010).

However the recent findings are not necessarily as contradictory to the traditional model as they might seem. Alexander et al. (1986) recognized the possible concurrent activation of the opposing pathways in order to fulfil a dual role of the BG within the motor system to both reinforce and suppress selected movement. Of note, the 'centre-surround model' of BG function is predicated on simultaneous activation of opposing BG pathways (Nambu et al., 2002). Within this model the faster direct pathway disinhibits only the selected motor program out of all possible motor actions, causing execution of only the desired movement. The slower indirect pathway then extensively inhibits the same executed motor program to terminate the movement at the necessary time. This would suggest the direct and indirect pathways synapse onto the same population of neurons within GPi and SNpr. The 'centre-

surround' model necessitates the concurrent activation of opposing direct and indirect pathways.

The 'centre-surround' model of BG function also includes the hyperdirect pathway. As previously mentioned, the effects of the hyperdirect pathway are observed first during simultaneous activation of all three pathways due to a decreased conduction time. Prior to movement initiation, the hyperdirect pathway is responsible for inhibiting thalamic and cortical representations for both the selected and competing motor programs (Mink, 1996; Nambu et al., 2002). The initial suppression of the selected motor program presumably prevents premature responses. The subsequent focused reinforcement of the selected motor program via the direct pathway coupled with suppression of potentially conflicting motor programs, is analogous to the 'inhibitory surround' model seen in various sensory systems. Even in 1990, Alexander and Crutcher recognized such a dual role of the BG "could result in the focusing of neural activity underlying each cortically initiated movement" (Alexander and Crutcher, 1990a). Such an idea dictates that the direct and hyperdirect pathways synapse onto separate populations of neurons within GPi and SNpr, thereby increasing the discharge rate of some neurons while decreasing it in others.

Single-cell recordings from primate studies have revealed the dynamics of information processing within the motor network. Changes in neuronal firing are sometimes evident in the motor cortical regions prior to any changes in activity within subcortical structures (Crutcher and Alexander, 1990; Tanji and Kurata, 1982; Thacher, 1978). This sequential firing pattern indicates serial processing of information within this loop, initiated in the cortex and proceeding in a 'top-down' manner. However during the movement burst, activity within the cortical and subcortical levels of this network appears to temporally overlap (Crutcher and Alexander, 1990). This implies motor processing is occurring in parallel. It therefore appears that both serial and parallel information processing is performed within the motor network.

Changes to neuronal firing in the motor network are sometimes observed prior to any movement initiation. Significant alterations to discharge rate can occur in cortical motor fields following information indicating an imminent stimulus-driven movement in a specific direction (Alexander and Crutcher, 1990c; Georgopoulos et al., 1989; Thach, 1978). Such activation changes remain until the cue for movement is presented and thus signify the neural correlate of 'motor set', the preparatory aspect of motor control. Interestingly, only subpopulations of putamen and GPi neurons exhibit such preparatory activation (Alexander, 1987; Alexander and Crutcher, 1990c). Individual neurons within these subcortical structures seem to be activated during either preparation or execution of movement. It there-

fore appears that the preparation and execution of movement is mediated via functional subdivisions within the motor network.

The cognitive network

The prefrontal cortex (PFC) is responsible for higher aspects of motor control. An important function of PFC is to weigh up the consequences of responses and then to plan and organize them accordingly. This is especially true when essential cues are not available in the environment at the time of execution and need to be recalled from working memory (Jacobsen, 1937). The PFC is a collection of cortical areas that project to and receive projections from the sensory system, motor system and several subcortical structures. There are three interconnected main regions: the lateral, medial and orbitofrontal PFC. The dorsolateral PFC (dlPFC) is located on the lateral surface of the frontal lobe anterior to the premotor regions. The dlPFC has preferential connections with motor structures and forms part of the dlPF network involved in cognitive control of movement. As movement becomes more goal-directed (i.e. requiring greater voluntary control), a larger extent of cognitive power is necessary. The dlPF network is often implicated in a wide range of executive functions including the control of goal-directed movement.

The dlPF network loops solely onto the dlPFC but originates more diffusely from the dorsolateral, medial and orbitofrontal PFC. Outputs converge and project between specific subdivisions responsible for cognitive functions within BG nuclei (Figure 2.1B). Within the striatum cognitive function is localized to the dorsolateral caudate nucleus and anterior putamen (Draganski et al., 2008; Nakano et al., 2000). These two regions project directly to the dorsomedial portion of GPi and indirectly to the rostral portion of SNpr. The indirect and hyperdirect cognitive pathways project via the medial portion of STN (Haynes and Haber, 2013). The cognitive regions of the BG output nuclei project to the ventroanterior and mediodorsal thalamic nuclei, and from there back to the dlPFC.

In order to modify voluntary movement, the dlPF network must influence cortical motor regions. The dlPFC can indirectly influence M1 via connections through SMA and preSMA (Haggard, 2008; Miller and Cohen, 2001). There are also direct connections between dlPFC and the anterior section of the dorsal PMC in nonhuman primates (Luppino et al., 2003). The dorsal PMC is implicated in higher-order motor control (Picard and Strick, 2001) and even hypothesized to be a gateway between cognitive and motor networks (Hanakawa, 2011).

To understand the influence of the dlPF network during goal-directed movement consider the ability to select a relatively weaker, task-relevant response in the presence of a

stronger task-irrelevant response, as in an antisaccade task. A saccade is a small, rapid movement of the eye from one fixation point to another. An antisaccade task requires suppression of an automatic saccade towards a presented visual stimulus, and instead a saccade toward the opposite, un-cued direction (the antisaccade). Nonhuman primates demonstrate impaired performance on an antisaccade task during transient dlPFC deactivation. Impairment is evident on antisaccade trials through higher error rates and increased reaction times on correct trials (Koval et al., 2011). The dlPF network is therefore recruited to facilitate the switch from a more automatic response to one requiring higher levels of cognitive control.

The limbic network

The limbic system is a collection of structures including the cerebral cortex, BG, midbrain and posterior forebrain on either side of the thalamus. It supports a variety of functions, including mood and emotional state, and can have strong influences over the manner in which voluntary behaviours are executed.

The limbic network follows the same basic architecture as the motor and cognitive networks (Figure 2.1B). The medial and orbitofrontal PFC send glutamatergic projections to the nucleus accumbens (NAcc), which is an important limbic structure situated within the ventral striatum (Groenewegen et al., 1999; Heimer et al., 1997). The NAcc has GABAergic projections to the ventral pallidum. Because the ventral pallidum is not as structurally segregated relative to the demarcation between GPi and GPe (Alexander and Crutcher, 1990b), the direct and indirect pathways of the limbic network are less clearly differentiated than those of the other networks. Evidence exists for a prefrontal-STN hyperdirect limbic pathway, projecting to the medial tip of STN (Haynes and Haber, 2013; Parent and Hazrati, 1995). The ventral pallidum sends GABAergic projections to the mediodorsal thalamus which in turn has glutamatergic projections back to the medial PFC (mPFC) to close the loop (Churchill et al., 1996).

The limbic network is comprised of subnetworks including: the mesolimbic, mesocortical and anterior cingulate networks. The mesocorticolimbic (MCL) network has an important role in reward, motivation, learning, memory and voluntary movement. The mPFC is part of the MCL network and sends major glutamatergic projections to NAcc. The NAcc also receives glutamatergic input from limbic structures such as the amygdala and hippocampus (Groenewegen et al., 1999). Similar to the posterior putamen serving as the motor-sensory interface of the BG, NAcc is described as the limbic-motor interface (Mogenson et al., 1980). The NAcc plays a vital role in goal-directed behaviour (movement) by

integrating contextual information from the hippocampus and emotional information from the amygdala with PFC cognitive functions, in order to select appropriate responses (Grace, 2000; Mogenson et al., 1980).

Changes to dopaminergic neurotransmission have important implications for the flow of information through the MCL network. The midbrain contains the majority of dopaminergic neurons within the brain, split mainly between SNpc which forms part of the dopaminergic nigrostriatal system (discussed in the following chapter), and the ventral tegmental area (VTA). The VTA is located medially to the SN and forms part of the dopaminergic MCL network. VTA dopaminergic neurons innervate the hippocampus, mPFC, amygdala and notably NAcc (Goto and Grace, 2005; Kalivas and Nakamura, 1999). The NAcc receives dense dopaminergic innervations from VTA and has inhibitory projections back to VTA (Kalivas and Nakamura, 1999; Nauta et al., 1978) forming a feedback loop. Dopaminergic tone within VTA has two modes of influencing goal-directed behaviour through its dopaminergic connections in the MCL network: i) directly modulating dopamine at the site of limbic-motor integration within NAcc; ii) modulating dopaminergic tone within PFC, which also has an additional effect on NAcc via frontostriatal connections. The pattern of excitatory and inhibitory connections between VTA, PFC and NAcc within the dopaminergic MCL network results in the PFC and midbrain having reciprocal influences on each other.

The dopaminergic MCL network plays a central role in the neurobiology of addiction (Blum et al., 2012), depression (Vaillancourt et al., 2013; Van den Heuvel and Pasterkamp, 2008), and schizophrenia (Weinberger et al., 1992). Most importantly for the present thesis, the MCL network is implicated in impulse control disorders in the presence of dopaminergic medication (Sawamoto et al., 2008; Vaillancourt et al., 2013). The inability to correctly modulate dopaminergic activity within the MCL network due to a persistent hyperdopaminergic state is hypothesized to contribute to the development of impulse control disorders on dopaminergic medication. How might this occur? Phasic bursts of dopamine release and D1 dopamine receptor activation within the MCL network signal reward and lead to contextual behaviour reinforcement (Goto and Grace, 2005; Morita et al., 2013). Phasic decreases in dopamine likewise modify synaptic plasticity to suppress cortical activity associated with the current response to decrease the likelihood of repeat behaviour. In a healthy state, tonic dopamine release from VTA neurons is maintained at a level such that phasic increases or decreases to dopamine levels can modulate behaviour through attention, reward and reinforcement learning (Goto and Grace, 2005; Rebec et al., 1997; Schultz, 2002). Tonic dopaminergic activity in the MCL circuit is believed to be elevated with dopaminergic medication. Enhanced tonic levels of dopamine prevent phasic decreases in dopamine from

being effective, thereby potentially reinforcing behaviours which are inappropriate or detrimental that would otherwise normally have resulted in phasic decreases to prevent future repetition. The net result: poor impulsive control and compulsive behaviour.

Separation and integration between networks

It is currently unclear as to the exact level of segregation between the motor, cognitive and limbic networks. The functional integration within the putamen and NAcc discussed above would argue against a strictly segregated network hypothesis. Furthermore, anatomical subdivisions within BG nuclei have been proven to be less distinct than once thought. Mapping the connectivity profile of distinct cortical projections to STN reveals significant topological overlap between anatomical regions of STN in both macaques (Haynes and Haber, 2013) and humans (Lambert et al., 2012). On the other hand, single cell recordings in animals have shown remarkable preservation of functional specificity at the level of individual neurons in the different networks (DeLong et al., 1984). It seems unlikely that such functional specificity could be possible without relatively strict topographical specificity within sequential projections of the networks. The idea of increasing convergence or 'funnelling' from the level of the cortex to the thalamus in the networks has been around for almost three decades (Alexander et al. 1986) (Figure 2.1B). The debate still exists as to the extent of integration within versus between networks.

The three networks have traditionally been considered as closed loops conducive to serial processing of information, with little or no flow of information between networks. For example, a decision to act would be made in the cognitive network and then passed to the motor network. However evidence from more contemporary connectionist models argues for a more interactive real-time form of information processing between the networks (for a review see Cisek and Kalaska 2010). The connectionist view necessitates a more open loop and interconnected design. Consider SNpr, which is traditionally classified as part of the motor network. Its output projects preferentially to PFC (Ilinsky et al., 1985) and it is therefore postulated to be heavily involved in nonmotor aspects of behaviour (Wichmann and Kliem, 2004). This architecture implies that motor information emanating in the motor network would also be directed to nonmotor prefrontal regions. Similarly, as mentioned, dorsal PMC has connections with both motor and cognitive cortical structures (Luppino et al., 2003). Such open loop architecture would enable information flow bi-directionally between motor and cognitive networks. Similar open loop design may also exist between cognitive and limbic networks. The idea of open cognitive-limbic loops is supported by

mPFC involvement in both cognitive and MCL networks and that the MCL network has an important influence on the cognitive functions of the dlPFC.

Any level of separation between the motor, cognitive and limbic networks, be it functional or anatomical, would necessitate that the output of the different control systems must at some point converge onto lower level motor structures that generate motor output. The exact site of this proposed 'final common motor path' is currently unknown. M1 is one likely candidate and therefore a good location to examine the combined effect of all networks on motor output. On the other hand, the exact role of each network cannot be delineated at this level as such convergence would allow any voluntary movement to be under varying levels of control from any, or all, of the networks. Interventions or investigatory methods that aim to target subcomponents of movement control must therefore still be interpreted in the context of all three motor, cognitive and limbic networks. This is also an important consideration when interpreting the behavioural effects of BG dysfunction.

2.2 Inhibition of voluntary movement

Situations may arise in which a prepared movement suddenly becomes unnecessary or inappropriate. For example, when a car suddenly pulls out as you're about to cross the road, the ability to rapidly cancel your movement becomes vitally important. RI engages a right-lateralized brain network. The RI network includes several of the structures in the motor, cognitive and limbic networks discussed previously: PFC, several BG nuclei, thalamic regions and M1. The specific components activated within the RI network depend on inhibition goals, i.e. stopping all or only part of a response.

RI has traditionally been investigated using a stop-signal or go/no-go task. These tasks have the advantage of well-defined go and stop cues, but they require participants to respond to external cues (i.e. a signalled response). Externally cued movements require less involvement of the BG system compared to internally generated movements (Jahanshahi et al., 1995). An anticipatory response inhibition (ARI) task (based on Slater-Hammel 1960) allows investigation of internally cued anticipated motor responses. For descriptions of each task see Chapter 3 Section 3.3. These different task designs investigate three distinct subdivisions of RI; action restraint/withholding (go/no-go task), action postponement (stop-signal task, SST) and action cancellation (ARI task). This section will discuss findings from all three tasks which have provided useful insight into the role of RI network components and how they interact to suppress motor output during complete and partial movement cancellation.

2.2.1 Components of the response inhibition network

Inferior frontal cortex

The PFC is an integral part of the RI network. Evidence over the last decade supports a vital role of the right inferior frontal cortex (rIFC) (for a review see Aron et al. 2014). A significant proportion of this evidence comes from functional magnetic resonance imaging (fMRI). This MRI technique detects the increased blood flow and corresponding proportional reduction in deoxyhemoglobin in local vasculature associated with neuronal activation by measuring a blood-oxygen-level dependent (BOLD) signal. Using this technique, rIFC activation can be detected during motor inhibition (Aron et al., 2007b; Aron and Poldrack, 2006; Garavan et al., 1999; Liddle et al., 2001; Rubia et al., 1999, 2003). These findings suggest that rIFC is an agent of RI and may exert inhibitory effects onto downstream components of the RI network. However Sharp et al. (2010) use fMRI during a modified version of the SST to argue that the rIFC is preferentially involved in attentional capture of the stop signal, and not RI per se. Sharp and colleagues added Continue trials to the traditional SST as a control that presented a salient stimulus without requiring RI. Right IFC activation for successful cancellation during Stop trials was essentially no different than that during Continue trials. The authors concluded that rIFC was activated during attentional capture of the salient stimulus in both Stop and Continue trials. This single study provides robust observations that challenge a body of literature regarding the role of rIFC in RI. The incompatibility between studies reminds us of the limitations of fMRI for identifying region-specific cognitive function.

There is another important caveat when interpreting fMRI study results in the context of RI. A common data analysis approach to isolate stopping-related activation is to contrast successful with unsuccessful Stop trials. However a stopping process is likely still initiated on an unsuccessful Stop trial, albeit too late to prevent the movement. The method of contrasting would therefore cancel out a large proportion of the stopping related activity which is present in both trial outcomes. Contrasting successful with unsuccessful Stop trials might therefore lead to erroneous conclusions and contribute to the discrepancy between neuroimaging findings in the RI literature.

The role of rIFC has also been investigated in patients with cortical damage. Damage to rIFC can impair inhibitory control (Aron et al., 2003), and the impairment seems to be positively correlated with the extent of lesion damage (Clark et al., 2007). However this is not always the case. Only one of five patients with rIFC lesions presented with decreased inhibitory control in a study by Floden and Stuss (2006). Low frequency repetitive transcranial magnetic stimulation (rTMS) can produce a 'virtual lesion' in neurologically

healthy participants by transiently suppressing excitability of the stimulated region. When administered to the rIFC by Chambers et al. (2006) rTMS impaired inhibitory control. This effect was not reproducible in a second session however, questioning the reliability of this finding. It is also worth noting that all the above mentioned results that demonstrate impaired inhibitory control with disruption of rIFC could be from an inability to attend to the stop signal (which would support the results of Sharp et al. 2010). The exact function may still be under debate, but the majority of evidence leads to the conclusion that rIFC is involved in the RI network, be it to register or react to the stop signal.

Supplementary motor regions

In humans, SMA and preSMA are in the dorsomedial frontal cortex within the superior frontal gyrus (Picard and Strick, 1996, 2001). The preSMA only has a small number of direct connections with M1 (Civardi et al., 2001; Picard and Strick, 1996). However, preSMA has afferent input to SMA, which has a strong influence over M1 (Picard and Strick, 1996; Tanji and Mushiake, 1996) and makes a substantial contribution of about 10 % to the corticospinal tract in nonhuman primates (Dum and Strick, 1991; He et al., 1995). PreSMA and SMA are both capable of modulating output from the corticospinal pathway and therefore have the ability to inhibit voluntary motor output.

Lesions encompassing both right SMA and preSMA impair RI performance (Floden and Stuss, 2006). However there are opposing views as to the role of SMA versus preSMA in inhibitory control. Electrophysiological recordings from nonhuman primates demonstrate increased activity of SMA neurons in response to a sensory cue to withhold movement (Kurata and Tanji, 1985; Schall, 1991). Degree of SMA activation is also positively correlated with speed (but not success) of inhibition on the SST (Li et al., 2006). In comparison, anodal transcranial direct current stimulation (TDCS) increasing excitability of the preSMA improves success (but not speed) of inhibition on the same task (Hsu et al., 2011). However there are caveats regarding spatial specificity when using TDCS to distinguish the roles of adjacent cortical regions. Nevertheless, action restraint in a simple go/no-go task (Mostofsky et al. 2003, see also the meta-analysis by Simmonds et al. 2008) and inhibition during the SST (Aron and Poldrack, 2006; Sharp et al., 2010) are associated with increased preSMA activation in healthy adults. Temporary inactivation of preSMA via low frequency rTMS decreases success and speed of RI in healthy adults, but again this effect was not robustly reproduced in a second session (Chen et al., 2009).

In contrast, case studies of very focal lesions to preSMA that leave SMA untouched demonstrate no deficits in simple stopping performance (Nachev et al., 2007; Roberts and

Husain, 2015). Focal preSMA lesions instead produce deficits during stop-change tasks requiring switching from one response plan to another. These findings suggest SMA proper has a role in simple movement inhibition and preSMA is preferentially recruited during more complex RI tasks involving task switching. Mounting evidence suggests preSMA is involved in resolving response conflict and reprogramming responses during task switching. This will be discussed further in Section 2.2.2 in the context of partial RI.

The IFC, preSMA and SMA are interconnected in nonhuman primates (Luppino et al., 1993) and humans (Aron et al., 2007a; Johansen-Berg et al., 2004). These areas therefore interact during RI, especially under conditions of increased task difficulty.

Basal ganglia

Along with PFC, the BG are another proposed agent of RI that exerts inhibitory effects on downstream thalamic and cortical structures. The neuroanatomy of cortico-BG-thalamocortical networks and BG pathways has been discussed in detail. The purpose of the following section is to firstly highlight the contribution of the indirect and hyperdirect BG pathways to RI performance, and secondly to highlight how PFC components discussed above recruit these BG pathways as part of the RI network.

Diffusion imaging enables the investigation of anatomical connectivity between RI network components. Diffusion tensor imaging (DTI) allows in vivo visualization of brain white-matter microstructure and integrity (Lehericy et al., 2012; Marino et al., 2012). This technique is used to visualize the random movement (diffusion) of water molecules in tissue. The degree of anisotropy of water diffusion along fibre tracts is quantified by the fractional anisotropy (FA) measure (Lehericy et al., 2012; Marino et al., 2012). Decreased anisotropy of white matter indicates water diffusion is less constrained along the direction of the nerve fibres due to decreased structural integrity. For example, tissue damage due to neurodegeneration or normal ageing is represented by a decreased FA value and an increase in global or whole brain diffusivity signifies cellular atrophy of grey matter. Tractography utilizes anisotropy measures to map fibre tracks. Tractography is based on the assumption that the local orientation of white matter fibres can be determined from the main diffusion direction within a voxel. Fibre tractography has helped elucidate the cortico-BG connectivity in the RI network.

DWI tractography has identified direct white matter connections between rIFC-STN and preSMA-STN in humans (Aron et al., 2007a). This finding extends previous evidence from nonhuman primates (Inase et al., 1999; Nambu et al., 1996) of direct projections from preSMA to STN. The integrity and strength of these hyperdirect connections to STN from

rIFC and preSMA can predict the efficiency of inhibitory control in healthy individuals (Coxon et al., 2012). Coxon and colleagues found larger FA values, representing greater structural integrity, for hyperdirect connections between rIFC and right STN correlated with a faster stopping process for younger and older participants on the ARI task. The strength of hyperdirect connections between bilateral preSMA and STN predicted the latency of the stopping process in older individuals. Previous fMRI results have shown associated activation of rIFC, preSMA and STN (Aron and Poldrack, 2006). Importantly, though, STN is part of both the indirect and hyperdirect BG pathways. Activation on fMRI alone does not conclusively distinguish which pathway is recruiting STN. Tractography results on the other hand verify the importance of STN within hyperdirect pathways for RI.

The indirect pathway is capable of producing more selective inhibition onto BG output nuclei than the hyperdirect pathway. The increased latency of the indirect pathway implies it is better suited for RI without an immediate time constraint. For example, when participants are given a cue that stopping probability is higher in the ARI task, they show a proportional increase in striatum activation (Zandbelt and Vink, 2010). This suggests a role of the striatum in anticipation of stopping when more time is available to implement the stopping process. Likewise, action withholding in the go/no-go task is implemented in a less time crucial manner and has been associated with striatum activation (Menon et al., 2001). Neuroanatomical evidence of connections in nonhuman primates (Inase et al., 1999) and associated fMRI activation in humans (Zandbelt et al., 2013; Zandbelt and Vink, 2010) demonstrate that IFC and SMA/preSMA can recruit the indirect pathway via the striatum in certain RI contexts.

PFC regions within the RI network are able to recruit either indirect or hyperdirect BG pathways via the striatum or STN, respectively. As STN is part of both pathways, there is consensus STN plays a key role in RI. The relative importance of the two pathways during RI likely depends on the time constraints of stopping. Rapid termination of movement would necessitate recruitment of the faster hyperdirect pathway that has more divergent inhibitory effects on downstream structures within the RI network.

Primary motor cortex

The primary motor cortex (M1) is a downstream target for inhibitory control. Cortico-BG pathways directly or indirectly decrease excitability within M1 to prevent prepared voluntary movement. RI networks have different mechanistic ways to ultimately decrease M1 excitability: 1) direct postsynaptic inhibition of M1 pyramidal neurons, 2) withdrawal of direct excitatory input onto pyramidal neurons, 3) presynaptic inhibition of excitatory

synapses onto pyramidal neurons, or 4) excitation of inhibitory circuits onto pyramidal neurons. Any of these mechanisms would decrease pyramidal neuron excitability and are not mutually exclusive. The output of any corticospinal neuron is the net effect of its excitatory and inhibitory inputs. Excitability of the corticomotor pathway from M1 can be probed using noninvasive brain stimulation techniques such as TMS (for a more detailed discussion on single and paired-pulse TMS see Chapter 4 Section 4.1).

TMS is routinely used to examine task-dependent effects on M1. It has been used to investigate temporal modulation of corticomotor excitability (CME) during movement preparation. Even in studies designed to investigate RI, it is prudent to examine CME on Go trials: i) to ensure the default response is being reliably initiated when expected; ii) to compare with temporal modulation of CME on Stop trials. The beginning of a Stop trial (in the stop-signal and ARI task) is indistinguishable from a Go trial, so initial CME modulation should be comparable. TMS reveals an increase in agonist muscle representation excitability in the 100 ms preceding onset of electromyography (EMG) activity for a simple motor response (Chen and Hallett, 1999; Coxon et al., 2006; Duque et al., 2010; Leocani et al., 2000; Marinovic et al., 2011; Pascual-Leone et al., 1992). This increase in CME is likely reflecting depolarization of pyramidal neurons that is exerting a subthreshold effect on the alpha motoneuron pool. For this reason, it seems most appropriate to distinguish the onset of CME increase as the switch from movement preparation to movement initiation. Movement initiation is seen about 150 ms prior to the target on Stop trials in the ARI task (Coxon et al., 2006). This confirms the stop signal in an ARI task is triggering rapid termination of an initiated movement i.e. reliably investigating action cancellation.

When a stop cue is presented during movement preparation, CME is suppressed 100 – 200 ms after the stop or no-go cue (Cai et al., 2012; Coxon et al., 2006; Hoshiyama et al., 1997, 1996; Majid et al., 2012; Yamanaka et al., 2002; Yamanaka and Nozaki, 2013). The latency reflects stop cue perception, recognition of the need for cancellation and then the cortico-BG-thalmocortical inhibitory network exerting an effect onto M1. For complete cancellation of simple unimanual responses, CME suppression is observed not only for the task-relevant muscle, but also for task-irrelevant (Badry et al., 2009; Cai et al., 2012; Majid et al., 2012) and antagonist muscles (Hoshiyama et al., 1996). Furthermore, Coxon et al. (2006) demonstrated elevated intracortical inhibition during Stop relative to Go trials of a nearby muscle representation as well as of the agonist. Collectively, the nonfocal suppression and inhibition during complete RI implies downstream effects from activation of the hyperdirect pathway, leading to divergent inhibitory effects onto muscle representations in M1.

The majority of the studies mentioned above investigated CME during complete cancellation of simple unimanual responses. Less is known about temporal modulation of CME during partial RI.

2.2.2 Partial response inhibition

Response inhibition does not always occur in an all-or-nothing context. Situations often require inhibitory control where some undesired responses are inhibited, while others must proceed unimpeded. Partial cancellation of movement is investigated in Chapters 5 to 7. The following section discusses the main behavioural observation and possible underlying neural mechanisms during this form of RI without repeating discussion in subsequent chapters.

Behavioural observation

The behavioural selectivity of RI can be investigated by cueing the cancellation of only a subset of a prepared multi-component response. Interestingly, the requirement for partial cancellation substantially delays the remaining executed component. The response delay following an unexpected stop signal has been reported in the range of 105 – 118 ms using the SST (Aron and Verbruggen, 2008; Claffey et al., 2010; Ko and Miller, 2011). The response delay was first demonstrated with the ARI task in 2007 (Coxon et al., 2007). Coxon and colleagues showed that the delay could be up to 100 ms or more, which has since been replicated in young (Coxon et al., 2009; Yamanaka, 2014) and older adults (Coxon et al., 2014, 2012). Why might this response delay be present?

Response delays are observed even in the presence of explicit advance warning of stopping goals. Using a bimanual choice SST, Majid et al. found that response delays could be reduced to an average of 74 ms by providing foreknowledge of which hand may need to be stopped in the future (Majid et al., 2012). On the other hand, other studies providing foreknowledge of stopping goals still report delays up to 184 ms (Aron and Verbruggen, 2008; Cai et al., 2011; Claffey et al., 2010). Advance information of the stopping goal is associated with suppression of the precued corticomotor hand representation, even before the go signal (Cai et al., 2011). Cai and colleagues demonstrated a decrease in motor evoked potential (MEP) amplitude of the right first dorsal interosseous muscle after the participants received a cue that the right hand might need to stop. This has been referred to as proactive inhibition. The mechanisms leading to proactive suppression before the go signal may be very different to reactive suppression after an unexpected stop signal (Duque et al., 2010). It

can be argued that the most vital and time-sensitive inhibitory responses in everyday life are most commonly associated with sudden and unexpected events where no warning is available. Proactive RI is acknowledged in the current thesis but not discussed in depth. The current experiments examine RI in a purely reactive context.

A recent paper has challenged the validity of the response delay (Xu et al., 2014). This study used a modified SST that presented an imperative for two responses: a manual choice response between left or right index fingers (cued by an arrow) and an invariant foot response. Over four experimental sessions the subsequent stop signal only ever related to the manual response; the arrow turned red (two consecutive sessions), or the relevant response key was vibrated. Monetary incentive was given in an attempt to prevent participants from delaying their foot response when Stop trials were introduced.

Xu et al. (2014) contended that the delay observed in the foot RTs when the hand response was cancelled merely reflected sampling bias. In the archetypical SST, the reaction times (RTs) from unsuccessful Stop trials arise, on average, from the early half of the overall Go RT distribution i.e., Go responses that were executed too quickly for the Stop process to intervene. Consequently, they inferred that successful RTs during partial RI are inherently delayed compared to the mean Go RT, representing a "sampling bias". When using the highly compatible tactile stop signal (key vibration) and their statistical model, Xu and colleagues argued that the response delay can be eliminated after multiple practice sessions even without providing foreknowledge. This contrasts with the consistent response delays across multiple sessions of the ARI task. Xu and colleagues concluded that the response delay in other studies, using either stop-signal or ARI paradigms, "may be the result of a statistical artefact inherent in the standard way of assessing this delay" (Xu et al., 2014). So are response delays robust or not?

Although the model of Xu and colleagues has merit, important caveats exist surrounding the data to which it is applied. Firstly, and most importantly, the authors have attempted to generalize across results obtained from different paradigms. The overlap between Go and Partial RI distributions attributable to sampling bias may be evident in the SST. However, this sampling bias is unlikely to apply to the ARI paradigm due to the tighter and normally distributed Go response distributions inherent to this task (explored in more detail in Chapter 7). Secondly, the inter-limb hand and foot responses in Xu et al. (2014) are less strongly coupled than bimanual responses, especially those comprised of homologous muscles. Weaker coupling may have decreased the response delay in the Xu et al. (2014) study (see below). Thirdly, the very short stop signal delays (SSDs) between the imperative and stop signal in Xu et al. (2014) (88 – 106 ms) probably influenced how the task was achieved.

These short SSDs, which are shorter than a standard simple RT, raise the possibility that the stop signal was presented prior to reliable preparation of a multi-component response. Combined with a de-emphasis on stopping through their reward scheme for participants, the short SSDs may have essentially changed the Stop trials to a go signal for the invariant foot response. It is therefore somewhat unsurprising that the authors observed smaller/absent response delays. These factors may also explain why the delays only reduced under very specific conditions. The authors might have reached a different conclusion had they applied their modelling approach to data obtained using an experimental setup that wasn't so carefully designed to reduce the delay in the first instance.

Other studies which have investigated the response delay have cued partial cancellation of a *bimanual* response. In this context the transient structural constraints of bimanual movement need to be considered. The coactivation of muscles involves transient coupling of movement characteristics during motor programming (for a review see Heuer 1993) which occurs most strongly between homologous muscles (Kelso, 1984). Importantly in the context of RI tasks, the effect of coupling on response time depends on whether programming occurs before or after the response signal. The SST bimanual RT involves a choice between two possible bimanual pairings at the time of the imperative e.g. both index or middle fingers. Therefore in the SST coupling can only occur after the go signal and would be expected to influence RT. This may partly explain the slow, right-skewed distribution of bimanual RTs during the SST (discussed in more detail in Chapter 7). Furthermore, response times in the SST would be expected to depend on the strength of coupling between components (c.f. Xu et al. 2014). On the other hand, in the bimanual ARI task there is always advance specification of the muscle groups involved. This is because the same response is anticipated on every trial and there is no choice component. Response programming and thus coupling can occur before internal generation of the response and therefore have no affect on response time. Bimanual response times are also not expected to depend on the strength of coupling between response components (i.e. homologous versus nonhomologous muscle pairs, explored in more depth in Chapter 5).

Although the duration of the response delay depends on the experimental approach, the majority of studies indicate the behavioural observation is a robust phenomenon. However the question remains: what are the neural mechanisms giving rise to this delay?

Selective versus nonselective neural mechanisms

Although cancellation can be achieved selectively at a *behavioural* level, there is contention about whether or not RI is being implemented via a selective *neural* mechanism in this

context. As such, there is currently an active debate regarding the neural mechanisms underlying the response delay during partial RI.

It has been suggested that partial cancellation *with prior knowledge of stopping goals* can be implemented via a selective stopping mechanism onto just the muscle cued to stop (Aron and Verbruggen, 2008; De Jong et al., 1995). De Jong et al. (1995) did not set out to investigate proactive inhibition by providing participants with explicit warning of the stopping goal, as done by Aron and Verbruggen (2008). However the block design of stopping conditions meant each block of 96 trials only consisted of one Stop trial type (e.g. Stop Left only). Participants would therefore have quickly learned the stopping goal for the block i.e. gained prior knowledge of which was the 'critical' hand that may stop. This would explain the significantly delayed Go RT for the critical hand (by 37 ms) compared to the noncritical hand in this study. The authors themselves acknowledged this RT discrepancy indicates participants were likely delaying the response with the critical hand to increase the chance of successfully withholding the response when necessary. This waiting strategy may also explain why the (additional) response delay following partial cancellation in this study was only 44 ms, compared to delays of 100 – 118 ms following an unexpected stop signal (Aron and Verbruggen, 2008; Claffey et al., 2010; Coxon et al., 2007; Ko and Miller, 2011).

Response delays were still observed in the studies by De Jong et al. (1995) and Aron and Verbruggen (2008) even with advance/explicit warning. The authors proposed detection of the stop signal recruits the slower indirect BG pathway that exacts inhibition which is selective at a neural level. However this appears to be incompatible with their reported response delays of 99 ms (Aron and Verbruggen, 2008) and 44 ms (De Jong et al., 1995). A truly selective stopping mechanism acting on only the cancelled response would be expected to have no effect on the noncancelled hand. Of note, even if a participant has advance warning about which hand may stop, they are still required to respond reactively and very rapidly to the stop signal when it is detected. An alternate interpretation of these results is therefore that even if advance warning is given, the rapid response to a partial stop signal engages a nonselective stopping mechanism which terminates all prepared output. The required (partial) response is then initiated. Time requirements for these processes would result in an inevitable response delay.

The alternate, nonselective stopping mechanism is likely via the hyperdirect BG pathway. The structural integrity of hyperdirect connections between IFC and STN and the strength of connections between preSMA and STN are inversely correlated with not only outright stopping, but also the response delay on the ARI task (Coxon et al., 2012). The same hyperdirect pathway recruited for sudden outright stopping is therefore also activated in partial

cancellation in reaction to the unexpected and perceptually salient stop signal (Wessel and Aron, 2013). Activation of this pathway, which is nonselective at a neural level, leads to the termination of all prepared movement. Importantly, this is where partial cancellation requirements deviate from outright stopping — execution of a (partial) response is still required. How then can this be achieved?

The terminated multi-component response must be reprogrammed and a new response must be generated to meet the new task requirements. For example, a prepared bimanual response is reprogrammed to switch to a (controlled) unimanual response. Action reprogramming and task switching in the presence of response conflict activate neurons in preSMA (Dove et al., 2000; Isoda and Hikosaka, 2007; Mars et al., 2009; Nachev et al., 2005; Rushworth et al., 2002) and STN (Isoda and Hikosaka, 2008) and lead to response delays. Activation of STN during task switching may be revealing its functional role in the hyperdirect pathway to rapidly terminate all movement when response conflict is detected, as a means to implement cognitive control (Frank, 2006). Indeed Kenner et al. (2010) used fMRI during a unimanual switching task to show common recruitment of rIFC, preSMA and BG structures during simple RI and task switching. The authors inferred that the same rapid, nonselective stopping mechanism for simple RI supports rapid response switching when paired with the new appropriate response (Kenner et al., 2010). Surprisingly, Kenner and colleagues did not find activation of preSMA during task switch trials over and above that during simple RI, suggesting it was not recruited for response reprogramming. On the other hand, preSMA is activated to a higher degree during partial Stop trials of the ARI task (Coxon et al., 2009). PreSMA activation above outright stopping levels may signal the occurrence of reprogramming during partial RI on the ARI task. It seems likely that the time requirements for reprogramming and unimanual execution are contributing to the response delay.

M1 is a downstream target of inhibitory control. Therefore examining CME after presentation of the stop signal may elucidate whether partial RI involves a selective or nonselective stopping mechanism. Majid et al. (2012) recorded CME at a single time point following the stop signal during partial RI. They used the SST to cue partial cancellation of a bimanual choice response and recorded MEP amplitude from the left tibialis anterior muscle. Majid and colleagues showed that CME of the task-irrelevant leg muscle was not suppressed 200 ms after presentation of the stop signal if foreknowledge of the future stopping goal was provided. They concluded that RI can be selective and applied to only one component of the bimanual response i.e. motor cortex suppression is not 'global' following a partial stop signal. However they did not examine CME of either task-relevant hand muscle which

comprised the bimanual response. The temporal modulation of CME for prepared versus unprepared muscle representations is likely to be fundamentally different.

The underlying mechanisms of RI that give rise to the response delay are still not fully understood and are investigated in Chapters 5 to 7. These chapters seek to answer the question: is the behavioural selectivity of RI achieved at the neural level through a simultaneous and selective Stop and Go mechanism, or a sequential nonselective Stop then Go mechanism? Elucidating the mechanisms involved may determine if this form of RI has potential utility in clinical populations which experience dysfunction in frontal and BG regions e.g. Parkinson's disease.

2.3 Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disease that affects around 6.3 million people worldwide (Apaydin et al., 2002; Braak et al., 2004; EPDA, 2014). The disease takes several years to develop, with 69 – 80 being the average age at diagnosis (Chillag-Talmor et al., 2011; Liu et al., 2015). Currently PD cannot be cured. PD does not necessarily decrease life expectancy, but it has a large impact on quality of life. The main aim of treatment is to maintain quality of life for as long as possible.

The pathological progression of PD targets multiple regions within the human nervous system (Apaydin et al., 2002; Braak et al., 2004; Saladin, 2011). The typical motor symptoms of PD include a pill-rolling tremor at rest, muscular rigidity, postural instability, bradykinesia (slowing of movement) and gait disturbance. Although motor symptoms are common landmarks for diagnosis and staging, PD also involves disturbances in cognitive, limbic and autonomic systems. Nonmotor symptoms include, but are not limited to: anosmia (loss of smell sensation), dementia, anxiety, depression, digestive disturbance, executive dysfunction and rapid eye movement (REM) sleep behavioural disturbance (RBD). The expression of symptoms can vary greatly between individuals. This variability is potentially due to individual factors (e.g. genetics), but also due to the extent of neurodegeneration.

Chapter 3 proposes that RI tasks have potential utility during the very early stages of PD to tap into mechanisms of injury and help with earlier diagnosis. RI tasks may be able to reveal subtle, subclinical motor abnormalities during this prediagnostic stage. When included as part of an objective test battery, RI tasks may help shorten the prediagnostic stage to facilitate better treatment and ultimately better quality of life. As PD includes substantial nonmotor symptoms, nonmotor biomarkers should also be included in the test battery. The following sections provide some background as to why measures of olfactory

function and RBD would be particularly useful. Measures obtained from MRI techniques may also complement the early behavioural manifestations of PD. Combined with a RI task, these measures may provide a useful objective test battery for identifying the insidious motor and nonmotor changes during the prediagnostic stage of PD, to aid earlier diagnosis.

2.3.1 Progression of Parkinson's disease

There are six neuropathological stages to the progression of PD (Braak et al., 2003, 2004). These stages can be further subdivided into two phases: presymptomatic and symptomatic. The underlying pathology of the disease begins a substantial amount of time prior to the exhibition of symptoms, starting in the brainstem and moving upwards to the cerebral cortex.

Presymptomatic phase (stages 1 – 3)

Over the course of PD, there is continual development of distinctive inclusion bodies in the somata of affected neurons (Apaydin et al., 2002; Braak et al., 2003, 2004; Takahashi and Wakabayashi, 2001). These intraneuronal inclusions are present in the form of Lewy bodies (globular) and Lewy neurites (thread-like) and are the hallmark of the presymptomatic disease phase. The inclusion bodies consist mainly of clusters of α-synuclein, a presynaptic protein which becomes misfolded (Dickson, 1999; Wakabayashi et al., 1992). The exact function of α-synuclein is still being revealed, but the protein is postulated to be involved in maintaining a supply of presynaptic vesicles, which is critical for neurotransmitter release and therefore neurotransmission. The healthy form of the protein appears to be important for the regulation of dopamine release.

It is hypothesized that trigger factors, perhaps genetic or environmental, cause a cascade of events which includes the misfolding and dysfunction of α-synuclein (Recchia et al., 2004). The mechanism by which dysfunctional α-synuclein causes or contributes to neuronal cell toxicity and death is complex and still unknown. Also unknown, is why the neurons are unable to eliminate the abnormal protein. Alpha-synuclein is naturally abundant within the nervous system, with predominant expression in the SN, hippocampus, olfactory bulb, striatum, neocortex, thalamus and cerebellum (Iwai et al., 1995; Nakajo et al., 1994). As neurons within these structures have large amounts of α-synuclein, they are especially susceptible to developing these abnormal aggregations.

Neuronal damage from PD does not occur in a random pattern of lesion distribution, but follows a coherent sequence (Braak et al., 1998). Changes first occur in the dorsal

motor nucleus of the glossopharyngeal and vagal nerves, olfactory bulb and sections of the reticular formation (Braak et al., 2003, 2004). The pathology in these areas worsens and spreads throughout the following stages. During stage 2, neuronal damage extends to other reticular formation nuclei which constitute the 'gain setting' system important for motor control. These gain setting nuclei regulate the excitability of medullary and spinal premotor and motor neurons, placing them in a heightened state of preparedness for action (Holstege, 1996; Nieuwenhuys, 1996). Of note, by the end of stage 2 the pathology is still largely confined to the olfactory bulb, medulla oblongata and pons tegmentum. The medulla oblongata (Schenkel and Siegel, 1989) and pons (Sanford et al., 1994) are critical areas involved in RBD, and anosmia results from damage to the olfactory bulb. Although cardinal motor symptoms are not yet apparent (hence presymptomatic), anosmia and RBD are consistently experienced by patients in this stage of the disease.

Measures of olfactory function and RBD are ideal nonmotor biomarkers for detecting PD during this phase of the prediagnostic stage. Olfactory dysfunction combined with reduced striatal dopamine transportor binding can identify first-degree relatives of PD patients who will develop the disease (Berendse et al., 2001; Ponsen et al., 2004). Profoundly impaired olfactory function has been particularly associated with patients who experience RBD (Stiasny-Kolster et al., 2005). RBD can be defined as "a multi-faceted parasomnia involving REM sleep and the motor system in which there is problematic behavioural release that is usually experienced by the individual as enactment of distinctly altered, unpleasant, and combative dreams" (Schenck and Mahowald, 2002). It is objectively diagnosed through a loss of muscle paralysis (atonia), abnormally raised EMG tone and excessive limb twitching during REM sleep (Stiasny-Kolster et al., 2005). There is a definite link between RBD and neurodegenerative disorders, with an estimated 50 % of people who present with RBD ultimately developing a neurodegenerative disorder (for a review see Iranzo et al. 2009; Postuma et al. 2009). Timely identification of these nonmotor symptoms, along with other criteria for the diagnosis of prodromal PD (Berg et al., 2015), holds the key for utilizing this crucial time within the disease when damage to dopaminergic neurons may be preventable, or at least delayed.

The basal portions of the midbrain and forebrain, specifically SNpc, do not develop Lewy neurites until stage 3 (Braak et al., 2004). Damage to the dopaminergic neurons in SNpc is what ultimately leads to the characteristic motor symptoms of PD. Therefore, if it were possible to diagnose PD in stages 1 or 2 (before the appearance of motor symptoms) and apply immediate causal therapy, any subsequent damage to SNpc may be preventable.

Biomarkers derived from MRI may also complement the early behavioural manifestations of PD. Recent developments have made it possible to visualize and extract MRI biomarkers from the dopaminergic SN (Lehericy et al., 2012). In addition to conventional MRI, several advanced MRI techniques have shown sensitivity to neurodegenerative processes in PD. Diffusion imaging can detect diffusion abnormalities (Du et al., 2012, 2011; Marino et al., 2012; Peran et al., 2010; Vaillancourt et al., 2009; Yoshikawa et al., 2004) and widespread microstructural damage (Gattellaro et al., 2009; Tessa et al., 2008) in the BG and frontal white matter of early PD patients. Functional MRI can identify early abnormalities in the recognition memory network (Ibarretxe-Bilbao et al., 2011), abnormal frontostriatal activity during executive function (Lewis et al., 2003; Rowe et al., 2008) and a correlation between disease severity and reduced activation in BG nuclei during a precision hand grip task (Prodoehl et al., 2010). Iron-sensitive sequences demonstrate that iron content is increased in SN of PD patients (Berg et al., 2001; Dexter et al., 1989; Du et al., 2012, 2011) even in early stages (Martin et al., 2008; Peran et al., 2010). All these imaging techniques show initial promise in identifying *de novo* PD patients. Although imaging is mentioned here in the context of prediagnostic PD, imaging is also potentially useful post diagnosis, to objectively monitor disease progression and treatment effect.

Symptomatic phase (stages 4 – 6)

Only the symptomatic phase of the degenerative process is currently able to be clinically assessed. Clinical assessment relies on the presentation of overt signs, which usually occur somewhere between stages 3 – 4 The development of symptoms reflects that the individual's 'neurophathological threshold' has been exceeded. Essentially, the cortical pathology during stages 4 – 6 follows the pattern of cortical myelination in reverse.

During stage 4, the cerebral cortex begins to exhibit neuronal damage. The poorly myelinated portion of the temporal mesocortex is the region specifically affected during this stage (Braak et al., 2003). The anteromedial temporal mesocortex projects to the hippocampal formation and amygdala, both areas which are damaged during the symptomatic stage (Braak et al., 2004) and which have further connections to PFC. Impairment of PFC pathways can cause cognitive decline (Dubois and Pillon, 1997) and memory dysfunction (Zola-Morgan and Squire, 1993). Cognitive impairment (Lewis et al. 2003; Muslimovic et al. 2005; Owen et al. 1992; Siepel et al. 2014 for a review see Ray and Strafella 2012), but not always memory deficits (Owen et al., 1992; Siepel et al., 2014), can be exhibited by *de novo* patients.

In the final 2 stages of PD, the entire neocortex is gradually affected. Inclusion bodies appear in PFC and high-order sensory association areas of the neocortex, then spread to the

premotor and first-order sensory association areas (Braak et al., 2004). Vulnerable portions of SN are virtually void of pigment (Braak et al., 2004). Macroscopic inspection reveals the characteristically pale complexion of SN at this point. By this time, the autonomic, limbic and motor systems are all severely damaged and it is possible for patients to exhibit the full range of PD-associated clinical symptoms.

2.3.2 The role of genetics

How an individual physiologically responds to PD and different treatment options may depend on their genetic profile. Branches of genetic research into PD have focused on the family of genes called PARK, for Parkinson's disease. Genes within this family, such as LRRK2, are associated with the hereditary form of PD. However, Chapters 3 and 8 do not focus on the role of genetics in the development of PD, but rather the importance of genetics post diagnosis. This section provides more detail on specific dopaminergic genes which are both integrally involved in the functioning of the three BG-thalamocortical networks and postulated to be important in determining how a patient responds to dopaminergic medication. The interrelated factors of dopaminergic genes and medication manipulate cortical and subcortical dopamine concentrations which influences performance on cognitive-motor tasks. It is therefore important to consider these interrelated factors when discussing the role of an impulse control task (e.g. RI task) in the context of PD.

Inter-individual differences in deoxyribonucleic acid (DNA) sequences can exist as a result of mutations. These differences are referred to as polymorphisms. In the context of dopamine, polymorphisms in specific genes encoding for dopamine receptors and degradation enzymes can significantly influence dopamine neurotransmission. Genetic variation in the dopaminergic system can influence certain traits modulated by dopamine, such as impulsivity (Nandam et al., 2013; Nemoda et al., 2011). Genetic variability is likely to have the greatest influence on behavioural performance when dopamine deviates from close-to-optimal levels. This means that polymorphisms in dopamine genes are likely to play a more important role during any kind of dopamine dysregulation. Genetically determined baseline dopamine neurotransmission levels are further influenced by ageing, disease status and the addition of dopaminergic medications.

There are distinguishing characteristics of the mesocortical dopamine projections to PFC that mean genetic polymorphisms which affect dopamine can have significant effects on dopamine levels in PFC. The dopaminergic neurons which project from VTA to PFC are distinct from those which project to NAcc, dorsal striatum and anterior cingulate (Carr and

Sesack, 2000). Dopaminergic neurons projecting to PFC from VTA have a higher baseline firing rate and a higher rate of dopamine turnover (Tam and Roth, 1997; Thierry et al., 1977). Therefore extracellular dopamine is especially increased in PFC when dopamine degradation proteins are functioning suboptimally and synaptic dopamine clearance reduces. Increased extracellular dopamine concentrations in the synaptic cleft will increase dopaminergic postsynaptic and extrasynaptic activation i.e. increase dopaminergic neurotransmission. An increase in dopaminergic PFC neurotransmission through genetic factors may not be detrimental in isolation. However, when occurring in conjunction with the increased PFC dopaminergic tone seen in early PD, as well as the pharmacological increase in dopamine from prescribed medications, dopamine dysregulation and impaired PFC function may result.

Polymorphisms within five genes are proposed to be of particular significance in dopamine neurotransmission as the different resulting alleles result in altered molecular function; the catechol-O-methyltransferase (COMT) and dopamine transporter (DAT) genes which influence dopamine levels within the synaptic cleft, and the genes which encode for dopamine receptors D1 (DRD1), D2 (DRD2) and D3 (DRD3) (Nemoda et al., 2011; Pearson-Fuhrhop et al., 2013). The combined effect on the dopamine system of polymorphisms within these five genes can be quantified by calculating a dopamine genetic risk score, as recently proposed by Pearson-Fuhrhop and colleagues (Pearson-Fuhrhop et al., 2014, 2013) and explored in Chapter 8. Briefly, different alleles are assigned values of 1 or 0, depending on whether they act to increase or decrease dopamine transmission, respectively. All five values are summed to obtain an dopamine genetic risk score, with higher scores corresponding to higher overall dopaminergic neurotransmission.

Genetic variation within individual dopamine receptor genes can act to either increase or decrease signal transduction and dopamine neurotransmission. One method of influencing signal transduction is through the cyclic adenosine monophosphate dependent signal transduction pathway. Adenylate cyclase is responsible for converting adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP) (Murayama and Ui, 1983). The presence of cAMP facilitates signal transduction by relaying extracellular signals to intracellular effectors. The two main types of dopamine receptors have opposite functions on adenylate cyclase, causing opposite effects on their respective BG pathways. Activation of postsynaptic D1-like receptors, i.e. D1 and D5, activates adenylate cyclase (Nemoda et al., 2011). Conversely, activation of postsynaptic D2-like receptors (D2, D3 and D4) inhibits adenylate cyclase (Nemoda et al., 2011). D1 and D2 are the most widely expressed

dopamine receptors throughout the brain (Nemoda et al., 2011) and are central components of cortico-BG networks (Gerfen et al., 1990; Goto and Grace, 2005; Surmeier et al., 1996).

The DRD1 gene has no functional polymorphisms. However it can have an A to G single nucleotide polymorphism (SNP) in its un-translated regulatory region (Cichon et al., 1994). The presence of the G allele leads to higher dopamine neurotransmission and has been associated with impaired inhibitory control (Comings et al., 1997). Dopamine neurotransmission can also be increased by a SNP from T to C in the coding region of the DRD3 gene. Conversely, a Glu to Lys amino acid substitution in the DRD2 gene as a result of a C to T SNP acts to reduce dopamine neurotransmission (Thompson et al., 1997). This polymorphism is associated with reduced D2 receptor availability and binding (Pohjalainen et al., 1998; Thompson et al., 1997) and a 40 % reduction in D2 receptor expression in the striatum. Initially, a decrease in D2 receptor activation might suggest an increase in neurotransmission through reduced inhibition of adenylyl cylase and greater amounts of cAMP. However D2 receptors are also located presynaptically, suggesting they are also important in controlling dopamine release into the synaptic cleft (Nemoda et al., 2011). Reduced concentrations of synaptic dopamine will decrease postsynaptic receptor binding and therefore dopamine transmission. D2 dopamine receptors are specifically implicated in RI performance (Colzato et al., 2010a; Ghahremani et al., 2012; Hamidovic et al., 2009; Nandam et al., 2013) and their impact is magnified during ageing (Colzato et al., 2013).

Dopamine neurotransmission is influenced by the levels of dopamine within the synaptic cleft. The principal method for regulating synaptic dopamine levels differs between the BG and PFC. Within the caudate nucleus of the striatum it is predominantly the DAT enzyme that is responsible for synaptic dopamine degradation. The DAT gene has a 40 base-pair sequence in its untranslated region which usually occurs in either 9 or 10 repeats. Alleles that code for 11 repeats are also possible and behave like 10-repeat alleles (Inoue-Murayama et al., 2002). The allele coding for 9 repeats is associated with a decrease in DAT protein levels, and therefore with less dopamine degradation and greater synaptic dopamine for a given level of dopamine neuronal activity in the BG (Heinz et al., 2000; VanNess et al., 2005). Dopamine neurotransmission is thereby elevated by allele mutations in the DAT gene causing fewer base-pair repeats.

The COMT enzyme also regulates dopamine concentrations within the synaptic cleft, in addition to degrading other catecholamines such as epinephrine and norepinephrine (Cooper et al., 1996; Tunbridge et al., 2006). The COMT enzyme is particularly important for dopamine degradation in prefrontal areas due to the lack of DAT activity in this region (Chen et al., 2004; Diamond et al., 2004; Robbins and Arnsten, 2009; Vallelunga et al., 2012).

A SNP from G to A can occur on chromosome 22, at codon 108 or 158 of this gene, producing a methionine (met) instead of valine (val) allele (Lachman et al., 1996). This substitution results in a form of the COMT enzyme with about a three to four-fold decrease in efficiency of dopamine inactivation (Chen et al., 2004; Lachman et al., 1996), and therefore increased dopamine neurotransmission within PFC through increased synaptic concentrations. Polymorphisms in the COMT gene affect executive function, including inhibitory control (Blasi et al., 2005; Colzato et al., 2010b; Congdon et al., 2009; Diamond et al., 2004; Fallon et al., 2013; Farrell et al., 2012; Foltynie et al., 2004; Kramer et al., 2007; Williams-Gray et al., 2008, 2007), however this is not always the case (Hoogland et al., 2010). Despite finding no association between executive function and COMT genotype alone, Hoogland and colleagues did reveal that COMT genotype determined how a patient's executive function was affected by medication status.

Individuals will most likely have a combination of polymorphisms which collectively determine their overall level of dopamine neurotransmission. The frequency of mutation differs amongst the five genes discussed above. For example, mutations within the COMT gene are relatively common. In Caucasian populations, about 50 % of the population are heterozygous (val/met), roughly 28 % are homozygous for the met allele (met/met) and only the remaining 22 % are homozygous for the val allele (val/val) (Lajin et al., 2010; Palmatier et al., 1999). However, mutations within genes encoding D2-like dopamine receptors are less common. The frequency of the SNPs in DRD2 (rs1800497) and DRD3 (rs6280) genes in Caucasian populations is about 10 % and 35 %, respectively (201, 2013).

Genetic variation within the dopaminergic system might explain why some PD patients (about 20 %) develop impulse control disorders (ICDs) when taking dopaminergic medication, especially dopamine agonists. This is explored further in Chapter 8. A mutation within DRD1 has been associated with impulsive behaviours such as compulsive eating, shopping and gambling in people without PD (Comings et al., 1997). On the other hand, directly comparing PD patients with and without ICDs, Vallelunga and colleagues found no difference in frequency for polymorphisms within COMT, DAT and DRD2 genes (Vallelunga et al., 2012). Variants within these dopaminergic genes were not associated with the risk of developing ICDs. Yet the study did not include quantitative and objective measures of impulse control. It is possible an effect could be uncovered through an interaction between genetics and objective behavioural measures of impulse control. Or perhaps focusing on individual genes will not reveal a risk for ICDs. Instead the combined effects of genes on overall dopamine neurotransmission may need to be considered by incorporating tech-

niques like the dopamine genetic risk score. The experiment in Chapter 8 is the first to investigate a polygenic dopamine score in the context of impulse control.

Chapter 3

Does Response Inhibition Have Pre- and Postdiagnostic Utility in Parkinson's Disease?

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Terminology: The current chapter uses DA to denote dopamine agonist, as opposed to dopamine.

Abstract

Parkinson's disease (PD) is the second most prevalent degenerative neurological condition worldwide. Improving and sustaining quality of life is an important goal for Parkinson's patients. Key areas of focus to achieve this goal include earlier diagnosis and individualized treatment. In this review the authors discuss impulse control in PD and examine how measures of impulse control from a response inhibition task may provide clinically useful information (i) within an objective test battery to aid earlier diagnosis of PD and (ii) in postdiagnostic PD, to better identify individuals at risk of developing impulse control disorders with dopaminergic medication.

3.1 Introduction

Parkinson's disease (PD) is a relatively common progressive neurodegenerative disease affecting about 6.3 million people worldwide (Apaydin et al., 2002; Braak et al., 2004; EPDA, 2014). The pathological process that underlies PD relentlessly progresses to the full-blown clinical syndrome over several years (Braak et al., 2004). PD is associated with the degeneration of dopaminergic nigrostriatal neurons in the substantia nigra pars compacta (SNpc) (Apaydin et al., 2002; Cameron et al., 2010; Gradinaru et al., 2009)), as well as several other nuclei of the brainstem (Grinberg et al., 2010). Although motor symptoms are common landmarks for diagnosis and staging, PD also involves disturbances in cognitive, limbic and autonomic systems.

Currently there is no definitive test for PD, making diagnosis relatively subjective. Clinical presentation of the disease can fluctuate over time, complicating disease monitoring and treatment evaluation. In addition, the pathology of this disease is only diagnostic in the brainstem, which is difficult to study during life, adding to the challenge of unbiased and objective monitoring. The time between the onset of neurodegeneration and the ability to clinically diagnose PD is termed the preclinical phase (Gaenslen et al., 2011; Truong and Wolters, 2009). During the preclinical phase unspecific symptoms appear in isolation. For this reason, such symptoms are only confirmed retrospectively after clinical diagnosis, but it is also possible for healthy individuals to exhibit many of these unspecific symptoms as part of normal ageing (e.g., impaired sense of smell, disturbed sleep, balance disturbance, muscle stiffness). Although the simple occurrence of select symptoms is not sufficient for a PD diagnosis (Gaenslen et al., 2011), the presentation of certain symptoms in a predicted chronological order (Braak et al., 2003; Przuntek et al., 2004) may identify a higher risk for PD. It has been proposed that at least two positive tests on potential preclinical symptoms may be considered sufficient evidence to diagnose a patient as clinically possible to have PD and begin protective therapy (Truong and Wolters, 2009). Affirmation of this probable diagnosis may be acquired through a response to PD treatment. During the preclinical phase, irretrievable dopaminergic neuron loss in SNpc has not yet reached the threshold for diagnosis. This phase presents an opportunity for treatment optimization through earlier diagnosis using tools that are sensitive enough to identify early changes in biological systems. The aim of earlier diagnosis would be to enable early neuroprotective therapies to prevent or delay further neuron degeneration (Berg and Poewe, 2012).

Once diagnosed, there are further challenges presented to patients and clinicians from treatment side effects. The two most common forms of treatment are medication and surgery

(e.g., deep brain stimulation, pallidotomy). One prevalent and detrimental side effect of dopaminergic medication treatment is the development of impulse control disorders, which manifest as impulsive and compulsive behaviours in a variety of contexts. There is currently no available screening method to identify patients at high risk of developing impulse control disorders. Treatment decisions would be aided by an objective method to predict and classify an individual's risk of impulsivity with dopaminergic treatment.

In this review we focus on impulse control in PD and how objective measures of impulse control could be used clinically pre- and postdiagnosis. The review has three main aims. First, to review and summarize functional changes in frontostriatal and basal ganglia-thalamocortical networks in PD and their effect on impulse control, specifically response inhibition. Second, to introduce the potential of standardized response inhibition paradigms from motor behaviour research to provide useful measures within an objective test battery to identify insidious motor and nonmotor changes during the preclinical phase, and aid earlier diagnosis. Third and finally, we introduce the idea of combining information obtained from response inhibition tasks with genetic analysis in the postdiagnostic phase of PD to better identify mechanisms which predispose individuals to impulse control disorders with dopaminergic treatment.

3.2 Impulse control in Parkinson's disease

Execution of premature or inappropriate responses reflects poor impulse control (Duque and Ivry, 2009). There are two aspects of impulse control: cognitive/psychological and motor/behavioural (Nemoda et al., 2011). Impulsive decision making (i.e., dysfunctional cognitive impulse control) manifests as an inability to evaluate the potential consequences of a decision and modify the decision accordingly, and has been associated with inferior structural integrity of white matter projections between the prefrontal cortex (PFC) and striatum (Peper et al., 2013). The inability to suppress an unnecessary action (i.e., impaired response inhibition) is an example of the motor/behavioural aspect (Nemoda et al., 2011).

There is a general decrease in impulse control with ageing, seen in motor (Braver and Barch, 2002; Fisk and Sharp, 2004), and cognitive impulse control (Fisk and Sharp, 2004). The age-related deterioration of motor impulse control is exacerbated with basal ganglia (BG) dysfunction as is evident in focal dystonia (Stinear and Byblow, 2004) and PD (Bokura et al., 2005; Cooper et al., 1994; Gauggel et al., 2004; Obeso et al., 2011). A dose-dependent inverted-U relationship (Goldman-Rakic et al., 2000) has been hypothesized to explain observed behavioural changes in impulse control associated with changes in dopamine

neurotransmission in PFC (Robbins and Arnsten, 2009). For those with lower levels of dopamine neurotransmission, increasing PFC dopamine concentration promotes better motor (Congdon et al., 2009) and cognitive impulse control (Diamond et al., 2004) and decreased impulsivity (Farrell et al., 2012).

3.2.1 Evidence for motor tests as biomarkers for Parkinson's disease

Deterioration of the motor system occurs well in advance of the clinical diagnosis of PD. Evidence of subtle motor deficits exists during the preclinical stage. Therefore salient tests of motor function could become possible biomarkers as part of a larger test battery or diagnostic algorithm. Years before clinical diagnosis patients subjectively report increased stiffness, slowness of movement, changes in gait pattern, reduced arm swing, tremor and postural imbalance (de Lau et al., 2006; Gaenslen et al., 2011). Movement tasks are capable of providing objective measures of these abnormalities which may be sensitive but not necessarily specific to preclinical PD in isolation. However the presentation of these subtle motor abnormalities following specific nonmotor symptoms in a predicted chronological order may identify a higher risk for PD. Tasks of visuomotor control (Hocherman and Giladi, 1998) and handwriting (Horstink and Morrish, 1999) have identified deficits in the asymptomatic hand of patients in the early stage of PD. Movement tasks which are able to detect subtle deterioration of motor control show greatest potential as biomarkers as part of a larger test battery.

Motor deficits are present in *de novo* PD patients compared to healthy age-matched controls. For example, de novo PD patients show impaired upper limb performance during bimanual (Ponsen et al., 2006) and unimanual (Pfann et al., 2001; Ponsen et al., 2008) movements. During a complex bimanual circle-drawing task, measures of success rate and accuracy are lower in PD patients, especially in the nondominant hand (Ponsen et al., 2006). However, even simple unimanual movement tasks reveal impairments in modulation of muscle activity and coordination in *de novo* patients (Pfann et al., 2001; Ponsen et al., 2008). Pfann et al. (2001) demonstrated that electromyography (EMG) can reveal an inability to modify movements according to task demands (impaired motor set) in *de novo* PD patients during a rapid elbow flexion task. EMG traces of patients reveal an impaired modulation of muscle bursting during upper limb movements of both single-joint (Hallett and Khoshbin, 1980; Vaillancourt et al., 2004) and multijoint movements (Farley et al., 2004). EMG activity patterns are therefore a potentially sensitive motor measure for identification of PD, with one study finding 90 % sensitivity at differentiating individuals with PD from healthy controls

during single-joint point-to-point flexion movements (Robichaud et al., 2009). Of note, one healthy control that demonstrated abnormal EMG was subsequently diagnosed with PD 30 months later. Ultimately, evidence exists that noninvasive and objective motor measures from EMG have the potential to reveal subclinical neurophysiological abnormalities during the preclinical stage.

3.2.2 Response inhibition in Parkinson's disease

Functional changes in basal ganglia-thalamocortical networks with Parkinson's disease

Nuclei of the BG are an integral part of the sensorimotor system, forming a cortico-subcortico-cortical loop involved in planning, executing and cancelling responses. Response inhibition (RI) depends critically upon interactions between the right frontal cortex (in particular, the right inferior frontal gyrus) and the BG (Aron et al., 2007b; Aron and Poldrack, 2006; Coxon et al., 2012; Jahfari et al., 2011; Robbins, 2007; Swann et al., 2011; Zandbelt and Vink, 2010). Striatal gray matter atrophy has been linked to impaired RI in PD (O'Callaghan et al., 2013). The striatum is the main input to the BG, receiving projections from the cerebral cortex, midbrain and thalamus (Figure 3.1). The striatum is divided into dorsal (caudate nucleus and putamen, separated by the internal capsule) and ventral regions (Kandel et al., 2013). BG sensorimotor networks comprise the motor portions of the putamen (i.e., dorsal striatum (Alexander and Crutcher, 1990a; Kandel et al., 2013).

Projecting from the dorsal striatum are two parallel pathways through the BG: the direct and indirect pathways (Figure 3.1). Both pathways modulate thalamic output to the cortex by either increasing (direct) or decreasing (indirect) thalamocortical drive (Alexander and Crutcher, 1990a; Danion and Latash, 2011). The subthalamic nucleus (STN) has been recognized as another significant input structure of the BG (Coizet et al., 2009; Lanciego et al., 2004). A third hyperdirect pathway projecting from the cortex can rapidly decrease thalamocortical drive (i.e., an inhibitory pathway) without synapsing onto the striatum, but rather directly onto STN (Nambu et al., 2002). Figure 3.1 illustrates examples of hyperdirect pathways from the inferior frontal cortex and the presupplementary motor area (preSMA) connecting directly to STN. Evidence suggests that hyperdirect pathways are critical for successful response inhibition (Aron et al., 2007a; Aron and Poldrack, 2006; Coxon et al., 2012; King et al., 2012).

The main BG output nuclei are internal globus pallidus (GPi) and substantia nigra pars reticulata (SNpr). These two structures provide sustained inhibitory input onto thalamocortical neurons. The general consensus is that movement initiation (through facilitation of the

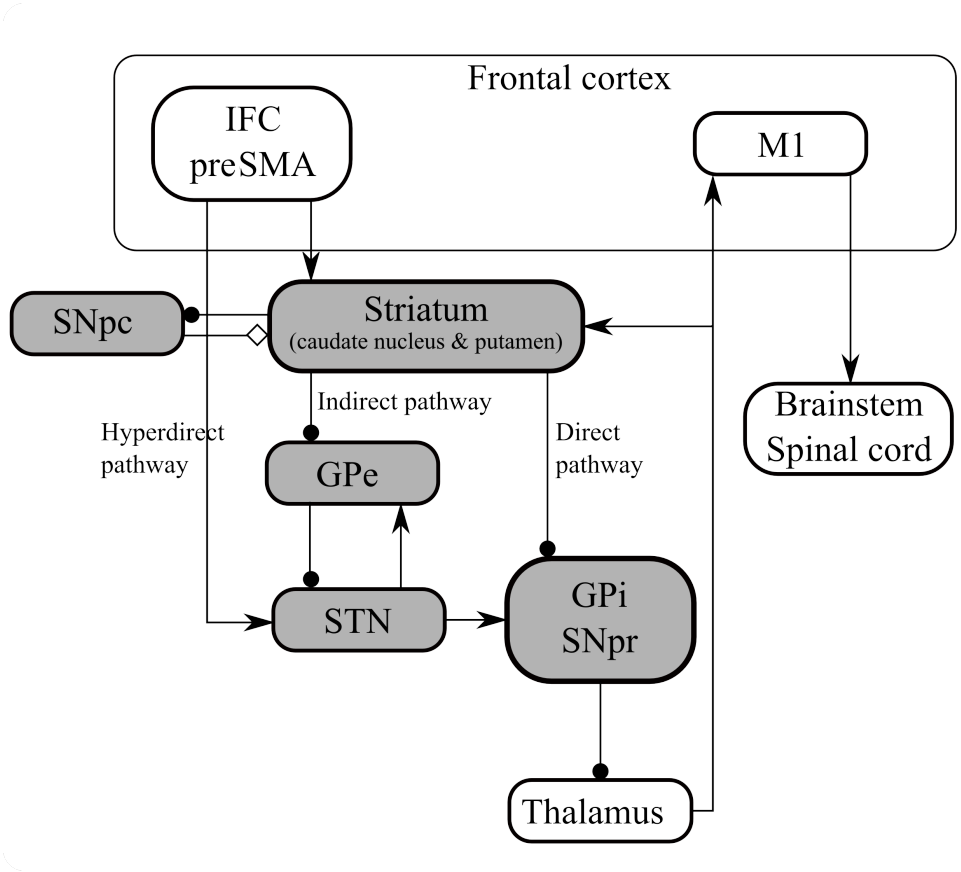

Figure 3.1 Basal ganglia sensorimotor network. Model of the cortico-basal ganglia-thalamocortical sensorimotor networks involved in movement execution and inhibitory control. The direct, indirect and hyperdirect pathways are represented at a basic level. Grey boxes indicate nuclei of functional basal ganglia; arrows indicate facilitatory input; filled circles indicate inhibitory input; open diamond indicates dopamine-dependent input. IFC: inferior frontal cortex; SNpc: substantia nigra pars compacta; GPe: globus pallidus externus; STN: subthalamic nucleus; GPi: globus pallidus internus; SNpr: substantia nigra pars reticulata; preSMA: presupplementary motor area; M1: primary motor cortex.

direct pathway) is an active process, requiring a pause in tonic inhibition and disinhibition of the thalamus. The default state of the motor system is analogous to driving with the brakes on, or the 'hold your horses' model (Ballanger et al., 2009). The spatial and temporal recruitment of the direct, indirect and hyperdirect pathways gives rise to the complex functionality of the BG.

The balance of neuronal output from the three BG pathways is usually maintained by dopamine through dopaminergic projections from SNpc to all BG nuclei, but most significantly through the dense connections to the dorsal and ventral striatum (Bjorklund and Dunnett, 2007). The origins of the direct and indirect pathways are from separate populations of striatal medium spiny neurons. The direct pathway originates from neurons expressing predominantly D1 dopamine receptors (DRD1), and the indirect pathway from neurons expressing predominantly D2 receptors (DRD2). Dopaminergic projections from SNpc differentially activate the two striatal neuronal populations due to the different dominant postsynaptic receptors. Dopamine binding to DRD1 facilitates the direct pathway, whereas dopamine binding at DRD2 suppresses the indirect pathway (Danion and Latash, 2011; Gerfen et al., 1990; Kandel et al., 2013; Obeso et al., 2013). The presence of dopamine therefore modulates movement control by reinforcing any cortically initiated activation of BG-thalamocortical networks leading to disinhibition of thalamocortical neurons (Alexander and Crutcher, 1990a).

In PD, RI is disrupted by dopamine disturbance within the sensorimotor BG-thalamocortical network. The degeneration of nigrostriatal dopaminergic neurons reduces the dopaminergic modulation through reduced striatal dopamine levels (Kandel et al., 2013). Reduced striatal dopamine results in less activation of striatal DRD1 and DRD2 affecting the direct and indirect pathways, respectively. Through decreased activation of DRD2s, striatal inhibitory projections to GPe become more active through reduced suppression. There is increased striatal inhibition of GPe, subsequent disinhibition of STN and therefore STN hyperactivity within the indirect pathway. Simultaneously, striatal projections to GPi and SNpr become less active through decreased DRD1 activation (Alexander and Crutcher, 1990a). As a result of increased STN excitation and reduced striatal inhibition, there is increased activity of GPi and SNpr, and a subsequent increase in tonic inhibition of the thalamocortical projection neurons. Therefore, with PD, maladaptive modulation of tonic inhibition of the thalamus through the separate striatal neuron subpopulations and subsequent BG pathways (Albin et al., 1989) has a crucial impact on motor impulse control (i.e., response inhibition).

Functional changes in frontostriatal networks with Parkinson's disease

In PD, abnormal modulation of striatal and PFC dopamine results in dysfunction within frontostriatal networks (Shepherd, 2013) and impaired impulse control. Networks involving the PFC and striatum are implicated not only in motor control, but also in several cognitive functions, including memory, action selection, behaviour reinforcement, and contextual conditioning (Alexander and Crutcher, 1990a; Goto and Grace, 2005; Pennartz et al., 2009). Dysfunction of frontostriatal networks can therefore contribute to a multitude of symptoms. As with many biological systems the key to optimizing function is balance. The optimal range for dopaminergic neurotransmission for frontostriatal networks is best illustrated by the inverted-U relationship. For example, the optimal range of PFC dopaminergic neurotransmission is surrounded by that above or below optimal (Figure 3.2), resulting in decreased PFC function. However the relationship between dopamine and functional performance is also complex, and includes several contributing factors.

Reducing dopamine neurotransmission can impair certain functions while enhancing others. The functional state of PFC relates to RI performance. RI tasks are sensitive to cognitive deficits as well as motor impairments, and are essentially cognitive-motor tasks. In addition to proficient motor impulse control, RI also requires efficient attention control (199, 1997; Tachibana et al., 1997) and cognitive flexibility (Cooper et al., 1994), both of which recruit PFC. Decreasing prefrontal dopamine promotes cognitive flexibility in young (Blasi et al., 2005; Colzato et al., 2010b) and older (Fallon et al., 2013) healthy individuals and PD patients (Cools et al., 2010), at the expense of cognitive stability. These findings are in line with Dual State Theory (Durstewitz and Seamans, 2008) whereby a DRD1 dominated system contains high-energy barriers between neural state representations. This system therefore favors stability and perseveration. Conversely, a DRD2 dominated system favors switching between representational states through low energy barriers. Direct neurophysiological evidence for Dual State Theory is supported by rodent models (Goto and Grace, 2005). The inverted-U relationship explains why equivalent changes to dopaminergic neurotransmission can have opposite effects on cognitive functions.

In early PD, dopamine concentrations are decreased within regions of the SN and striatum, yet paradoxically dopamine concentration is increased in PFC (Kaasinen et al., 2001). This counterintuitive increase in PFC dopamine could reflect compensation within the mesocorticolimbic (MCL) network (Rakshi et al., 1999; Zigmond et al., 1990). It could be due to reduced striatal dopamine levels, given the wellstudied inverse relationship between MCL and nigrostriatal dopaminergic systems (Akil et al., 2003; Carr and Sesack, 2000; Carter and Pycock, 1980; Jahanshahi et al., 2010; Kolachana et al., 1995; Pycock et al., 1980; Roberts et al.,

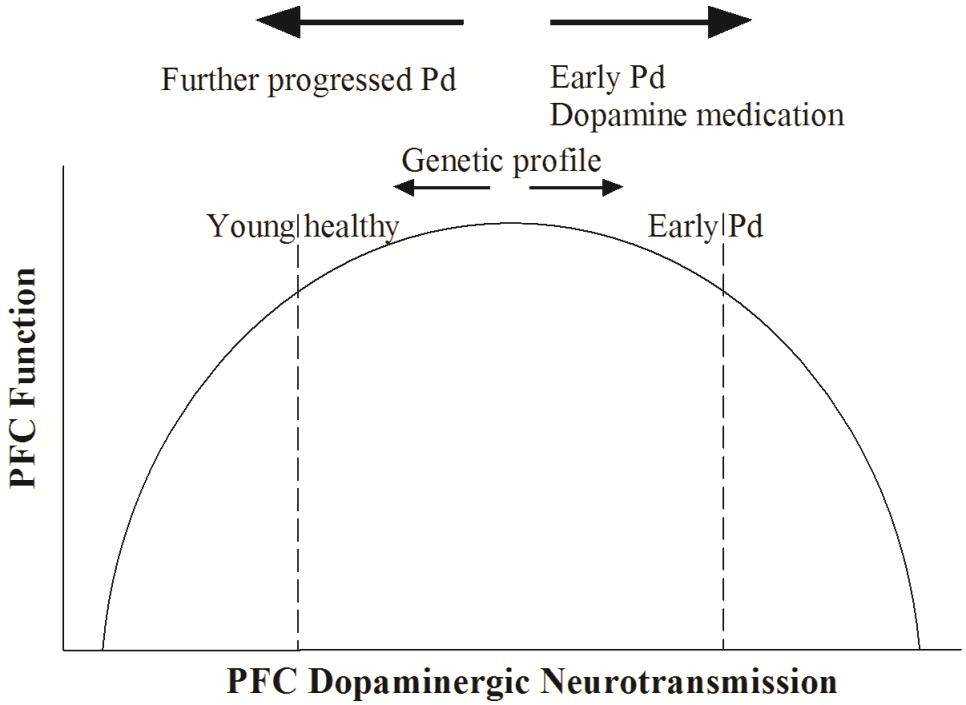

Figure 3.2 Inverted-U relationship between function and dopamine neurotransmission. The task-dependent inverted-U relationship between function and dopaminergic neurotransmission in the prefrontal cortex (PFC). Area on the curve between dashed vertical lines denotes optimal function and transmission of dopamine. Healthy young adults lie to the left of the curve, early Parkinson's disease (PD) patients to the right. Factors that move individuals to the right of the curve include dopaminergic medication and neurophysiological changes in early PD. As PD progresses, an individual moves toward the left along the curve. An individual's position and movement along the curve will also depend on their dopaminergic genetic profile, and whether it causes higher or lower baseline dopamine neurotransmission.

1994; Sawamoto et al., 2008). A hyperdopaminergic MCL network causes greater dopamine transmission between the ventral tegmental area and PFC. In the early stages of PD, the increase in PFC dopamine effectively shifts patients to the right of the curve compared to healthy controls. A shift to the right may increase or decrease cognitive performance by moving the individual into or beyond the optimal range of dopamine for a task. Average young healthy individuals cluster toward the left of the inverted-U while early PD patients tend to cluster toward the right (Figure 3.2). Higher prefrontal dopamine enhances attentional control (required for RI) in healthy individuals (Blasi et al., 2005) but impairs it in patients (Williams-Gray et al., 2008). These findings illustrate how increasing dopamine in early PD has opposite effects on prefrontal function and neural activity compared to younger healthy individuals (Fallon et al., 2013).

Measures of RI demonstrate strong potential to objectively identify abnormalities in the frontostriatal and sensorimotor BG-thalamocortical networks inherent to PD. Midbrain and cortical regions such as the striatum, SN, STN, globus pallidus, SMA/preSMA and PFC all demonstrate impaired activity in PD as described previously. These areas form part of the right-lateralized inhibitory control network that projects input to the primary motor cortex via the thalamus (Figure 3.1) (Aron et al., 2003; Aron and Poldrack, 2006; Bellgrove et al., 2004; Coxon et al., 2006, 2009; Garavan et al., 1999; Liddle et al., 2001; Mostofsky et al., 2003; Picard and Strick, 1996; Rubia et al., 2003; Stinear et al., 2009). Furthermore, involvement of PFC could mean RI tasks are sensitive to prefrontal cognitive deficits present in the disease. Here we examine only RI tasks that require observable motor behaviour, as opposed to other types of behavioural inhibition, such as the Stroop color-word test or tests of deferred gratification.

3.3 Response inhibition tasks in preclinical Parkinson's disease

Motor RI has traditionally been investigated using a stop-signal or go/no-go task. These tasks involve externally cued motor responses. An anticipatory response inhibition (ARI) task (Slater-Hammel, 1960) allows investigation of internally cued anticipated motor responses. All three RI tasks have provided useful insights into the initiation and inhibition processes required for successful control of a motor response. The primary dependent measures for each task and the expected affect of PD on each measure is presented in Table 3.1. Subtle design differences between the tasks enables the examination of cancelling three funda-

Table 3.1 The primary dependent measures for the three main types of motor response inhibition tasks, and the expected affect of Parkinson's disease on each measure

Task	Primary dependent measures	Expected effect of Parkinson's disease
Go/no-go	Go reaction time	Lengthen
	Error frequency on no-go trials	Increase
Stop-signal	Go reaction time	Lengthen
	Stop trial success rate	Decrease
	Stop signal reaction time	Lengthen
	Stop signal delay for p(respond) = .5	Shorten
Anticipatory response inhibition	Go response time	Increase variability
	Stop trial success rate	Decrease
	Stop signal reaction time	Lengthen
	Stop signal offset from target for p(respond) = .5	Lengthen

p(respond) = .5 = 50 % probability of a behavioural response.

mentally different processes; a planned, externally generated or internally generated action. There is therefore the question as to which task design is optimally suited to identify PD biomarkers. To date there are published studies using go/no-go and stop-signal paradigms in PD, but no published studies using an ARI task with PD patients.

3.3.1 Go/no-go task

The majority of trials in the motor go/no-go task require participants to make a motor response as quickly as possible when a go cue is presented. Occasionally the go signal is replaced by a no-go signal (Figure 3.3A), indicating the participant should make no response. The go/no-go task design examines the ability to withhold a planned response (i.e., action restraint), which is often necessary to resolve preresponse conflict. The go/no-go task has been used to examine RI in PD. Individuals with PD have delayed reaction times (RTs) (Cooper et al., 1994; Tachibana et al., 1997) and greater error rates (Bokura et al., 2005) compared to healthy controls on this task, supporting ideas of impaired conflict resolution in PD (Cooper et al., 1994). However, unlike the earlier studies, Bokura et al. (2005) found no significant difference in RTs between PD patients and controls. Yet the decreased accuracy

of patients, specifically the higher rate of false alarm responses, may indicate the presence of a speed-accuracy tradeoff; RTs shortened at the expense of accuracy. More recent studies conflict with the results of earlier studies. For example, no difference in error rate or RT between PD patients and healthy controls (Beste et al., 2010). Furthermore, RTs and error rates on the go/no-go task were unable to distinguish between healthy controls and patients with early PD (Baglio et al., 2011). RT could not differentiate between *de novo*, early treated and chronic PD patients . Overall the contradictory findings suggest the go/no-go task lacks sufficient sensitivity in the context of PD. The lack of sensitivity and correlation to disease severity suggests measures from this type of RI task are inappropriate biomarkers for PD.

3.3.2 Stop-signal task

The stop-signal task has played an integral part in elucidating the role of BG and cortical structures which form the right-lateralized inhibitory control network. The majority of trials again require a motor response as quickly as possible to an external go signal. On some trials, a stop signal is presented at a variable delay after the go signal (stop signal delay [SSD]; Figure 3.3B, left). Longer SSDs increase the probability of an incorrect response. The SSD can change dynamically during the task using a staircase procedure to ensure convergence to a stop time that results in 50 % probability of successful inhibition: p(respond) = .5. The task design enables the measurement of the efficacy and the latency of the inhibitory process, calculated as the difference between the stop signal for p(respond) = .5 and mean RT on Go trials (stop signal reaction time [SSRT]; Figure 3.3B, right). Interpretation of the SSRT is based on the 'horse-race' model (De Jong et al., 1990; Logan and Cowan, 1984), built on the premise of independent excitatory and inhibitory mechanisms. Response execution is a result of excitatory mechanisms, triggered by the go signal. Inhibitory mechanisms are triggered by the stop signal, which prevent response execution. Whichever mechanism wins the race determines whether a motor response is generated. The SSRT signifies the latency at which each mechanism wins half the time. SSRT is often used to examine the integrity of inhibitory mechanisms.

The stop-signal task has been used to examine motor control in PD. Mild to moderately advanced PD patients have difficulty initiating and inhibiting responses during the stop-signal task (Gauggel et al., 2004; Mirabella et al., 2012; Obeso et al., 2011; Swann et al., 2011) compared to controls, manifesting as slower RTs and longer SSRTs. RI motor deficits are accompanied by deficits in volitional inhibition on cognitive tests (Obeso et al., 2011),

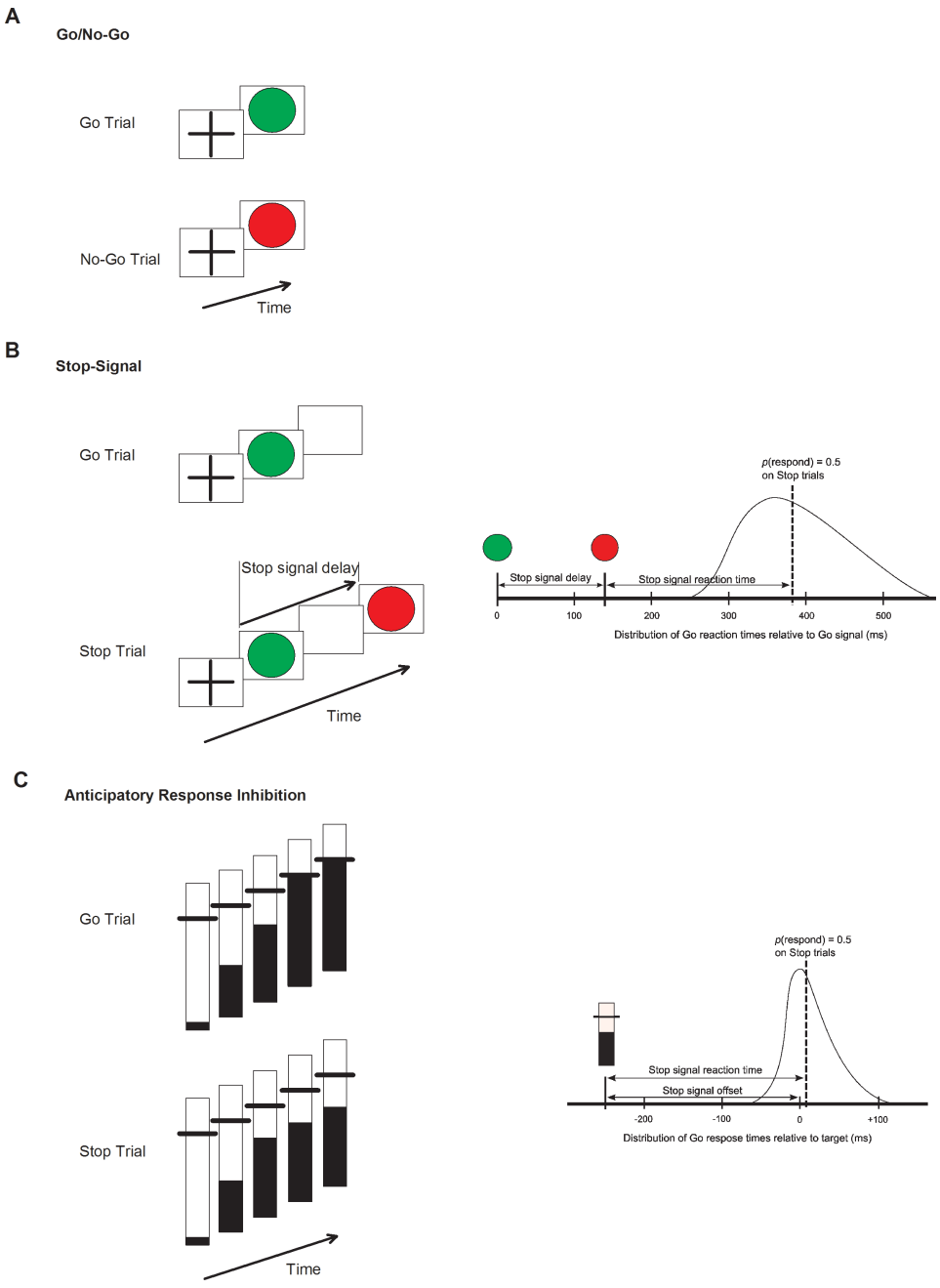

Figure 3.3 Task designs to investigate response inhibition. Schematics of go/no-go (A), stop-signal (B), and anticipatory response inhibition (C) task displays during execution and inhibition trials. The distribution of Go responses is represented for the stop-signal and anticipatory response inhibition tasks (right), demonstrating how the latency of the inhibition process is calculated (stop signal reaction time) using assumptions of the race model. p(respond) = probability of a response.

supporting the presence of generalized impulse control deficits in PD. Curiously, Gauggel et al. (2004) were unable to find a correlation between impaired RI and disease severity in PD.

To be sensitive to the progressive degeneration associated with disease severity, a task needs to adequately recruit and challenge the BG system. Although the stop-signal and go/no-go tasks offer advantages from having well-defined go and stop cues, they require participants to respond to external cues (i.e., a signalled response). Externally cued movements require less involvement of the BG system compared to internally generated movements (Jahanshahi et al., 1995). Therefore, measures taken during inhibition of externally generated movements are less likely to be sensitive to the ongoing deterioration of the BG network integrity during PD. Additionally, probability of successful inhibition on the stop-signal task increases with slower RTs to the go signal (Lappin and Eriksen, 1966). Lappin and Eriksen were the first to observe that participants could delay their response to improve their chance of successful inhibition if a stop cue was presented. More recently, it has again been acknowledged that the stop-signal task allows adjustments to response strategies (e.g., slowing of responses) to balance the requirements of execution and inhibition (Verbruggen and Logan, 2009). The stop-signal task may therefore be better described as investigating action postponement. If patients are aware of their deteriorating impulse control, they may adjust their response strategy and slow down, or postpone, their response to enable better reaction to the stop cue. The delayed patient RTs reported by Gauggel et al. (2004) may be reflecting such a strategy.

3.3.3 Anticipatory response inhibition tasks

The ARI paradigm is based on that of Slater-Hammel (1960). In the original study, healthy young participants anticipated and stopped the sweep dial of a clock face at a target position by depressing a switch. Subsequent studies have used a rising or filling bar (Coxon et al., 2007; MacDonald et al., 2012 Chapter 5; Yamanaka and Nozaki, 2013; Zandbelt et al., 2013; Zandbelt and Vink, 2010). The stop signal consists of the indicator automatically stopping before the target (Figure 3.3C, left). Slater-Hammel (1960) found that participants had a 50 % probability of successfully inhibiting their prepared response when the sweep dial stopped 166 ms before the target. With ARI the closer in time that the stop signal is to the target position, the greater the probability that a go response will be generated. As with the stop-signal task, the timing of the stop signal can be programmed to converge on a stop time that produces 50 % successful inhibition to allow the calculation of SSRT. Thus, ARI tasks also permit the estimation of latency and accuracy of inhibition (Figure 3.3C,

right). In the ARI task, response execution is relatively constrained compared to other RI tasks, as response times are tightly distributed around a defined target. This is because ARI tasks require participants to internally generate and inhibit an anticipated motor response rather than react to a signal. The anticipatory nature of the default response enables the examination of volitional inhibition during preparation of an internally generated response.

ARI tasks produce interesting results with individuals with BG disorders. For example, patients with focal hand dystonia (FHD) have an increased latency and decreased efficacy of their motor inhibitory process (Stinear and Byblow, 2004). In this study, the indicator had to stop a greater distance from the target position for patients than healthy controls, to obtain a 50 % probability of successful inhibition (lower R50, Figure 3.4A). When patients did successfully inhibit their response, they demonstrated a greater probability of partial EMG bursts in the agonist muscle even with no overt movement (Figure 3.4B), indicating the production of an incomplete response. Overall, ARI measures and EMG revealed that FHD patients had greater difficulty inhibiting their anticipated motor response compared to healthy age-matched controls.

Although much is known about deficits in simple and choice reaction times in PD based on externally cued tasks, less is known about the self-initiation and cancellation of anticipatory responses. An ARI task has not yet been used in a published study with PD patients. Nevertheless, preliminary data with *de novo* patients and healthy age-matched controls indicate novel insights into elements of voluntary control using an ARI task (unpublished data). Apart from decreased accuracy on execution trials, *de novo* patients also show abnormal EMG patterns of activation prior to initiation of the motor response (Figures 3.4C and 3.4D). Patients demonstrate a predominance of multiple, ineffective EMG bursts during execution trials, contributing to indications that EMG activity patterns may be a sensitive motor measure for identification of PD (Farley et al., 2004; Hallett and Khoshbin, 1980; Pfann et al., 2001; Vaillancourt et al., 2004). Taken together, the variability in response times and abnormal EMG patterns signify patients have difficulty suppressing their imminent response and timing it correctly to intercept the target, indicating deficits in predictive internal motor timing. Temporal processing and movement timing, required for successful predictive internal motor timing, recruit PFC (Jahanshahi et al., 2010) and dopaminergic BG pathways (Meck, 1996; O'Boyle et al., 1996), specifically SN (Fan et al., 2012). So it logically follows that PD patients would experience internal motor timing deficits (Harrington et al., 1998; Malapani et al., 1998; Pastor et al., 1992), as indicated by the response times and EMG patterns from the pilot data. Nevertheless, this is not always the case (Bares et al., 2010). On the other hand, Bares et al. (2010) only reported behavioural results. The novel motor

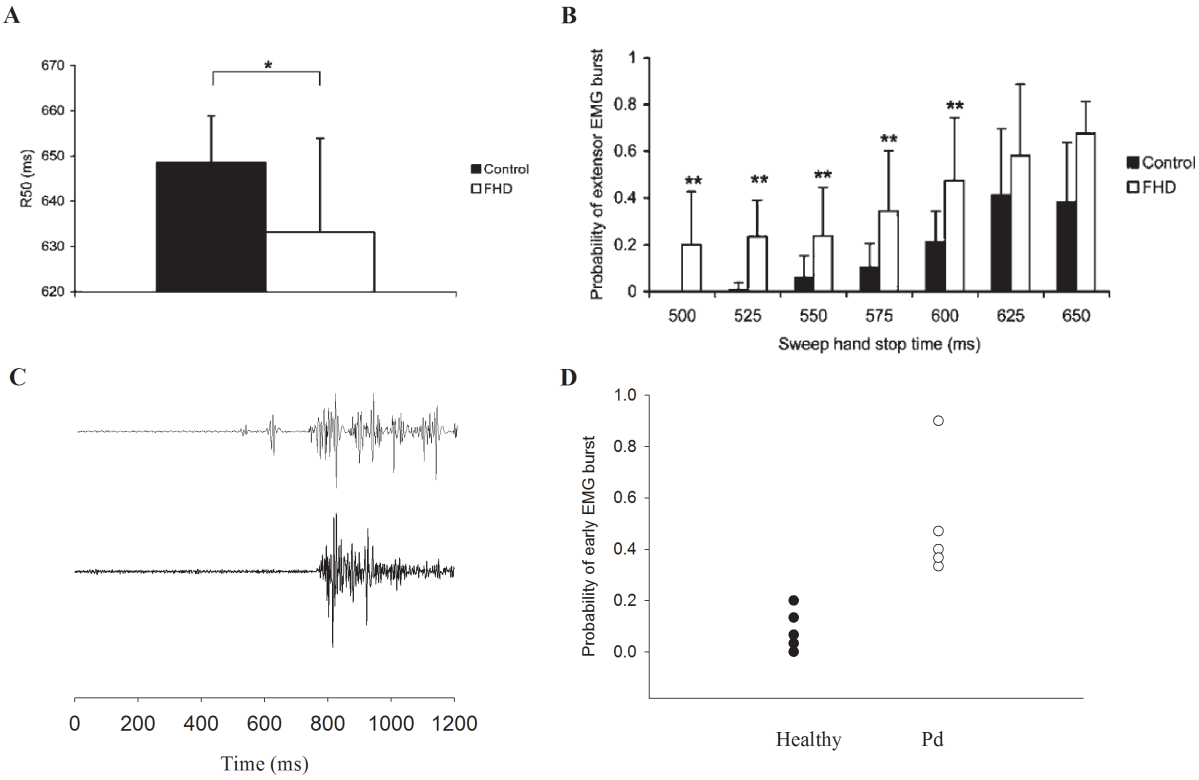

Figure 3.4 The effect of focal dystonia and Parkinson's disease on anticipatory response inhibition task performance. Results from an anticipatory response inhibition task with individual's with focal hand dystonia (FHD; A, B) and *de novo* Parkinson's disease (PD) patients (C, D). The target is presented at 800 ms in both studies. A: Patients with FHD require an earlier mean stop time to achieve 50 % successful inhibition (R50) compared to healthy age-matched controls. B: At the majority of stop times prior to the target, patients with FHD demonstrate a greater probability of EMG bursts during successfully inhibited responses compared to controls. FHD patients had greater difficulty inhibiting their preplanned response than controls. (Stinear and Byblow 2004; reproduced with permission). Error bars denote standard deviation. $*P < .05$, $**P < .01$. C: Electromyography traces from extensor digitorum communis during an ARI execution trial. Top: Individual trace from a *de novo* PD patient, motor response at 815 ms. Note the two small bursts of EMG prior to the muscle activity that produced the motor response. Bottom: Individual trace from a healthy age-matched adult, motor response at 792 ms. Note the lack of EMG activity prior to the burst of muscle activity that produced the motor response (unpublished data). D: Individual data from five *de novo* PD patients and five healthy age-matched adults, showing the probability of these early, ineffective bursts of EMG activity. *De novo* PD patients are more likely to produce these premature EMG responses (W. D. Byblow & C. M. Stinear, unpublished data).

control deficits revealed by the pilot study were not evident at a purely behavioural level. EMG recordings were used in combination with the task to reveal the abnormalities. An ARI task, in combination with EMG, may be able to reveal abnormalities of motor function beyond current clinical examination abilities.

Interestingly, the preliminary results with the ARI task were able to distinguish between *de novo* patients and controls on Go trials, with the EMG and behavioural data revealing deficits in internal motor timing. Given these results, and the fact that SSRT does not always correlate with disease severity (Gauggel et al., 2004), Go trials in the context of an RI task might provide the more sensitive and useful biomarkers during the preclinical period.

Overall, the ARI task satisfies the three criteria necessary to obtain quantitative, objective and sensitive measures of the motor deficits during the preclinical phase of PD (Maetzler and Hausdorff, 2012): (i) ARI challenges the BG system by requiring generation and cancellation of internally- generated movements, (ii) used in combination with EMG measures, ARI can be used to assess motor function beyond clinical evaluation standards, and (iii) ARI can distinguish between patients and controls at the earliest phase of the disease. Given these three main criteria, ARI may also be able to monitor PD progression, although further research will be required to test this.

The positive results produced using the go/no-go and stop-signal tasks in the context of PD serve to motivate the use of RI tasks with PD patients in the preclinical stage. Theoretically, for reasons stated above, an ARI task may perform even better at differentiating between healthy controls and preclinical PD patients. This theory is supported by the pilot data using an ARI task with *de novo* patients. However more research is certainly needed and it is currently unclear which RI task would reveal the most salient biomarkers of PD.

3.3.4 Bimanual response inhibition

The majority of RI studies have investigated execution and cancellation of simple unimanual responses, with or without a preceding choice decision. Fewer studies have investigated execution and cancellation of unitary, bimanual responses using either the stop-signal (Aron and Verbruggen, 2008; Claffey et al., 2010; Ko and Miller, 2011; Majid et al., 2012) or ARI task (Coxon et al., 2007, 2012; MacDonald et al., 2012 Chapter 5). There is evidence to suggest that bimanual RI tasks may be even more salient than unimanual RI in the context of PD. Individuals with PD demonstrate impaired bimanual coordination, especially in an antiphase pattern (Almeida et al., 2002; Byblow et al., 2002; Geuze, 2001; Ponsen et al., 2006) or when performing two different movements simultaneously (Brown et al.,

1993). Importantly, bimanual coordination dysfunction is present in *de novo* PD (Ponsen et al., 2006). In-phase movements require symmetric activation of homologous muscles, whereas anti-phase movements require simultaneous activation of nonhomologous muscles. MacDonald et al. (2012 Chapter 5) investigated bimanual ARI performance and compared homologous versus nonhomologous muscles. Surprisingly, healthy younger adults are able to perform the task equally well with both muscle pairings. However PD patients would be expected to exhibit worse performance using nonhomologous muscle pairings. Importantly, because the ARI task effectively constrains the Go response, it should provide a valid estimate of the inhibitory process in PD patients. A bimanual RI task may reveal more subtle motor deficits than unimanual RI for preclinical PD.

Another advantage of a bimanual task is that it permits the examination of partial response cancellation, a cognitively and neurophysiologically demanding behaviour. When a subset of an action must be cancelled while the remaining components continue, the remaining components are substantially delayed (Aron and Verbruggen, 2008; Claffey et al., 2010; Coxon et al., 2007, 2009; Ko and Miller, 2011; MacDonald et al., 2012 Chapter 5). Furthermore the subsequently delayed response is executed at a higher gain as indicated by a greater rate of EMG onset and force production (Coxon et al., 2007; Ko and Miller, 2011; MacDonald et al., 2012 Chapter 5). The delay and gain of EMG is greater with homogeneous digit pairings compared to heterogeneous pairings (MacDonald et al., 2012 Chapter 5). Given the expected damage to gain setting nuclei in the brainstem that accompanies early PD (Braak et al., 2004; Grinberg et al., 2010), the bimanual ARI paradigm of MacDonald et al. (2012 Chapter 5) may be salient for detecting the motor onset of PD.

3.4 Preclinical Parkinson's disease: Response inhibition tasks as a component of an objective test battery

We propose that RI tasks have potential utility during the preclinical stage to reveal subtle, subclinical motor abnormalities to aid with earlier diagnosis of PD. The diagnosis of PD currently remains a clinical one, with no definitive biochemical or genetic diagnostics. The only definitive PD diagnosis is through a postmortem. Diagnosis is particularly difficult in the very early stages of the disease, and is based on the presentation of motor symptoms and a positive response to PD medication. Unfortunately, there is a substantial length of time between the onset of neurodegeneration and the ability to clinically diagnose PD. This period is known as the preclinical (prodromal) phase, also referred to as the premotor

phase, and can last up to ten years (Gaenslen et al., 2011; Gonera et al., 1997). However our contention is that premotor is not an appropriate term given the evidence of motor abnormalities during this time. For simplicity we refer to this stage as preclinical.

Biomarkers are objectively measurable characteristics indicative of normal biological processes (Michell et al., 2004). One of the most basic goals for biomarkers is to help shorten the preclinical stage of PD, and to facilitate better treatment and ultimately better quality of life. It is estimated that 50 – 70 % of irretrievable dopaminergic neuron loss is needed in SNpc to develop the characteristic symptoms required for clinical diagnosis (Fearnley and Lees, 1991; Marino et al., 2012; Riederer and Wuketich, 1976). This means the extent of degeneration has not yet reached this critical point during the majority of the preclinical phase, providing a window of opportunity for early neuroprotective therapies to prevent or delay further neuron degeneration. The goal of earlier diagnosis is therefore an important one. For example, if it were possible to diagnose PD early in the preclinical stage and a causal therapy was available, then further neuronal loss in the SNpc may even be preventable (Braak et al., 2003).

For a measure to be useful for early detection in PD, it is necessary to prospectively investigate a group of individuals at risk of developing the disease. However, the first step is to examine whether the measure is capable of discriminating between a diagnosed group at the earliest stage of the disease and healthy age-matched controls. Before a test is deemed to have clinical utility, research is required to verify its sensitivity, specificity and plausibility. If one can assume that severity distinguishes between the preclinical and early clinical (*de novo*) state, it can be inferred that tests which are successful at differentiating between de novo patients and controls also show promise for differentiating during the preclinical stage.

Several techniques are currently under investigation for identifying early and subtle nonmotor changes to biological processes during the preclinical stage (for a review see Michell et al. 2004). These include magnetic resonance imaging (MRI) (Gattellaro et al., 2009; Lewis et al., 2003; Martin et al., 2008; Peran et al., 2010; Tessa et al., 2008), transcranial sonography (Izawa et al., 2012), cerebral spinal fluid analyses (Goldstein et al., 2012), rapid eye movement (REM) sleep disturbance, olfactory function, protein build-up in colonic neurons (Shannon et al., 2012), among others. A full discussion of nonmotor biomarkers is beyond the scope of this review. However it is worth noting that the most prevalent nonmotor symptoms of PD involve specific brainstem nuclei (for a review see Grinberg et al. 2010). For example, neurodegeneration in the olfactory bulb leads to olfactory dysfunction and changes within the medulla oblongata and pontine tegmentum are involved in REM sleep behavioural disorder (Braak et al., 2003, 2004; Del Tredici et al., 2002). Due to the

neurobiological pattern of PD progression, olfactory and REM sleep behaviour disorder symptoms appear before degeneration of SNpc neurons, which cause motor symptoms. For this reason, we regard these nonmotor biomarkers as optimal for combined use with an RI task into an objective test battery, to utilize the crucial period when damage to dopaminergic neurons may be preventable, or at least delayed. Biomarkers derived from MRI may also complement the early behavioural manifestations of PD and prove useful in objectively monitoring disease progression. It is unlikely that any single biomarker will be perfect for PD. Due to the heterogeneity of the disease, it is more likely that a faction of biomarkers will be required.

3.5 Postdiagnostic Parkinson's disease

3.5.1 Response inhibition and impulse control disorders

Response inhibition tasks may also have utility in postdiagnostic PD and for evaluating treatment options. One prevalent, detrimental and underreported side effect of dopaminergic medication in PD is the prevalence of impulse control disorders (ICDs). The incidence of ICDs in PD patients is as high as 20 % (Weintraub, 2009), and suggests some individuals have greater susceptibility for developing ICDs than others. The identified risk factors for ICDs include age at PD onset with ICD more prevalent in younger patients, being male, being single, having a family or personal history of addictive behaviours, dopamine agonist (DA) medication in combination with levodopa treatment, high doses of dopaminergic medication, long duration of dopaminergic treatment and a personality profile characterized by impulsiveness (Ceravolo et al., 2009; Giladi et al., 2007; Klos et al., 2005; Voon et al., 2007; Weintraub et al., 2010, 2006). ICDs manifest as addictive behaviours including pathological gambling, compulsive shopping, binge eating and hypersexuality (for a review see Voon et al. 2007). Treatment decisions would be aided by an objective method to predict and classify an individual's risk of developing impulsive side effects.

Impaired impulse control is associated with an increased risk of developing ICDs. PD patients on dopamine replacement therapies exhibit higher levels of impulsivity (Isaias et al., 2008) and disinhibition (Pontone et al., 2006) than healthy controls, which are both associated with an increased probability of impulsive disorders. There are several reasons to suspect that a RI paradigm could provide a quantifiable measure of risk for ICD development. For instance, D2 dopamine receptors are specifically implicated in RI (Colzato et al., 2013, 2010a; Eagle et al., 2011; Ghahremani et al., 2012; Hamidovic et al., 2009; Nandam et al.,

2013) and are a common target of several routinely prescribed DA medications known to cause ICDs. Second, RI is impaired in pathological gamblers and individuals with an ICD manifesting as Tourette syndrome (Goudriaan et al., 2006). Poletti and Bonuccelli (2012) identified that difficulty on executive tasks requiring high levels of impulse control such as a RI task may signal increased risk for the development of ICDs in medicated PD patients, but this has not yet been tested. As impaired inhibitory control has been specifically implicated in individuals with ICDs, SSRTs produced from a RI task may be the most useful dependent variable to provide a quantifiable measure of risk for ICD development.

Without question, the development of ICDs are associated with DA medication (Dodd et al., 2005; Grosset et al., 2006; Klos et al., 2005; Voon et al., 2006; Weintraub et al., 2006) — pramipexole, pergolide and ropinirole (Tyne et al., 2004). The incidence of ICDs is about 14 – 20 % in patients prescribed DAs (Weintraub, 2009; Weintraub et al., 2010, 2006). Although *de novo* PD patients can also develop ICDs in the absence of dopaminergic medication (Antonini et al., 2011; Avanzi et al., 2006), the risk is no higher than for healthy controls (Weintraub et al., 2013). One idea is that early detection of impaired impulse control may prevent ICDs from developing by informing clinicians and guiding medication selection and timing. Once dopaminergic therapy begins, early detection of impaired impulse control would signal the need for monitoring at-risk patients (Voon et al., 2007).

It is worth briefly re-examining how dopaminergic medication may trigger ICDs. ICDs are essentially extreme cases of dopaminergic dysregulation of voluntary and goal-directed behaviours. The current hypothesis on the mechanistic root of ICDs is the hyperdopaminergic state of the MCL system in early PD (Cools, 2006; Sawamoto et al., 2008), which is then exacerbated by dopaminergic medication. Medication is targeted at optimizing motor function by augmenting depleted nigrostriatal dopamine. Unfortunately medications lack network specificity. Therefore the relatively preserved ventral striatum, caudate nucleus and PFC within cognitive and MCL networks can become hyperdopaminergic (Cools, 2006; Vaillancourt et al., 2013), deviating from their optimal dopaminergic activity and function along their individual inverted-U curve. Increasing tonic dopamine activity in PFC and ventral striatum disrupts associative learning and behaviour modification (Goto and Grace, 2005; Schultz, 2002). Contextual behaviour modification is impaired during healthy ageing (Chowdhury et al., 2013) and in PD patients (Rowe et al., 2008). Further disruption of this behavioural mechanism through dopamine dysregulation is hypothesized to contribute to the development of ICDs. Interestingly however, at a group level DA administration does not necessarily impair RI in PD (Antonelli et al., 2013). Using the delay discounting task and go/no-go RI task, Antonelli et al. (2013) found pramipexole increased impulsivity during

the delay discount task but had no effect on reaction time or frequency of unsuccessful no-go trials in the RI task. Treatment with pramipexole influenced cognitive impulse control (impulsive choice), but not motor impulse control (impulsive action). The lack of effect on motor impulse control may be partly due to the go/no-go task design, as discussed in Section 3.3.1. Nevertheless, Wylie et al. (2012) found measures of motor impulse control could not dissociate between PD patients with and without ICDs.

3.5.2 Does genetic makeup predispose some individuals to impulse control disorders?

As in many pathological conditions, responses to both disease and treatment options may depend on an individual's genetic profile. Here we briefly review what is known about genes involved in dopaminergic transmission. Dopamine regulating genes are integrally involved in the functioning of BG-thalamocortical networks and are postulated to dictate response to dopaminergic medication. Inter-individual differences in DNA sequences exist as a result of mutations, referred to as polymorphisms. Genetic variation within the dopaminergic system can influence traits known to be modulated by dopamine, such as impulsivity (Nandam et al., 2013; Nemoda et al., 2011). Genetic variability will have the greatest influence on behaviour when dopamine neurotransmission deviates from close-to-optimal levels (i.e., dopamine dysregulation). For example, at either extreme end of the inverted-U relationship (Figure 3.2).

Here we identify five genes that are particularly influential in dopamine neurotransmission, most of which have received some attention related to ICDs. Catechol-O-methyltransferase (COMT) and dopamine transporter (DAT) genes influence synaptic dopamine concentrations. COMT polymorphisms affect executive function, including impulse control (Blasi et al., 2005; Colzato et al., 2010b; Congdon et al., 2009; Diamond et al., 2004; Fallon et al., 2013; Farrell et al., 2012; Foltynie et al., 2004; Hoogland et al., 2010; Kramer et al., 2007; Williams-Gray et al., 2008, 2007).

Polymorphisms within the genes encoding for the dopamine D1 (DRD1, rs4532), D2 (DRD2, rs1800497), and D3 (DRD3, rs6280) receptors can affect dopamine neurotransmission (Nemoda et al., 2011; Pearson-Fuhrhop et al., 2013). DRD2s are specifically implicated in RI performance (Colzato et al., 2010a; Ghahremani et al., 2012; Hamidovic et al., 2009; Nandam et al., 2013) and their impact is magnified during ageing (Colzato et al., 2013). Mutations within DRD1 (Comings et al., 1997) and DRD3 (Lee et al., 2009) have been associated with impulsive behaviours. D3 receptors are abundant in the ventral striatum (Gurevich and

Joyce, 1999), which forms part of the MCL network. The link between DRD3 polymorphisms and impulsive behaviour in PD provides further support for the involvement of the MCL network in ICDs.

The combined effect on dopaminergic neurotransmission of mutations within these five genes has recently been quantified by determining a dopamine gene score for 50 individuals engaged in a motor learning task (Pearson-Fuhrhop et al., 2013). The effect of dopaminergic medication on motor learning varied with dopamine gene score: participants with lower levels of dopamine neurotransmission showed an improvement in motor learning on dopaminergic medication, whereas medication had a detrimental effect on those with higher dopamine gene scores. Dopaminergic genes may also determine how an individual responds to dopaminergic medication in the context of impulse control. Indeed, DAs produce opposite individual effects on impulse control that are dependent on a patient's baseline performance without medication (Wylie et al., 2012). It is our contention that investigating individual dopamine genetic profiles in combination with cognitive-motor impulse control measures may reveal important information that can account for the divergent DA effects on impulse control and possible susceptibility to ICDs, which in turn could lead to more individualized treatment of PD. For these reasons, considering only the effect of dopaminergic medication on RI performance, without allowing for dopaminergic gene profiles, may not be capable of identifying risk of ICDs.

3.6 Conclusion

Motor, cognitive and limbic systems are impaired in PD due to dopaminergic dysregulation. RI may offer potential utility and RI tasks may provide salient biomarkers which inform diagnostic criteria as well as identifying individuals at risk of developing ICDs. Given the contextually rich dataset provided by an RI task, the salient measures provided during the pre- and postdiagnostic stage are most likely to be in different behavioural contexts. Execution trials of an RI task, rather than SSRT, might provide the most sensitive and useful biomarkers during the preclinical period. In contrast, it is more likely that SSRT measures will provide the more useful markers postdiagnosis when evaluating ICD risk. Our contention is that further research is warranted to determine if RI tasks should form part of an objective, combined motor and nonmotor test battery, to assist with earlier diagnosis. To inform individualized treatment decisions postdiagnosis, the risk of ICDs may best be determined through assessments and screening that may include RI measures and obtaining a dopaminergic genetic profile.

Chapter 4

Overview of Experimental Techniques and Methods

4.1 Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a noninvasive tool used to stimulate the brain and make inferences about the underlying neurophysiological processes within the central nervous system of humans. TMS has provided a safe and painless way of assessing neuromotor function since 1985 (Barker et al., 1985) by stimulating the brain via electromagnetic induction. A stimulator induces a rapid pulse of high voltage current by discharging a capacitor. The current is passed through an attached wire coil, which creates a brief surrounding magnetic field. A changing magnetic field induces a current in conductive material. When the coil is held tangentially against the scalp, the magnetic field passes unimpeded through the skin and skull, creating an electric field and oppositely directed current flow within underlying neural tissue. The electric field modifies the transmembrane current of neurons which can in turn depolarize the neuron and generate an action potential if the stimulus is of sufficient intensity. TMS intensity can be set in 1 % increments from 0 to 100 % of maximum stimulator output (commonly 2 Tesla). If held at the correct angle and location TMS can activate pyramidal neurons of the corticospinal tract within M1. In Chapter 6 TMS was delivered over M1 using a Magstim 200 stimulator and a flat figure-of-eight coil.

When applied over M1, a single pulse of TMS can produce a motor evoked potential (MEP) in the contralateral target muscle. The MEP is recorded via surface electromyography (EMG) from electrodes placed on the skin over the target muscle. A typical MEP latency for intrinsic hand muscles is 20 – 25 ms, dependent on the limb length of the individual. The MEP comprises multiple descending volleys labelled as direct (D) and indirect (I) compo-

nents (for a review see (Di Lazzaro et al., 2008). D-waves have the shortest latency as a result of direct stimulation of pyramidal neuron axons whereas the I-waves represent indirect depolarization of the pyramidal neurons trans-synaptically (Di Lazzaro et al., 2004). The threshold for TMS is lower in humans for I-waves than D-waves so the observed MEP in target muscles is mostly contributed to by I-wave activity, except at very high intensities (Day et al., 1989; Rothwell et al., 1991). The activation thresholds differ between inhibitory interneurons, excitatory interneurons and corticomotor neurons (Ilic et al., 2002). It is therefore possible to examine the excitability of separate intracortical circuits by altering stimulation intensities. In Chapter 6, intracortical inhibitory function was examined via a subthreshold TMS pulse.

The optimal location, or 'hotspot', for stimulation of the target muscle must be determined for each individual. The optimal orientation will be one inducing a posterior to anterior current perpendicular to the precentral gyrus (Day et al., 1989; Rossini et al., 1994). Due to the underlying neural topology, the initial coil orientation is commonly with the handle directed posteriorly at a 45 degree angle. The coil is then gradually moved around the scalp in roughly a 1 cm grid along M1 until the location is determined that produces the largest MEP amplitudes for a given stimulation intensity. This location is marked on the scalp to ensure consistent coil placement. The hotspot represents the location of highest corticomotor neuron density and lowest activation threshold for the target muscle. The target muscle during TMS experiments was the left first dorsal interosseous (FDI).

Motor thresholds are determined at the cortical hotspot either with the muscle at rest (rest motor threshold, RMT) or minimally activated (active motor threshold, AMT). The activation state of a muscle is reflected by the root mean square of EMG activity (rmsEMG) within a specified time window (e.g. 50 ms) immediately prior to stimulation. Muscles are considered to be at rest with rmsEMG values below 10 – 15 μV, which is an important criteria when determining RMT. Calculation of AMT requires the participant to maintain an isotonic contraction of the target muscle around 10 – 20 % of maximum voluntary contraction during stimulation. Motor threshold is defined as the lowest stimulation intensity that evokes MEPs of at least 50 (RMT) or 100 μV (AMT) amplitude in 50 % of recorded stimulations (e.g. in 4 out of 8 stimulations) (Rossini et al., 1994). AMT is always lower than RMT as voluntary muscle contraction facilitates cortical and spinal motor neuron membrane potential. Similarly, RMT is generally more variable than AMT as resting membrane potential for individual neurons are at more variable distances from firing threshold. RMT and AMT are frequently used to set TMS intensities for experimental paradigms, as described in Chapter 6.

TMS can be administered as a single pulse or pairs of pulses to assess corticomotor excitability or the state of intracortical circuits, respectively. The measures from both techniques relevant to the current experiments are described below.

4.1.1 Single-pulse TMS

Single-pulse is the most common form of TMS and measures corticomotor excitability (CME) by stimulating M1 and evoking MEPs in the contralateral target muscle. Peak-to-peak amplitude of the MEP can be used as a measurement of the excitability of the entire corticomotor pathway at the time of stimulation i.e., the net effect of facilitatory and inhibitory inputs to all synapses between the coil and muscle. One method of investigating CME is to progressively increase stimulation intensity to generate a stimulus-response curve. These sigmoidal curves reflect the increasing excitability of synaptic inputs to corticomotor neurons in response to progressively increasing TMS intensities (Devanne et al., 1997). Alternatively, the temporal dynamics of CME can be investigated by using a constant TMS intensity and varying stimulation time (as in the current thesis). An increase in MEP amplitude evoked by the same intensity reflects an increase in responsiveness (i.e. excitability) of the corticomotor pathway. MEP amplitude of involved motor representations progressively increases during preparation of a simple motor response in the 100 ms preceding onset of EMG activity (Chen and Hallett, 1999; Coxon et al., 2006; Duque et al., 2010; Marinovic et al., 2011; Pascual-Leone et al., 1992).

When using TMS to investigate CME dynamics during motor control studies it is important to consider the timing and strength of TMS. Suprathreshold TMS delivered to M1 during the premovement period close to the presumed movement onset can delay RT (Hashimoto et al., 2004; Leocani et al., 2000; McMillan et al., 2004; Pascual-Leone et al., 1992). The consensus is that suprathreshold stimulation interferes with central motor commands and causes a refractory period in the corticomotor neurons at a time when they would have been firing to initiate movement, causing a delayed movement time. Conversely, subthreshold TMS during the same time period can shorten RT (Hashimoto et al., 2004; Pascual-Leone et al., 1992; Sawaki et al., 1999). The shortening of RT is speculated to be from a reduction in the time to transfer a motor command from premotor and supplementary motor regions to M1, without interfering with the motor program. Alternatively, decreased RT may be from less specific intersensory facilitation. Intersensory facilitation describes the effect of an accessory stimulus being presented close in time to a response signal (Terao et al., 1997). Stimulation intensity and timing are therefore crucial factors when designing a TMS

experiment to investigate the temporal modulation of CME in the context of RI. By using a constant subthreshold stimulation intensity around each participant's motor threshold (determined during a minimal key press), Coxon et al. (2006) successfully avoided interfering with behaviour in the ARI task.

There are two main advantages to using TMS when investigating movement preparation and cancellation. Firstly, TMS enables very high temporal resolution. TMS can be delivered with millisecond accuracy, providing high resolution information about the dynamic state of the pathway throughout an active task. Secondly, TMS can be used to preferentially target inhibitory or excitatory neurons. Cortical inhibitory interneurons have a lower threshold than excitatory interneurons. This means lower stimulation intensities are relatively selective for inhibitory interneurons, a feature exploited by the paired-pulse technique described below. Therefore TMS is ideal for investigating the temporal dynamics of both CME and inhibition during movement preparation and cancellation.

4.1.2 Paired-pulse TMS

Paired-pulse TMS enables investigation of intracortical mechanisms exerting an effect on M1. This technique is predicated on conditioning a MEP with a second TMS volley delivered via the same, or a second coil. Depending on the relative timing and location of the conditioning (second) stimulus, mechanisms of intracortical and interhemispheric inhibition/facilitation can be examined.

One common method of investigating inhibitory function within M1 is to measure short-interval intracortical inhibition (sICI). This involves preceding a suprathreshold test stimulus (TS) with a subthreshold conditioning stimulus (CS) by 1 – 6 ms (Kujirai et al., 1993; Pascual-Leone et al., 2002). The first pulse generates an inhibitory postsynaptic potential in the corticomotor neuron, thereby suppressing the response to the second stimulus. The amount of suppression of the nonconditioned MEP reveals the influence of intracortical inhibitory circuits. Gamma amino butyric acid (GABA) is the main inhibitory neurotransmitter in the brain. Pharmacological studies demonstrate that sICI is mediated by certain $GABA_A$ receptors. Administration of the nonspecific $GABA_A$ agonist Lorazepam can increase sICI (Ilic et al., 2002; Teo et al., 2009), whereas specific activation of the $GABA_A$ $\alpha 1$ receptor via Zolpidem has no effect (Teo et al., 2009).

The intensity and timing of the CS can affect levels of sICI. Intensity of the CS influences sICI in a U-shaped manner (Chen et al., 1998a) with maximal sICI occuring at different CS intensities for different muscles at a given interstimulus interval (ISI). Inhibition at different

ISIs may be mediated by different inhibitory circuits (Roshan et al., 2003). Selection of the appropriate ISI (timing) also has a large impact on the amount of sICI that can be detected, as facilitatory processes may contaminate sICI at certain ISIs. For intrinsic hand muscles, such as FDI, an ISI of 2 ms and CS intensities from 100 – 120 % of AMT produce maximal sICI (Peurala et al., 2008). To investigate modulation of sICI throughout an experimental protocol, an initial target of 30 – 50 % inhibition is often chosen as it allows both increases and decreases in sICI (Fisher et al., 2002; Stinear and Byblow, 2003). At 2 ms ISI, approximately 50 % inhibition can be achieved with a CS between 65 – 90 % AMT, as was done in the paired-pulse experiment in Chapter 6.

Specific factors should remain constant to allow valid and comparable measures of sICI. Nonconditioned MEP amplitudes within 1 – 4 mV are optimal for investigating sICI, with amplitudes outside this range reducing sICI (Daskalakis et al., 2002; Roshan et al., 2003; Sanger et al., 2001). Consequently it is common to set TS intensity to elicit a nonconditioned MEP amplitude around 1 – 1.5 mV, and then adjust TS intensity throughout the experiment to maintain this amplitude range (Byblow and Stinear, 2006; Daskalakis et al., 2002; Roshan et al., 2003). However nonconditioned MEP amplitude can change dynamically throughout an active task. This can make it very difficult to maintain MEP amplitudes at a level that enables a reliable comparison of sICI throughout the task. In addition, levels of voluntary activity can both fluctuate during an active task and influence sICI (Stinear and Byblow, 2003). It is therefore important to ensure comparable background muscle activity when measuring sICI during an active task. To this end, trials were excluded from analysis in the current sICI experiment if rmsEMG exceeded 14 µV.

4.1.3 Safety and experimental considerations

TMS is considered a safe technique provided participants are correctly screened and the appropriate guidelines are adhered to (screening questionnaire Appendix F). All information provided by participants on the screening checklist is seen and signed off by a neurologist. Guidelines for the safe and ethical application of TMS are driven by best practice recommendations (Rossi et al., 2009; Wassermann, 1998). For all research conducted in the Movement Neuroscience Laboratory, information is provided to participants prior to recruitment regarding the techniques and interventions to be used in the study. This is provided in the form of an approved participant information sheet that is specific to each study and approved by the necessary ethics committee (available in Appendices C and H). Written consent is always obtained from participants after explanation of the potential risks

(Appendices D and I). It is acknowledged that TMS is still a relatively new technique, with extensive use over only the last 20 years. The longer term side effects are therefore unknown and cannot be completely discounted.

Seizures are considered the most serious acute adverse effect and are the main consideration when screening participants (Anand and Hotson, 2002). Contraindications which may signal an increased risk of seizures include previous concussion, head injury and a personal or familial history of epilepsy. The risk of seizures is less than 1 % in healthy adults and more likely to occur with repetitive, rather than single or paired-pulse, TMS (Rossi et al., 2009). Additional contraindications to TMS include implanted electronic devices (e.g. pacemakers) and metallic hardware above shoulder level. These devices may malfunction when the TMS coil is discharged. Less severe potential side effects include local pain and discomfort from recording electrodes or stimulation of scalp and facial muscles, headaches and psychological discomfort if the technique is unfamiliar. TMS is also not recommended for pregnant women.

There is natural variability in MEPs recorded from TMS, both within and between participants. Within subject factors that can contribute to variability include time of day for the experimental session (Sale et al., 2007), caffeine consumption (Cerqueira et al., 2006) and sleep deprivation (Lanza et al., 2015). These factors can be partially controlled through consistent timing of experimental sessions and questionnaires. Between subject factors include handedness (MacDonell, 1991), age (Pitcher et al., 2003), and medication (Ziemann, 2004). For these reasons, the current TMS studies recruited only right handed individuals within a specified age range and questions regarding prescribed and nonprescribed medication usage were included in the screening checklist. Methodological factors which can contribute to inter-trial MEP variability include coil orientation and placement, and background muscle activity. Neuronavigation techniques are becoming more common in order to enhance stimulation precision. Data trimming is a common analysis technique and was used in the current TMS experiments prior to averaging in order to counter the potential effect of outliers in the MEP data. Trimming can involve removal of MEPs above and below a specified number of standard deviations from the mean, or, as in the current experiments, removal of an absolute percentage (e.g. 10 % of the smallest and largest MEPs.

4.2 Pharmacological intervention

Dopamine plays a diverse and complex role in the brain. There are various pharmacological options available to increase dopamine neurotransmission. Synthetic forms of levodopa pro-

vide the precursor substrate to dopamine and activate endogenous dopaminergic synthesis pathways within the brain to increase dopamine production (for a review of the history of levodopa see Hornykiewicz 2002). This method of increasing dopamine neurotransmission remains the gold standard for treating clinical symptoms of PD. Other pharmacological options to increase dopamine neurotransmission include COMT inhibitors, monoamine oxidase B (MAO-B) inhibitors and dopamine agonists (DAs). DAs were initially introduced as adjunctive therapy to levodopa treatment for PD, but can also be used as monotherapy in patients with *de novo* PD and restless legs syndrome (Ondo 1999; Walters et al. 2004, for a review see Matheson and Spencer 2000). DAs mimic the neurotransmitter and directly activate receptors in the absence of dopamine (Brooks, 2000; Tintner and Jankovic, 2003). There are five main DA drugs used in the treatment of PD: pramipexole, rotigotine, apomorphine, bromocriptine and ropinirole. The most common orally prescribed DAs are ropinirole and pramipexole. The proposed mechanisms underlying the development of ICDs on DAs have been discussed in Chapter 3. The following section will consider the basic mechanisms and safety considerations for ropinirole, the dopamine agonist relevant to the current research.

Ropinirole (SKF-101468) is a nonergoline D2-like dopamine receptor agonist, showing little or no interaction with nondopaminergic receptors. D2-like receptors encompass D2, D3 and D4. Ropinirole, as with all DAs, acts on D2 dopamine receptors with postsynaptic activation believed to be most important for antiparkinsonian effects, and presynaptic activation possibly providing neuroprotection (Iida et al., 1999; Kuzel, 1999; Tulloch, 1997). However, the preferential affinity for ropinirole is D3 > D2 > D4 (Coldwell et al., 1999; Perachon et al., 1999) with D2 and D3 being the primary targets. This order of affinity is similar to that of dopamine. Of most relevance to the current research, is the activation of presynaptic D2-like autoreceptors by ropinirole in the nigrostriatal and mesocorticolimbic pathways (see Matheson and Spencer 2000).

Ropinirole is widely distributed throughout the body and rapidly absorbed following oral administration. Peak plasma concentrations and prominent effects on the central nervous system (CNS) occur after 1 – 2 hours in healthy participants and PD patients (Brefel et al., 1998; Ramji et al., 1999). Co-administration with food does not affect the extent of absorption as assessed by systemic availability, however it significantly delays time to peak concentration (Brefel et al., 1998). A delayed time to peak concentration may reduce the incidence of nausea but has important implications in the context of experimental protocols. Revealing the effect of a single dose of ropinirole, as in the current research, necessitates maximal sensitivity of experimental measures. Logically this would occur at peak drug concentrations. Therefore in a research setting it is advisable to standardize timing of drug

administration to food intake. Ropinirole was always administered in the current experiment after 1 – 2 hours of fasting.

Ropinirole therapy is initiated at a low dose and gradually increased to achieve maximum therapeutic response. The recommended starting dose for oral administration in patients is a total of 0.75 mg per day (Matheson and Spencer, 2000). Doses up to 1 mg have also been successfully administered and tolerated in healthy participants (Acton and Broom, 1989; Monte-Silva et al., 2009). In Chapter 8, ropinirole was administered at both 0.5 mg and 1.0 mg to healthy participants.

4.2.1 Side effects and safety considerations

Although orally administered ropinirole is targeted at D2-like receptors in the CNS, transient side effects can occur from peripheral activation of dopamine receptors. Activation of peripheral D4 receptors inhibits stimulus-evoked release of noradrenaline and may lead to hypotension, bradycardia and regional vasodilation (Parker et al., 1994). Single doses of ropinirole up to 1.0 mg may cause transient side effects in healthy participants consistent with peripheral D2 dopaminergic effects (de Mey et al., 1990). Postural symptoms can include nausea, faintness, dizziness and sweating. These can mostly be avoided through pretreatment with domperidone which is a peripheral D2 receptor antagonist (de Mey et al., 1991). Ropinirole monotherapy is also commonly associated with somnolence. Participants in the current research were therefore advised, for safety reasons, not to drive or operate heavy machinery for up to 6 hours after taking the medication i.e. for the duration of the elimination half-life (Hubble et al., 2000). In addition, participants were advised not to consume CNS depressants (e.g. alcohol) on days of experimental sessions.

Ropinirole is generally well tolerated in combination with commonly administered drugs such as antidepressants, ibuprofen and antihistamines. However when screening potential participants, all prescription and nonprescription/herbal products used, allergies and medical history should be recorded to identify any contraindications or reasons for caution. All participants in the current research were screened by a neurology registrar using an approved checklist (Appendix L). Contraindications for ropinirole and/or domperidone include a known hypersensitivity to ropinirole, domperidone, or any of the excipients; history of acute or chronic psychiatric disorder; history of severe cardiac, hepatic or renal disease; history of severe systemic disease; history of severe dizziness or fainting; a prolactin-releasing pituitary tumour; currently breast feeding; current tobacco smoking or nicotine

patch; lactose intolerance; glucose/galactose malabsorption; any medications which may interact with ropinirole or domperidone, or themselves cause drowsiness.

4.3 Neuropsychological assessment

Dopaminergic tone can affect both motor and cognitive behaviour. The ARI task was used in Chapter 8 to measure the effect of dopamine agonist medication on motor impulse control, while cognitive impulse control was assessed through performance on the Balloon Analogue Risk Task (BART) and global cognitive function was assessed using the Central Nervous System Vital Signs (CNSVS) computerized test battery. The ARI task is common to all thesis experiments and therefore discussed in each experimental chapter as well as compared to other RI tasks in Chapter 3, so will not be discussed again in this section. The following section will instead discuss the BART and CSNVS test battery as they relate to the experimental work presented in Chapter 8.

4.3.1 Balloon analogue risk task (BART)

The BART is a computerized, laboratory-based task designed to measure decision making capabilities and risk taking propensity (Lejuez et al., 2002). Akin to real-world situations, taking risks on the task is rewarded until a point at which further risk results in worse outcomes. Briefly, each mouse click on a 'Pump up the balloon' button either i) incrementally inflates an onscreen balloon, causing a realistic inflation sound effect and visual increase in balloon size, adding 5 cents to an accumulating monetary reward, or ii) inflates the balloon past its individual explosion point, thereby bursting the balloon, generating a popping sound effect and visual, and resulting in no money earned for that balloon. Each balloon explodes after a randomly determined number of pumps, which occurs at any point from the first pump all the way to the balloon expanding to fill the entire screen. On each button press, a number is randomly selected from an array of N numbers without replacement. Selection of a specific number is designated to indicate a balloon explosion. Successive pumps therefore result in an increased probability of a balloon explosion (e.g. 1/N, 1/N-1 etc) to model real-world situations in which increasing risk often results in diminishing returns. However it is possible to stop pumping the balloon after any number of pumps, collect the accumulated money, and progress to the next balloon. Each pump of the balloon therefore requires an evaluation of the potential consequences and a decision about how to behave. This is the essence of cognitive impulse control.

The most commonly used measure from the BART to denote decision making has traditionally been adjusted average number of balloon pumps. This is computed by averaging the number of balloon pumps using only trials in which the participant made the decision to collect the accumulated money. This 'adjusts' for trials in which the number of pumps was artificially low due to the random nature of the balloon explosion. However more recent studies have utilized alternate methods of assessing BART performance. These include measuring the coefficient of variation for adjusted pumps (DeMartini et al., 2014) and the change in adjusted pumps following collected versus exploded balloons (Ashenhurst et al., 2014). The method used by Ashenhurst and colleagues accounted for behaviour on a trial-by-trial basis as an index of loss and reward reactivity. This method of measuring BART performance seems most valid in the context of cognitive impulse control. Increased reactivity to positive or negative task reinforcement would denote greater impulsiveness in decision making as behaviour is being too readily modified.

The BART has demonstrated acceptable test-retest reliability (White et al., 2008). The random element of balloon explosion provides the opportunity to minimize the learning effect if the BART is used as part of a multiple session research design. It is still possible to assess a participant's ability to learn and react to the probability of balloon explosion by exposing them to varying sized arrays from which to randomly pick the number to denote explosion, as was done in the initial study by Lejuez et al. (2002). However the intention in the current research was to reduce the opportunity for reinforcement learning. To this end, participants performed only a single block of 30 trials that had the same probability of balloon explosion in each experimental session.

Scientists and clinicians alike often use behavioural measures to assess decision making capabilities. Common tasks used by clinicians include delay discounting tasks such as the Iowa Gambling Task (Bechara et al., 1994). This type of task examines the ability to control the urge for immediate reward in order to obtain larger rewards after more time or effort, therefore assessing the capacity to evaluate immediate gains over long-term losses and judge relative risk. Choosing between options can be in the context of 'cold' and 'hot' decision making, utilizing deliberate calculations versus more emotional reactions, respectively. The BART predominantly measures 'hot' decision making as opposed to the Iowa Gambling Task and Columbia Card Task (Figner and Voelki, 2004) which assess more deliberate calculation of risk and benefits. It has been suggested that these three different tasks therefore measure distinct decision making processes (Buelow and Blaine, 2015). It remains open to debate which task would be best suited to measure decision making in the

context of ICDs. However the BART seems a viable option as impulsive decision making involves spontaneous, emotional reactions before sufficient evaluation of the consequences.

There have been reports that delay discounting tasks can have poor correlation with self-reported measures of impulsivity (Mitchell, 1999; Petry, 2001) e.g. Barrat Impulsiveness total score. In contrast, the BART shows a consistent correlation with self-reported impulsivity and real-world risk behaviours (Ashenhurst et al., 2014; DeMartini et al., 2014; Lejuez et al., 2007, 2003, 2002; MacPherson et al., 2010). The BART therefore appears to be ecologically valid for measuring impulsive decision making and was chosen to reflect cognitive impulse control in Chapter 8.

Experimental considerations

The number of pumps on the BART is sensitive to the probability of an explosion (Lejuez et al., 2002). The starting size of the array for explosion probability (N) is therefore an important consideration. The average explosion point for a balloon will be N/2, which also reflects the average number of balloon pumps that would maximize earnings. Restricting the range for possible number of pumps limits the likelihood that performance on the BART will reflect real-world decision making. A sufficiently wide range is also required to capture inter- and intra-individual variability. On the other hand, inappropriately large arrays will result in such low probability of explosion that participants are likely to disengage from the task and performance will again not be a reliable measure of decision making. An array size of 85 was chosen in the current research in an attempt to maximize validity of task performance.

To model decision making in real-world risk-reward situations, participants should receive a monetary reward equal to their final winnings on the task. Crucially participants need to be informed of this reward to highlight the consequences of their decisions. In Chapter 8, participants were informed in advance that they would receive their reward immediately upon task completion, and this was indeed the case in each session of the study.

4.3.2 Central nervous system vital signs (CNSVS) test battery

The CNSVS is a computerized neurocognitive test battery developed as a tool to assess cognitive and executive aspects of behaviour (Gualtieri and Johnson, 2006). It draws from a very large normative database of 1,069 healthy individuals between 7 and 90 years old, thereby enabling the comparison of participants to their peers. Test scoring is automated which eliminates evaluator bias. Raw test scores are based on correct responses, error

responses, number of responses and reaction times. Standard scores are generated by normalizing raw scores to the age-matched normative dataset. Cognitive domain scores are determined from single or multiple test scores. An overall neurocognition index score is also calculated as the average of domain standard scores and is an indication of global cognitive function.

The core CSNVS battery consists of seven tests based on or adapted from well-established neuropsychological tests: verbal memory, visual memory, finger tapping, symbol digit coding, shifting attention, continuous performance and the Stroop test. It is possible to add and remove tests to this core group. For example, the current research used the ARI task to measure motor function so the finger tapping test was removed from the CNSVS core test battery. The 4-part continuous performance test was included instead to measure working memory, which has been shown to be modulated by dopaminergic tone in PD patients (Costa et al., 2009; Lewis et al., 2005). Combined, the tests chosen for the current research battery assessed a range of cognitive domains: composite memory (including verbal and visual), processing speed, executive function, reaction time, complex attention, cognitive flexibility, working memory and sustained attention. The overall neurocognition score was the average of composite memory, reaction time, complex attention and cognitive flexibility. A basic description of each test used in the current research and the cognitive domain it contributes to is shown in Table 4.1.

Ethical and experimental considerations

CNSVS is designed for serial administration and is therefore suitable for research involving multiple experimental sessions. Additional research benefits of the CNSVS battery include the automated instructions for participants, millisecond temporal resolution and minimal number of response keys involved which reduces the influence of keyboard skills on test performance. Test-retest reliability across two sessions spaced 62 days apart ranges from $r = 0.45 - 0.87$ for individual tests (except for one aspect of the Stroop Test at $r = 0.31$) and from $r = 0.65 - 0.87$ for domain scores (Gualtieri and Johnson, 2006). However conventional and computerized cognitive test batteries can fall prey to test-based learning effects (Beglinger et al., 2005; Falleti et al., 2006). It was therefore necessary to counterbalance session order across participants in the multiple session design used in Chapter 8 to control for any such learning effects.

It is important to note that the CNSVS is not intended for use as a stand-alone clinical diagnostic tool. It can only provide an indication of an individual's level of cognitive function at a specific point in time. Clinical interpretation of test results and any diagnosis requires

Table 4.1 Descriptions for CNSVS battery tests and associated cognitive domains

Test	Description	Cognitive Domains
Verbal memory	Series of 15 words are displayed to remember and recognize. Presented amongst 15 distractors immediately following, and again at the end of the test battery.	Verbal memory Composite memory
Visual memory	Series of 15 geometric shapes are displayed to remember and recognize. Presented amongst 15 distractors immediately following, and again at the end of the test battery.	Visual memory Composite memory
Symbol digit coding	A grid of paired symbols and numbers is displayed. Enter numbers to match presented symbols for 120 seconds.	Processing speed
Stroop test	Part One: respond to any word presented. Part Two: respond if colour and name of word match. Part Three: respond if colour and name of word do not match.	Reaction time Complex attention Cognitive flexibility
Shifting attention	Respond to changing rules of 'match colour' and 'match shape' between changing pairs of shapes.	Complex attention Cognitive flexibility Executive function
Continuous performance	Respond to presentation of 'B' in a series of letters for 5 minutes.	Complex attention
4-Part continuous performance	Part One: respond to any shape presented. Part Two: respond to specified shape. Part Three: respond if two consecutive shapes match. Part Four: respond if shape N matches N – 2 in series.	Working memory Sustained attention

a skilled clinician to integrate test scores with additional information from several different sources. For this reason, participant reports (showing standardized scores) which are automatically generated upon completion were not displayed to participants.

4.4 Computational modelling

Chapter 7 presents a parameter optimization model to examine the neural processes underlying response inhibition. The computational model explored a conceptual framework to capture the neural processes giving rise to the empirical findings from Chapters 5 and 6 and was based on the original model presented in Chapter 6. The model was predicated on the evolution of excitability in the motor system over time leading to the behavioural response. In summary, predicted EMG and MEP data were generated with Monte Carlo simulation reliant on a number of parameters describing the facilitatory and inhibitory processes hypothesized to underlie the movement response. Summary statistics (means and standard deviations) of predicted data were fitted to equivalent EMG and single-pulse MEP data from Chapter 6 by minimizing a Pearson Chi-square statistic (Boucher et al., 2007; Hu et al., 2014) (Figure 4.1). A summed Chi-square was minimized using the unconstrained Nelder-Mead simplex algorithm (Nelder and Mead, 1965).

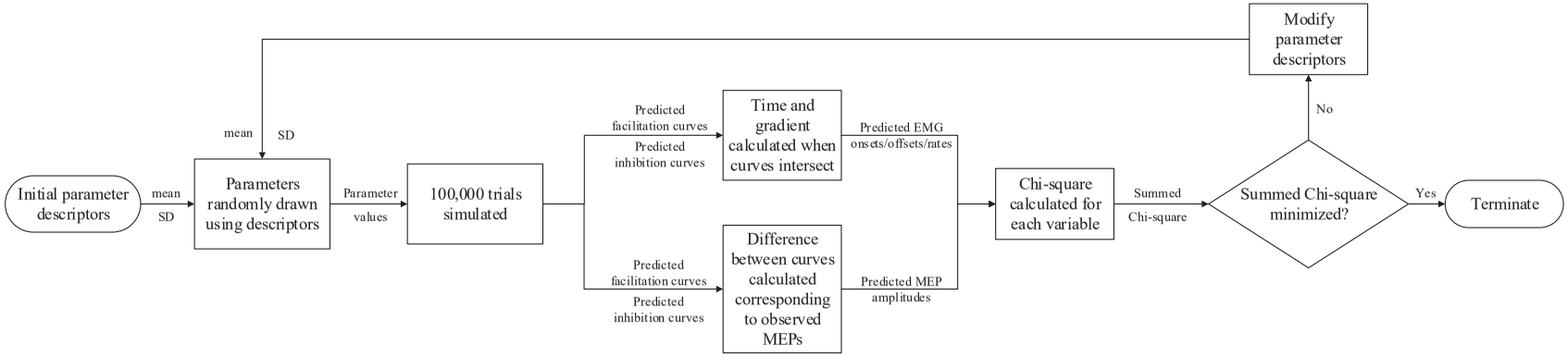

Figure 4.1 Activation threshold model flowchart. Means and standard deviations (SD) were estimated for each model parameter to account for physiological variability in the characteristics of the Go and Stop process. MEP: motor evoked potential; EMG: electromyography

The model specifically optimized parameters to fit data collected during execution and partial cancellation of bimanual movement. Model parameters were estimated to fit the following experimental observations: i) an average response delay of 82 ms on Partial compared to Go trials; ii) a 50 % decrease in CME on Partial compared to Go trials at equivalent time points preceding an EMG burst prior to response; and iii) a higher eventual EMG burst gain on Partial versus Go trials to generate the response.

A complete time course of information across an entire response inhibition trial cannot be gained directly with TMS MEPs because of EMG contamination. The benefit of computational modelling is that it is possible to use MEPs from uncontaminated times to generate new hypotheses about the neural mechanisms underlying response inhibition, including those which occur at the time of movement execution.

The model was required to simultaneously optimize up to 8 parameters by cycling through up to 200 iterations simulating 100,000 trials each. Given the time-intensive nature of these parameter optimizations, simulations were run on a high performance computing cluster operated by the University of Auckland Centre for e-Research as part of the New Zealand e-Science Infrastructure (NeSI) framework. NeSI provides state-of-the-art high performance computing integrated platforms to support research across the public and private research sectors. Their two Nvidia M2090 graphical processing units (GPUs) were utilized to run the optimization within a reasonable time (e.g. 5 – 10 min).

It was assumed that the empirical data for the model came from the a single normal distribution (healthy young adults) so the model was applied to aggregated group data. The Python code for the model is available in Appendix G.

4.5 Experimental setup for the anticipatory response inhibition task

The ARI task is common to all studies in the current thesis. The experimental setup for the task was very similar across experiments (Figure 4.2). Details about task design (e.g. number of each trial type, total number of trials) which are specific to each experiment are detailed in the appropriate chapters. However the details regarding software and hardware are necessarily brief for publication. The following section therefore provides a more detailed rationale regarding the software and hardware used to control the ARI task.

Carefully designed and precisely executed behavioural tasks are crucial in fields such as cognitive, behavioural and systems neuroscience. Temporal precision was especially

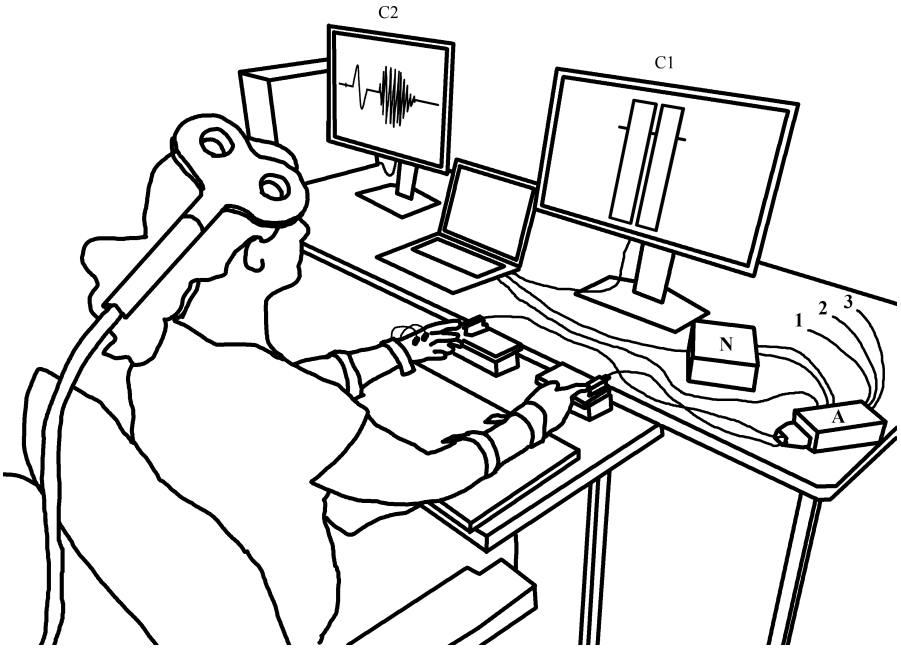

Figure 4.2 Experimental setup during anticipatory response inhibition (ARI) task. Variations in experimental setup regarded the use of TMS (as depicted, only Chapter 6) and whether EMG was recorded from bilateral first dorsal interosseous (FDI) (Chapter 8), bilateral extensor indicis proprius and abductor pollicis brevis (Chapter 5), or only left FDI (as depicted, Chapter 6). Participants depressed two microswitches to control the ARI task on one computer (C1) while EMG (and MEP) data were recorded in Signal on a separate computer (C2). The arduino (A) constantly monitored the state of the switches and sent output to Signal (1) at trial onset. The arduino was responsible for triggering the TMS stimulator(s) (output 2 and 3). The National Instruments data acquisition device (N) interfaced between Matlab and the arduino. Participants were lightly restrained to prevent wrist and elbow movement and ensure fingers were lifted off the switches using only the target muscle(s).

important in the current experiments as behavioural responses are measured on a millisecond timescale. Furthermore, examining the modulation of excitability/inhibition during behavioural trials required precise control of stimulation timing, especially for paired-pulse TMS. Stimulation needed to occur at an accurate and reliable time point relative to trial onset and stop signal presentation. While a high level of temporal precision can often be achieved with low-level programming languages (e.g. C or Pascal), the same level of precision and flexibility is possible with high-level languages, such as Matlab. High-level interpreted (rather than compiled) programming languages offer the advantage of rapid program development. Matlab in particular provides a friendlier development environment and access to several in-built toolboxes. There are however a few considerations to ensure reliable and accurate timing in a high-level interpreted software environment. Thankfully many of the potential issues are well known and have generally accepted solutions. When these potential issues are managed appropriately, behavioural control software written in programs like Matlab can achieve millisecond-scale temporal accuracy and reproducibility.

The ARI task in the current experiments was controlled using custom software written with Matlab. The original coding structure was created by a previous laboratory member and adapted for the current studies. The dataset for each experiment was pseudorandomly generated by custom code as subtly different constraints were required for each experimental hypothesis. For example, Chapter 5 investigated response asynchronies during bimanual execution following successful Stop trials. This necessitated that a specified number of each Stop trial type be followed by a Go trial. Likewise, while Go Left – Stop Right trials were the primary Stop trial of interest in Experiment 1 in Chapter 6, they were presented with equal probability as other Stop trials in all other experiments.

When Matlab is run in the default mode there are a few obstacles which can render its millisecond-scale temporal resolution unreliable (Asaad and Eskandar, 2008). Firstly, the visual display is refreshed with relatively slow periodicity that is not synchronized to a participant's time-varying behavioural output. Secondly, there are potential issues from running a time-sensitive task in a nonreal-time operating system like Microsoft Windows, as Matlab may be interrupted by competing applications and processes. Thirdly, behavioural data recorded continuously as an analog signal are not available for monitoring until the temporarily stored data are transferred to motherboard memory, which is done at relatively infrequent intervals . These issues have important implications and may result in unexpected and unpredictable distortions in task control and monitoring if not controlled.

The first issue was solved by utilizing available Matlab toolboxes. Matlab does not provide hardware control needed for precise stimulus display. This capability was added via the

additional Psychophysics Toolbox (Psychtoolbox Version 3) which provides accurately timed displays designed for vision and neuroscience research. Psychtoolbox contains specific functions designed to minimize the lag between the software call to activate a stimulus and its appearance. In addition, Psychtoolbox time-stamps the visual display refresh to give an accurate indication of when a visual stimulus was actually displayed to the participant.

Psychtoolbox mitigates some of the timing issues from running the task with Windows OS by running Matlab at 'highest priority'. However Psychtoolbox alone is unable to completely eliminate these potential delays. Since the studies in Chapters 6 required accurately timed TMS relative to behavioural events, an arduino device was employed to control time-crucial processes apart from the visual display. The arduino constantly monitored the state of two custom-made switches (Figure 4.2) and thereby registered participant responses with microsecond accuracy. Matlab checked the input from the arduino once per screen refresh to update the visual display. The arduino was not interrupted by applications running on the PC, had a faster average cycle rate and less temporal jitter than Matlab. The arduino therefore eliminated the temporal variance from running the task in Windows. This meant the arduino was reliably able to trigger the TMS with microsecond accuracy during the task.

A potential timing issue arises from the manner in which analog data is transferred from a data acquisition device to Matlab. However this was not an issue in the current experimental setup as EMG data was recorded by separate software (Signal, CED). The arduino triggered the recording software at trial onset and Signal was preset to record muscle activity for the full trial duration (1 second). The EMG recording did not influence any event controlled by the task. Two separate computers were used to record EMG and run the task to eliminate the chance of any interference.

The hardware setup included a National Instruments data acquisition device (National Instruments USB-6009) to interface between Matlab and the arduino. However the device was not used to record analog EMG signal (as indicated above). Instead, it was used to communicate digitally with the arduino in the absence of a parallel port.

Controlling for these potential issues ensured adequate temporal precision so that behavioural and neurophysiological data were recorded with reliable temporal resolution during the ARI task in the following thesis experiments.

4.6 Data analysis for the anticipatory response inhibition task

The experimental designs in the current experiments necessitated recording between 300 – 900 trials in each session, for every participant. Data analysis was therefore automated to

reduce the risk of data handling errors. It also meant data could be processed in a timely manner between experimental sessions.

In brief, a custom data analysis program written in Matlab paired EMG data with behavioural data outputted from the task into Excel. The program requested input from the user regarding any study specifics (e.g. number of EMG channels to analyze) and participant code. The user manually chose the correct EMG and behavioural files to input into the program. EMG traces for all conditions of interest were displayed to the user for visual inspection to ensure the program was accurately capturing EMG and/or MEP data. For example, MEP data could be manually rejected if contaminated by an EMG burst. Following visual inspection, dependent measures were computed and outputted into an Excel file for group level analysis.

Chapter 5

Uncoupling Response Inhibition

This experiment has been reported in Journal of Neurophysiology, MacDonald et al., Uncoupling response inhibition. (2012); 108(5); 1492-1500

Terminology: The terminology used for trials in the anticipatory response inhibition task that require cancellation of one finger and execution of the other has evolved over the course of the thesis. The current chapter is presented as published and refers to these as Selective trials, referring to the behaviourally selective nature of cancellation that is required. However subsequent chapters refer to Partial trials to avoid confusion, as we contend the neural stopping mechanism is not able to be selective on these trials.

Abstract

The ability to prevent unwanted movement is fundamental to human behaviour. When healthy adults must prevent a subset of prepared actions, execution of the remaining response is markedly delayed. We hypothesized that the delay may be sensitive to the degree of similarity between the prevented and continued actions. Fifteen healthy participants performed an anticipatory response inhibition task that required bilateral index finger extension or thumb abduction with homogeneous digit pairings, or a heterogeneous pairing of a combination of the two movements. We expected that the uncoupling of responses required for selective movement prevention would be more difficult with homogeneous (same digit, homologous muscles) than heterogeneous pairings (different digits, nonhomologous muscles). Measures of response times (and asynchrony between digits) during action execution, stopping performance and electromyography from EIP (index finger extension) and APB (thumb abduction) were analyzed. As expected, Selective trials produced a delay in the remaining movement compared to execution trials. Successful performance in the se-

lective condition occurred via suppression of the entire prepared response and subsequent selective reinitiation of the remaining component. Importantly, the delayed reinitiation of motor output was sensitive to the degree of similarity between responses, occurring later but at a faster rate with homogeneous digits. There were persistent after-effects from the selective condition on the motor system which indicated greater levels of inhibition and a higher gain were necessary to successfully perform Selective trials with homogeneous pairings. Overall the results support a model of inhibition of a unitary response and selective reinitiation, rather than selective inhibition.

5.1 Introduction

Response inhibition requires prevention of unwanted movement and is fundamental to human behaviour. It is challenging because it requires higher order control, and is often impaired in neurodegenerative conditions (Gauggel et al., 2004; Stinear et al., 2009). Response inhibition engages a right-lateralized brain network comprised of the inferior frontal cortex (IFC), supplementary motor areas (SMA), nuclei of the basal ganglia, thalamic regions and primary motor cortex (M1) (Aron, 2011; Aron et al., 2003; Aron and Poldrack, 2006; Coxon et al., 2006; Garavan et al., 1999; Liddle et al., 2001; Mostofsky et al., 2003; Rubia et al., 2003; Stinear et al., 2009). The specific regions activated depend on the goal of the inhibition: inhibition of all movement or inhibition of only a subset of movement components (Coxon et al., 2009).

Response inhibition is traditionally investigated using a stop-signal or go/no-go paradigm (or variations of these paradigms), both in humans and animals (Aron et al., 2003; Aron and Poldrack, 2006; Aron and Verbruggen, 2008; Eagle and Robbins, 2003; Kenner et al., 2010; Leocani et al., 2000; Mars et al., 2009; Sharp et al., 2010). Although the stop-signal paradigm offers advantages with respect to well defined go and stop cues, this paradigm allows adjustments to response strategies (e.g. slowing of responses) to balance the requirements of the execution and inhibition conditions (Verbruggen and Logan, 2009). It is important that a response has been planned or initiated at the time of the stop signal for calculation of the latency of the stop process (stop signal reaction time, SSRT), which is used as an index of inhibitory control. An anticipatory response inhibition (ARI) task (Slater-Hammel, 1960) ensures Go response preparation in the presence of stop cues. Coxon et al. (2007, 2009) and Stinear et al. (2009) used the ARI task to investigate the selectivity of inhibitory control by requiring some, but not all, prepared movements to be inhibited in response to a selective stop cue. This requirement produced markedly delayed execution of the remaining Go re-

sponse. Coxon and colleagues speculated that this delay was the result of rapid nonselective suppression of all prepared movements and subsequent selective reinitiation of the required movement. Movement reselection and initiation processes are thought to occur within SMA and M1 (Coxon et al., 2009).

An alternative way to conceptualize the process of selective movement prevention is the suppression of a single unitary response, which is comprised of all prepared movement components 'coupled' together. The key distinction here is that, rather than preparing multiple separate movements that are executed together, all movements are coupled together into one response which now consists of multiple subcomponents (Ko and Miller, 2011). Movement prevention would therefore affect all subcomponents of the single response simultaneously. The response would then need to be separated into its subcomponents before selective reinitiation of only the required component could occur. This separation would be achieved through uncoupling all the response components. If our model is correct, the uncoupling and reinitiation processes should be sensitive (under time pressure) to the strength of coupling between subcomponents in the prepared movement.

The strength of coupling between movement subcomponents can be investigated using a bimanual task. Bimanual response inhibition tasks are accomplished by functionally coupling movements which facilitates their coordination and synchronization (De Jong, 1993; De Jong et al., 1995). This functional coupling produces movements with the same structural or topological characteristics, such as movement direction and extent (Newell, 1985). The dynamics of rhythmic bimanual coordination reveal greater coupling between the hands during in-phase movements (homologous muscles activated simultaneously) compared to anti-phase movements (nonhomologous muscles activated simultaneously) (Kelso, 1984). Therefore, in the present study, movements requiring synchronous activation of homologous muscles were expected to have greater functional coupling between them than movements from synchronous activation of nonhomologous muscles.

The aim of the present study was two-fold: firstly, to further investigate the aforementioned reselection and initiation processes presumed to occur during selective movement prevention tasks; and secondly, to investigate whether the delay in responding that occurs on Selective trials depends on the degree of coupling between independent components of the previously prepared movement. The second aim was met by altering digit pairings during a bimanual ARI task employed previously (Coxon et al., 2007). By manipulating pairing we intended to produce a strongly coupled homogeneous pairing and a more weakly coupled heterogeneous pairing. We examined the influence of pairing on behavioural measures of response inhibition and response execution, the identification of anomalous EMG bursts,

the rate of EMG development and EMG burst onsets and offsets. We hypothesized that the requirement for selective response prevention would cause a delay in the remaining response, compared to standard Go trials, as previously observed (Coxon et al., 2007). EMG was recorded to capture any motor-level contribution to this response delay (Coxon et al., 2007; Ko and Miller, 2011). Secondly, we hypothesized that the delay would be greater (with a different underlying EMG profile) in homogeneous pairings than heterogeneous pairings, as the expected stronger coupling between movement subcomponents would take longer to uncouple. Finally, we hypothesized that the carry-over effects of uncoupling during Selective trials would be more prominent in the nondominant hand during homogeneous pairings, indicative of more stringent coupling of the nondominant to the dominant hand than vice versa (Byblow et al., 2000; Carson, 1993).

5.2 Methods

5.2.1 Participants

Fifteen healthy adults with no neurological impairment were included in the study (mean age 25 yr, range 20 – 32 yr, 9 male). All participants were right handed (mean laterality quotient 0.94, range 0.79 – 1.0) as assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). The study was approved by the University of Auckland Human Participant Ethics Committee and written informed consent was obtained from each participant.

5.2.2 Behavioural task

The bimanual ARI task is based on the paradigm by Slater-Hammel (1960), adapted previously for examining selective response inhibition (Coxon et al., 2007). Participants sat 1 m in front of a computer display while performing the task. The display consisted of two vertically orientated indicators, 18 cm tall and 2 cm wide, separated by 2 cm (Figure 5.1). The left indicator corresponded to the left hand digit and the right indicator to the right hand digit. The task was controlled using custom software (MatLab R2011a) interfaced with two custom made switches. Each trial commenced after a variable delay when both switches were depressed. Both indicators moved upwards from the bottom at the same rate, reaching the target after 800 ms.

The majority of trials (66 %, main experiment) involved releasing both switches in time to stop both indicators at the target (Go trials). To emphasize that trials were to be performed as accurately as possible, visual feedback was displayed at the completion of each trial,

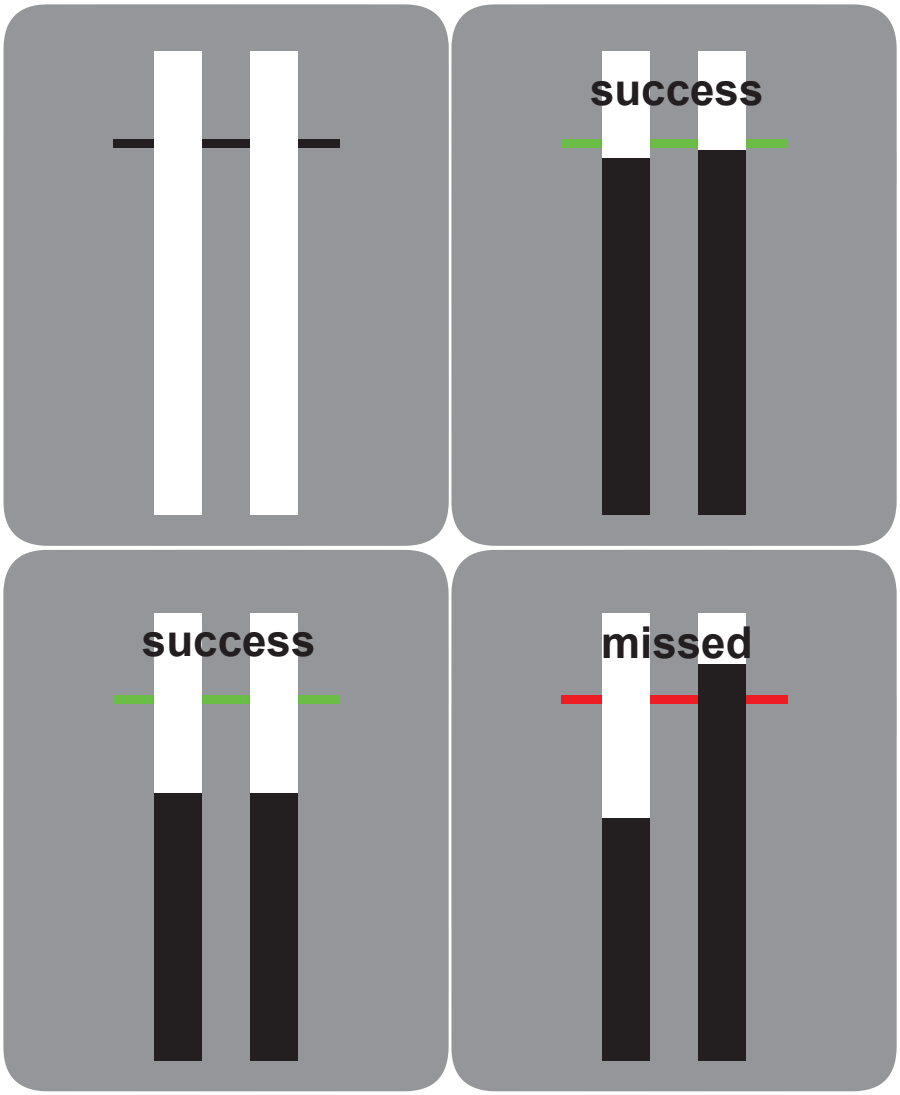

Figure 5.1 Anticipatory response inhibition task display. Visual display at the start of a trial (top left) when trial type is ambiguous; successful Go trial (top right) when the participant has stopped both indicators at the target; successful Stop Both trial (bottom left) when the participant kept both digits on the switches when the two indicators automatically stopped early (600 ms); typical successful Selective trial (Stop Left) when the left response was correctly inhibited but the right response was delayed (bottom right). Other selective condition (Stop Right) is not shown. The target line was black at the start of a trial and while the bars were rising. On Go trials, if both bars were stopped within 30 ms of the target the line would go green to indicate success. Otherwise the target line would go red to indicate that the participant had missed the target. On Stop Both trials, the target line would go green only if the participant had successfully kept both fingers on the switches. On Partial trials, the target line would only go green if the correct finger had remained on the switch and the other bar had been stopped within 30 ms of the target.

stating whether the indicator(s) had been stopped sufficiently close to the target (within 30 ms) (See Figure 5.1). Occasionally one or both indicators stopped automatically before reaching the target. In this case, participants were required to not lift the corresponding digit(s) (Stop trials). There were three types of Stop trials: Stop Both, when both indicators stopped automatically and Stop Left and Stop Right (Selective trials), when only the left or right indicator stopped, respectively. Selective trials still required the participant to stop the other indicator as accurately as possible at the target, by lifting the corresponding digit. Feedback also indicated whether inhibition of one or both responses was successful.

The indicator for each Stop trial type was initially set to stop automatically at 600 ms and the indicator stop time changed dynamically throughout the task. Following successful inhibition, the stop time was delayed by 25 ms on the subsequent Stop trial (increasing difficulty); following unsuccessful inhibition, the stop time was set 25 ms earlier. This staircase procedure ensured convergence to a stop time that resulted in a 50 % probability of successful inhibition for each type of Stop trial. The task consisted of 8 blocks, each comprising 30 trials. The first two blocks involved only Go trials. Of the remaining 180 trials (6 blocks), 120 were Go trials and 60 were Stop trials (20 trials per Stop type). Go and Stop trials were pseudorandomized across the 6 blocks. Each participant completed the task four times in different digit pairing combinations, with the pairing combinations counterbalanced across participants. Each pairing required either bilateral index finger extension or thumb abduction (homogeneous pairings), or a combination of the two (heterogeneous pairings).

5.2.3 Recording procedure

Electromyography (EMG) data were recorded from bilateral extensor indicis proprius (EIP) and abductor pollicus brevis (APB) muscles. Electrodes were placed in a belly tendon montage and ground electrodes were placed over the lateral surface of the wrist (for APB) and the lateral surface of the olecranon of the elbow (for EIP). EMG signals were amplified (CED 1902, Cambridge, United Kingdom), bandpass filtered (20 – 1000 Hz) and sampled at 2 kHz (CED 1401, Cambridge, United Kingdom). Data were saved for later offline analysis using Signal (CED, Cambridge, United Kingdom) and custom software (MatLab R2011a).

5.2.4 Dependent measures

Individual trial and average lift times (LTs) and EMG burst onsets preceding the response were determined for Go and selective trials. EMG burst onset was defined as a rise of 3 SD above baseline causing the lift response (Hodges and Bui, 1996). LT and EMG burst onsets

from successful Selective trials correspond to the responding digit. Average LT was calculated after removing LTs more than 3 SD from the mean (on average 1.8 ± 0.3 % were removed for Go LT averages, none were removed for Selective trial LT averages). Lift time asynchrony (LTA), EMG burst onset asynchrony, LTs and EMG burst onset times were calculated on Go trials following Go trials and following successful Stop trials. Asynchronies were calculated from (left digit) – (right digit) and reported in milliseconds.

For Stop trials, stop signal reaction time (SSRT) and staircased indicator stop time (producing 50 % probability of success) were determined for each trial type. Staircased indicator stop time refers to the time the indicator was programmed to stop relative to the trial onset due to the staircase procedure. SSRT was calculated using the mean method (Logan and Cowan, 1984) as the staircase procedure ensured a success rate of 50 %.

Some Selective trials exhibited an initial EMG burst in both muscles (partial bursts) followed by a delayed main EMG burst in only the responding muscle (lifting burst), referred to as dual burst trials. Partial bursts are reported as a percentage of total successful Stop trials for each stop type. Partial bursts were recorded when they occurred in both muscles on Selective trials and when they occurred in either inhibited muscle on Stop Both trials. Offset times (drop below 3 SD of baseline) of both partial EMG bursts on Selective trials were calculated. Peak rate of onset for the main EMG lifting burst was determined for Selective trials and Go trials, calculated using a dual-pass 20 Hz Butterworth filter prior to differentiation (Coxon et al., 2007). Electromechanical delay (EMD) was determined for Go and Selective trials. EMD was calculated as the time (ms) between the main EMG lifting burst onset and LT (EMD = LT - EMG onset).

5.2.5 Statistical analysis

Partial EMG burst offset times on Selective trials and LTs on Go trials in same and different pairings were subjected to correlation analyses. The significance of the difference between the correlation coefficients for same and different pairings for the two dependent measures was tested using Fisher's z_r transformation. Average LTs on Go trials were compared with average LTs on unsuccessful Stop trials using paired t tests.

All remaining dependent measures were subjected to repeated measures (RM) analysis of variance (ANOVA) with post hoc comparisons when necessary. A four-way RM ANOVA tested for differences in mean LT, EMG lifting burst onset, EMD and peak rate of EMG onset between Go and Selective trials, with factors Side (Left, Right), Digit (Thumb, Index), Pairing (Same, Different) and Trial Type (Go, Selective).

Go trials preceded by a successful Stop trial were sorted according to Stop trial type. The average LT for the left and right digit and the LTA were calculated. The average EMG lifting burst onset for the left and right digit and EMG burst onset asynchrony were also calculated. LTA, EMG burst onset asynchrony, average LTs and average EMG burst onsets were also determined for Go trials preceded by Go trials (not Stop trials) for comparison. Differences in average LTA and EMG burst onset asynchrony were analyzed with a three-way RM ANOVA, factors Digit, Pairing and Preceding Trial Type (Go, Stop Left, Stop Right, Stop Both). The LTs and EMG burst onsets were analyzed with a four-way RM ANOVA, factors Side, Digit, Pairing and Preceding Trial Type. LTs and EMG burst onsets were also analyzed using a four-way RM ANOVA with Stop Both trials removed.

A three-way RM ANOVA with factors Digit, Pairing and Trial Type (Stop Left, Stop Right, Stop Both) tested for differences in mean staircased indicator stop time, SSRT and percentage partial bursts. A three-way RM ANOVA tested for differences in average percentage of dual burst trials with factors Digit, Pairing and Trial Type (Stop Left, Stop Right).

For nonspherical data, the conservative Greenhouse-Geisser P value was reported. Criterion for statistical significance was $\alpha = 0.05$. Post hoc t tests were used to test main effects or interactions. All results are shown as group means ± standard error (SE).

5.3 Results

5.3.1 Lift time correlation between digits on Go trials

The lift times for the right and left digits on Go trials showed a significant strong correlation in homogeneous ($r = 0.79, P < 0.001$) and heterogeneous pairings ($r = 0.75, P < 0.001$). There was a significant difference between the two correlation coefficients ($z = 4.24, P < 0.001$) with homogeneous pairings producing a stronger correlation between lift times, indicative of stronger coupling with homogeneous pairings.

5.3.2 Lift times for Go and Selective trials

Lift times are shown in Figure 5.2. For Go trials, LTs occurred within the target range (811 ± 2 ms), indicative of successful task performance and similar to those reported previously (Coxon et al., 2006, 2007). Of interest was the delay in LTs during the selective condition (901 ± 5 ms) compared to Go trials (main effect of Trial Type ($F_{1,14} = 465.9, P < 0.001$)) (Figure 5.2). There was a main effect of Side ($F_{1,14} = 6.3, P = 0.025$) but no effect of Digit ($F_{1,14} < 1$) or Pairing ($F_{1,14} = 1.5, P = 0.243$). For Go and Selective trials combined, LTs for the left digit

(859 ± 3 ms) were slower than the right (852 ± 4 ms). There were no other main effects or interactions (all $P > 0.1$).

5.3.3 EMG lifting burst onset time, rate and EMD during Go and Selective trials

For EMG burst onset time, there was a main effect of Pairing ($F_{1,14} = 10.9, P = 0.005$), a main effect of Trial Type ($F_{1,14} = 299.9, P < 0.001$) and a Pairing x Trial Type interaction ($F_{1,14} = 8.7, P = 0.011$) (shown in Figure 5.3A). In support of the LTs, Selective trials exhibited a greatly delayed EMG lifting burst onset (827.1 ± 5.4 ms) compared to Go trials (734.2 ± 3.5 ms). For Go and Selective trials combined, homogeneous pairings (784.9 ± 4.1 ms) produced an EMG lifting burst onset later than heterogeneous pairings (776.4 ± 3.7 ms). There was a larger delay in EMG burst onset time between Selective trials (834.9 ± 5.9 ms) and Go trials (734.9 ± 3.6 ms, $t_{14} = 18.3, P < 0.001$) for homogeneous pairings than for heterogeneous pairings (Selective trials, 819.2 ± 5.9 ms; Go trials, 733.6 ± 3.6 ms, $t_{14} = 13.6, P < 0.001$). These results provide a physiological marker of coupling effects on delays induced by selective stopping tasks. There were no other main effects or interactions (all $P > 0.057$).

For EMD there was only a main effect of Pairing ($F_{1,14} = 5.5, P = 0.035$), where EMD was shorter with homogeneous (74.0 ± 2.4 ms) than heterogeneous (77.1 ± 2.8 ms) pairings (Figure 5.3B), again indicating an effect of coupling mediated by digit pairing.

The rate of EMG burst onset showed a main effect of Digit ($F_{1,14} = 5.0, P = 0.042$), Pairing ($F_{1,14} = 5.3, P = 0.038$) and Trial Type ($F_{1,14} = 8.6, P = 0.011$), as well as a Digit x Pairing interaction ($F_{1,14} = 5.0, P = 0.042$) but no effect of Side ($F_{1,14} = 4.2, P = 0.059$). Peak rate of onset was higher during Selective trials (5.9 ± 0.5 mVs^{-1}) than Go trials (5.5 ± 0.5 mVs^{-1}) (Figure 5.3C), indicative of higher gain during these trials. Peak rate of onset in the APB (thumb) was higher during homogeneous (7.5 ± 0.9 mVs^{-1}) than heterogeneous pairings (6.2 ± 0.8 mVs^{-1}, $t_{14} = 2.4, P = 0.031$) but pairing had no effect on EIP (index finger) (Figure 5.3D). There were no other main effects or interactions (all $P > 0.08$).

5.3.4 Percentage of partial EMG bursts on Stop trials

Partial bursts occurred during successful Stop Both (Figure 5.4A) and Selective trials (Figure 5.4B). These bursts indicate the preparation and initial execution of an expected Go response prior to rapid termination. There was a main effect of Trial Type ($F_{2,14} = 15.9, P < 0.001$) and post hoc tests revealed Stop Both (35.1 ± 2.1 %) had a higher percentage of partial bursts than Stop Left (22.9 ± 2.8 %, $t_{14} = 4.9, P < 0.001$) and Stop Right (27.3 ± 2.1 %, $t_{14} = 5.9, P < 0.001$),

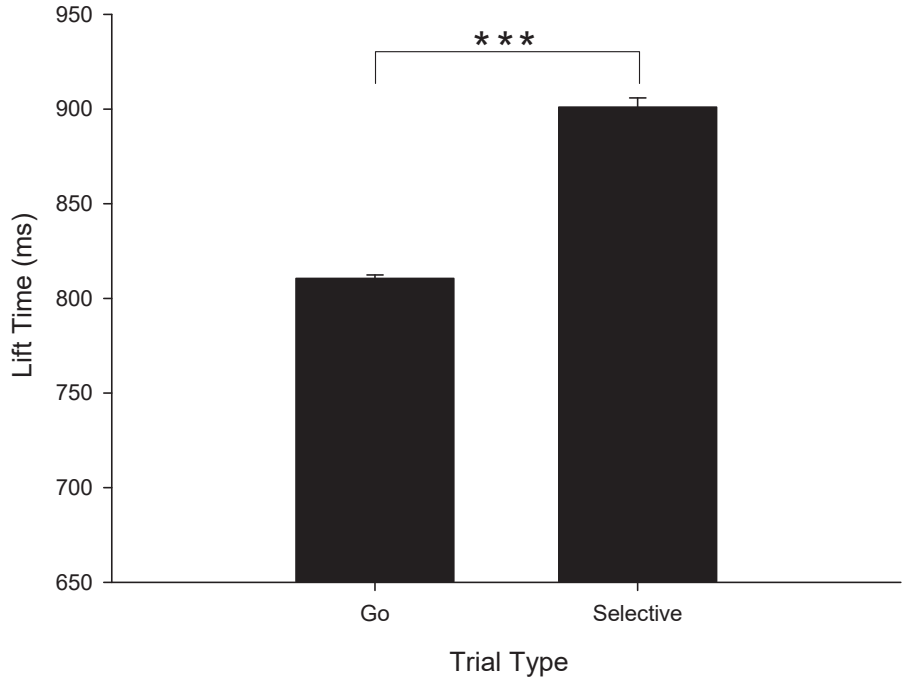

Figure 5.2 Lift times for Go and Selective trials. Group LT for Go and Selective trials collapsed across Side, Digit and Pairing. For Selective trials, LT is from the responding digit following inhibition and selective reinitiation. Asterisks indicate significant differences for paired t tests: $***P < 0.001$. Error bars indicate 1 SE.

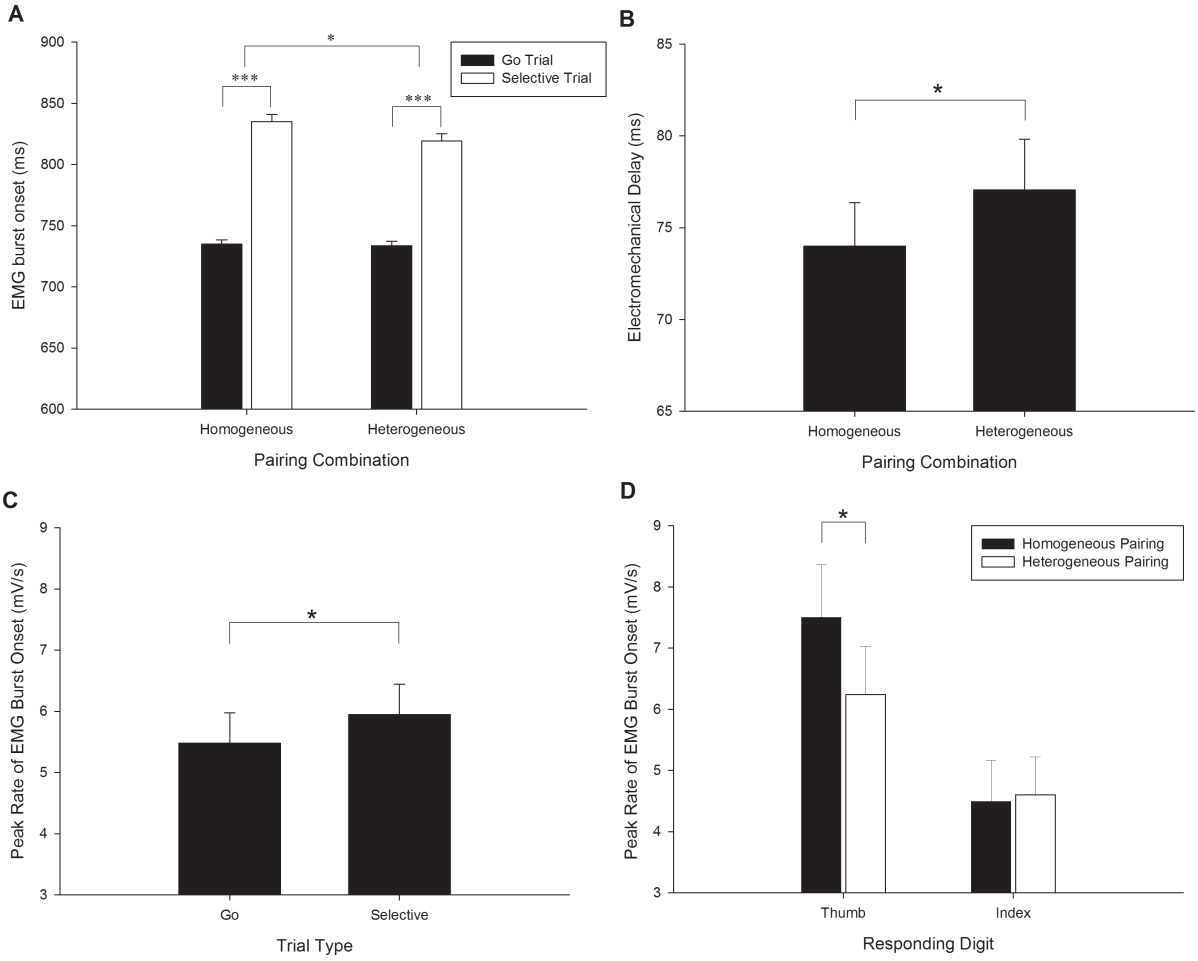

Figure 5.3 EMG results for Go and Selective trials. Group results for lifting EMG burst onset time (A), electromechanical delay (B) and peak rate of lifting EMG burst onset across trial types (C) and digits (D) for Go and Selective trials. Electromechanical delay = lift time – lifting EMG burst onset time. In A: black bars, Go trials; white bars, Selective trials. In D: black bars, homogeneous pairings; white bars, heterogeneous pairings. Asterisks indicate significant results from post hoc t tests: $*P < 0.05$, $***P < 0.001$. Error bars indicate 1 SE.

which did not differ from each other ($t_{14} = 1.7, P = 0.111$). There was a Digit x Pairing x Trial Type interaction ($F_{2,14} = 4.6, P = 0.028$) that did not decompose meaningfully. There were no other main effects or interactions (all $P > 0.5$).

5.3.5 Partial EMG bursts on Selective trials

Some successful Selective trials showed two important characteristics: 1) a partial burst in *both* muscles as well as 2) a lifting EMG burst in only the responding muscle (Figure 5.4B). These trials were expressed as a percentage of the total number of successful Selective trials. These trials occurred with both digit pairings and both types of Selective trials. There was a main effect of Trial Type ($F_{1,14} = 8.1, P = 0.013$) but no effect of Pairing ($F_{1,14} < 1$) or Digit ($F_{1,14} = 1.2, P = 0.291$). There was a higher percentage of these trials during the Stop Right (26.2 ± 4.3 %) than Stop Left (18.6 ± 3.3 %) condition. There were no other main effects or interactions (all $P > 0.07$).

The offsets of the partial EMG bursts were correlated between the two muscles (Figure 5.5). There was a significant correlation in homogeneous ($r = 0.52, P < 0.001$) and heterogeneous pairings ($r = 0.57, P < 0.001$). There was no significant difference between the two correlation coefficients ($z = 0.56, P = 0.58$).

5.3.6 Lift and EMG burst onset times for Go trials preceded by Go versus successful Stop trials

There was a Side x Preceding Trial Type interaction for lift times ($F_{3,14} = 24.6, P < 0.001$) and EMG burst onset times ($F_{3,14} = 12.1, P < 0.001$). The interactions were preserved for both lift times ($F_{2,14} = 33.3, P < 0.001$) and EMG burst onset times ($F_{2,14} = 19.5, P < 0.001$) when Stop Both trials were removed. The following results are from the analyses with Go and Selective trials only.

Post hoc tests on LT data revealed a faster average Go LT with the left side immediately after a Stop Right trial (806 ± 4 ms) compared to after a Go trial (814 ± 2 ms, $t_{14} = 2.6, P = 0.022$) (Figure 5.6A). There were no differences between Go LTs with the right side. There was no effect of Digit ($F_{1,14} = 1.3, P = 0.277$) or Pairing ($F_{1,14} < 1$) and no other interactions (all $P > 0.07$). Figure 5.6B and C show the Side x Preceding Trial Type interaction for homogeneous and heterogeneous pairings respectively.

Post hoc tests of EMG burst onset revealed an earlier average Go EMG burst onset time with the left side immediately after a Stop Right trial (729.5 ± 4.1 ms) compared to after a Go trial (736.8 ± 3.8 ms, $t_{14} = 2.6, P = 0.023$). There were no differences between Go EMG burst

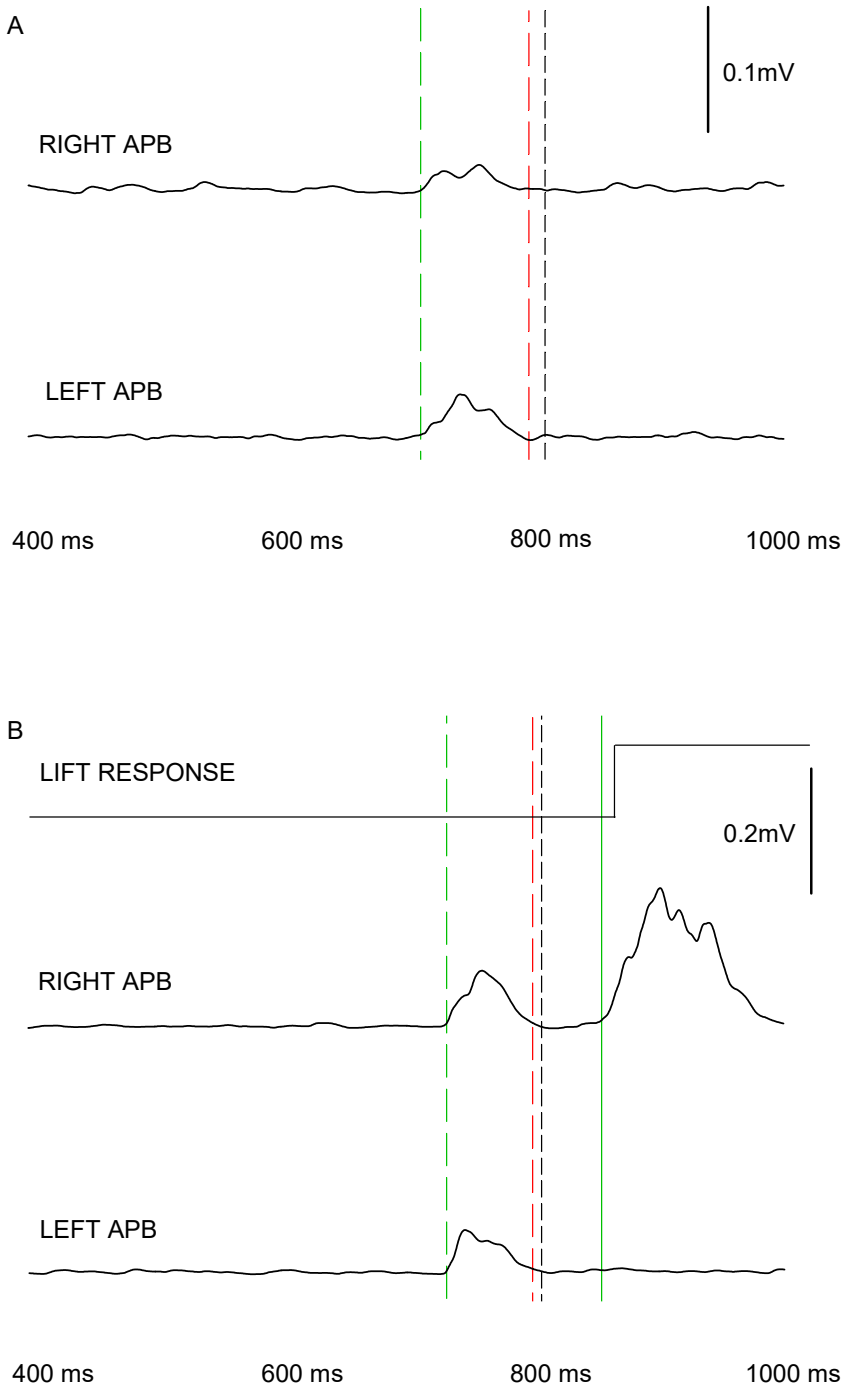

Figure 5.4 Example individual EMG trace for Selective trials. EMG traces from an individual participant representing a successful Stop Both (A) and Stop Left (B) trial with a homogeneous pairing. Black dashed vertical line indicates target line. B: Middle: Responding muscle. Bottom: Nonresponding muscle. Dashed green line, bilateral response initiation; dashed red line, inhibition following stop signal; solid green line, selective reinitiation of the responding muscle; APB, abductor pollicis brevis.

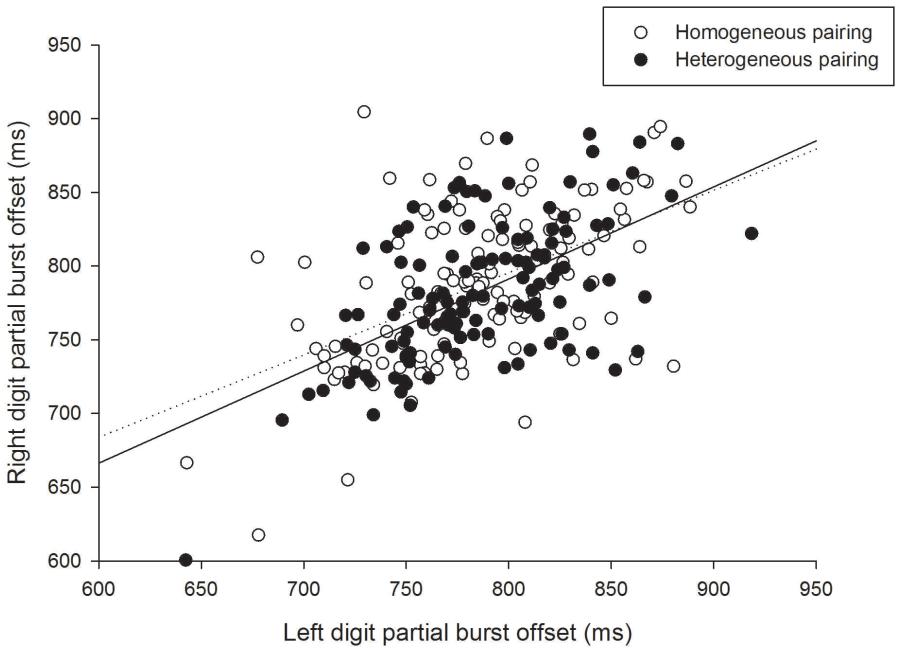

Figure 5.5 Correlation between partial EMG burst offsets on Selective trials. Linear regression between EMG partial burst offsets for the two different types of pairings. White circles and dashed line, homogeneous pairing ($y = 348.8 + 0.56x, r = 0.52$); black circles and solid line, heterogeneous pairing ($y = 291.6 + 0.62x, r = 0.57$). Both $P < 0.001$.

onset times with the right side. There was no effect of Pairing ($F_{1,14} = 1.2, P = 0.290$) and no other main effects or interactions (all $P > 0.075$).

5.3.7 Lift time and EMG onset asynchrony on Go trials preceded by Go versus successful Stop trials

For LTA, there was a main effect of Preceding Trial Type ($F_{3,14} = 24.6, P < 0.001$) and a Digit x Pairing interaction ($F_{1,14} = 5.2, P = 0.039$). There were no other effects or interactions (all $P > 0.06$). LTA on Go trials was larger when preceded by Stop Left trials (11 ± 3 ms), than by Go trials (3 ± 3 ms, $t_{14} = 5.4, P < 0.001$), indicating that the left LT lagged the right to a greater extent when the left digit was previously inhibited (Figure 5.7). Conversely, LTA on Go trials was less when preceded by Stop Right trials (-2 ± 3 ms), than by Go trials ($t_{14} = 4.9, P < 0.001$). There was no difference in LTA following Stop Both compared to Go trials ($t_{14} = 1.0, P = 0.349$). The Digit x Pairing interaction arose because LTA was larger with the heterogeneous pairing when the left digit was the thumb (8 ± 3 ms) rather than the index finger (-1 ± 4 ms, $t_{14} = 2.2, P = 0.047$), but there was no difference between digits for homogeneous pairings ($t_{14} = 1.3, P = 0.204$).

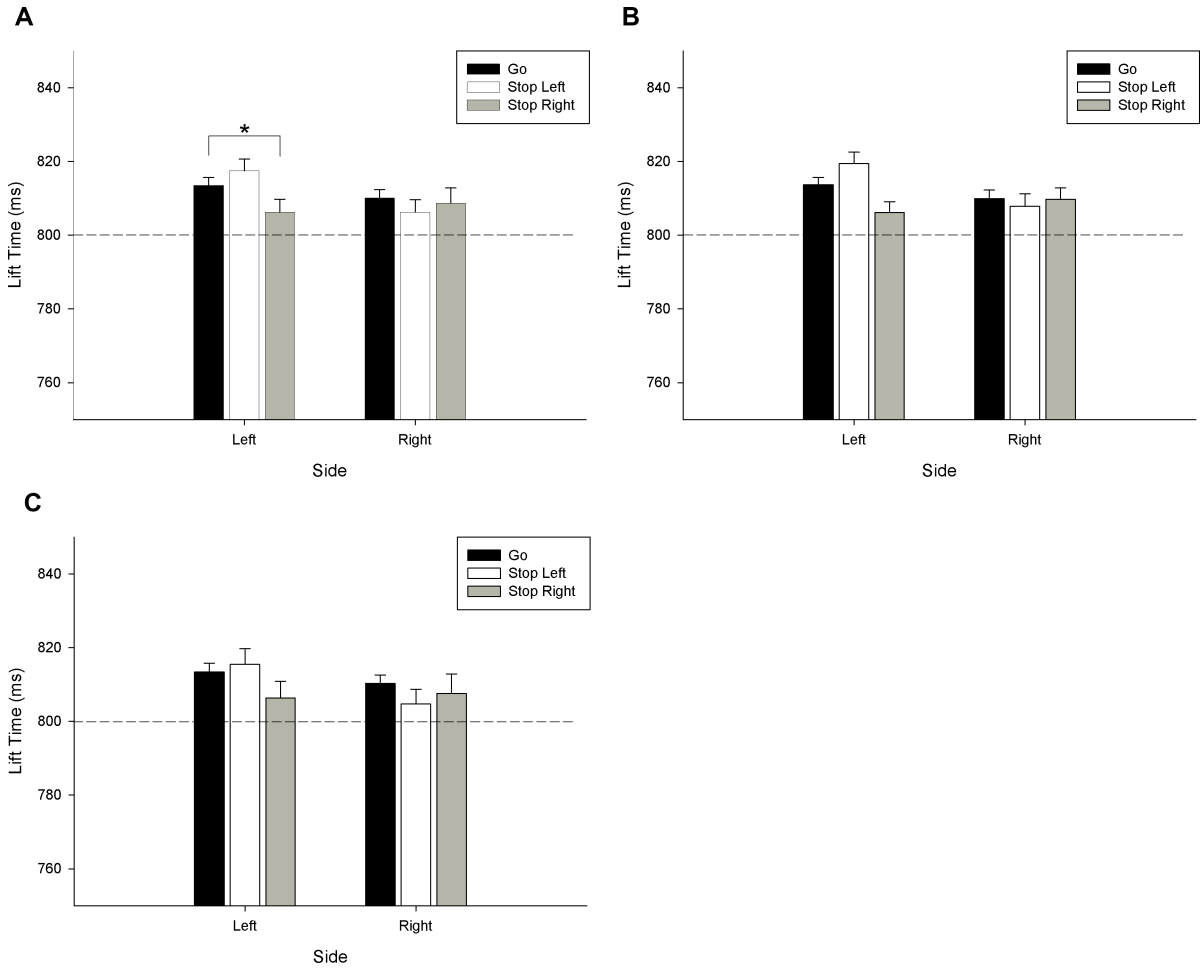

Figure 5.6 Lift times following successful Go and Selective trials. Group average LTs for Go trials only, preceded by Go or successful Selective trials. Collapsed across Digit and Pairing (A) and separated into homogeneous (B) and heterogeneous pairings (C). Black bars, Go is preceding trial type; white bars, Stop Left is preceding trial; grey bars, Stop Right is preceding trial. Horizontal dashed line indicates target line at 800 ms. Asterisk indicates significant difference from post hoc paired t test: $*P < 0.05$. Error bars indicate 1 SE.

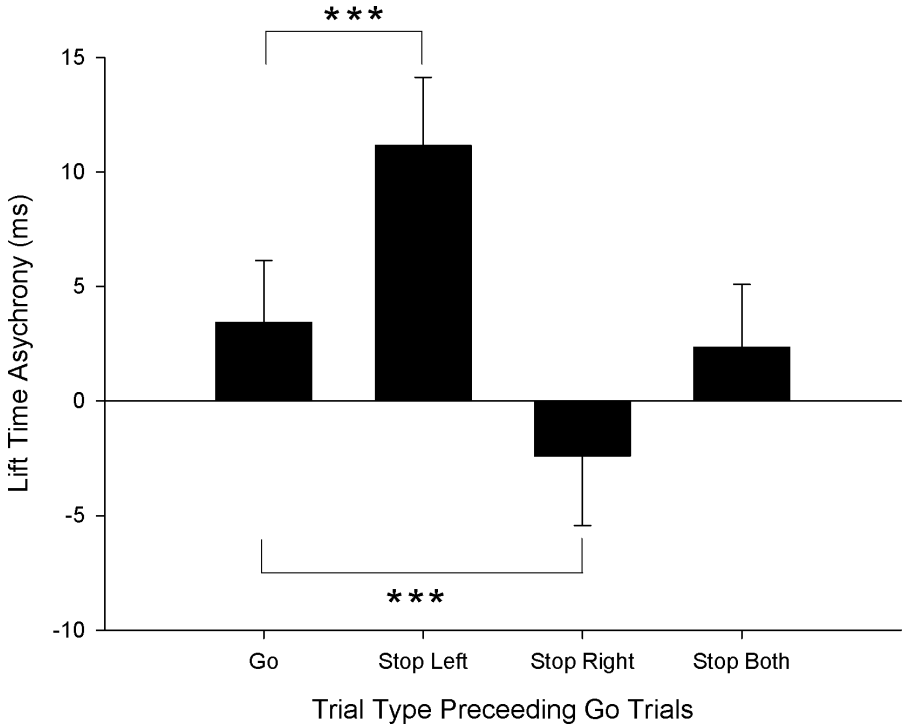

Figure 5.7 Lift time asynchrony (LTA) following Go and Stop trials. Positive LTA indicates right digit lifted before the left. Asterisks indicate results of paired t tests: $***P < 0.001$. Error bars indicate 1 SE.

For EMG burst onset asynchrony, there was a main effect of Preceding Trial Type ($F_{3,14} = 12.2, P < 0.001$) and Digit ($F_{1,14} = 8.9, P = 0.010$). EMG burst onset asynchrony on Go trials was larger when preceded by Stop Left trials (8.7 ± 2.4 ms), than by Go trials (4.8 ± 2.1 ms, $t_{14} = 3.3, P = 0.005$), supporting the LT data that the left digit response lagged the right digit to a greater extent when the left digit was previously inhibited. On the other hand, EMG burst onset asynchrony was less when preceded by Stop Right trials (-1.9 ± 2.2 ms), than by Go trials ($t_{14} = 4.2, P = 0.001$). Again, there was no difference in asynchrony following Stop Both trials compared to Go trials ($t_{14} = 1.7, P = 0.109$). When the left digit was the thumb, the EMG burst onset asynchrony was greater (9.5 ± 3.0 ms) than when the left digit was the index finger (-2.5 ± 2.7 ms).

5.3.8 Stop signal reaction time on Stop trials

There was a main effect of Trial Type ($F_{2,14} = 9.3, P = 0.003$). The SSRT for Stop Both trials (208 ± 4 ms) was faster than Stop Left (242 ± 9 ms, $t_{14} = 4.3, P = 0.001$) and Stop Right (250 ± 10 ms, $t_{14} = 4.6, P < 0.001$) trials, which did not differ from each other ($t_{14} = 0.6, P = 0.556$). This effect was precipitated by an effect of Trial Type ($F_{2,14} = 11.8, P = 0.001$) on the time at which the staircase procedure stopped the indicator on Stop trials to achieve a 50 % success rate. The staircase procedure stopped the indicator later for Stop Both trials (603 ± 5 ms) than Stop Left (567 ± 9 ms, $t_{14} = 4.8, P < 0.001$) and Stop Right (562 ± 9 ms, $t_{14} = 4.9, P < 0.001$) trials, which did not differ from each other ($t_{14} = 0.4, P = 0.690$). There were no other main effects or interactions (all $P > 0.3$).

5.3.9 Lift times for unsuccessful Stop trials

Average LTs were later for the left digit on unsuccessful Stop Left trials (828 ± 4 ms) compared to Go trials (812 ± 2 ms, $t_{14} = 3.6, P = 0.003$) and for the right digit on unsuccessful Stop Right trials (833 ± 4 ms) compared to Go trials (809 ± 2 ms, $t_{14} = 5.7, P < 0.001$). The average LT between digits on unsuccessful Stop Both trials (809 ± 2 ms) was not significantly different than the average LT between digits on Go trials (811 ± 2 ms, $t_{14} = 0.9, P = 0.383$).

5.4 Discussion

The novel finding in support of our main hypothesis was that Selective trials involved movement reinitiation processes that were sensitive to response coupling. As predicted, pairings of same digits were more strongly coupled than pairings of different digits, and the effects

of uncoupling the digit pairs during Selective trials were more prominent in the nondominant than the dominant hand. The persistent effects of the Selective trials on the motor system were also dependent on coupling and hand dominance. Successful performance on Selective trials temporarily altered the gain of involved motor representations. These novel findings indicate that stopping the prepared, coupled response was a unitary phenomenon, followed by uncoupling of the response to allow selective initiation of one component. As such, the task may be better described as a selective *reinitiation* task than a selective *stopping* task. Given that the task caused pairing-dependent changes in motor output, it may be sensitive to the onset of basal ganglia dysfunction which impairs task-dependent modulation of motor set.

Firstly, it is important to note that participants performed the task correctly. During Go trials participants did not delay their response to allow possible detection of a stop cue, as can be the case with stop-signal tasks (Verbruggen and Logan, 2009). Go LTs were on average within 11 ms of the target (811 ± 2 ms). These results show that the task was reliably investigating the ability to suppress a preplanned motor response.

The behavioural outcomes for Stop Both trials also indicated the task was being performed correctly. The staircase procedure resulted in later indicator stop times and shorter SSRTs during Stop Both trials than during Selective trials, as expected (Coxon et al., 2007). The behavioural results for Stop Both trials can potentially be accounted for by the race model. In the context of the stop-signal task, the race model proposes a race between execution and inhibition processes initiated by presentation of the stop signal (Logan and Cowan, 1984). On nonselective inhibition trials in this paradigm (i.e. Stop Both trials), whichever process 'wins the race' determines the resulting behaviour (i.e. whether the lift responses are made or prevented). This binary outcome can be explained by the race model, but the substantially delayed lift times on Selective trials appear to violate the assumptions of the model.

Lift times and EMG lifting burst onsets were delayed when one part of the movement was prevented, compared to when the complete prepared movement was executed, as previously observed (Aron and Verbruggen, 2008; Cai et al., 2011; Claffey et al., 2010; Coxon et al., 2007, 2009; Dove et al., 2000). In the present study there was a substantial delay in the lift time of the responding digit during Selective trials (average of 90 ms) (Figure 5.2). There was also a significant delay in the onset of the EMG burst causing the lift response (average of 93 ms). It has been speculated that the delayed reaction time is due to rapid, nonselective suppression of all prepared movements (Aron and Verbruggen, 2008; Coxon et al., 2007; Kenner et al., 2010) via a nonselective neural pathway (Coxon et al., 2006; Leocani et al., 2000). A candidate

neuro-anatomical substrate is the 'hyperdirect' pathway between the inferior frontal gyrus and subthalamic nucleus (Aron and Poldrack, 2006). Our EMG data clearly illustrate a rapid suppression of prepared movement during Selective trials, where the partial EMG bursts were rapidly suppressed in both digits (Figure 5.6B). We propose that this reflects the suppression of a single prepared movement, which would have been performed by a pair of digits, rather than the nonselective suppression of two separately prepared movements. This proposition is supported by the synchronized offset of the partial EMG bursts during Selective trials (Figure 5.5). Importantly, the partial EMG burst was rapidly suppressed in both muscles at the same time regardless of the whether digit pairings were homogeneous or heterogeneous. Therefore suppression of the prepared movement is a unitary phenomenon, insensitive to the strength of coupling, posture or hand dominance. This indicates that regardless of pairing, planned movements were integrated together into a unitary response during Go trials (and at the beginning of Stop trials when trial type was unknown), indicative of immediate "conceptual binding" within the motor system (Wenderoth et al., 2009). It therefore logically follows that suppression of this single, coupled response would affect all of its components equally, even though the intention may be to selectively suppress one component of the response only.

Once a prepared response is suppressed on a Selective trial, the desired component is selectively reinitiated by engaging execution pathways potentially via structures such as the presupplementary motor area (Coxon et al., 2009; Isoda and Hikosaka, 2007; Van Gaal et al., 2011). The time required for this process accounts for the delay in EMG burst onset and lift time (Coxon et al., 2009; Kenner et al., 2010). The present data highlight the role of uncoupling of movement representations in this process. To successfully reinitiate the desired component of the prepared movement, synchronized neural activity between coupled cortical movement representations must be sufficiently uncoupled. After uncoupling, each response component can then be separately suppressed or executed. The execution of the desired response was delayed to a greater extent in homogeneous compared to heterogeneous pairings (Figure 5.3A). This indicates that uncoupling was more difficult and took longer to achieve with homogeneous digit pairings, as expected. It is possible that more inhibition was required to achieve uncoupling of homogeneous pairings, and that this in turn was responsible for the longer delay in subsequent Selective responses. However, the longer delay was offset by a higher gain, shown by a shorter EMD (Figure 5.5B) and faster rate of EMG onset (Figure 5.5D) with homogeneous pairings. Ko and Miller (2011) also indicated a higher gain in the responding muscle, which produced more forceful responses during Selective trials compared to execution trials. Therefore when the prepared movement

components are strongly coupled, an increase of both inhibition and gain seem necessary to successfully uncouple the prepared movement and reinitiate only the desired component.

What are the consequences of selective response reinitiation on the motor system? Coxon et al. (2007) found that uncoupling of the digits on successful Selective trials had carry-over effects on subsequent Go trial performance, and the present study confirms and extends these findings (Figure 5.4). For example, after a Stop Left trial, the left digit was delayed relative to the right on a subsequent Go trial. Whereas after a Stop Right trial, the right digit was delayed relative to the left on a subsequent Go trial, as also observed by Coxon et al. (2007). The novel finding here was that after a Stop Right trial, the left digit was lifted sooner (with an earlier EMG burst onset). This carry-over effect was specific to the nondominant hand, and aligns with previous findings that the nondominant hand is more strongly coupled to the dominant hand than vice versa during bimanual tasks (Byblow et al., 2000; Carson, 1993). However, this interpretation must be considered with caution as any effect due to hand dominance cannot be ascertained definitively from only right handed participants.

The behavioural carry-over effects observed in the nondominant hand were also influenced by digit pairings. Only homogeneous pairings exhibited the speeding up of left digit LT following Stop Right trials. Furthermore, only homogeneous pairings showed a slower left digit LT following Stop Left trials compared to after Go trials, possibly due to persistent inhibition (Coxon et al., 2007; Kennerley et al., 2002). Neurophysiological investigation using techniques such as transcranial magnetic stimulation would be required for confirmation of persistent changes to inhibition levels. Taken together, the carry-over effects observed in the nondominant hand may reflect asymmetric coupling between the hands during the uncoupling and selective reinitiation of finger movements. Importantly, we found no evidence of uncoupling after successful Stop Both trials. Therefore, only *selective reinitiation* temporarily altered the execution of motor responses.

Previous studies have shown that impaired response suppression is associated with basal ganglia dysfunction resulting from Parkinson's disease and focal hand dystonia (Gauggel et al., 2004; Stinear and Byblow, 2004). The present results indicate that a selective response task may be usefully applied in studies involving patients with impaired basal ganglia function, and may assist in the prognosis of basal ganglia dysfunction. For example, damage of gain setting nuclei is believed to accompany early changes in Parkinson's disease (Braak et al., 2004). Therefore, parameters derived from this type of task may provide sensitive biomarkers of Parkinson's disease and warrant further investigation.

In summary, this study has demonstrated that selective movement prevention occurs through rapid suppression of the prepared movement and subsequent reinitiation of the desired component of the response. This process results in a movement delay and is more difficult to achieve when the prepared response is comprised of strongly coupled components. The rapid suppression of the prepared response was not affected by the strength of coupling between digits. However, the reinitiation of the desired movement component was delayed and occurred at a higher rate when the prepared response involved same pairings of digits. This is the first study to show that a higher gain and possibly greater levels of inhibition are necessary to successfully perform selective reinitiation in strongly coupled postures. The carry-over effects observed in the lift times of the left hand with homogeneous pairings further support this idea. Further research is needed to elucidate the neurophysiological mechanisms underlying the observed effects.

Chapter 6

The Fall and Rise of Corticomotor Excitability with Cancellation and Reinitiation of Prepared Action

These experiments have been reported in Journal of Neurophysiology, MacDonald et al., The fall and rise of corticomotor excitability with cancellation and reinitiation of prepared action. (2014); 112(11); 2707-2717

Abstract

The sudden cancellation of a motor action, known as response inhibition (RI), is fundamental to human motor behaviour. The behavioural selectivity of RI can be studied by cueing cancellation of only a subset of a planned response, which markedly delays the remaining executed components. The present study examined neurophysiological mechanisms that may contribute to these delays. In two experiments, healthy human participants 21 to 37 years of age received single- and paired-pulse transcranial magnetic stimulation while performing a bimanual anticipatory response task. Participants performed most trials bimanually (Go trials) and were sometimes cued to cancel the response with one hand while responding with the other (Partial trials). Motor evoked potentials were recorded from left first dorsal interosseous (FDI) as a measure of corticomotor excitability (CME) during Go and Partial trials. CME was temporally modulated during Partial trials in a manner that reflected anticipation, suppression and subsequent initiation of a reprogrammed response. There was an initial increase in CME, followed by suppression 175 ms after the stop signal, even though the left hand was not cued to stop. A second increase in excitability occurred

prior to the (delayed) response. We propose an activation threshold model to account for nonselective RI. To investigate the inhibitory component of our model, we investigated short-latency intracortical inhibition (sICI), but results indicated that sICI cannot fully explain the observed temporal modulation of CME. These neurophysiological and behavioural results indicate that the default mode for reactive partial cancellation is suppression of a unitary response, followed by response reinitiation with an inevitable time delay.

6.1 Introduction

The ability to suddenly cancel an action is perhaps as fundamental to human behaviour as action itself. Cancellation or 'stopping' engages a right-lateralized cortico-subcortical inhibitory network, with downstream effects on the primary motor cortex (M1) (Aron et al., 2003; Aron and Poldrack, 2006; Coxon et al., 2009, 2012; Garavan et al., 1999; Liddle et al., 2001; Rubia et al., 2003; Stinear et al., 2009; Zandbelt et al., 2013; Zandbelt and Vink, 2010). Sometimes a subset of the action must be cancelled while the remaining elements continue. How the motor system prepares for this eventuality relates to the presence or absence of foreknowledge, termed proactive and reactive inhibition, respectively (Aron, 2011; Cai et al., 2011). When foreknowledge about stopping is available, the costs associated with partial cancellation are reduced (Aron and Verbruggen, 2008; Cai et al., 2011; Claffey et al., 2010). However, the most vital and time-sensitive inhibitory responses in everyday life are most commonly associated with sudden and unexpected events where no warning is available, e.g., avoiding a car accident. Without foreknowledge, partial cancellation of movement is difficult and executed components are markedly slowed (Aron and Verbruggen, 2008). For example, in a bimanual anticipatory response task, partial cancellation of self-initiated responses leads to marked delays in the responding effector (Coxon et al., 2007, 2012; MacDonald et al., 2012 Chapter 5). It is our contention that delays during reactive partial cancellation reflect neuroanatomical constraints that limit the ability to selectively suppress prepared actions.

Transcranial magnetic stimulation (TMS) is routinely used to noninvasively examine task-dependent effects on M1. Single- pulse TMS of M1 probes excitability of the entire corticomotor pathway, i.e., the net effect of facilitatory and inhibitory inputs to all synapses between the coil and muscle. Corticomotor excitability (CME) of involved motor representations increases during motor preparation, in advance of execution (Chen et al., 1998b; Marinovic et al., 2011; Pascual-Leone et al., 1992). When a stop signal is presented during preparation, CME is suppressed 100 – 200 ms after the stop signal (Coxon et al., 2006;

Hoshiyama et al., 1997; Yamanaka et al., 2002; Yamanaka and Nozaki, 2013). Suppression is observed not only for the task-relevant effector but also for task-irrelevant effectors, suggesting that RI is associated with 'global' effects on the motor system (Badry et al., 2009; Cai et al., 2012; Coxon et al., 2006; Greenhouse et al., 2012; Majid et al., 2012; Wessel et al., 2013). The majority of the above studies investigated CME during cancellation of simple unimanual responses, with or without a preceding choice decision. Majid et al. (2012) examined partial cancellation of a bimanual response in the context of proactive stopping, but they did not examine CME in the task-relevant effectors. In the present study we examine how CME is modulated in the task-relevant effectors during partial cancellation of a bimanual response without foreknowledge. Crucially, we are only examining cancellation of task-relevant muscles, which are always prepared to respond at the beginning of a trial.

Our main aim was to investigate temporal modulation of CME preceding and during partial cancellation of movement (experiment 1) in a reactive RI task requiring bimanual response preparation. Participants performed a bimanual anticipatory response inhibition (ARI) task requiring execution (Go trials) and occasional complete or partial cancellation (Partial trials) of responses. We hypothesized that partial cancellation would reveal neuroanatomical constraints on behaviourally selective suppression. This would be evident in CME, which would initially increase in both Go and Partial trials, then subsequently decrease after the stop cue in Partial trials, followed by a second increase and a substantially delayed response. We present a computational model encapsulating the empirical data. Based on the model, we tested whether short-latency intracortical inhibition (sICI) during Partial trials could explain the inhibitory component of the model (experiment 2). We hypothesized that modulation of sICI during Partial trials would coincide with changes in CME.

6.2 General methods

6.2.1 Participants

Fifteen healthy adults with no neurological impairment participated in experiment 1 (mean age 25.5 yr, range 21 – 37 yr , 8 male). Thirteen of the same participants took part in experiment 2 (mean age 26.1 yr , range 24 – 37 yr, 6 male). All participants were right handed (laterality quotient: experiment 1 mean 0.73, experiment 2 mean 0.78, range 0.36 – 1) as assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). The study was approved by the University of Auckland Human Participant Ethics Committee, and written informed consent was obtained from each participant.

6.2.2 Anticipatory response inhibition task

The bimanual ARI task is based on the paradigm by Slater-Hammel (1960), adapted for investigating the behavioural selectivity of RI (Coxon et al., 2007; MacDonald et al., 2012 Chapter 5). Participants were seated 1 m in front of a computer display while performing the task. The display consisted of two vertically oriented indicators 2 cm apart, each 18 cm in length and 2 cm in width (Figure 6.1). The left indicator corresponded to the left hand index finger and the right indicator to the right hand index finger. The forearms rested on a table, positioned midway between supination and pronation. The task was controlled using custom software written with MATLAB (R2011a, version 7.12; MathWorks) and interfaced with two custom made switches, attached via an analog-to-digital USB interface (NI-DAQmx 9.7; National Instruments). The medial aspect of each index finger was used to depress the switches (index finger adduction). Each trial commenced after a variable delay when both switches were depressed. Following the delay, both indicators moved upward from the bottom at equal rates, reaching the target after 800 ms.

The majority of trials (66 % in experiment 1, 70 % in experiment 2) involved index finger abduction to release both switches in time to stop both indicators at the target (Go trials, GG). Visual feedback was displayed at the completion of each trial, indicating whether the indicator(s) had been stopped sufficiently close to the target (within 30 ms), to emphasize that trials were to be performed as accurately as possible. Occasionally, one or both indicators stopped automatically before reaching the target, cueing the participant to inhibit responding with the corresponding digit(s) (Stop trials). There were three types of trials requiring RI: Stop Both (SS), when both indicators stopped automatically, and Partial trials, which included Stop Left-Go Right (SG) and Go Left-Stop Right (GS), when only the left or right indicator stopped, respectively. SS trials were included as catch trials so that GS trials could not be anticipated (experiment 1) and to investigate neurophysiological mechanisms during complete cancellation of the bimanual response for comparison with partial cancellation (experiment 2). The pairing of letters (e.g., GS) represents the spatial mapping of index fingers: the letter on the left denotes the action of the left index finger, and the letter on the right denotes the action of the right index finger.

A colour-coded feedback display indicated whether inhibition of one or both responses was successful. A green target line indicated successful inhibition and a red target line indicated that a finger lift had been detected. The indicator was set to stop automatically 250 ms before the target on Partial trials and 200 ms before the target on Stop Both trials, both producing about 50 % probability of success as determined using the staircase design in previous research (MacDonald et al., 2012 Chapter 5). Predetermined stop times allowed

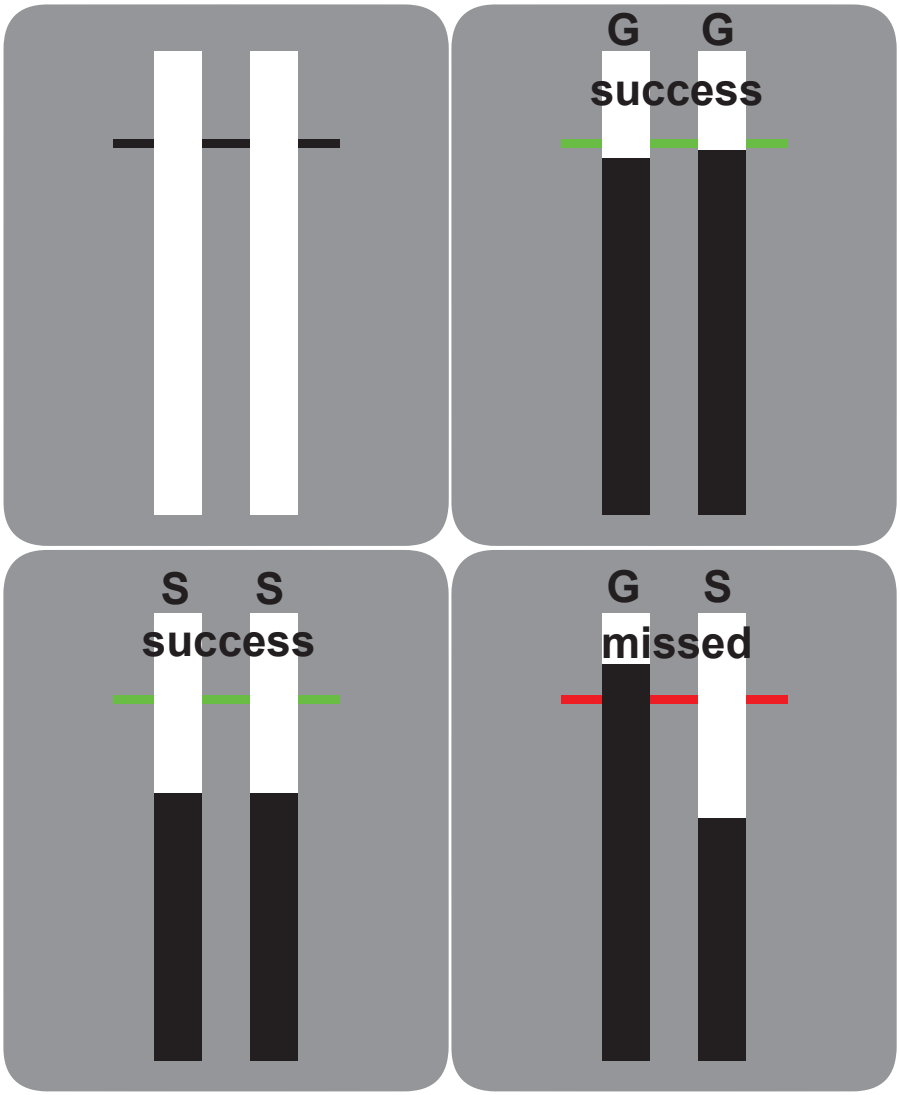

Figure 6.1 Anticipatory response inhibition task display. Visual display is shown at the start of each trial (top left) when trial type is ambiguous, for a successful Go (GG) trial (top right) when both bars were stopped at the target by the participant, for a successful Stop Both (SS) trial (bottom left) when both bars automatically stopped before reaching the target (−200 ms) and the response was correctly inhibited by the participant, and for a successful Partial (Go Left – Stop Right, GS) trial (bottom right) when the right hand response was correctly inhibited but the left hand response missed the target and was delayed. S and G labels were not displayed to participants. Visual feedback ("success" or "missed") was displayed after each trial.

comparison of motor evoked potentials (MEPs) between subjects at the same absolute stimulation times during the trial. All participants completed preliminary practice blocks consisting of only Go trials in both experiments (40 – 80 trials). Practice blocks were used for participant familiarization and to set TMS intensities.

6.2.3 Recording procedure

MEPs were recorded from left first dorsal interosseous (FDI), since the nondominant hand is more strongly affected than the dominant hand by the processes required to successfully cancel a subset of a motor action (MacDonald et al., 2012 Chapter 5). Surface electromyography (EMG) was recorded from left FDI using a belly-tendon montage. The ground electrode was placed on the posterior surface of the hand. EMG signals were amplified (CED 1902; Cambridge, UK), bandpass filtered (20 – 1000 Hz), and sampled at 2 kHz (CED 1401; Cambridge, UK). The EMG collection system was triggered when the indicators started to rise in the behavioural task, and EMG was recorded for 1 s. Data were saved for off-line analysis using Signal (CED, Cambridge, UK) and custom software (MATLAB R2011a, version 7.12).

6.2.4 Transcranial magnetic stimulation

TMS was applied to right M1 using a figure-of-eight D702 coil and Magstim200 unit (Magstim, Dyfed, UK) or through a Bistim unit (Magstim) connected to two Magstim200 units (experiment 2). The optimal coil position was found (and marked on the scalp) that elicited MEPs of the largest amplitude in the left FDI using a slightly suprathreshold stimulus intensity. The coil was positioned tangentially to the head with the handle directed posteriorly at a 45° angle to the midline of the head, inducing a current directed posterior to anterior in the underlying cortical tissue.

6.3 Experiment 1

6.3.1 Methods

Protocol

The task consisted of 12 blocks, each comprising 36 trials. There were 432 trials in total, of which 288 (66 %) were Go trials and 144 (33 %) were Stop trials pseudorandomized across the 12 blocks. The high proportion of Go trials ensured that this was the default response. The main trials of interest were GG and GS trials. SS and SG conditions made up 30 catch

trials of no interest that did not include stimulation. Catch trials were included to ensure that participants could not anticipate a GS response and guarded against the task being performed in a choice reaction manner (between GG and GS).

Task motor threshold (TMT) was determined while the participants pressed the left switch as they would in the task. TMT was defined as the minimum stimulus intensity required to evoke FDI MEPs of at least 50 µV amplitude in 4 of 8 stimuli. Test stimulus (TS) intensity was initially set at the participant's TMT and increased by 1–2 % of maximum stimulator output (MSO) if necessary to obtain a MEP amplitude of 0.1–0.2 mV during practice blocks, without affecting behavioural performance. Timing of TMS is reported relative to the anticipated response target (0 ms). For Go trials, single-pulse TMS was delivered at 7 time points from 250 to 100 ms before the target in 25 ms intervals (i.e., −250, −225, −200, −175, −150, −125 and −100 ms) to obtain 12 stimuli at each time (Figure 6.2A). There were 204 Go trials with no TMS interspersed throughout the blocks. Of the Stop trials, the 114 GS trials were of most interest. To compare GS with Go trials, the 7 time points for single-pulse TMS were offset on GS trials by 100 ms, delivered at −150, −125, −100, −75, −50, −25 and 0 ms (12 stimuli per stimulation time; Figure 6.2A), because responses are delayed by about 100 ms on Partial trials (Coxon et al., 2007, 2012; MacDonald et al., 2012 Chapter 5). Stimulation times were pseudorandomized. Practice blocks consisted of only Go trials, and stimulation occurred at −200 ms relative to target, before the onset of FDI muscle activity. The TS intensity remained constant for the remaining data collection.

Dependent measures

Lift times (LTs) were determined for successful Go and Partial trials. Average LTs were calculated after outliers (±3 SD) were removed (1.0 ± 0.1 % and 0.2 ± 0.2 %, respectively). LTs from successful Partial trials correspond to the responding digit. All LTs are reported in milliseconds relative to the target.

Percentages of successful trials and stop signal reaction time (SSRT) were determined for only GS trials. SSRTs were calculated using the integration method (Logan and Cowan, 1984; Verbruggen et al., 2013) so that SSRT was estimated by subtracting the fixed stop time from the finishing time of the Stop process. The Go LTs were rank ordered and the nth LT selected, where n was obtained by multiplying the number of Go LTs by the probability of responding to a stop signal.

Mean MEP amplitude and mean pretrigger root mean squared (rms) EMG was determined for each subject and stimulation time, for GG and GS trials. The difference in MEP amplitudes between GG and GS trials was of primary interest. MEP amplitudes from 110

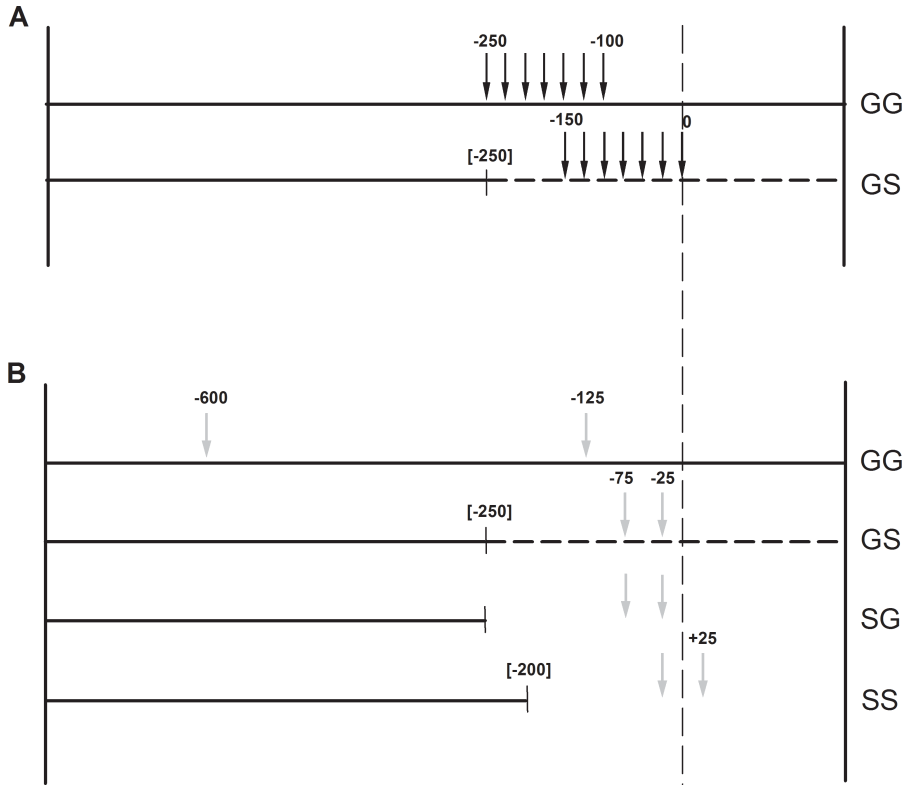

Figure 6.2 Experimental design for experiment 1 and 2. Schematics of experiment 1 (A) and experiment 2 (B) design showing trial types of interest. Horizontal solid lines represent time relative to trial onset (−800 ms). The vertical dashed line represents the target (0 ms). Stop times on Stop trials are represented by the short vertical lines. Horizontal dashed lines on GS trials indicate that the left digit is still required to respond. Black vertical arrows indicate the pseudorandom times at which single-pulse transcranial magnetic stimulation (TMS) was delivered over right primary motor cortex (M1) (25 ms intervals, experiment 1). Gray vertical arrows show the times when paired-pulse (short-latency intracortical inhibition, sICI) and single-pulse TMS were delivered over right M1 (experiment 2). These timings were derived from the results of experiment 1. All numbers indicate time in milliseconds relative to target.

to 170 ms prior to group-average LT for GG and GS trials were also plotted separately to compare the rate of rise in CME leading to the lift response. Peak rate of onset for the main EMG burst was used as an index of motor output gain as described previously (Coxon et al., 2007; MacDonald et al., 2012 Chapter 5). Peak rate of EMG onset was determined for GG and GS trials, calculated using a dual-pass 20 Hz Butterworth filter prior to differentiation.

Statistical analysis

Dependent measures were subjected to repeated measures (RM) analysis of variance (ANOVA) with post hoc and planned comparisons when necessary. LT was examined in a two Digit (Left, Right) × two Trial Type (Go, Partial) RM ANOVA, and the predetermined indicator stop times were checked by comparing the percentage of successful Stop trials against 50 % using one-sample t tests. The criterion for statistical significance was $\alpha = 0.05$. Greenhouse-Geisser P values are reported for nonspherical data. All results are shown as group means ± SE.

A two Trial Type (GG, GS) × seven Stimulation Time Relative to Lift RM ANOVA tested for differences in MEP amplitude and pretrigger rmsEMG between GG and GS trials. Differences in peak rate of EMG onset between GG and GS trials was tested with a one-way RM ANOVA with Trial Type (GG, GS) as the factor. A paired-sample t test compared rate of increase in CME prior to the lift response between GG and GS trials. Rate was calculated using the linear gradient of change in MEP amplitude from 110 to 170 ms prior to average LT for both trial types.

6.3.2 Results

Behavioural data: lift times and SSRT

For Go trials, LTs occurred on average 14 ± 2 ms after the target, indicating successful timed response performance as reported previously (Coxon et al., 2007; MacDonald et al., 2012 Chapter 5). All LTs are shown in Table 6.1. There was a main effect of Trial Type ($F_{1,14} = 421.3, P < 0.001$), with LTs delayed to an average of 98 ± 4 ms after the target on Partial trials. There was a main effect of Digit ($F_{1,14} = 4.6, P = 0.049$), with left LT faster than right LT when collapsed across Trial Type (51 ± 3 vs. 61 ± 4 ms relative to the target). There was no Trial Type × Digit interaction ($F_{1,14} = 0.8, P = 0.393$).

The success rate during GS trials of 48.3 ± 5.5 % was as expected and was not different from 50 % ($t_{14} = -0.3, P = 0.759$). SSRT for GS trials was 260 ± 5 ms.

Table 6.1 Lift times for Go and Partial trials for each participant in experiment 1

Subject	GG trial: left digit LT, ms	GG trial: right digit LT, ms	GS trial: left digit LT, ms	SG trial: right digit LT, ms
1	10	3	71	81
2	0	28	79	155
3	1	12	69	76
4	−4	5	73	109
5	22	35	112	67
6	7	2	101	118
7	5	38	78	117
8	3	20	79	NA
9	15	15	93	72
10	9	10	137	NA
11	20	28	90	122
12	10	14	105	119
13	8	11	65	NA
14	22	17	115	121
15	19	20	102	102
Average	10	17	91	105
SD	8	11	21	26
SE	2	3	5	8

Lift time (LT) is represented relative to target at 800 ms. GG, Go trial; GS, Go Left-Stop Right trial; SG, Stop Left-Go Right trial; NA, no successful trials available.

Neurophysiological data: MEP amplitude and pretrigger rmsEMG

TMT was 35 ± 2 % MSO, and TS intensity was 37 ± 2 % MSO (106 % TMT). For the ANOVA of MEP amplitude on successful GG and GS trials, there was a Trial Type × Stimulation Time Relative to Lift interaction ($F_{6,84} = 3.5, P = 0.039$; Figure 6.3A), a main effect of Stimulation Time Relative to Lift ($F_{6,84} = 11.9, P < 0.001$), and no main effect of Trial Type ($F_{1,14} = 1.8, P = 0.197$). For Go trials, MEP amplitude increased from −250 ms relative to target (0.10 ± 0.01 mV) to −175 ms (0.16 ± 0.02 mV; $t_{14} = 3.1, P = 0.007$) and remained facilitated (all $P < 0.013$). Comparing GG and successful GS trials, average MEP amplitude did not differ at −150 ms ($t_{14} = 0.9, P = 0.363$) but trended toward larger MEPs on GG trials at −125 and −100 ms (both $t_{14} = 2.1, P = 0.052$). For successful GS trials, MEP amplitude increased from −150 ms (0.15 ± 0.03 mV) to −100 ms (0.40 ± 0.09 mV; $t_{14} = 2.5, P = 0.025$). This increase in MEP amplitude was not sustained, with MEP amplitude decreasing from −100 to −75 ms before the target (0.18 ± 0.02 mV; $t_{14} = 2.3, P = 0.039$) even though the left digit was not cued to stop. MEP amplitude increased again from −75 to −25 ms before the target (0.44 ± 0.07 mV; $t_{14} = 3.9, P = 0.002$) and remained facilitated at 0 ms (0.40 ± 0.05 mV; $t_{14} = 4.5, P = 0.001$).

On unsuccessful GS trials, the temporal pattern of MEP amplitude modulation mirrored that on successful trials (Figure 6.3D). MEP amplitude decreased from −100 to −75 ms (from 1.03 ± 0.63 to 0.47 ± 0.33 mV; $t_{14} = 3.6, P = 0.003$). Importantly, between these two time points, MEP amplitude decreased to a lower absolute level on successful than on unsuccessful trials ($t_{13} = 3.0, P = 0.010$). This indicates that MEP suppression occurred during unsuccessful GS trials, likely reflecting that a reactive stopping mechanism was recruited but was insufficient to suppress the bimanual response.

There was a trend for MEP amplitude to increase more rapidly prior to the lift response on GG trials compared with GS trials ($t_{12} = 1.8, P = 0.090$; Figure 6.3C). Mean pretrigger rmsEMG level was 10 ± 1 µV, indicating that the FDI was sufficiently at rest at the time of stimulation. There were no effects or interactions for pretrigger rmsEMG (all $P > 0.09$).

EMG data: peak rate of EMG onset

There was a main effect of Trial Type ($F_{1,14} = 17.5, P = 0.001$). Peak rate of EMG onset was higher on GS trials (6.8 ± 1.2 mV s^{-1}) than on Go trials (5.6 ± 1.1 mV s^{-1}), indicative of a higher gain during GS trials.

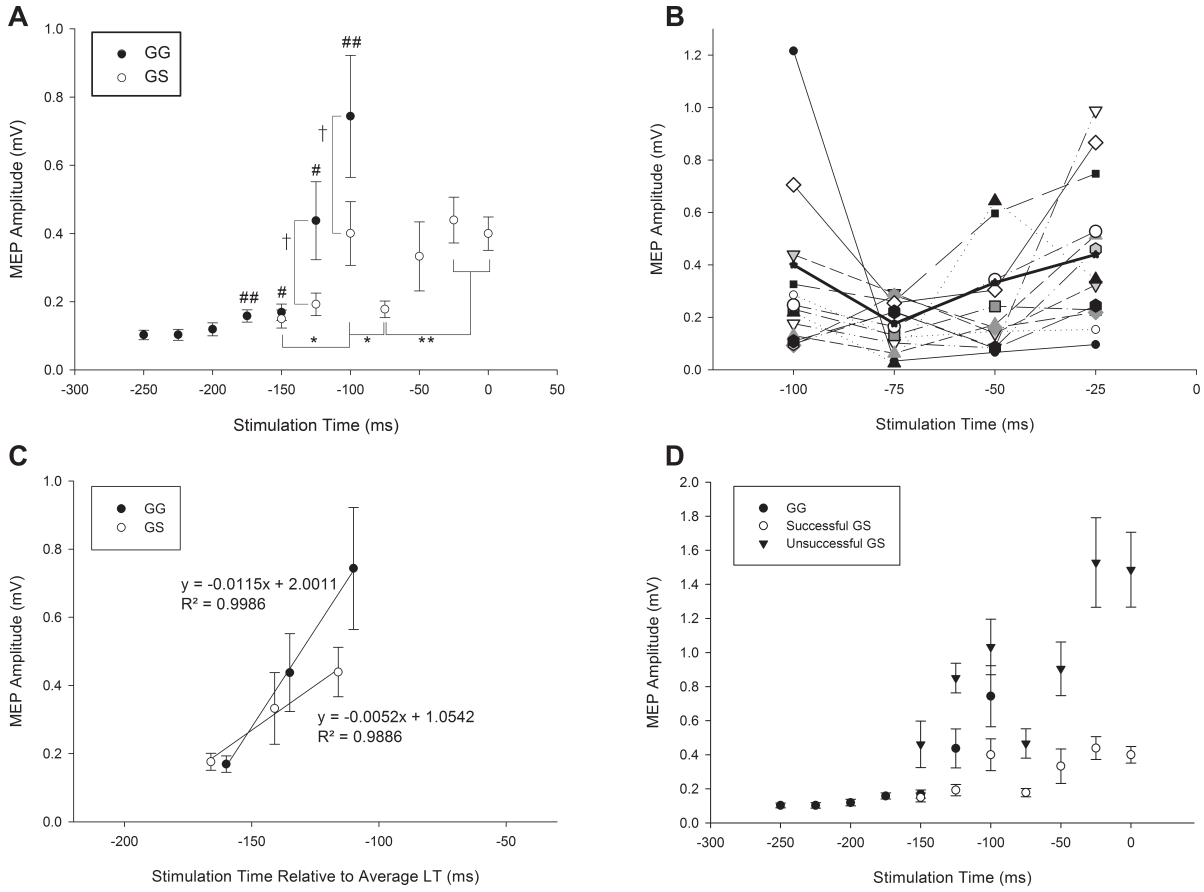

Figure 6.3 Modulation of corticomotor excitability during Go and GS trials. Modulation of left first dorsal interosseous (FDI) corticomotor excitability (CME) in experiment 1. A: Left FDI motor evoked potential (MEP) amplitudes during Go trials (GG) and Partial trials (GS) ($n = 15$). B: Individual participant data showing the temporal evolution of CME following the Partial stop cue (GS). This demonstrates that the dip in CME on GS trials was highly consistent ($n = 13$; 2 participants had a missing data point in this range). C: Rate of CME increase leading up to the response for Go and GS trials ($n = 13$ as for B). LT, lift time. Note that the slope for GS is half that for GG. D: Reillustration of A including MEP amplitudes during unsuccessful GS trials for comparison. Significant differences are not identified. Stop cue was given at −250 ms on GS trial. Stimulation time in A, B and D is relative to target. Values are means ± SE. $\#P < 0.05$; $\#\#P < 0.01$ represent significant increases relative to baseline during GG trials. $\dagger P = 0.052$ denote trends. $*P < 0.05$; $**P < 0.01$ represent significant differences during GS trials.

Modelling

An activation threshold model (ATM; Figure 6.4) is proposed to account for variation in lift time, CME and EMG (gain) between Partial and Go trials. The ATM is predicated on modulation of CME, which is the net balance of facilitatory and inhibitory processes that compete upstream of the final common motor pathway. The activation threshold is initially set by a tonic inhibitory input to maintain a resting state (Figure 6.4, A and B). Responses only occur when facilitation surpasses inhibition, i.e., the activation threshold. Facilitation is modelled as a ramp function with slope k_{facGo} and time constant τ_{facGo} to reflect sensorimotor processing.

$$\text{Facilitation} = 1/k_{facGo}[\text{time} - \tau_{facGo}(1 - e^{-\text{time}/\tau_{facGo}})]$$

On Partial trials, inhibition increases in response to a step input (I; Figure 6.4, C and D) with amplitude A_{inh}, slope k_{inh}, and time constant τ_{inh} to reflect stop signal processing.

$$I = \text{inhibition} + A_{inh}/k_{inh}(1 - e^{-\text{time}/\tau_{facGo}})$$

On Partial trials, an additional facilitatory drive (F; Figure 6.4C) reflects the initiation of the new, reprogrammed (single component) response at a higher gain. This is modeled as a ramp function of slope $k_{facGoNew}$ and time constant $\tau_{facGoNew}$ and is additive to the pre-existing Go trial facilitation.

$$F = \text{facilitation} + 1/k_{facGoNew}[\text{time} - \tau_{facGoNew}(1 - e^{-\text{time}/\tau_{facGoNew}})]$$

To capture the empirical data, model parameters were identified to reflect the following: a 50 % decrease in CME slope on GS trials compared with Go trials (Figure 6.3C); the higher gain of the reinitiated response on Partial trials as evident from EMG (Figure 6.4); and the average left LT delay of 82 ms on GS trials (Table 6.1). By arbitrarily setting an amplitude of inhibition increase $A = 1.555$, values of gain (k) and time delay (τ) parameters could be found to capture the empirical results described above. With $k_{facGo} = 0.2$, $\tau_{facGo} = \tau_{inh} = 0.8$, $k_{inh} = 1.2$, $k_{facGoNew} = 0.091$, and $\tau_{facGoNew} = 2.4$, the ATM captures behavioural and neurophysiological effects of Partial (GS) trials (Figure 6.4).

6.3.3 Discussion

The rise, fall and rise again of CME during Partial (GS) trials is a novel finding in support of our hypothesis of a nonselective neural RI mechanism. Suppression occurred on GS

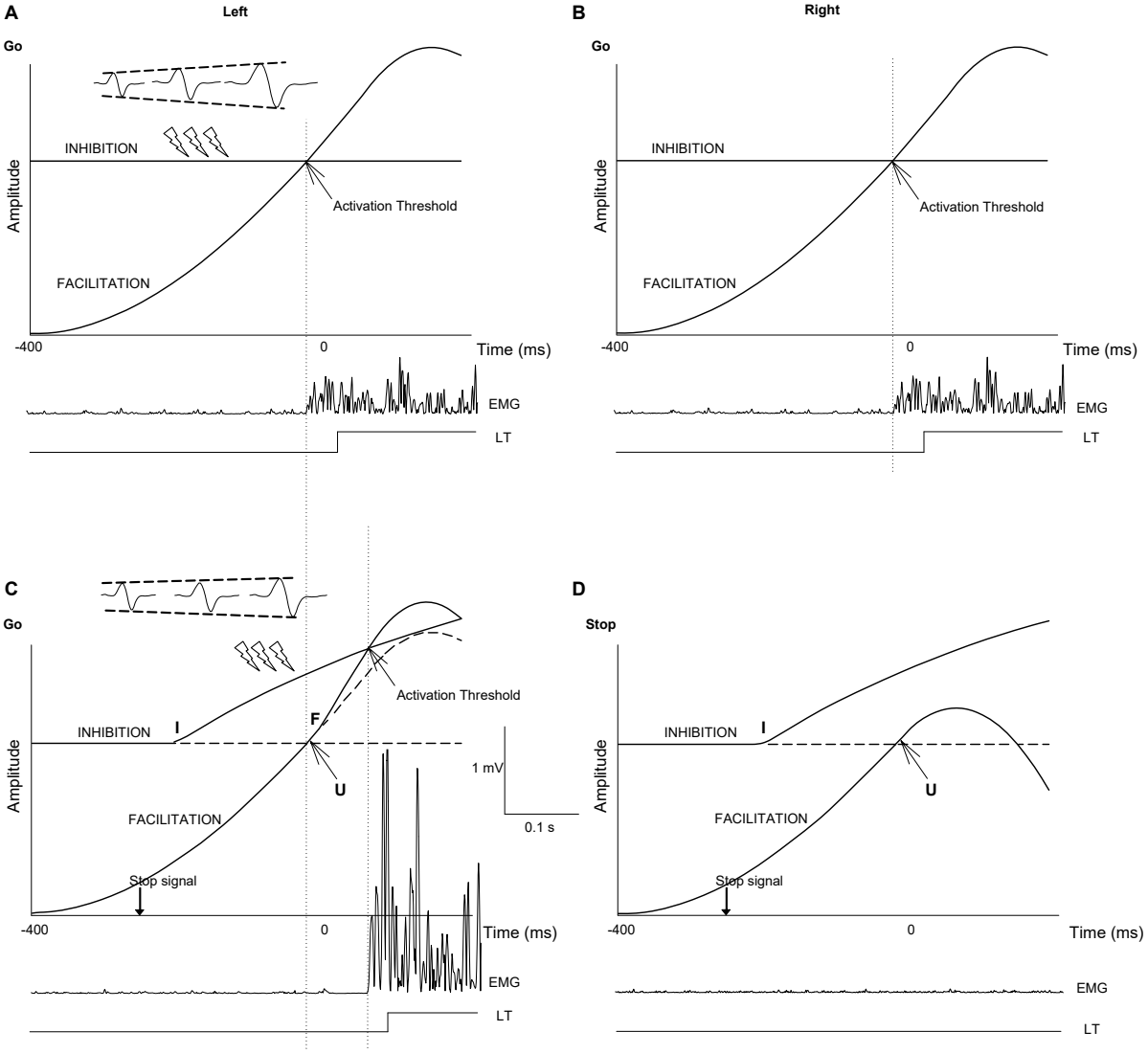

Figure 6.4 The activation threshold model for response inhibition. An activation threshold model (ATM) can account for CME modulation preceding movement initiation on Go trials (A and B) and the delayed reinitiation at a higher gain on GS trials (C). The ATM represents coexisting facilitatory and inhibitory processes that compete upstream of the final common motor pathway preceding muscle activity. The y-axis is unitless and reflects amplitude. Dotted vertical lines identify when the facilitation exceeds the activation threshold, corresponding to the generation of muscle activity. Lightning bolts represent the timing of single-pulse transcranial magnetic stimulation. The single vertical arrow represents the timing of the stop signal (C and D), causing a step input to inhibitory levels (I), raising the activation threshold. A new ramp facilitatory input (F) causes deviation of the facilitatory slope in C, representing the facilitation and initiation of the reprogrammed response (comprising 1 component) after uncoupling of the unitary response (U). Left digit is modelled using result data (A and C); right digit is hypothesized (B and D). Rectified electromyography (EMG) traces are from an individual participant, representing a GG (A) and GS trial (C) in experiment 1.

trials even though the left hand was not cued to stop. This modulation of CME reflects anticipation, suppression and subsequent initiation of a reprogrammed response. The novel neurophysiological findings are in line with previous behavioural data that also demonstrate nonselective RI (Coxon et al., 2007, 2012; MacDonald et al., 2012 Chapter 5). Overall, these results support the idea that neuroanatomical constraints prevent purely selective inhibition, at least when foreknowledge about cancellation is unavailable (Cai et al., 2011). The default process appears to be suppression of a unitary response and initiation of a reprogrammed response with an inevitable time delay. Selective inhibition therefore may only be possible in the context of proactive inhibition.

Anticipation of action modulates excitability of involved motor representations prior to execution (Chen et al., 1998b; Duque et al., 2010; Marinovic et al., 2013, 2011; Pascual-Leone et al., 1992). FDI MEP amplitude was facilitated above baseline from 175 ms before target on Go trials (Figure 6.3A). This confirms that CME reliably increases in a temporally appropriate manner during internally generated movements intrinsic to the ARI task (Coxon et al., 2006). Similarly, MEP amplitude increased 150 – 100 ms before target on GS trials as the default response was initiated. Pretrigger rmsEMG remained at resting levels, confirming MEP amplitude facilitation reflects modulation upstream of the alpha-motoneuron pool and is presumably cortical in origin.

Unimanual RI studies show MEP amplitude attenuation 100 – 200 ms after stop signal presentation (Coxon et al., 2006; Hoshiyama et al., 1997, 1996; Yamanaka and Nozaki, 2013). The present study extends these findings to a bimanual task requiring partial response cancellation. As predicted, the initial rise in CME on GS trials was followed by a significant decrease in excitability 175 ms after the stop signal (Figure 6.3A). Left FDI MEP amplitude decreased despite the left hand not being cued to stop. From this key finding, we contend that inhibition cannot be purely selective for this task. Preplanned multicomponent responses are integrated into a single unitary response through conceptual binding (Wenderoth et al., 2009). Suppression of this unitary response affects all components equally, decreasing excitability of all coupled motor representations. Our data indicate that a unitary response was cancelled through suppression of both FDI motor representations.

Delayed responses on Partial trials can be conceptualized as follows. Movement components are uncoupled after termination of the unitary response (MacDonald et al., 2012 Chapter 5). Uncoupling leads to separation of components, thus allowing the initiation (or selective reinitiation) of only the left response (Figure 6.4C), albeit delayed relative to target. The delayed response occurs at a higher gain than on execution trials (Coxon et al., 2007; Ko and Miller, 2011; MacDonald et al., 2012 Chapter 5). The higher gain may arise from a

steeper rise in facilitatory input to overcome inhibition that resulted from cancellation of the original response.

On unsuccessful GS trials, a bimanual response was made in error. Even on these occasions, left FDI MEP amplitude decreased 175 ms after the stop signal (Figure 6.3D). This indicates that the inhibitory process was activated but was unable to sufficiently suppress the preprogrammed response. The temporal pattern of CME for unsuccessful GS trials (Figure 6.3D) was 'shifted to the left' of Go trials, indicating that the excitability of involved motor representations was at a higher level and the excitatory process was further progressed when the stop signal was processed. Akin to the horse-race model, the excitatory process, likely belonging to the earlier part of the response distribution, "won the race" and the bimanual response was generated (De Jong et al., 1990; Logan and Cowan, 1984). Note, however, that the temporal consistency of CME suppression suggests independence between the excitatory and inhibitory processes, fulfilling another crucial assumption of the horserace model. Therefore, the bimanual response was generated because the excitatory process was initiated earlier, whereas the latency of the inhibitory process, in response to the stop signal, remained the same. In summary, the pattern of CME modulation on successful and unsuccessful GS trials adheres to the principles of the horse-race model. Furthermore, it appears that a decrease in CME to some threshold relative to baseline is necessary to terminate the preprogrammed response in advance of successful selective response reinitiation.

The activation threshold model (ATM) can be used to explain CME modulation during the selective reinitiation process. During simple action execution, muscle activity is not initiated until facilitatory inputs onto M1 exceed resting (tonic) inhibitory inputs (Figure 6.4, A and B) (Dacks et al., 2012; Duque et al., 2010; Jaffard et al., 2008). This idea is consistent with existing "hold your horses" models of stop signal reaction time tasks (Ballanger et al., 2009). During partial response cancellation, however, the activation threshold is elevated due to nonselective processing of the stop signal. The ATM accounts for the trend for decreased MEP amplitude during initial anticipation of the response on GS trials relative to Go (Figure 6.3A, −125 and 100 ms; $P = 0.052$). With an equivalent initial rise in facilitatory drive and a simultaneous increase in inhibition, the rate of CME increase must be less. This is supported by the 50 % lower rate of CME increase on GS trials compared with GG trials (Figure 6.3C), although this trend was not significant ($P = 0.09$). After uncoupling, a greater facilitatory drive is generated in the responding muscle to surpass the elevated activation threshold and initiate the reprogrammed response (Figure 6.4C). Once facilitatory inputs overcome inhibitory inputs, the response is necessarily at a higher gain, as can be seen in

the rate of EMG onset and the example EMG traces (compare Figure 6.4, A and C) and as shown previously (Coxon et al., 2007; MacDonald et al., 2012 Chapter 5).

If foreknowledge about cancellation was provided, the ATM would predict the same inhibitory response for the responding component, from reactive processing of the stop signal, and an earlier change to facilitatory drive from prior knowledge of which component to reinitiate. An equivalent inhibitory increase but an earlier facilitatory response would lead to a shorter LT delay in Partial trials. This is speculative and remains to be tested in the context of the ARI task in a future study. Importantly, however, the present and previous results indicate that an elevated threshold is obligatory for reactive processing of a stop signal.

6.4 Experiment 2

During motor preparation the amplitude of MEPs from TMS over involved motor representations may partly reflect GABAergic inhibition, which tonically suppresses inappropriate or premature movements (Dacks et al., 2012; Duque et al., 2010; Jaffard et al., 2008). Tonic GABAergic inhibition potentially includes cortical (Duque et al., 2010; Jaffard et al., 2008), spinal (Duque et al., 2010), and subcortical inhibitory circuits (Ballanger et al., 2009). Paired-pulse TMS can be used to investigate local M1 intracortical inhibition, by pairing a subthreshold conditioning stimulus with a subsequent suprathreshold test stimulus (Coxon et al., 2006; Fisher et al., 2002; Kujirai et al., 1993; Peurala et al., 2008; Roshan et al., 2003), and can examine the contribution of M1 intracortical circuits to inhibition during motor preparation (Coxon et al., 2006). Experiment 2 examined whether sICI within M1 was responsible for the elevated threshold within our model during Partial trials. We investigated whether modulation of sICI would coincide with modulation of CME from the first experiment.

6.4.1 Methods

Protocol

The task and procedure were identical to those of experiment 1 with the following exceptions. All three stop conditions (SS, GS, SG) were of interest and equiprobable. There were 817 trials in total, 565 Go (70 %) and 252 Stop trials (30 %). Go and Stop trials were pseudorandomized across 19 blocks of 43 trials.

For paired-pulse TMS, an interstimulus interval (ISI) of 2 ms was chosen for investigating sICI (Peurala et al., 2008) to examine $GABA_A$-mediated intracortical inhibitory processes

within M1 (Di Lazzaro et al., 2000; Ziemann et al., 1996). Active motor threshold (AMT) was determined while the participant maintained an isometric left FDI contraction at about 5 % of maximal voluntary contraction. TS and conditioning stimulus (CS) intensity were determined during practice of Go trials at −600 ms, prior to M1 movement preparation associated with switch release (Coxon et al., 2006). TS intensity was set to consistently evoke a MEP of about 1.5 mV with only minimal interference of task performance. CS intensity was determined by starting at 65 % AMT and increasing in 1 % MSO increments until the conditioned (C) MEP amplitude was 50 % of nonconditioned (NC) MEP (CS50) (Coxon et al., 2006; Fisher et al., 2002; Stinear and Byblow, 2003).

The sICI protocol necessitated a more narrow range of stimulation times to ensure a tolerable experiment duration. TMS was delivered early or late, at −75 and −25 ms on Partial trials, −25 and 25 ms on SS trials, and −600 and −125 ms on GG trials (Figure 6.2B). Stimulation on Go trials at −600 ms ensured a baseline measure prior to trial-related modulation of CME. Stimulation at −125 ms enabled the comparison of CME to −25 ms on GS trials, following findings from experiment 1. Stimulation on all Stop trials was 175 and 225 ms post stop signal, to examine sICI at the time of MEP suppression and subsequent increase. Twenty single and paired-pulse TMS trials were collected in each condition in pseudorandom order. All three Stop trial conditions included stimulated trials.

Dependent measures

LTs were determined for successful Go and Partial trials. Average LTs were calculated after outliers (±3 SD) were removed (1.2 ± 0.2 % and 0.2 ± 0.1 %, respectively). LTs from successful Partial trials correspond to the responding digit. All LTs are reported in milliseconds relative to the target. SSRT was determined for each stop condition using the integration method as described for experiment 1.

MEP amplitude for both C and NC trials, percent inhibition (%INH) and pretrigger rmsEMG were determined. %INH was calculated as [(NC MEP - C MEP)/NC MEP] × 100. NC MEP amplitudes were compared within and between GG and Partial trials using planned comparisons, following results from experiment 1. Primary measures of interest were the differences in %INH among the three types of Stop trials. Pretrigger rmsEMG was calculated within a 50 ms window preceding TMS, and trials were discarded if rmsEMG was above 14 µV. Trials were visually inspected and discarded if activity was present between the stimulus and MEP onset.

Statistical analysis

Dependent measures were subjected to RM ANOVAs, as in experiment 1, with the same criteria for statistical significance. LT and predetermined indicator stop times were analyzed as in experiment 1. All results are shown as group means ± SE.

NC MEP amplitude and pretrigger rmsEMG were examined in four Trial Type (GG, SG, GS, SS) × two Stimulation Time (Early, Late) RM ANOVAs. The sICI protocol was checked by examining %INH on Go trials (−600 ms) against zero using a one-sample t test. %INH on Stop trials was examined in a three Stop Trial Type (SG, GS, SS) × two Stimulation Time (Early, Late) RM ANOVA. For Go trials, %INH was examined using a two-tailed paired t test. Linear regression was performed to determine if the change in %INH between GG and GS trials (−125 ms on GG vs. −25 ms on GS) was associated with LT delay. SSRTs were analyzed using a one-way RM ANOVA with Stop Condition (SG, GS, SS) as factors.

6.4.2 Results

Behavioural data: lift times and SSRT

LTs are shown in Table 6.2. For Go trials, LTs occurred on average 14 ± 2 ms after the target, indicating successful performance as reported previously and in experiment 1. There was a main effect of Trial Type ($F_{1,12} = 321.6, P < 0.001$), with LTs delayed on Partial trials to 100 ± 5 ms after the target. There were no other main effects or interactions (all $P > 0.130$). Go LTs were not significantly different between stimulated (at −125 ms) and unstimulated trials ($t_9 = 1.8, P = 0.099$), indicating that TMS did not have an appreciable affect on behaviour.

For SSRT there was a main effect of Stop Condition ($F_{2,24} = 27.3, P < 0.001$). The SSRT for SS trials (222 ± 4 ms) was faster than that for SG (254 ± 6 ms; $t_{12} = -7.6, P < 0.001$) and GS trials (252 ± 5 ms; $t_{12} = -5.9, P < 0.001$), which did not differ from each other ($t_{12} = 0.5, P = 0.644$). Success on GS trials was greater than 50% (65.6 ± 5.0 %; $t_{12} = 3.1, P = 0.009$) and significantly higher than in experiment 1 ($t_{12} = 3.9, P = 0.002$). Success on SG (60.6 ± 6.1 %) and SS trials (42.7 ± 4.4 %) did not differ significantly from 50% successful inhibition ($t_{12} = 1.7, P = 0.108$ and $t_{12} = -1.7, P = 0.124$, respectively).

Neurophysiological data: MEP amplitude, sICI and pretrigger rmsEMG

Due to an insufficient number of MEPs after rejection of trials with pretrigger rmsEMG >14 μV, three participants were removed from the neurophysiological data for experiment

Table 6.2 Lift times for Go and Partial trials for each participant in experiment 2

Subject	GG trial: left digit LT, ms	GG trial: right digit LT, ms	GS trial: left digit LT, ms	SG trial: right digit LT, ms
1	5	12	71	108
2	2	6	80	82
3	24	22	146	101
4	24	−1	113	79
5	12	22	115	85
6	6	3	95	128
7	18	12	103	74
8	18	12	91	75
9	29	9	120	111
10	25	16	120	108
11	20	13	81	74
12	21	13	90	88
13	13	16	134	141
Average	17	12	105	96
SD	8	7	22	22
SE	2	2	6	6

Lift time (LT) is represented relative to target at 800 ms.

2, leaving 10 participants in the analysis. AMT was 38 ± 3 % MSO, TS intensity was 55 ± 4 % MSO, and average CS50 was 29 ± 2 % MSO (76.0 ± 2.3 % of AMT). The conditioning protocol successfully produced sICI using TS and CS intensities set during practice blocks. Average NC MEP amplitude on Go trials (−600 ms) was 1.48 ± 0.20 mV. Average %INH during Go trials decreased compared with that in practice blocks but was still significantly larger than zero (28.4 ± 7.8 %; $t_9 = 3.6, P = 0.005$), as observed previously (Coxon et al., 2006).

For %INH on Stop trials there was a main effect of Stimulation Time ($F_{1,9} = 9.1, P = 0.015$) but no effect of Stop Trial Type ($F_{2,18} = 0.3, P = 0.847$) or Stop Trial Type × Stimulation Time interaction ($F_{2,18} = 1.9, P = 0.173$). %INH was on average greater at the later (33.0 ± 4.5 %) compared with early (28.2 ± 4.7 %) stimulation time on Stop trials. On Go trials there was no group level significant difference between %INH at early (−600 ms; 28.4 ± 7.8 %) and late (−125 ms; 37.0 ± 4.6 %) stimulation times ($t_9 = 1.0, P = 0.355$). This nonsignificant difference arose from participants with lower sICI at −600 ms increasing %INH during task Go trials, whereas participants with higher sICI at −600 ms decreased %INH during Go trials ($r = 0.85, P = 0.002$; Figure 6.5). The change in sICI was correlated with baseline levels of sICI at −600 ms. The opposing modulation of sICI during Go trials resulted in the nonsignificant group effect. A paired-sample t test (1- tailed) for greater %INH on GS trials at −25 ms compared with GG trials at −125 ms was not significant (30.9 ± 5.4 % on GS vs. 37.0 ± 4.6 % on GG; $t_9 = 1.1, P = 0.151$). There was no correlation linking change in %INH between GG and GS trials and LT delay ($r = 0.20, P = 0.587$).

For NC MEP amplitude there was a Trial Type × Stimulation Time interaction ($F_{3,27} = 6.0, P = 0.003$, Figure 6.6), a main effect of Stimulation Time ($F_{1,9} = 17.0, P = 0.003$), and no main effect of Trial Type ($F_{3,27} = 1.3, P = 0.284$). On Go trials NC MEP amplitude increased from −600 ms (1.48 ± 0.20 mV) to −125 ms (2.62 ± 0.39 mV; $t_9 = 3.6, P = 0.006$), indicating that CME increased on GG trials as demonstrated in experiment 1. On GS trials NC MEP amplitude increased from −75 ms (2.17 ± 0.30 mV) to −25 ms (2.75 ± 0.40 mV; $t_9 = 3.0, P = 0.014$), mirroring the increase in CME between these stimulation times in experiment 1. On SG trials NC MEP amplitude also increased from −75 ms (2.01 ± 0.23 mV) to −25 ms (2.51 ± 0.39 mV; $t_9 = 2.4, P = 0.042$). On SS trials NC MEP amplitude did not differ between stimulation times ($t_9 = 1.2, P = 0.247$). There was a significant decrease in NC MEP amplitude at −75 ms on GS trials compared with −125 ms on GG trials ($t_9 = 2.0, P = 0.041$), mirroring results of experiment 1. NC MEP amplitude also decreased at −75 ms on SG trials compared with −125 ms on GG trials ($t_9 = 2.1, P = 0.030$). Based on results of experiment 1, a planned comparison tested for a difference in NC MEP amplitude between −125 ms on Go

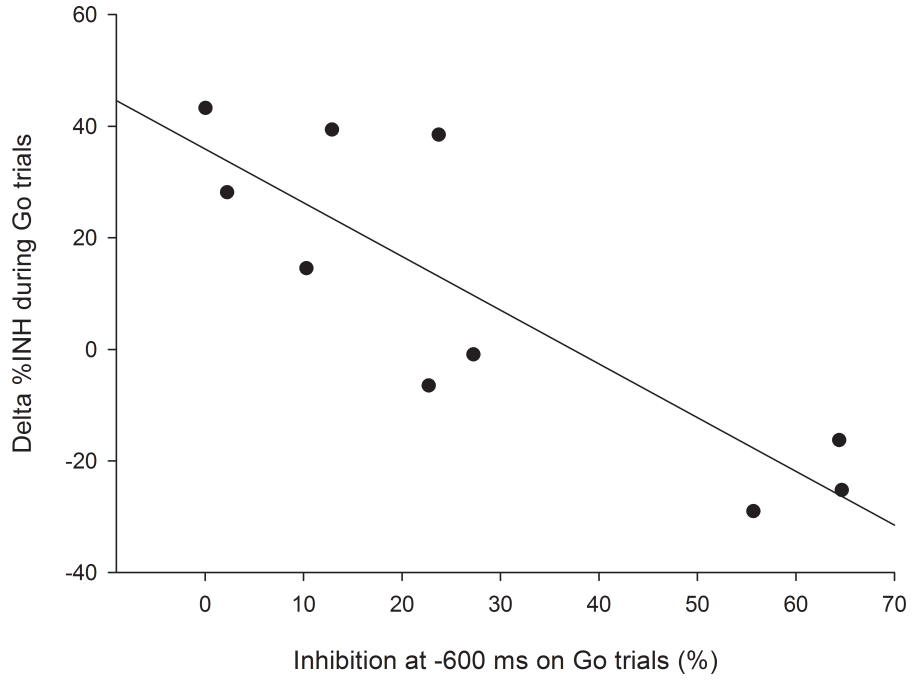

Figure 6.5 Short-latency intracortical inhibition during Go trials. Linear regression between percent inhibition (%INH) at −600 ms and change in (delta) %INH ($r = 0.85, P = 0.002$) on Go trials in experiment 2. Participants with higher %INH at −600 ms demonstrated a decrease in %INH during Go trials, whereas those with lower baseline %INH demonstrated an increase in %INH during Go trials.

trials and −25 ms on GS trials. No significant difference was found ($t_9 = 0.8, P = 0.452$), as expected.

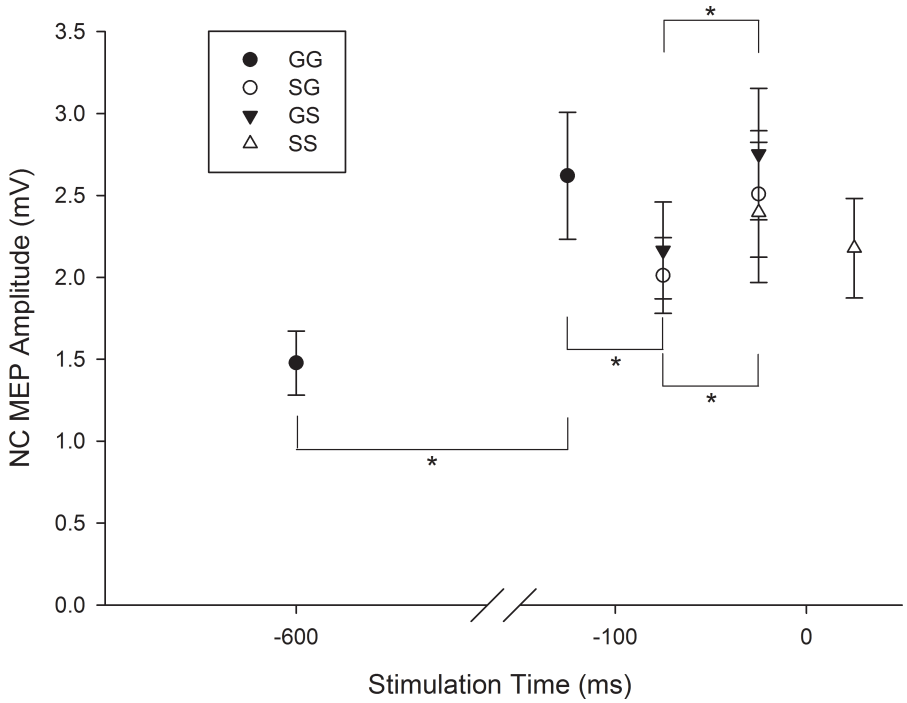

Figure 6.6 Nonconditioned MEP amplitudes. Modulation of corticomotor excitability in experiment 2. Left first dorsal interosseous nonconditioned (NC) motor evoked potential (MEP) amplitudes are shown for stimulation at −600 and −125 ms on GG trials, −75 and −25 ms on SG (Stop Left-Go Right) and GS trials, and −25 and 25 ms on SS trials. Values are means ± SE ($n = 10$). $*P < 0.05$ between stimulation times for GG, SG, and GS trials.

Mean pretrigger rmsEMG level was 8 ± 1 μV, indicating that the FDI was sufficiently at rest at the time of stimulation. There were no main effects or interactions for pretrigger rmsEMG (all $P > 0.099$).

Discussion

Experiment 2 was designed to investigate the inhibitory component of the ATM. In support of the model, sICI showed an overall increase over the course of Stop trials. However, contrary to our second hypothesis, there was no modulation of M1 sICI during GS trials that could account for the observed CME modulation. CME suppression 175 ms after the stop cue on GS trials of experiment 1 does not appear to rely purely on M1 intracortical inhibitory mechanisms. We did not observe a significant increase in sICI at this time point on GS trials. Given this disparity between CME and sICI data on GS trials, it is unlikely that

the $GABA_A$-mediated intracortical inhibitory processes within M1 (Di Lazzaro et al., 2000; Ziemann et al., 1996) probed at an ISI of 2 ms can fully account for attenuated left FDI MEP amplitude after the right finger was cued to stop. Our results suggest M1 sICI is unlikely to be the primary mechanism contributing to the decrease in excitability on Partial trials and the increased activation threshold within the ATM.

Experiment 2 was successful at validating the main results from experiment 1 and extending the model. NC MEP amplitude increased during Go trials of experiment 2 (Figure 6.6), further confirming that CME reliably increases in a temporally appropriate manner during movement anticipation in the ARI task (Coxon et al., 2006). NC MEP amplitude was suppressed at −75 ms on GS trials relative to −125 ms on GG trials, mirroring CME suppression in experiment 1. NC MEP amplitude was also suppressed at −75 ms on SG trials, indicating this same dip in CME is seen whether the left side is cancelled or executed in a Partial trial. The decrease in NC MEP amplitude on both GS and SG trials (Figure 6.6) informed the ATM by indicating an equivalent increase in inhibition for both digits (Figure 6.4, C and D) following processing of the stop cue. The subsequent equivalent increase in CME for canceled and executed digits from −75 to −25 ms (Figure 6.6) would indicate full uncoupling between response representations has not yet occurred at these time points. We propose uncoupling on Partial trials is achieved between −25 and 0 ms prior to facilitation of the reprogrammed, single-component response ("U," Figure 6.4, C and D).

M1 sICI at 2 ms ISI is unlikely to be the primary mechanism contributing to the decrease in excitability on Partial trials and the increase in the activation threshold. sICI demonstrated an overall increase over the course of Stop trials as our model would predict, indicating cancellation of a prepared bimanual response recruits sICI in this context (Coxon et al., 2006). However, the delayed increase at 225 ms would indicate it is not the inhibitory mechanism responsible for CME suppression 175 ms post stop signal on GS trials. For a comparable level of corticomotor pathway excitability (−125 ms on GG vs. −25 ms on GS trials), sICI was not comparably higher on GS trials. Furthermore, there was no correlation between the difference in sICI between GG and GS trials and the extent of LT delay. Although M1 sICI appears to be modulated during Stop trials of a bimanual ARI task, it is unlikely to be the sole inhibitory mechanism producing the dynamic modulation of CME on GS trials or the increased threshold within our model.

Nonsignificant results are difficult to interpret, and there are a couple of considerations for this study. First, MEPs are pointwise measures of CME and can be influenced by multiple co-occurring and/or temporally overlapping processes (Duque et al., 2010). For example, sICI and interhemispheric inhibition (IHI) may be occurring simultaneously during this

bimanual task. sICI is significantly reduced in the presence of IHI (Daskalakis et al., 2002). It is possible that IHI masked the true involvement of sICI during Go and Partial trials. Because our study did not include any direct measures of IHI, we can only speculate as to its role on sICI measures. Second, the inherent dynamic excitability of involved motor representations prior to an anticipated response resulted in significant differences in NC MEP amplitude during Go and Partial trials. It can be exceedingly difficult to match NC MEP amplitudes during an active task. Unfortunately, a change in NC MEP amplitude complicates the comparison of sICI across and between trials (Daskalakis et al., 2002; Sanger et al., 2001). Nevertheless, it is important to note that TS intensities consistently produced average NC MEP amplitudes between 1.5 and 2.8 mV, within the optimal range for sICI (Sanger et al., 2001).

If sICI is not the primary mechanism contributing to the raised activation threshold within the model, other likely mechanisms include cortico-subcortical loops through the basal ganglia or cortico-cortical afferents (Alexander and Crutcher, 1990a; Ballanger et al., 2009; Danion and Latash, 2011; Di Lazzaro et al., 2008; Jahfari et al., 2011; Mattia et al., 2012). The involvement of cortico-subcortical loops during Partial trials for the ARI task would align with two recent studies (Coxon et al., 2012; Majid et al., 2013). Further research is warranted into the inhibitory mechanisms involved in this bimanual task.

6.5 General discussion

Participants performed the task correctly, assuring validity of the study. First, Go LTs confirmed that participants did not delay their response in anticipation of a stop cue. The traditional stop-signal task can allow adjustments to response strategies (i.e., response slowing) to balance the requirements of the execution and inhibition conditions (Lappin and Eriksen, 1966; Verbruggen and Logan, 2009). However, due to task design (stop signal occurring before the target), an ARI task ensures Go response preparation in the presence of stop cues. The current study is therefore reliably investigating CME modulation during partial cancellation of an initiated bimanual response. Second, partial trial LTs were significantly delayed compared with complete movement execution, as shown previously. Finally, LTs were comparable between experiments and with previous studies using this task (Coxon et al., 2007; MacDonald et al., 2012 Chapter 5), so TMS did not affect behavioural performance. Therefore, the data reflect the unpredicted (reactive) cancellation of an initiated response.

6.6 Conclusion

These studies provide novel insight into RI. Partial response cancellation requires complex temporal modulation of CME in a pattern consistent with the anticipation, suppression and subsequent selective reinitiation of the response. The proposed activation threshold model can account for CME modulation leading to delayed reinitiation of the reprogrammed response at a higher gain. Elucidating the mechanisms responsible for RI and CME modulation during such a cognitively demanding task is challenging and may involve a combination of cortical and subcortical processes. Whatever the underlying mechanism, it appears that neuroanatomical constraints prevent purely selective inhibition in a reactive context.

Chapter 7

An Activation Threshold Model for Response Inhibition

This experiment has been submitted for peer review.

Abstract

Reactive response inhibition (RI) is the cancellation of a prepared response when it is no longer appropriate. Selectivity of RI can be examined by cueing the cancellation of one component of a prepared multi-component response. This substantially delays execution of other components. There is debate regarding whether this response delay is due to a selective or nonselective neural mechanism. Here we propose a computational activation threshold model (ATM) and test it against behavioural and neurophysiological data from partial RI experiments. The ATM comprises both facilitatory and inhibitory processes that compete upstream of motor output regions. Summary statistics (means and standard deviations) of predicted muscular and neurophysiological data were fit to equivalent experimental measures by minimizing a Pearson Chi-square statistic. The ATM successfully captured behavioural and neurophysiological dynamics of partial RI. The ATM demonstrated that the observed modulation of corticomotor excitability during partial RI can be explained by nonselective inhibition of the prepared response. The inhibition raised the activation threshold to a level that could not be reached by the original response. This was necessarily followed by an additional phase of facilitation representing a secondary activation process in order to reach the new inhibition threshold and initiate the executed component of the response. The ATM offers a mechanistic description of the neural events underlying RI, in which partial movement cancellation results from a nonselective inhibitory event followed

by subsequent initiation of a new response. The ATM provides a framework for considering and exploring the neuroanatomical constraints that underlie RI.

7.1 Introduction

The most time-sensitive inhibitory responses in everyday life are commonly associated with unexpected events. Without foreknowledge of such events, cancellation of a response is difficult (Aron and Verbruggen, 2008). The cancellation of prepared movement when it is no longer appropriate is termed response inhibition (RI). A "horse-race" model provides a conceptual framework for RI (Logan and Cowan, 1984). This model posits that response execution results from neural facilitation triggered by an imperative cue, and that RI results from neuronal inhibition triggered by a stop signal. Whichever process "wins the race" to a point of no return somewhere along the neuroaxis determines whether or not a response is generated.

An anticipatory response inhibition (ARI) task conforms to the assumptions of the horse-race model with the added benefit of time-locking Go responses to a predictable event. In the ARI task Go responses can be anticipated and are therefore internally generated (Coxon et al., 2007; Zandbelt and Vink, 2010), rather than made in response to an unpredictable imperative cue. The sudden cancellation of a single component of the prepared response can delay the remaining executed component by up to 100 ms (Coxon et al., 2007, 2009; MacDonald et al., 2014 Chapter 6, 2012 Chapter 5) or more in older adults (Coxon et al., 2014, 2012). Interestingly, the response delay occurs regardless of whether the task requires dual responses made by different digits within the same hand (unimanual) or between hands (bimanual) (Coxon et al., 2007).

The response delay during partial RI has been confirmed across numerous studies performed by different groups (Aron and Verbruggen, 2008; Cai et al., 2011; Claffey et al., 2010; Coxon et al., 2007, 2009; Ko and Miller, 2011; MacDonald et al., 2014 Chapter 6, 2012 Chapter 5; Majid et al., 2012; Smittenaar et al., 2013), even when the intention is to demonstrate that such delays can be minimised under certain conditions (Xu et al., 2014). The delay appears robust to variations in the experimental paradigm e.g. whether the Go response requires reacting to an imperative or intercepting a stationary target. Here we will use the term response delay to reflect what others have called a stopping interference effect, or restart cost. The underlying mechanisms of response delays in the context of partial RI are not fully understood and have been explored with a variety of experimental paradigms, combining behavioural, neurophsyiological and/or computational measures

(Figure 7.1, MacDonald et al. 2014 Chapter 6; Majid et al. 2012; Xu et al. 2014). These studies have investigated two important questions. What is the neural mechanism of the response delay observed during partial RI? And can a subset of a prepared multi-component response be selectively inhibited, with no delay in initiating the remaining response component?

We proposed an activation threshold model (ATM) to account for response delays during partial RI (MacDonald et al., 2014 Chapter 6). The ATM was predicated on the findings that CME for the responding muscle was temporally modulated during partial RI in a manner that reflected anticipation, suppression and subsequent initiation of a reprogrammed response. The model proposes preparation of a synchronous two-component response via neuronal "coupling" of effector representations. An unanticipated stop signal triggers the simultaneous inhibition of all components of the prepared response. Inhibition essentially terminates all prepared output. Therefore in order to execute the (partial) response, a new response comprised of a subset of the original effectors is proposed to be initiated after the stop cue. The termination and reinitiation of movement can account for the robust response delay.

In contrast, Majid et al. (2012) proposed a mechanism of selective inhibition and reduced delays, but only when knowledge about stopping is given in advance. Majid and colleagues employed a variation of the traditional stop-signal task (SST) that required a bimanual choice reaction time (RT) in response to an imperative cue on the majority of trials. A visual stop signal presented after the imperative cued the cancellation of one component of the bimanual response. Using a dual-task SST, Xu et al. (2014) suggested that selective inhibition is possible and the delay can be eliminated, even without foreknowledge. However, the study by Xu and colleagues showed robust delays across numerous conditions and minimal delays in a very specific condition: using a highly compatible tactile stop cue following relatively short stop signal delays (shorter than a standard simple reaction time), and only after multiple practice sessions in which a reward scheme de-emphasized accurate stopping. The disparate views about the selective nature of RI are likely a by-product of the paradigms used to investigate partial RI. To date, the Go response distributions between the ARI and SST paradigms have not been directly compared. Differences in the distribution of the underlying Go response may explain the different behavioural results that have lead to these opposing views.

The ATM predicts whether or not a response will occur, when it will occur, and with what gain, based on the net balance of facilitatory and inhibitory processes that compete upstream of motor output regions. Here we use a computational ATM, in conjunction with existing behavioural and neurophysiological data, to investigate hypotheses about the neural mechanisms of RI. First we validated and expanded the ATM by showing that optimized

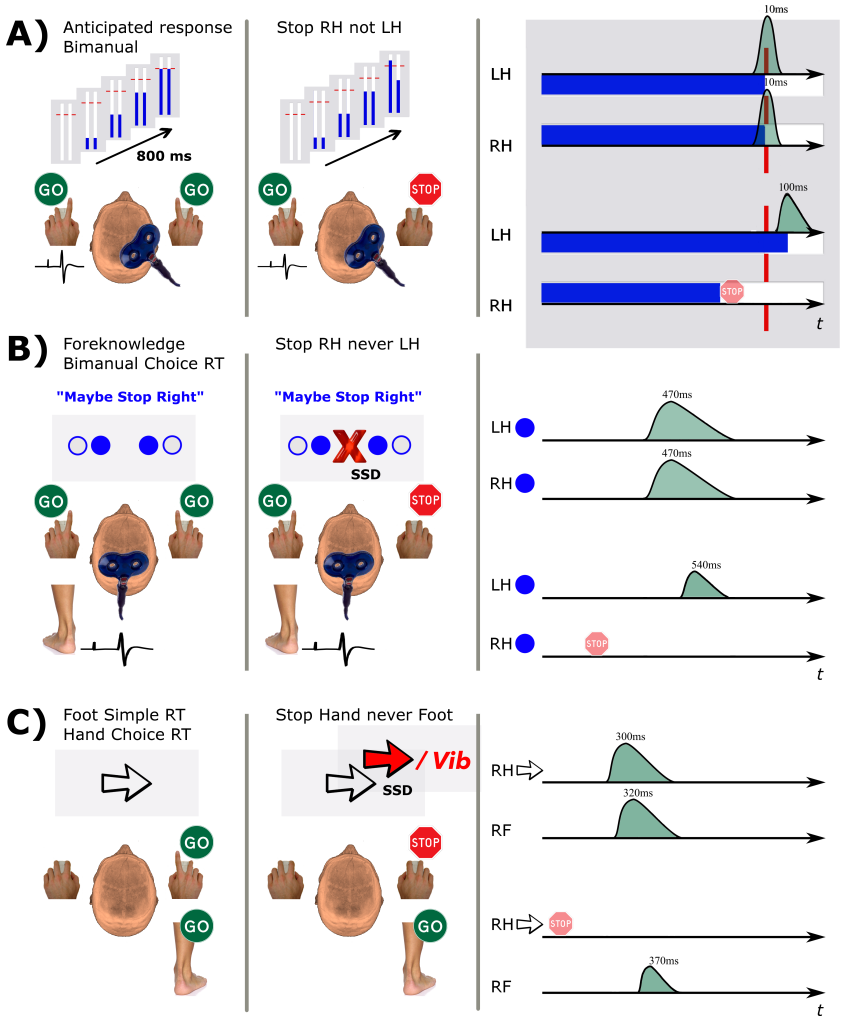

Figure 7.1 Experimental designs used to investigate the response delay. A: MacDonald et al. (2014 Chapter 6). Bimanual anticipatory response inhibition task. On a Partial trial, one bar unexpectedly stopped rising before the target, cueing cancellation of the corresponding hand. TMS was applied to the right primary motor cortex and motor evoked potentials (MEPs) were recorded from the task-relevant left FDI muscle. Mean response times (ms) are relative to the target positioned at 800 ms. B: Majid et al. (2012). In the foreknowledge stop-signal task, text was displayed to bias stopping expectations followed two seconds later by the imperative. Participants made a synchronous bimanual choice reaction time (RT) response with both index or both little fingers. On Partial trials, a central stop signal appeared after a stop signal delay (SSD) and the stopping rule held in working memory was implemented. MEPs were recorded from the task-irrelevant tibialis anterior muscle. C: Xu et al. (2014). In the dual-task version of the stop-signal task, participants always responded with their foot and performed a choice RT task, responding with the hand that corresponded to the direction of the arrow (imperative). On Partial trials, the arrow turned red (or the hand was vibrated) after a SSD and no hand response was required. RTs are relative to the imperative in B and C. RH: right hand, LH: left hand, RF: right foot, RT: reaction time, Vib: vibration.

parameters of the model could reproduce experimental Go trial data. Once validated, the model was used to explore the hypothesis that response delays are due to nonselective response inhibition followed by response reprogramming. We expected that response delays could not be simulated solely by elevating an activation threshold via increased inhibition, thereby increasing the time to cross threshold (movement execution). Instead we expected an increase in threshold would necessarily be followed by an additional phase of facilitation representing a secondary activation process in order to cross the threshold and execute the remaining component of the response. To compare response distributions between paradigms, we simulated empirical findings from the SST using results from Majid et al. (2012). We expected markedly different distributions of the underlying Go process (Ratcliff, 1979, 1993) between the ARI and SST, which may explain the opposing views on the source of the response delay.

7.2 Methods

Empirical data were taken from published work (MacDonald et al. 2014 Chapter 6; Experiment 1). Briefly, data are from the left hand of 15 neurologically healthy right handed adults between the ages of 21 – 37 yr, 8 male. Participants completed the bimanual ARI task (Coxon et al., 2007) while receiving single-pulse transcranial magnetic stimulation (TMS) of the right primary motor cortex (M1) over the first dorsal interosseous hotspot (Figure 7.1A). The default Go response was bimanual index finger abduction to intercept two rising indicators with an onscreen stationary target (Go trials). Occasionally one or both indicators stopped automatically before reaching the target (Stop trials), cueing the inhibition of the response with the corresponding digit(s). Partial movement cancellation was required when only one indicator stopped (Partial trials), as participants were still required to intercept the other indicator with the target. The current model fits data from the left hand during successfully performed Go left – Stop right (GS) trials, when only the right hand is cued to stop and the response delay is seen in the left hand (Figure 7.1A, middle). A similar response delay occurs in Stop left – Go right trials but we chose to model the nondominant hand as it is more strongly affected by uncoupling during the bimanual ARI task (MacDonald et al., 2012 Chapter 5). TMS was delivered from 250 – 100 ms before the target on Go trials and 150 – 0 ms on Partial trials, in 25 ms intervals. The stop signal on Partial trials always occurred 250 ms prior to the target. Typical lift time (LT) averages and distributions for this task are graphically depicted for Go (top) and GS trials (bottom) (Figure 7.1A, right).

7.2.1 General model assumptions

The ATM is based on that proposed in MacDonald et al. (2014 Chapter 6). In the present study the ATM has been fit to EMG onset times (as opposed to lift times) since these are more closely linked temporally to neural output. An assumption is that a response is not initiated until facilitatory inputs to the alpha motoneuron pool exceed inhibitory levels. In the lead up to a response, impulse control mechanisms (Dacks et al., 2012; Duque et al., 2010; Jaffard et al., 2008) keep the motoneurons below threshold until a movement is appropriate. This framework is consistent with models of saccades whereby the growth of activity in neurons predicts saccade initiation time (Dorris and Munoz, 1998).

Motor evoked potential (MEP) amplitudes recorded from first dorsal interosseous were used as a measure of the excitability of the corticomotor pathway in the lead up to the response. The MEP amplitude is equated with the difference between facilitation and the rise of inhibition above baseline (Figure 7.2A&B). This reflects the subliminal fringe of neurons close enough to threshold to be activated by the TMS pulse, as a consequence of the balance of facilitatory and inhibitory input (Devanne et al., 1997). A simple Gaussian function was chosen to model facilitation leading to ballistic finger movements. Our model therefore assumes between trial variability in the rate and starting point of CME accumulation reflecting an underlying ballistic facilitatory process. Increased inhibition following the stop signal is modelled with a step function including a time constant defining the rate of rise.

7.2.2 Model specifics

Predicted EMG and MEP data were generated by a Monte Carlo simulation reliant on a number of parameters describing the facilitatory and inhibitory processes hypothesized to underlie the movement response. Summary statistics (means and standard deviations) of predicted data were fitted to equivalent measures from experimental EMG and MEP data by minimizing a Pearson Chi-square statistic (Boucher et al., 2007; Hu et al., 2014) using the unconstrained Nelder-Mead simplex algorithm (Nelder and Mead, 1965).

$$\chi^2 = \sum_i \sum_j (o_{ij} - p_{ij})^2 / p_{ij} \tag{7.1}$$

where i indexes variables e.g. EMG onsets, MEP amplitudes, etc (Figure 7.2A&B). Within each variable, experimental data points or model predictions were categorized into one of 3 bins, representing upper, middle and lower thirds, indexed by j such that o_{ij} and p_{ij} are

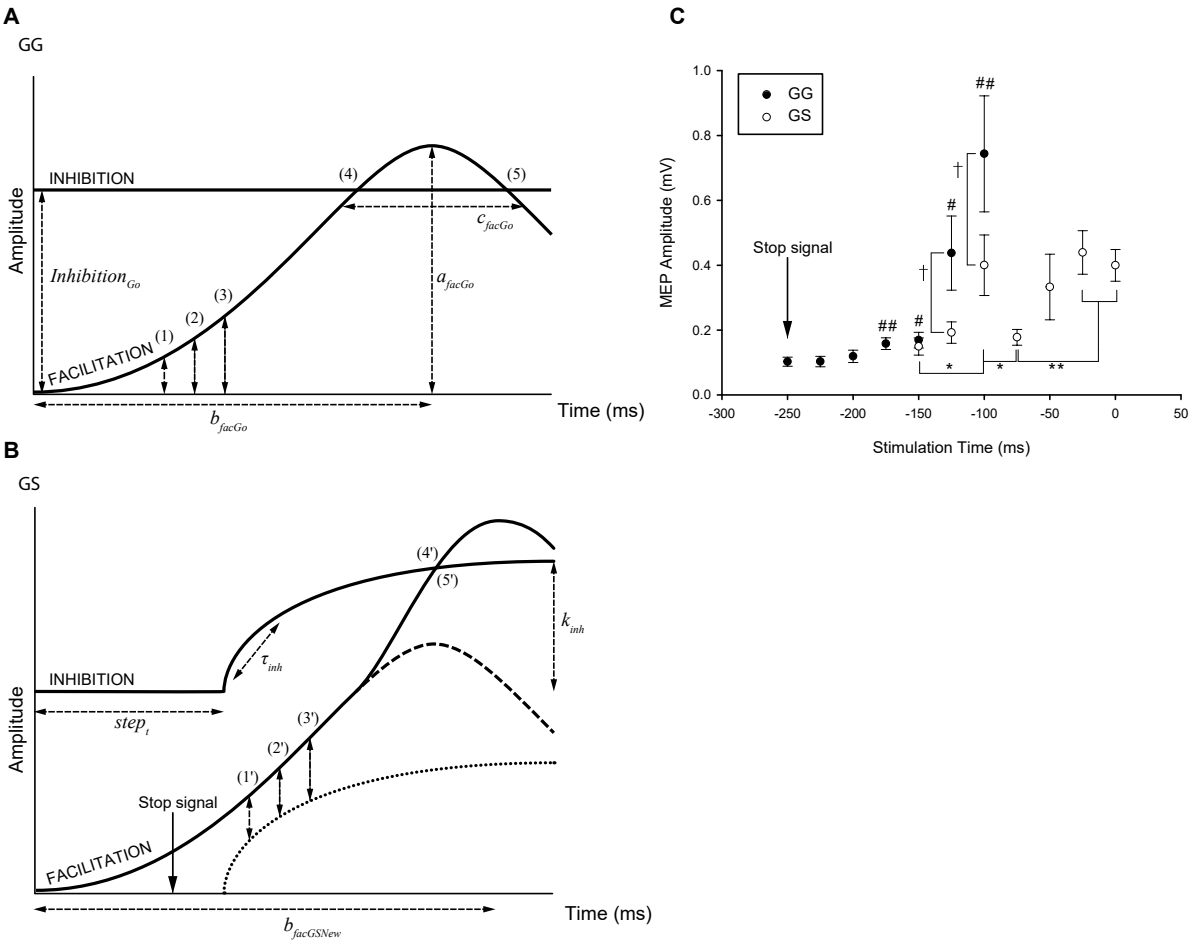

Figure 7.2 Experimental data used in the activation threshold model. Graphic depiction of the experimental data from Go and GS trials in MacDonald et al. (2014 Chapter 6) and the activation threshold model (ATM). A: The ATM accounted for increasing corticomotor excitability (CME) preceding movement execution on Go trials. Model parameters for facilitation and inhibition curves were simultaneously fitted to motor evoked potential (MEP) amplitude data collected 150 (1), 125 (2) and 100 ms (3) before the target, and electromyography (EMG) onset (4) and offset (5) times. B: The ATM accounted for modulation of CME following the stop signal on GS trials and the delayed initiation of muscle activity at a higher gain. Model parameters for the increased inhibition were fitted to MEP amplitudes 75 ($1'$), 50 ($2'$) and 25 ms ($3'$) before the target. Parameters for the secondary facilitatory input were fitted to EMG onset times ($4'$) and rates of onset ($5'$). C: Experimental results showing modulation of left first dorsal interosseous MEP amplitudes during Go (GG) and Partial (GS) trials. Stop signal was given at −250 ms on GS trials. Values are mean ± standard error. $\#P < 0.05; \#\#P < 0.001$ represent significant increases relative to baseline during GG trials. $\dagger P = 0.052$ denote trends. $*P < 0.05; **P < 0.01$ represent significant differences during GS trials. Reproduced from MacDonald et al. (2014 Chapter 6).

observation and prediction counts respectively. Minimizing a summed Chi-square across all variables allowed simultaneous fitting of MEP amplitude and EMG data.

Parameter values from the ATM (MacDonald et al., 2014 Chapter 6) were initially passed into the optimization function. To ensure convergence on a global minimum, values from points on either side of estimated values were also compared. Facilitation and inhibition curves for the ATM were determined across a time range spanning −400 to 200 ms relative to the target. A total of 100,000 trials were simulated with each set of parameters for all trial types. Given the time-intensive nature of the approach, simulations were run on a high-performance computing cluster operated by the University of Auckland Centre for e-Research as part of the New Zealand e-Science Infrastructure framework.

7.2.3 Go trials

MEP amplitudes and EMG data from Go trials (Figure 7.2A) were selected from all successful trials when TMS was delivered at 150, 125 and 100 ms prior to the target (N = 514). MEP amplitudes at these times depict the rise in corticomotor excitability (CME) above baseline prior to the lift response (Figure 7.2B). Facilitation curves were optimized to fit the observed MEP amplitudes. The level of inhibition was optimized to create intersection points with the facilitation curves to fit the experimentally obtained EMG onset and offset times.

To better capture the underlying neurophysiological processes associated with EMG onset/offset, the facilitation curve was modelled using a Gaussian base function (c.f., MacDonald et al. 2014 Chapter 6). The simple Gaussian function was derived as

$$Fac_{Go} = a_{facGo} e^{(-(time - b_{facGo})^2 / 2{c_{facGo}}^2)} \tag{7.2}$$

where a_{facGo} is amplitude, b_{facGo} is peak time, and c_{facGo} is curvature/width. As estimation of EMG offset times was noisy, offset times were generated based on the empirical average burst duration of 107 ms.

Means and standard deviations (SD) were estimated for each model parameter to account for: the speed of neuronal firing (curvature, c); the temporal and spatial summation of facilitatory inputs onto the alpha motoneuron pool (value at maximum, a); and the internal generation of an anticipated response to intersect the target (peak time, b). The activation threshold was set initially to reflect tonic inhibition in a resting state ($Inhib_{Go}$). For each simulated trial, parameter values were drawn randomly from the normal distribution with the currently estimated mean and SD. Predicted EMG onset and offset times reflect the times the facilitation curves cross and recross the tonic inhibition levels.

Since Gaussian curves have an infinite domain, a *threshold* value of 0.1 was set to calculate average time of onset (t_0) for the facilitation curves. A threshold value of 0.1 was chosen to denote a rise in CME above resting level, and reflects empirical MEP amplitudes (in mV). The parameter values producing the best fit were entered into the following equation.

$$t_0 = \sqrt{-2c_{facGo}^2 \log_e(threshold/a_{facGo})} + b_{facGo} \tag{7.3}$$

7.2.4 Partial trials

TMS and EMG data were available from 258 successful GS trials, where the left hand was required to respond and intercept the indicator with the target but the right hand needed to be inhibited. Compared to Go trials, TMS times were delayed by 100 ms on GS trials. The fitted stimulation times correspond to the suppression (−75 ms) and subsequent rise (−50 to −25 ms) in CME generating the delayed response in the left hand which was never cued to stop (Figure 7.2B).

Time points −150 to −100 ms (Figure 7.2B) illustrate the initial rise in MEP amplitude on GS trials, demonstrating participants were starting to initiate a bimanual response prior to the stop signal. Therefore, optimized Go parameters generated the initial facilitation curves on GS trials. However the rise appears less steep on GS trials, indicating the inhibitory process is starting to have an effect. The stop signal caused MEP suppression after 175 ms, conceptualized as nonselective inhibition acting on the bimanual response to raise the activation threshold. The elevated threshold must be surpassed in the left hand for a response to occur and is a candidate mechanism to explain the inevitable response delay.

Inhibition increased in response to a step input with size k_{inh} and time constant τ_{inh}

$$Inhib_{GS} = Inhib_{Go} + k_{inh}(1 - e^{-(time+step_t)/\tau_{inh}}) \tag{7.4}$$

where $step_t$ captured temporal variability in stop signal processing. Variables k_{inh} and τ_{inh} were not represented by normal distributions but rather by a single value for each trial given that variability in the Go process (facilitation), rather than the Stop process (inhibition), dictates behavioural outcome (Wiecki and Frank, 2013).

A second rise in CME occurs to generate the unimanual (left hand) response (Figure 7.2B). It was assumed that the neural facilitation mechanisms are comparable to the initial bimanual response i.e., $a_{facGo} = a_{facGSNew}$ and $c_{facGo} = c_{facGSNew}$. Mean and SD for $b_{facGSNew}$ were estimated for these secondary facilitation curves (equation 7.5). Facilitatory

inputs for the unimanual response were modelled as additive to the pre-existing bimanual facilitation at the level of the alpha motoneuron pool.

$$Fac_{GSNew} = Fac_{Go} + a_{facGSNew} e^{(-(time - b_{facGSNew})^2 / 2c_{facGSNew}{}^2)} \tag{7.5}$$

The resulting unimanual response is produced at a higher gain than the original (bimanual) response, and this is evident in an elevated rate of EMG onset (MacDonald et al., 2014 Chapter 6, 2012 Chapter 5) and greater force (Ko and Miller, 2011). This increased gain of the motor system was captured by the slope at the point of intersection with the activation threshold and has been estimated as 120 % of Go trials based on EMG data of MacDonald et al. (2014 Chapter 6).

7.2.5 Go trials in the stop-signal task

To compare bimanual Go distributions between the SST and ARI task, the ATM generated facilitation curves based on the RTs from (Majid et al. 2012, Experiment 2). For simplicity, RTs were transformed to the time scale used for the ARI task (SST go signal = −400 ms). Insufficient data existed to model Partial trials for the SST.

It was assumed that the fundamental neural characteristics of ballistic responses in the ARI task are comparable to the SST. Therefore optimized ARI values were used for $a_{facGoSST}$, $c_{facGoSST}$ and $Inhib_{GoSST}$. The mean and SD for $b_{facGoSST}$ were estimated based on the empirical RTs. The fitting process included the same steps, with the following exceptions:

1. Given that EMG onsets were not measured, we assumed a consistent electromechanical delay and the ATM parameters were optimized to match curve intersection points to behavioural RTs. Therefore the comparison of distribution patterns, but not absolute b values, is valid between tasks.

2. Experimental RT data were generated by randomly sampling from a right-skewed (Ratcliff, 1993; Verbruggen et al., 2013) skew normal distribution with a mean of 472 ms and SD of 49 ms (Majid et al., 2012).

Table 7.1 Model output for Go and Partial trials of the anticipatory response inhibition task.

Trial	Parameter	Estimated Value	Experimental Variable	χ^2	Summed χ^2
Go	a_{facGo} (mean)	2.576	MEPs 150 ms	0.005	0.012
	a_{facGo} (SD)	0.053	MEPs 125 ms	0.006	
	b_{facGo} (mean)	0.006	MEPs 100 ms	0.001	
	b_{facGo} (SD)	0.008	EMG onsets	$0.7x10^{-6}$	
	c_{facGo} (mean)	0.064	EMG offsets	$0.1x10^{-3}$	
	c_{facGo} (SD)	0.011			
	$Inhib_{Go}$ (mean)	1.798			
	$Inhib_{Go}$ (SD)	0.246			
	t_0	−0.157			
Partial	k_{inh}	1.887	MEPs 75 ms	0.822	1.392
	τ_{inh}	0.060	MEPs 50 ms	0.568	
	$step_t$ (mean)	0.133	MEPs 25 ms	0.003	
	$step_t$ (SD)	0.018			
	$b_{facGSNew}$ (mean)	0.108	EMG onsets	0.451	0.470
	$b_{facGSNew}$ (SD)	0.002	EMG rates	0.019	
	t_0	−0.055			

Estimated values for b and t_o reported in seconds relative to target. Experimental MEPs recorded at time in ms prior to target. SD: standard deviation; MEP: motor evoked potential; EMG: electromyography.

7.3 Results

7.3.1 Go trials

The rise in MEP amplitudes and distribution of EMG onsets and offsets for Go trials were reproduced by the ATM. Best-fitting parameters and Chi-square goodness of fit are provided in Table 7.1. Figure 7.3A illustrates 100 simulated trials with the optimized parameters. The model accurately captured the tight (small SD) distribution of onset times (Chi-square = 0.7×10^{-6}) that is a characteristic feature of EMG and LT data in the ARI task (Figure 7.1A, right). Average predicted onset time for facilitation curves was −157 ms, consistent with the experimentally observed rise in CME 175 (MacDonald et al., 2014 Chapter 6) to 150 ms (Coxon et al., 2006) before the target.

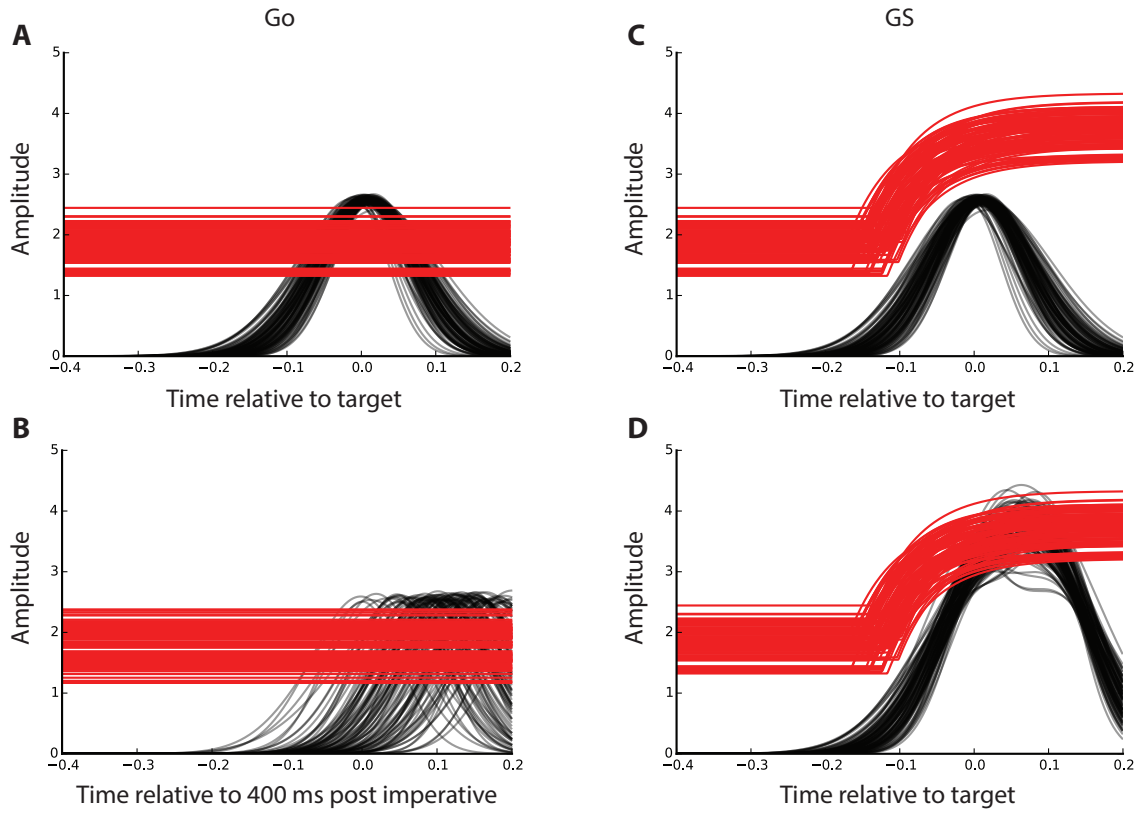

Figure 7.3 Model results for Go and GS trials. 100 simulated Go (A&B) and GS (C&D) trials using best fitting parameters produced by the model. A: The anticipatory response inhibition (ARI) task necessitates a tight distribution of bimanual facilitatory drive. B: Bimanual reaction times in the stop-signal task are captured with a much wider distribution of facilitatory drive. C: Facilitatory input for the Go response on ARI trials is unable to surpass the elevated activation threshold following nonselective inhibition of the bimanual response. D: A secondary facilitatory input is required to summate excitatory drive to pass the elevated threshold and generate a unimanual left hand response. Red: inhibitory input (activation threshold); black: facilitatory input.

7.3.2 Partial trials

Bimanual inhibition

The same bimanual facilitation curves derived for Go trials were used for GS trials. The temporal modulation of CME on GS trials was successfully recreated by increasing the activation threshold. The best fitting parameters and Chi-square values are provided in Table 7.1, and 100 simulated trials with these parameters are shown in Figure 7.3C. $step_t$ indicated that neural braking of the bimanual movement began on average 117 ms after the stop signal presented at −250 ms. Increased inhibition resulted in none of the simulations crossing threshold. Crucially, this model would incorrectly predict no response on successful GS trials. Initial facilitation curves that were suitable for simulating Go responses, were insufficient to cross the threshold on GS trials. Therefore an additional facilitatory input was needed to model the observed behaviour.

Unimanual facilitation

The ATM was able to capture EMG onsets of GS trials only with the inclusion of a second facilitation phase. The best fitting parameters and corresponding Chi-squares for the new facilitation curve are provided in Table 7.1. Figure 7.3D shows the combined facilitatory inputs passing the elevated activation threshold, thereby generating a response. The model also successfully characterized the elevated gain of the delayed partial response. Average predicted onset time (t_0) for the second facilitation phase was −55 ms i.e., *after* nonselective inhibition at −75 ms. This second facilitatory input can be conceptualized as a newly programmed left hand response, subsequent to the cancellation of the default bimanual (Go) response.

7.3.3 Go trials in the stop-signal task

The ATM successfully captured the distribution pattern of RTs from Majid et al. (2012) on the SST, as indicated by very low Chi-square values. The best fitting values for $b_{facGoSST}$ are reported in Table 7.2 and 100 simulated trials with these values are shown in Figure 7.3B. Figure 7.3A and B contrast the distribution of the Go responses between the ARI task and SST.

Table 7.2 Model output for Go trials of the stop-signal task.

Trial	Parameter	Estimated Value	Experimental Variable	χ^2
Go	$b_{facGoSST}$ (mean)	0.129	RTs	0.001
	$b_{facGoSST}$ (SD)	0.048		

Estimated values for b reported in seconds relative to target. SD: standard deviation; RT: reaction time.

7.4 Discussion

A computational model of neuronal activity was put forward to explain the dynamics of RI. The ATM successfully fitted neural excitability (MEP) and muscle activity (EMG) data observed empirically during execution and partial cancellation of movement. The ATM demonstrated that MEP suppression on Partial trials can be explained by nonselective inhibition. This inhibition raises an activation threshold to a level that cannot be reached by the preprepared Go response. In support of our hypothesis, additional facilitatory input was required to account for the delayed response executed at a higher gain. The ATM can also accommodate the much wider Go distribution of the SST compared to the ARI task. There are several reasons why the ATM provides a framework for understanding why partial RI may occur without delay on the SST, but not the ARI task.

The ATM captures the tight temporal distribution of excitatory drive for the required bimanual responses of the ARI task, and the broad distribution of responses in the SST. The anticipatory nature of the ARI task allows participants to perform Go trials very accurately (Zandbelt et al., 2013; Zandbelt and Vink, 2010). Participants begin each trial in this task intending to make a (default) bimanual response to stop both indicators at the stationary target. The standard deviation for the Go response for young adults is normally 20 – 30 ms (Coxon et al., 2007) and was 8 ms for the EMG distribution in our model. The ATM provides computational evidence that it is not possible to produce the delayed response on Partial trials by merely sampling from the later part of the Go distribution (c.f. Xu et al. 2014). The tightly distributed execution process signifies that response delays in ARI tasks are immune to such "sampling bias". This important difference means that the ARI task allows a more valid examination of the response delay during pure (reactive) RI than the SST.

The ATM reflects neural activity underlying the bimanual response. Average response asynchrony on Go trials for the ARI task is typically 3 – 8 ms (Coxon et al., 2007; MacDonald et al., 2012 Chapter 5). Regardless of muscle pairing, movement components are integrated

together into a unitary response during movement preparation (Ko and Miller, 2011; MacDonald et al., 2014 Chapter 6), indicative of transient conceptual binding (Wenderoth et al., 2009). Functional coupling between hands is especially strong when homologous muscles are activated simultaneously (Heuer, 1993; Kelso, 1984), as in the experimental data used in this study. The modulation of neural input captured by the model on Go trials therefore accurately represents the generation of a unitary response which is anticipated as the default on every trial.

On Partial trials, the stop cue introduces response conflict as the default response is no longer appropriate. The subsequent modulation of CME on these trials can be explained solely by an increase in inhibition (i.e. the activation threshold). The increased threshold may explain the empirical suppression of CME that occurs 100 – 200 ms after the stop signal (Cai et al., 2012; Coxon et al., 2006; Hoshiyama et al., 1997; MacDonald et al., 2012 Chapter 5; Majid et al., 2012; Yamanaka and Nozaki, 2013). In the presence of conflict, the presupplementary motor area (preSMA) activates the subthalamic nucleus via the nonselective inhibitory 'hyperdirect' basal ganglia pathway to rapidly terminate the prepotent response (Coxon et al., 2009; Frank, 2006; Isoda and Hikosaka, 2007, 2008; Wiecki and Frank, 2013). The functional role of this nonselective inhibition is similar to that described in the neural network model for an antisaccade task (Frank, 2006; Wiecki and Frank, 2013). Elevation of the threshold may represent the recruitment of an override mechanism during response conflict to suppress the default response and to enable executive control to take over. The empirical data show, and the model supports the contention, that nonselective inhibition suppresses all motor representations of the default (unitary) bimanual action.

Partial cancellation of multi-component movement involves task switching. Frank (2006) proposed that a raised threshold allows the switch from a prepotent to a controlled response to meet new task demands in the antisaccade task. On a successful antisaccade trial, an obvious switch in movement direction is seen. The ATM demonstrates that behaviour during partial movement cancellation can be explained by a comparable switching process, albeit less obvious: from a bimanual to unimanual response. The dorsolateral prefrontal cortex (Koval et al., 2011; Mansouri et al., 2007, 2009) and preSMA (Isoda and Hikosaka, 2007; Nachev et al., 2005, 2007; Rushworth et al., 2002) are activated during response conflict and facilitate a switch from a prepotent response to those requiring higher levels of cognitive control. The preSMA is activated during partial movement cancellation (Coxon et al., 2009), potentially signalling the switch from a (prepotent) bimanual to (controlled) unimanual response.

A second facilitatory input is required to meet Partial trial demands. A further argument against Partial responses being from the later part of the Go distribution (c.f. Xu et al. 2014) is that the neural activation for Go responses is unable to reach the elevated threshold, albeit according to the underlying assumptions of the model. An additional facilitatory process is recruited to add to and reshape excitatory drive. The second facilitatory component of the ATM may also explain evidence of lateralized event related potentials 200 – 300 ms after a partial stop cue (Yamanaka, 2014). The additional excitatory drive follows nonselective inhibition to generate a new (unimanual) response rather than the partial continuation of a previous response.

A participant's stop signal reaction time (SSRT) reflects the efficacy and latency of the inhibitory process during RI. SSRT is calculated as the difference between mean response time on Go trials and the stop signal resulting in 50% successful inhibition. The interpretation of the SSRT is based on the 'horse-race' model (De Jong et al., 1990; Logan and Cowan, 1984). The horse-race model assumes independence of the facilitatory and inhibitory processes. Cancelling one response and initiating a new one does not violate this independence assumption. A 'restart' model simulates a transient stopping, or pausing, of the prepared synchronous response, followed by restarting just one component of the *same* response (Xu et al., 2014). Xu et al. correctly state that a 'restart' model is inconsistent with the horse-race model as independence between the Go and Stop process is violated. This is in contrast to the ATM which conceptualizes cancellation of the prepared synchronous response, uncoupling of response components and switching to the initiation of a *new* (unimanual) response. The distinction between 'restarting' and 'initiating a new' response is important in the context of the horse-race model and interpreting SSRT values.

The ATM also successfully captures behaviour during complete cancellation of a multi-component response. If a second facilitatory drive is not present, the elevated threshold is not reached for either component and the ATM predicts no movement is generated. This behavioural outcome constitutes success on a trial requiring complete cancellation. Interestingly, the ATM can also recreate the experimental observation that participants (more often older adults) occasionally suppress their bimanual response following a partial stop cue, but are unable to generate a unimanual response within the time constraints. This may result from the inability to uncouple bimanual components via rapid recruitment of neurons within the supplementary motor area (Meyer-Lindenberg et al., 2002; Serrien et al., 2002) and/or sufficiently summate facilitatory drive.

The simulations indicated that the main difference between the ARI and SST is in the distribution of Go responses. In SSTs like those employed in Majid et al. (2012) and Xu et

al. (2014) (Figures 1B&C), a choice paradigm results in right skewed response distributions (Ratcliff, 1993; Verbruggen et al., 2013) with a larger standard deviation of up to 80 ms (Cai et al., 2011). Across studies, average RTs are typically in the range of 300 – 600 ms. Strategic slowing can further delay RTs in the SST (Smittenaar et al., 2013). Wider, right skewed RT distributions could make it difficult to determine whether responses are genuinely delayed on Partial trials, or from a Go response that was slow to begin with (Xu et al., 2014). We contend that the rate of EMG onset on Partial trials obtained in the SST may resolve this uncertainty. The novel prediction from the ATM is that EMG gain on Partial trials will not differ from Go trials for the SST, as it does for the ARI task, because the distribution of Go RTs negate the requirement for a second facilitatory drive.

The present study has some limitations. The model assumptions outlined in the Methods dictate the characteristics and performance of the model. While the underlying assumptions were based on valid neurophysiological mechanisms, they should nonetheless be kept in mind when interpreting the model results. There is also always a risk of over-fitting optimization models to produce parameters that precisely match data from only one experiment, thus limiting the usefulness of the model. One solution is to do cross-validation, but this relies on having sufficient amounts of data given the stochastic nature of our model. We therefore opted for a purely descriptive approach in the first instance. The ATM is unable to differentiate between neural inhibition occurring at cortical, subcortical and spinal levels. It represents a system-wide inhibitory process. However this is sufficient to examine whether a nonselective model is able to capture empirical data and can also be considered a strength of the model; the ATM is able to capture the combined influence of all sources of inhibition within the motor system upstream of the alpha motoneuron pool.

Further investigations of the ATM might examine other and future experimental findings. For example, the neural mechanisms behind temporal modulation of CME during unsuccessful Partial trials. The ATM may also offer new testable hypotheses such as how RI is affected during healthy ageing or with dopaminergic dysregulation, such as that occurring with Parkinson's disease.

Chapter 8

Dopamine Gene Profiling Can Predict Impulse Control and Effects of Dopamine Agonist Ropinirole

This experiment has been submitted for peer review.

Abstract

Background: Dopamine agonists can impair inhibitory control and cause impulse control disorders for those with Parkinson's disease, although mechanistically this is not well understood. We hypothesized that the extent of such drug effects on impulse control is related to specific dopamine gene polymorphisms in human subjects. **Objective**: This double-blind, placebo-controlled study aimed to examine the effect of single doses of 0.5 mg and 1.0 mg of the dopamine agonist ropinirole on motor and cognitive impulse control in healthy adults of typical age for Parkinson's disease onset. **Methods**: Motor impulse control was measured by stop signal reaction time (SSRT) on a response inhibition task and cognitive impulsivity by an index of impulsive decision making on the Balloon Analogue Risk Task. A dopamine genetic risk score quantified basal dopamine neurotransmission from the influence of five genes: catechol-O-methyltransferase (COMT), dopamine transporter (DAT), and those encoding receptors D1, D2 and D3. **Results**: With placebo, motor and cognitive impulse control was better for the high versus low genetic risk score groups. Ropinirole modulated impulse control in a manner dependent on a participant's genetic risk score. For the lower score group, both doses improved response inhibition (decreased SSRT) while the lower dose reduced impulsiveness in decision making. Conversely, the higher score group showed

a trend for worsened response inhibition on the lower dose while both doses increased impulsiveness in decision making. **Conclusion**: Dopaminergic genotyping in conjunction with baseline measures of motor and cognitive impulse control may identify people at risk of developing impulse control disorders on dopamine agonists.

8.1 Introduction

Impulse control is required to evaluate the potential consequences of a decision, modify behaviour and suppress undesirable actions. Dopamine is necessary for impulse control whereby dysfunctional levels of frontostriatal dopamine are associated with worse control (Pattij and Vanderschuren, 2008). People with Parkinson's disease (PD) are commonly prescribed dopamine agonist medication and approximately 20 % develop impulse control disorders (ICDs) as a result (Weintraub, 2009; Weintraub et al., 2006). It has been suggested that difficulty performing executive tasks requiring high levels of impulse control may signal an increased risk for the development of ICDs (Poletti and Bonuccelli, 2012). However the mechanisms of susceptibility to ICD development are not well understood.

One working hypothesis is that ICDs result from a hyperdopaminergic state of the mesocorticolimbic system in early PD, which is then exacerbated by dopaminergic medication. Dopamine agonists augment depleted nigrostriatal dopamine but a lack of network specificity consequently increases dopamine within the relatively preserved medial prefrontal cortex (PFC) and ventral striatum (Cools, 2006; Sawamoto et al., 2008; Vaillancourt et al., 2013). Subsequent dopamine dysregulation within the mesocorticolimbic system may cause deviation from optimal function, adversely influencing motor and cognitive control.

Variation in dopamine-regulating genes can influence impulse control (Nandam et al., 2013; Nemoda et al., 2011) and may affect response to dopaminergic medication. For example a dopamine gene score can predict the effect of Levodopa on motor learning in healthy participants (Pearson-Fuhrhop et al., 2013), based on the effect of polymorphisms within five genes that affect dopamine neurotransmission: catechol-O-methyltransferase (COMT), dopamine transporter (DAT), and DRD1, DRD2 and DRD3 which regulate the D1, D2 and D3 receptors. Interestingly, all of these genes have been implicated in impulse control.

To investigate why ICDs are developed by some people, but not others, we examined how dopamine agonist drugs interact with dopamine gene polymorphisms to influence impulse control. The present study was conducted with healthy adults spanning the typical age of onset for PD. Participants were administered ropinirole or placebo and one hour later

performed computerized tasks to measure motor and cognitive impulse control. We hypothesized that impulse control would be modulated by ropinirole, and that this would occur in a manner affected by dose and the participant's genetically determined dopamine profile. Specifically, we predicted that ropinirole would improve motor and cognitive impulse control in participants with lower basal dopamine neurotransmission i.e. lower dopamine genetic risk scores (GRS). Conversely, we predicted that ropinirole would worsen motor and cognitive impulse control in participants with higher basal dopamine neurotransmission (higher GRS). Global cognitive function was not expected to be affected by ropinirole and served as a control measure.

8.2 Methods

8.2.1 Participants

Healthy adults of typical age for Parkinson's disease onset were screened to determine eligibility for the study. Inclusion criteria were age 40 – 70 yr old, no neurological or cognitive impairment, nonsmoker, normal or corrected-to-normal vision and no contraindications to ropinirole or domperidone. The study was approved by the University of Auckland Human Participant Ethics Committee and Health and Disability Ethics Committee and written informed consent was obtained from each participant.

8.2.2 Pharmacological intervention

Participants were orally administered a single dose of placebo, 0.5 mg or 1.0 mg of the dopamine agonist ropinirole in three experimental sessions with a double-blind, randomized, counterbalanced design. A dose of 1.0 mg was chosen as it is around the commonly prescribed daily therapeutic starting dose for PD (Matheson and Spencer, 2000), and this dose has been tolerated in studies with healthy participants (Acton and Broom, 1989; Monte-Silva et al., 2009). A dose of 0.5 mg was included to investigate the dose-dependency of ropinirole effects. Overall these two doses are low compared to replacement doses for PD. The experimental sessions were spaced at least one week apart to prevent cumulative drug effects. To minimize drug-induced systemic side effects of ropinirole, 20 mg of domperidone was administered orally and participants refrained from caffeine and alcohol on the days of testing.

8.2.3 Experimental protocol

Prior to the first experimental session, all participants completed the Beck Depression Inventory (BDI-II) (Beck et al., 1996), Barratt Impulsiveness Scale (BIS-II) (Patton et al., 1995), and were assessed by a research nurse on the motor section of the Unified Parkinson's Disease Rating Scale (all available in Appendix).

Each experimental session began with administration of domperidone and ropinirole/placebo (after at least an hour fasting) one hour before beginning the computerized impulse control tasks. This timing interval coincides with peak ropinirole blood concentrations (Brefel et al., 1998). See Section 8.5 (Supplementary material) for additional task specifics.

Anticipatory response inhibition (ARI) task

The goal of the task was to lift the index fingers in time to stop rising indicators at a fixed target on a computer display (Figure 8.1A). Both indicators "filled" upward at equal rates, reaching the target line in 800 ms and terminating their rise in 1000 ms, unless stopped prior by releasing either or both switches. Each trial commenced after a variable delay. The default response on Go trials (GG, 66 % of trials) required the release of both switches in time to stop the indicators at the target. The remaining $1/3^{rd}$ of trials were Stop trials, where one or both indicators stopped automatically before reaching the target, cueing the participant to inhibit responding with the corresponding digit(s). There were three types of Stop trials: Stop Both (SS), when both indicators stopped automatically, and Partial Stop trials Stop Left - Go Right (SG) and Go Left - Stop Right (GS). For each Stop trial type the indicator was initially set to stop at 500 ms. A staircase procedure adjusted the indicator stop time dynamically throughout the task in 25 ms increments to convergence on a 50 % success rate. Electromyography (EMG) data were recorded from bilateral first dorsal interosseous (FDI) muscles.

Balloon analogue risk task (BART)

To perform the BART participants used a mouse to click on an icon that read 'Pump up the balloon' to incrementally inflate a red balloon on a laptop screen (Figure 8.1B). Each press would either i) incrementally inflate the balloon, causing a visual (and auditory) increase in balloon size, adding 5 cents to the monetary reward or ii) burst the balloon (with realistic visual and auditory effect), resulting in no money earned for that balloon. At any time the participant could click a 'Collect $$$' icon to end the trial and the current amount would

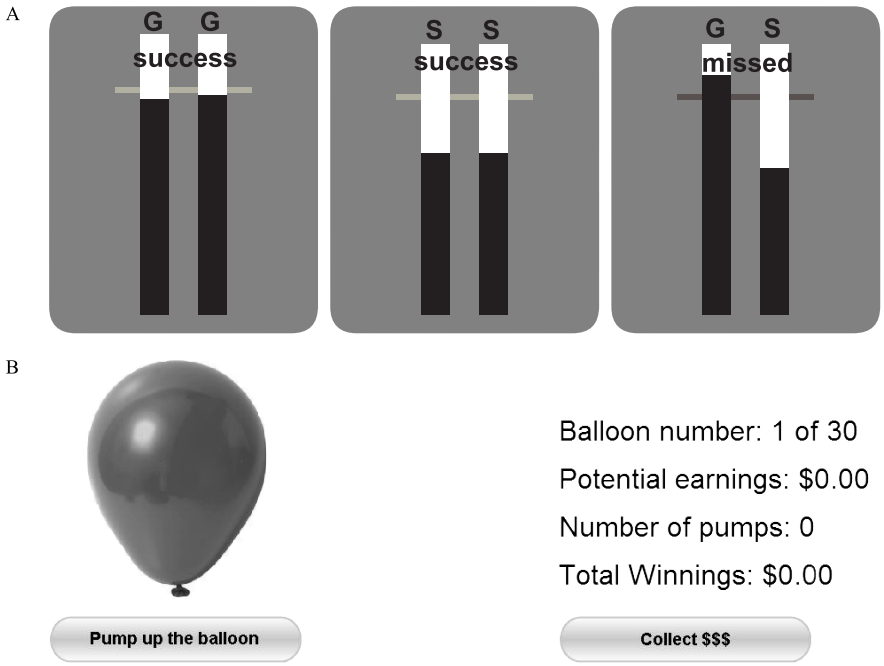

Figure 8.1 Impulse control tasks. A: Visual display for the anticipatory response inhibition task showing successful Go (GG, left), Stop Both (SS, middle) and Partial Stop trial (Go Left – Stop Right, GS, right). B: Visual display at the start of the balloon analogue risk task.

add to their total along with reinforcing auditory feedback. Each balloon was set to explode in a randomly determined manner anywhere from the first pump to filling the entire screen. Successive pumps resulted in increasing risk but diminishing returns. Participants were told that they would be given a monetary reward equivalent to the final money counter. Participants completed a single block of 30 trials.

Central nervous system vital signs (CNSVS) test battery

The CNSVS consisted of seven tests examining composite memory, verbal memory, visual memory, working memory, processing speed, executive function, reaction time, complex attention, cognitive flexibility and sustained attention. The four-part continuous performance test was added to six of the core tests (excluding the finger tapping test). Cognitive domain scores were computed as normalized standard scores (mean of 100) representing raw scores relative to age-matched normative data. An overall neurocognitive index (NCI) score was the average of standard scores for composite memory, reaction time, complex attention and cognitive flexibility.

8.2.4 Genotyping

Genotyping was performed (see Supplementary material Section 8.5) for DRD1 rs4532, DRD2 rs1800497, DRD3 rs6280 and COMT rs4680 single nucleotide polymorphisms and the 40 base pair variable number of tandem repeats (VNTR) in the untranslated regulatory region of the DAT gene (rs28363170). A participant's GRS represented the additive effects of the five polymorphisms affecting dopaminergic neurotransmission, as has been described and validated previously in relation to motor learning, Levodopa effects and cortical plasticity (Pearson-Fuhrhop et al., 2013), and more recently depression (Pearson-Fuhrhop et al., 2014). Each gene was initially equally scored based on the absence (0) or presence (1) of polymorphic alleles that increase dopamine neurotransmission (Table 8.1). Dopamine GRS could range from 0 (lowest basal dopamine neurotransmission) to 5 (highest neurotransmission). If an effect of GRS was present, subsequent analyses investigated a weighted GRS generated by substituting each single gene score into the model. We also investigated removing each gene sequentially in order of lowest weighting, to determine their contributions to the composite score (Pearson-Fuhrhop et al., 2013).

Table 8.1 Occurrence of polymorphisms and values for genetic risk score.

	DRD1 rs4532			DRD2 rs800497			DRD3 rs6280			DAT rs28363170			COMT rs4680		
	A/A	A/G	G/G	Glu/Glu	Glu/Lys	Lys/Lys	Ser/Ser	Ser/Gly	Gly/Gly	9/9	9/10	10/10	Val/Val	Val/Met	Met/Met
Score	0	1	1	1	0	0	0	1	1	1	1	0	0	1	1
Predict freq	0.29	0.50	0.14	0.68	0.29	0.03	0.33	0.49	0.18	0.49	0.42	0.09	0.28	0.50	0.23
Actual freq	0.21	0.64	0.14	0.68	0.29	0.04	0.36	0.43	0.21	0.43	0.54	0.04	0.25	0.54	0.21

DAT 11 alleles scored as 10 alleles. DRD1: dopamine receptor D1; DRD2: dopamine receptor D2; DRD3: dopamine receptor D3; DAT: dopamine transporter; COMT: catechol-O-methyltransferase; Lys: lysine; Glu: glutamic acid; Ser: serine; Gly: glycine; Val: valine; Met: methionine.

8.2.5 Dependent measures

ARI task

For Stop trials, stop signal reaction time (SSRT), indicator stop time (staircased to 50 % success), and percentage of successful trials were determined. SSRT on Stop Both (SS) trials (integration method (Logan and Cowan, 1984; Verbruggen et al., 2013) was the primary dependent measure for this task as it signifies the efficacy and latency of the inhibitory process in pure response inhibition (RI).

BART

The average number of button presses was calculated for 'collect' trials following a balloon burst and for 'collect' trials following no balloon burst. To calculate the effect of positive reinforcement the difference between the two averages was normalized to the mean number of presses on collect after burst trials. The effect of negative reinforcement was normalized to collect after collect trials. Proportions further from zero indicate greater behaviour modification as a result of reinforcement on a trial-by-trial basis and are also indicative of more impulsive decision making because behaviour is too readily modified.

CNSVS test battery

The primary dependent measure was NCI. Higher values represent better global cognitive function. Working memory was calculated separately from correct – incorrect responses on the four-part continuous performance test.

8.2.6 Statistical analysis

All dependent measures were analyzed with a mixed-effects linear regression model in SPSS Statistics (IBM Corporation, version 21). Each dependent measure was modelled as a function of Dose (PLA, ROP 0.5, ROP 1.0), Genetic Risk Score (GRS), Dose x GRS interaction and Age. Measures from the CNSVS were standardized scores so Age was removed from the model when predicting these dependent variables. A subject-specific random effect factor (μ) accounted for between-subject variation and all other effects ($\beta_0 - \beta_4$) were fixed.

$$y = \beta_0 + \beta_1(Dose) + \beta_2(GRS) + \beta_3(Dose \times GRS) + \beta_4(Age) + \mu \tag{8.1}$$

Table 8.2 Participant demographics and clinical assessment scores.

Age (y)	60 (44 – 75)
Weight (kg)	73 (52 – 96)
Gender	15F / 13M
Ethnicity	27 Caucasian, 1 Maori
BIS–11	59 (38 – 77)
UPDRS (III)	4 (0 – 14)
BDI–11	3 (0 – 15)
MoCA	28 (26 – 30)

Values are mean (range) unless otherwise noted. BIS: Barratt Impulsiveness Scale (max 120); UPDRS (III): Unified Parkinson's Disease Rating Scale motor scores (max 56); BDI: Beck Depression Inventory (max 63); MoCA: Montreal Cognitive Assessment (max 30).

To explore single-gene relationships, each single-gene score in Table 8.1 was independently inserted into the model in place of GRS. Model degrees of freedom were calculated using the Satterthwaite method.

Chi-squared tests were used to assess Hardy-Weinberg equilibrium for each gene. The criterion for statistical significance was $\alpha = 0.05$. All results are reported as group means ± standard error (SE).

8.3 Results

Thirty-seven participants were screened, 33 recruited and 30 completed all experimental sessions. Two withdrew due to drug-induced side effects (nausea: 1, dizziness: 1) and one due to scheduling problems. Generally, the medications were tolerated with the following exceptions for ropinirole (nausea: 2, vomiting: 1, drowsiness: 5) and domperidone (dry mouth: 1, headache: 1). Two participants were unable to adhere to one or more protocols. Results are reported for the remaining 28 participants (see also Supporting Material Table 8.3, 8.4) and their demographic details and clinical assessment scores are presented in Table 8.2. All genes were in Hardy-Weinberg equilibrium ($0.12 < P < 0.89$, Table 8.1). The distribution of dopamine GRS is shown in Figure 8.2A. Scores of 2 and 3 were grouped (Low, N = 12) as were scores of 4 and 5 (High, N = 16). No participants had the rare GRS of 0 or 1.

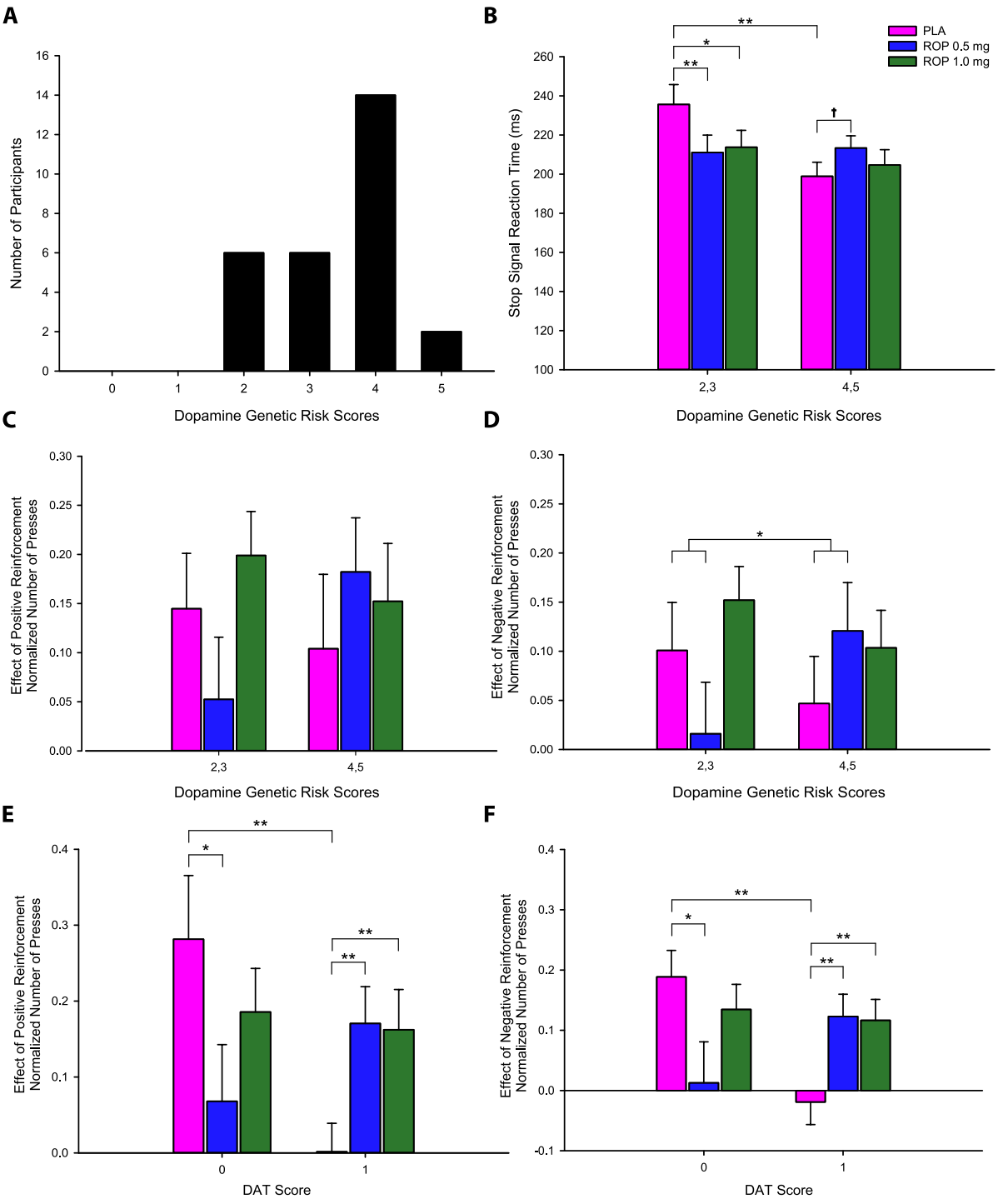

Figure 8.2 Dopamine genetic risk scores and associated performance on the impulse control tasks. A: Distribution of genetic risk scores. Stop signal reaction times (B) and impulsive decision making (C-F) for low versus high neurotransmission. PLA: placebo; ROP: ropinirole; DAT: dopamine transporter. $\dagger P = 0.072$, $* P < 0.05$, $** P < 0.01$.

8.3.1 ARI task

Go and Partial Stop trials were performed as expected (Supporting Information). Stop Both trials were performed as expected with a success rate just above 50 % (58.6 ± 1.8 %). The model predicted that SSRT for SS trials was dependent on Dose ($P = 0.025$), the Dose x GRS interaction ($P = 0.029$) and the intercept ($\beta_0 = 243$ ms, $t_{27} = 7.2, P < 0.001$). Predicted SSRT decreased by 66 ms with 0.5 mg ROP ($t_{27} = -2.6, P = 0.013$) and by 61 ms with 1.0 mg ROP ($t_{27} = -2.4, P = 0.021$). The pattern of interaction results for predicted SSRT is evident in the sample data (Figure 8.2B). Post hoc tests revealed participants with a low GRS had longer SSRTs at baseline (236 ± 10 ms) than those with high scores (199 ± 7 ms, unpaired t test: $t_{26} = 3.0, P = 0.008$). SSRT decreased with ROP for low GRS (paired t tests: 0.5 mg, 211 ± 9 ms, $t_{11} = -2.8$, $P = 0.008$; 1.0 mg, 214 ± 9 ms, $t_{11} = -2.2$, $P = 0.025$) but tended to increase with ROP for high scores, especially at the lower dose (paired t tests: 0.5 mg, 213 ± 6 ms, $t_{15} = 1.5$, $P = 0.072$; 1.0 mg, 205 ± 8 ms, $t_{15} = 0.6$, $P = 0.280$).

Entered into the model separately, no single gene significantly interacted with ROP to predict SSRT (Dose x Gene interactions: $0.06 < P < 0.64$). DRD3 had the highest weighting (0.32), then DAT (0.25), DRD1 (0.22), COMT (0.14), DRD2 (0.08). The Weighted GRS produced very similar results with a fixed effect of Dose ($P = 0.010$) and Dose x Weighted GRS interaction ($P = 0.012$). Removing the lowest-weighted gene DRD2 from the Weighted GRS had a negligible effect on the Dose x Weighted GRS interaction ($P = 0.011$). Removing COMT weakened the interaction ($P = 0.029$) and removing DRD1 produced no Dose x Weighted GRS interaction ($P = 0.159$). At least four genes were necessary to explain the Dose x GRS interaction for ARI task (SSRT) performance.

8.3.2 BART

Using the unweighted GRS to predict effect of negative reinforcement, there was a fixed effect of Dose ($P = 0.024$) with the predicted number of presses after burst trials decreasing less with 0.5 mg ROP ($t_{27} = -2.3$, $P = 0.027$) than PLA, with no difference between 1.0 mg ROP and PLA ($t_{27} = 0.3$, $P = 0.786$). There was a Dose x GRS interaction ($P = 0.031$, Figure 8.2D). Participants with a low GRS made fewer impulsive decisions on 0.5 mg ROP (PLA: 0.10 ± 0.05; ROP: 0.02 ± 0.05) whereas those with a high GRS made more (PLA: 0.05 ± 0.05; ROP: 0.12 ± 0.05), although these differences did not reach significance in post-hoc testing ($P > 0.17$). A similar pattern of means were observed for positive reinforcement (Figure 8.2C), but with no fixed effect of Dose ($P = 0.091$) or Dose x GRS interaction ($P = 0.107$).

Entered into the model separately, the DAT polymorphism interacted with ROP to predict an effect of both negative (Dose x DAT Score interaction: $P = 0.002$, Figure 8.2F) and positive reinforcement (Dose x DAT Score interaction: $P = 0.006$, Figure 8.2E). No other gene could predict this interaction (Dose x Gene interactions: $0.27 < P < 0.96$). At baseline participants with a DAT score of 0 (DAT_0, lower dopamine neurotransmission, N = 12) made more impulsive decisions than DAT_1 participants (higher dopamine transmission, N = 16) after negative (DAT_0: 0.19 ± 0.04; DAT_1: 0.02 ± 0.04, unpaired t test: $t_{26} = 3.6$, $P = 0.001$) and positive reinforcement (DAT_0: 0.28 ± 0.08; DAT_1: 0.00 ± 0.04, unpaired t test: $t_{26} = 3.0$, $P = 0.008$). DAT_0 participants *reduced* impulsivity with 0.5 mg ROP (paired t tests: both reinforcement $t_{11} < -1.9$, $P < 0.044$) but not 1.0 mg ROP (paired t tests: both $P > 0.176$). Conversely, DAT_1 participants *increased* impulsivity with 0.5 mg (paired t tests: both reinforcement $t_{15} > 2.6$, $P < 0.009$) and 1.0 mg ROP (paired t tests: both $t_{15} > 3.7$, $P < 0.002$).

DAT had the highest weighting (0.60) in the Weighted GRS, then DRD2 (0.24), DRD3 (0.08), COMT (0.05), DRD1 (0.03). The Weighted GRS produced a fixed effect of Dose ($P = 0.037$) and Dose x Weighted GRS interaction ($P = 0.017$) for positive reinforcement, and the effect of Dose ($P = 0.008$) and Dose x Weighted GRS interaction ($P = 0.003$) for negative reinforcement. Removing the lowest weighted genes in order (DRD1, COMT, DRD3) had a negligible effect on the Dose x Weighted GRS interaction for negative (all $P < 0.004$) and positive reinforcement (all $P > 0.015$). Therefore, the DAT polymorphism alone accounted for the Dose x GRS interaction for BART performance.

8.3.3 CNSVS test battery

The predicted NCI score was not dependent on Dose or a Dose x GRS interaction. There was a significant intercept ($\beta_0 = 112$, $t_{27} = 18.6$, $P < 0.001$) and a fixed effect of GRS ($P = 0.022$). However there was no systematic increase or decrease in NCI as a function of GRS ($t_{27} = -1.5$, $P = 0.130$) and post-hoc tests indicated no difference in NCI between GRS. Predicted working memory was not dependent on Dose, GRS, or a Dose x GRS interaction (all $P > 0.065$), only the intercept ($\beta_0 = 115$, $t_{27} = 9.1$, $P < 0.001$).

8.4 Discussion

This study produced several novel findings. Motor and cognitive impulse control of healthy adults differed between those with high and low levels of basal dopamine neurotransmission, as determined by a GRS. A single administration of ropinirole interacted with genetic varia-

tions in dopamine transmission to affect motor and cognitive impulse control in predictable ways. In support of our hypothesis, RI improved for those with a lower GRS when given a single dose of ropinirole. Whereas a polygenic risk score was necessary to account for motor impulse control with the ARI task, the DAT polymorphism alone determined cognitive impulse control with the BART. Ropinirole decreased impulsive decision making for those with the lower DAT score and increased it for those with the higher DAT score. Ropinirole had no effect on global cognitive function so the results appear to be specific to impulse control.

Consistent with previous studies, we propose an inverted-U relationship between dopamine levels and impulse control (Congdon et al., 2009; Farrell et al., 2012). Figure 8.3 illustrates how the GRS may determine a person's starting position on the curve. People with higher scores have near optimal levels of dopamine for motor RI whereas people with lower scores sit lower on the curve. In the present study this was verified by faster SSRTs for participants with a higher GRS. Adults with more optimal levels of dopamine neurotransmission also demonstrate greater neural activation within the RI network (Congdon et al., 2009). Interestingly, Congdon and colleagues did not find an effect on SSRT when contrasting polymorphisms within COMT and DAT individually. Variation in DRD2 expression alone can modulate motor RI (Colzato et al., 2010a; Ghahremani et al., 2012; Hamidovic et al., 2009). The current study extends these findings by quantifying the influence of a greater range of polymorphisms that influence dopamine neurotransmission and demonstrating that a dopamine GRS can be used to predict baseline measures of motor RI.

A single administration of ropinirole temporarily shifted participants rightwards along the inverted-U curve either into or beyond optimal dopamine concentrations for motor RI (Figure 8.3). Both doses of ropinirole shifted participants with a lower GRS towards optimal levels, as evident by decreased SSRTs. For participants with optimal or near optimal dopamine, 0.5 mg ropinirole caused a nonsignificant increase in SSRT ($P = 0.072$) indicating there was no dose-dependent effect of ropinrole on motor RI, perhaps due to the low dosages of ropinirole used in this study. The absence of dose-dependency may also be due to only two participants being at the highest range of basal neurotransmission (GRS of 5). Previously, a single administration of up to 1.0 mg ropinirole (Monte-Silva et al., 2009) and 0.5 mg pramipexole (Pizzagalli et al., 2008) was shown to influence plasticity and reinforcement learning in healthy participants, respectively. Consistent with these findings, the divergent effect of ropinirole on motor RI in this study was evident during peak dopamine agonist concentrations.

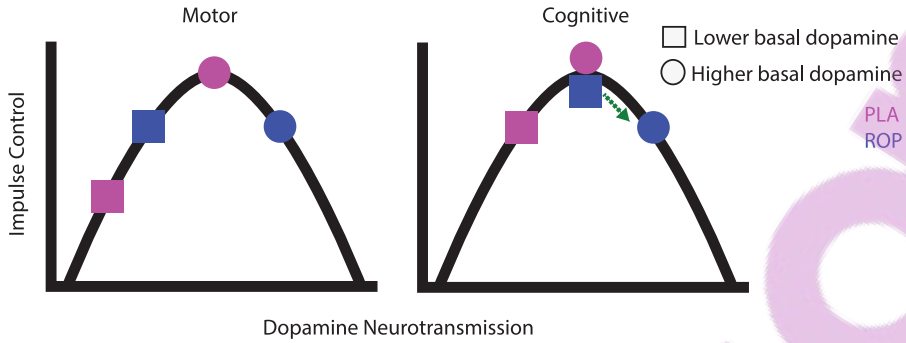

Figure 8.3 Inverted-U relationship between dopamine and impulse control. Relationship between dopamine neurotransmission and motor (left) and cognitive (right) impulse control. Squares: genetic risk scores 2, 3 for motor, DAT_0 for cognitive; circles: genetic risk scores 4, 5 for motor, DAT_1 for cognitive; PLA: placebo; ROP: 0.5 mg ropinirole.

The current study extends the use of a dopamine polygenic score into the context of impulse control. Variation within DRD3 has been associated with increased risk of ICDs in PD patients on dopaminergic medication (Lee et al., 2009) and the D3 receptor is a target of ropinirole (Matheson and Spencer, 2000). The present results indicate that DRD3 was weighted most heavily to predict the interaction between GRS and ropinirole on SSRT. However variation in DRD3 alone could not account for the effects of ropinirole. Motor RI might better be predicted by quantifying widespread dopaminergic neurotransmission rather than DRD3 alone, because of the differential expression of dopamine genes across the network of brain regions implicated in RI. This includes frontal cortical regions (e.g. right inferior frontal gyrus) in which COMT has a larger impact on dopamine neurotransmission. A four-gene score that omits DRD2 may be sufficient to capture the effect of ropinirole on motor RI and warrants further investigation. However, a strength of the five-gene score is that it was *a priori*, hypothesis-driven score based on previously published literature (Pearson-Fuhrhop et al., 2014, 2013). The ARI task might be clinically useful in the context of ICDs. Baseline measures of SSRT and dopamine GRS indicate a person's starting position on the inverted-U curve, and combined, may identify those at risk of developing ICDs when taking dopamine agonists.

Surprisingly, the DAT polymorphism alone predicted impulsive decision making. The DAT protein is involved in synaptic dopamine degradation and is particularly important in the striatum. Lower DAT activity results in less reuptake of synaptic dopamine and consequently higher levels of dopamine neurotransmission (Heinz et al., 2000; VanNess et al., 2005). DAT_1 participants (DAT score = 1) had presumably higher basal levels of striatal dopamine neurotransmission and demonstrated better impulse control than DAT_0

participants. Those with DAT_1 made fewer impulsive decisions on placebo after both positive and negative reinforcement. This is consistent with individual differences in general risk taking on the BART, with lower DAT activity being associated with less risky behaviour (Mata et al., 2012). Mata and colleagues inferred risk taking from average total number of button presses on collected trials. The present study quantified behavioural modification on a trial-by-trial basis as a result of rewards and losses to assess impulsive decision making (Ashenhurst et al., 2014) and extend the findings of Mata and colleagues to show how DAT polymorphism dictates impulsive decision making.

The DAT protein influences basal dopamine neurotransmission and tonic dopamine activity within the dorsal and ventral striatum. Striatal dopamine is associated with reinforcement learning from positive and negative outcomes (Cox et al., 2015; Frank et al., 2007). Increasing tonic dopamine activity in the ventral striatum beyond optimal levels disrupts behaviour modification (Goto and Grace, 2005; Schultz, 2002). In the present study, ropinirole interacted with the DAT polymorphism in a predictable way. This can be likened to shifting a participant rightwards along an inverted-U curve either into optimal levels of striatal dopamine neurotransmission (DAT_0) or beyond them (DAT_1). Figure 8.3 depicts the working hypothesis (green arrow) that 1.0 mg ropinirole degrades decision making in people with lower striatal dopamine neurotransmission, perhaps because striatal dopamine levels were near optimal at 0.5 mg. This may explain why 0.5 mg ropinirole improved decision making while 1.0 mg degraded it. When combined with DAT genotyping, the BART may assist in identifying people who may be more susceptible to developing a hyperdopaminergic state of the ventral striatum when given dopamine agonist medication.

Sample size is a limitation in the present study. We did not capture the full range of possible dopamine genetic risk scores, including no participants with scores of 0 or 1, and only two participants with scores of 5. Sample size also necessitated limiting the number of predictors in the model. For example weight was not included to avoid overparameterization. However this was not considered to have a major impact on our result as shown previously for gene score predictions of motor learning (Pearson-Fuhrhop et al., 2013). Caution is also advised when distinguishing between performance on the ARI task and BART as reflecting purely motor versus cognitive impulse control, respectively. For example, RI tasks are also sensitive to deficits in control of attention (Tachibana et al., 1997) and cognitive flexibility (Cooper et al., 1994). The current distinction relates to neural regions recruited and dopaminergic function, but is not intended to be a strict demarcation.

In summary, the effect of ropinirole on motor and cognitive impulse control can be conceptualized as shifting people rightward along an inverted-U curve, to their benefit or

detriment. The effect of this shift depends on their basal levels of dopamine neurotransmission, which are significantly influenced by genetic factors. Dopaminergic genotyping combined with baseline measures of motor and cognitive impulse control may be useful for identifying people at risk of developing ICDs on dopamine agonists. It remains to be determined if such an approach could lead to better individualized treatments for PD.

8.5 Supplementary material

8.5.1 Methods

Potential participants were screened by a neurology registrar (JK) for contraindications. A research nurse (LM) took a single blood sample for genetic analysis. The order of tasks was always ARI, BART, CNSVS. Collection and analysis of tasks and questionnaires were performed blind to medication (placebo, dose) and genotype.

ARI task

The ARI task was controlled using custom software written with MATLAB (MathWorks USA, R2012b), interfaced with two custom-made switches, an A/D USB interface (National Instruments, NI-DAQmx 9.7) and microcontroller (Arduino Uno). The forearms rested on a table, positioned midway between supination and pronation. The medial aspect of each index finger was used to depress the switches (index finger adduction). Electrodes were placed in a belly tendon montage and ground electrodes were placed over the posterior surface of the hand. EMG signals were amplified (CED 1902, Cambridge, United Kingdom), bandpass filtered (20 – 1000 Hz) and sampled at 2 kHz (CED 1401, Cambridge, United Kingdom). Data were saved for later offline analysis using Signal (CED, Cambridge, United Kingdom) and custom software (MATLAB R2012b).

Only Go trials were presented in the first two blocks and as 66 % of trials in the remaining eight blocks. Participants completed a total of 360 trials across the ten blocks. Upon trial completion visual feedback indicated “success” (within 30 ms of target) or “miss”, to emphasize that trials were to be performed as accurately as possible.

Lift times (LTs) were determined for successful Go (GG) and Partial (GS, SG) trials. Average LTs were calculated after removing outliers (± 3 SD) (1.0 ± 0.1 % and 0.2 ± 0.2 %, respectively). All LTs are reported in milliseconds relative to the target. Lift times were subjected to a repeated-measures analysis of variance with a three Dose (PLA, ROP 0.5, ROP 1.0) by two Digit (Left, Right) by two Trial Type (Go, Partial) design.

Indicator stop time, instead of SSRT, was used as a more direct measure of performance on Partial trials as the calculation of SSRT was not possible in instances where participants couldn't successfully perform these trials.

BART

The BART was controlled using Inquisit 3 (Millisecond Software, version 3.0.6.0). The balloon (i.e. trial) number, accumulated money for the current balloon, number of pumps for the current balloon and total winnings thus far were displayed to participants. The probability of explosion was determined by an array from 1 – 85. Each button press randomly selected a number without replacement. Selection of number one was designated as a balloon explosion.

CNSVS test battery

Standardized instructions were given. Test scoring was automated and generated from primary scores based on correct responses, error responses, number of responses and reaction times.

Genotyping

DNA was extracted from whole blood samples by salt precipitation. Genotyping for DRD1 rs4532, DRD2 rs1800497, DRD3 rs6280 and COMT rs4680 single nucleotide polymorphisms (SNPs) was performed using the Agena MassArray iPLEX assay (Agena Bioscience, San Diego, USA). The assay consisted of an initial locus-specific polymerase chain reaction (PCR), followed by single base extension using mass-modified dideoxynucleotide terminators of an oligonucleotide primer (Gabriel et al., 2009). The four SNPs were included in one multiplex well after accounting for the presence of proximal SNPs. Analysis was performed on the Bruker Mass Spectrometer using parameters optimized for iPLEX chemistry, allowing allele specific single base extensions to be resolved. The 40 base pair variable number of tandem repeats (VNTR) in the untranslated regulatory region of the DAT gene (rs28363170) underwent PCR with a labelled primer (Mata et al., 2012) and was assayed separately on a 3130XL genetic analyser. The results were analyzed using GeneScan and PeakScanner software.

8.5.2 Results

ARI task: Go trials

Go trials were completed successfully with LTs occurring 32 ± 2 ms after the target as is typical for older adults with this task (Coxon et al., 2012). There was a main effect of Trial Type ($P < 0.001$) with LTs delayed to an average of 96 ± 6 ms after the target on Partial trials. There was a main effect of Digit ($P = 0.018$) with right LT faster than left LT when collapsed across Trial Type and Dose (57 ± 5 ms vs 70 ± 3 ms). There was no effect of Dose ($P = 0.557$) or any interactions (all $P > 0.218$).

ARI task: Partial Stop trials

On average, Partial Stop trials were more difficult than Stop Both trials, with success rates just below 50 % (SG, 41.8 ± 3.3 %; GS, 36.4 ± 3.8 %). Eleven participants were unable to complete any successful trials for at least one Partial trial type in at least one session, even with the staircase procedure. Two participants were unable to perform any SG trials successfully (N = 26) and one couldn't perform GS trials successfully (N = 27).

The indicator stop time on GS and SG trials was dependent on the intercept ($t_{26} = 4.3$, $P < 0.001$ and $t_{25} = 5.9$, $P < 0.001$, respectively) but was not dependent on Dose, GRS, or a Dose x GRS interaction (all $P > 0.179$). Partial GS trials only showed a fixed effect of Age ($P < 0.001$). With each year increase in age, there was a 9 ms increase in the predicted indicator stop time relative to target.

8.5.3 Discussion

Performance on the bimanual ARI task was as expected for healthy older adults. Go LTs were typical for this age range (Coxon et al., 2012), occurring later than for younger adults performing an identical task (MacDonald et al., 2012 Chapter 5). As expected, LTs on Partial trials were delayed.(Coxon et al., 2007; MacDonald et al., 2014 Chapter 6, 2012 Chapter 5) Furthermore, partial cancellation on GS trials was more difficult with increasing age (Coxon et al., 2014, 2012). In contrast to SSRT obtained from Stop Both trials, performance on Partial trials was not influenced by genetic risk score or ropinirole dosage. Compared to simple RI, partial movement cancellation involves more complex neural mechanisms as the noncued movement component still needs to be executed. The delay in the executed component may reflect processes of inhibition, reprogramming and initiation (Coxon et al., 2007; MacDonald et al., 2014 Chapter 6). Partial trials may therefore engage mechanisms

Table 8.3 Main effects from mixed-effects linear regression models.

		Unweighted			Weighted		
Dependent measure	Model term	F	df	*P*	F	df	*P*
SSRT	Dose	4.0	2,51	**0.025**	5.0	2,51	**0.010**
	GRS	1.6	1,30	0.211	1.3	1,30	0.271
	Age	1.8	1,30	0.187	1.5	1,30	0.230
	Dose x GRS	3.8	2,51	**0.029**	4.8	2,51	**0.012**
Positive reinforcement	Dose	2.5	2,54	0.091	3.5	2,54	**0.037**
	GRS	0.2	1,31	0.639	0.3	1,31	0.585
	Age	0.0	1,31	0.904	0.0	1,31	0.882
	Dose x GRS	2.3	2,54	0.107	4.4	2,54	**0.017**
Negative reinforcement	Dose	4.0	2,54	**0.024**	5.4	2,53	**0.008**
	GRS	0.2	1,32	0.668	0.2	1,31	0.699
	Age	0.0	1,32	0.862	0.0	1,31	0.895
	Dose x GRS	3.7	2,54	**0.031**	6.4	2,53	**0.003**
NCI	Dose	0.5	2,48	0.636			
	GRS	5.9	1,27	**0.022**			
	Dose x GRS	0.3	2,48	0.711			
Working memory	Dose	2.7	2,48	0.080			
	GRS	3.7	1,26	0.066			
	Dose x GRS	2.5	2,48	0.089			

SSRT: stop signal reaction time; NCI: neurocognitive index; GRS: genetic risk score.

beyond pure impulse control as opposed to SSRT from Stop Both trials, and this may explain the differential sensitivity to dopaminergic factors between these two trial types.

Table 8.4 Main effects in balloon analogue risk task using DAT score.

Dependent measure	Model term	F	df	*P*
Positive reinforcement	Dose	3.0	2,55	0.059
	DAT	1.7	1,32	0.205
	Age	0.0	1,32	0.915
	Dose x DAT	5.6	2,55	**0.006**
Negative reinforcement	Dose	4.2	2,54	**0.021**
	DAT	1.1	1,31	0.313
	Age	0.0	1,31	0.862
	Dose x DAT	6.9	2,54	**0.002**

DAT: dopamine transporter.

Chapter 9

General Discussion

9.1 Summary of main findings

The current experiments examined the behavioural, neurophysiological and genetic elements for impulse control of an overt motor response. The mechanisms underlying motor impulse control in healthy adults were investigated using an ARI paradigm that cued complete, and partial cancellation of a prepotent bimanual response. The ARI task (in conjunction with cognitive impulse control measures) examined how dopamine agonist drugs interact with dopamine gene polymorphisms to influence impulse control. There were several novel results that further the understanding of how we achieve behaviourally selective impulse control of a multi-component response. Furthermore, the results of the final experiment provide the first evidence that baseline measures of impulse control in conjunction with dopaminergic genotyping can predict a person's response to dopamine agonist medication. This approach may be able to identify people at risk of developing impulse control disorders.

Chapters 5 to 7 investigated bimanual ARI performance and indicated that there are neuroanatomical constraints on behaviourally selective impulse control. Chapter 5 presented EMG evidence that regardless of muscle pairing, planned multi-component movements are integrated together into a single response in anticipation of execution. This meant that even when only one response component needed to be cancelled, stopping the coupled response had to be nonselective, causing rapid suppression of all prepared movement. The reinitiation of activity in the responding muscle was sensitive to the strength of coupling between components. This indicated that nonselective suppression was followed by uncoupling to allow selective initiation of one component.

Chapter 6 examined the possible neurophysiological mechanisms underlying the effects observed in Chapter 5. If the inhibitory mechanism triggered by the stop signal has an effect on all components of a unitary response, one would expect to see suppression of CME in a response component that was never cued to stop. The first experiment in Chapter 6 confirmed this by showing temporal modulation of CME in the noncancelled component that reflected anticipation, suppression and subsequent reinitiation of movement.

The second experiment in Chapter 6 demonstrated that sICI was modulated during simple inhibition on the bimanual ARI task, although sICI was unlikely to be the mechanism causing nonselective suppression during partial RI. However nonsignificant results are difficult to interpret and there are a few caveats regarding interpretation of these results which are discussed below and in Chapter 6.

Chapter 7 presented a computational model that accounted for the empirical data from previous chapters. The proposed activation threshold model supported that a secondary activation process was needed following nonselective suppression in order to execute the remaining component of the response. This second activation process can be conceptualized as the newly programmed unimanual response that is selectively initiated, subsequent to the cancellation of the default bimanual response. As such, it appears we achieve behaviourally selective impulse control of a multi-component response from neurally selective reinitiation of movement, as opposed to selective inhibition.

Chapter 8 used a bimanual ARI task to investigate the mechanisms underlying impulse control disorders developed by some people on dopaminergic medication. Simple RI performance on the bimanual ARI task was predicted by a person's basal levels of dopamine neurotransmission. Furthermore, when combined with a dopamine genetic risk score, baseline measures of motor impulse control from the ARI task predicted a person's response to dopamine agonist medication.

9.2 Potential limitations

There are several limitations to this research in addition to those discussed in the relevant chapters. These limitations should be kept in mind when interpreting the results summarized above.

All RI tasks inherently contain a potential confound of 'task-impurity'. Even though the ARI is predominantly a motor task, it requires a finely orchestrated and complex interplay between various brain regions throughout the frontal cortex and BG. Successful RI requires attention to task stimuli, retention of task goals in working memory and cognitive flexibility

to switch between task demands, amongst other executive functions. Therefore, RI also relies on cognitive and emotional elements of executive control (see Chapter 8). One needs to be careful when interpreting performance on this task as evidence of strictly motor control.

There is inherent variability in MEPs, especially during an active task (Chapter 6). In addition, reliably measuring SSRT in the two TMS experiments of this thesis necessitated setting an indicator stop time that produced around 50 % successful inhibition. Success was achieved randomly across stimulated and unstimulated trials for each participant. This resulted in average MEP amplitudes being calculated from varying numbers of successful stimulation trials, both between participants and across stimulation times. While the temporal modulation of CME that is indicative of nonselective suppression during partial RI is compelling, these combined sources of variability may have led to spurious results or an underestimation of a larger effect. A replication of the CME modulation demonstrating nonselective suppression seems prudent.

The experiments in Chapter 6 did not include a dynamic tracking algorithm for Stop trials. Stimulation times were all relative to a constant indicator stop time determined from the results of Chapter 5 and not individualized to each participant's SSRT. Participants required more time for partial RI (stop signal 250 ms before target) than simple RI (200 ms) in order to match the probability of responding at 50 %. Considering the robust CME suppression on GS trials observed in all participants with a complete dataset, the use of a nonindividualized stop time is unlikely to have significantly influenced the temporal modulation of CME. Nevertheless, dynamically adjusting the stimulation times relative to stop times is suggested for future experiments investigating temporal modulation of neurophysiological mechanisms during the ARI task.

A further caveat with the use of a single 'stop signal delay' is that participants may have been able to anticipate when they would need to stop and preactivate a stopping process. This is of particular consideration when GS trials occurred more frequently than other Stop trial types. However, preactivation of a Stop process seems unlikely given the performance on GS trials was not substantially better (when they were more common) compared to other studies and stopping conditions. Furthermore, LTs were not delayed on Go trials compared to other thesis experiments (which used the tracking algorithm and had an equal probability of Stop trial types). It does not appear that participants were able to predict the occurrence or type of Stop trial, although we cannot completely discount this possibility.

Chapter 6 illustrates the difficulty in measuring sICI while participants are functionally engaged in a task. Voluntary muscle activation fluctuates during an active task and influences sICI (Ridding et al., 1995; Stinear and Byblow, 2003). For this reason, three participants

had violated the rmsEMG criterion at the time of stimulation and their data were removed from the final analysis. While this ensured reliable measures of a true sICI effect, it reduced statistical power for neurophysiological data and may have contributed to the overall null effect.

Background muscle activation cannot explain why some participants showed a reduction in sICI on Go trials while others showed an increase. To produce voluntary movement inhibition must be reduced (Hasbroucq et al., 1999). Any increase in inhibition prior to initiation for selected response representations may reflect another process, such as that required to prevent premature responses (Duque and Ivry, 2009; Duque et al., 2010). It is currently unclear why we observed the opposing modulation of sICI during bimanual response initiation.

The absence of evidence for sICI during partial RI does not equate to evidence of absence. It is worth noting that Experiment 2 (Chapter 6) successfully produced robust sICI at a level enabling the detection of both increases and decreases in percent inhibition, despite no evidence of modulation. There are a few potential reasons why modulation of sICI could not account for the dynamic modulation of CME during partial RI (see also discussion in Chapter 6). As mentioned, MEPs are pointwise measures of CME and can be influenced by multiple co-occurring and/or temporally overlapping processes e.g. interhemispheric inhibition. The presence of long-latency ICI can also reduce sICI (Sanger et al., 2001). The persistent after-effects on the motor system from partial RI (lift time asynchronies LTAs, Chapter 5) may suggest involvement of $GABA_B$-mediated inhibitory circuits. The working hypothesis is that $GABA_B$ circuits responsible for long-latency ICI presynaptically inhibit the $GABA_A$ circuits responsible for sICI (Sanger et al., 2001). The current experiment constituted the first investigation of intracortical inhibitory circuits during performance of a bimanual RI task. Therefore further investigation is warranted to elucidate the role of inhibitory intracortical and interhemispheric mechanisms during partial RI.

It is currently unclear exactly when complete uncoupling of the default response is achieved during partial RI. The combined evidence from Chapters 5 to 7 suggest partial RI occurs via i) nonselective inhibition of a unitary response, ii) uncoupling of response components, iii) response reprogramming, and iv) initiation of a new unimanual response to meet trial requirements. The equivalent increase in CME for cancelled and executed digits on Partial trials from −75 to −25 ms would indicate full uncoupling of response components has not yet occurred 25 ms before the target. The activation threshold model suggests the average onset of the facilitatory input for the unimanual response (at −55 ms) occurs before uncoupling of response components is complete. However uncoupling must be complete

by the time of the overt (unimanual) response (around 100 ms after the target). Therefore, complete uncoupling of the default bimanual response seems to occur *after* onset of the second facilitatory input but *before* generation of the unimanual response.

Although we proposed an inverted-U relationship between dopamine levels and impulse control, the experiment in Chapter 8 did not include a direct measure of dopamine activity in the brain. We assumed an increase in dopamine concentration from 1 hour following dopamine agonist administration, in line with other studies (Brefel et al., 1998; Monte-Silva et al., 2009; Pizzagalli et al., 2008). Furthermore, we could only infer that basal dopamine neurotransmission was different between high versus low genetic risk scores. However our results and interpretations are consistent with other studies that have found an inverted-U relationship between dopamine levels and impulse control (Congdon et al., 2009; Farrell et al., 2012) or other executive functions (for a review see Robbins and Arnsten 2009). Our novel contributions came from i) using the polygenic risk score to quantify widespread effects of neurotransmission in the context of impulse control disorders rather than focusing on individual genes, and ii) using the ARI task to capture the genetic influence on quantitative measures of impulse control. Regardless, it is acknowledged that the findings reported in this thesis are only suggestive of an association and the underlying mechanisms. In addition, as discussed in Chapter 8, the sample size in this study was relatively small for the statistical model. The study was powered for 50 participants. Our findings therefore necessitate future work with a larger sample size, possibly integrating molecular and/or cellular level data (e.g. a $H_2{}^{15}O$ PET scan) with behaviour and genetic risk scores.

9.3 Future directions

Impulse control on and off dopamine agonist medication has yet to be examined in PD patients while accounting for genotype. Findings presented in Chapter 8 suggest dopaminergic genotyping combined with baseline measures of motor and cognitive impulse control may be useful for identifying people at risk of developing impulse control disorders on dopamine agonists. A possible next step is to use this experimental design with *de novo* PD patients to determine if these results can be replicated in early PD. An additional step would be to use this approach with PD patients who already have ICDs and those who do not. These additional studies would help determine whether this approach can lead to better individualized treatments for PD. PD can be viewed as a form of accelerated ageing (Surmeier, 2007) and as such, the effect found in healthy older adults might be heightened in PD patients.

PD causes abnormal control of CME. CME is altered in the less affected side of early PD patients and abnormal CME may be contributing to early clinical symptoms (Wu et al., 2007). PD patients demonstrate increased excitability at the level of the cortex and spinal cord (Cantello et al., 1991; Valls-Sole et al., 1994). Our activation threshold model suggests dysfunctional CME and BG-thalamocortical connections will disrupt modulation of the activation threshold during selective reinitiation of movement, and result in abnormal gain and gating of reinitiated movements. Future work with our computational model might generate hypotheses for testing in PD patients on the bimanual ARI task.

The ARI task may have prognostic value for other BG disorders. The unimanual version of the ARI task has proven sensitive to impaired impulse control in focal dystonia (Stinear and Byblow, 2004) as evident in EMG data on Stop trials. The present thesis also indicates that successful partial RI requires complex modulation of CME. BG disorders such as dystonia and Gilles de Tourette can cause abnormal control of CME (Orth, 2010; Trompetto et al., 2012). The bimanual task may therefore provide novel insight into the control of partial RI in BG dysfunction. Future work could explore the ability of the bimanual ARI task to assist in providing sensitive measures for identifying and monitoring BG disorders.

Serotonin and norepinephrine (NE) are other monoamines implicated in impulse control. NE is hypothesized to adaptively change the gain of neurons in the frontal cortex (Aston-Jones and Cohen, 2005). Pharmacological manipulation of NE via atomoxetine modulates RI performance as demonstrated in healthy adults and adults with attention-deficit hyperactivity disorder (Chamberlain et al., 2007). Of note, atomoxeine also improves impulse control in PD by increasing NE neurotransmission (Kehagia et al., 2014). In addition, serotonergic function is modulated by dopamine agonists such as ropinirole (Dhir and Kulkarni, 2007). These two monoamines represent other possible pharmacological avenues of investigation for impulse control and PD.

Appendix A

Supplementary Results to Experiment 2 in Chapter 6

LTA was analyzed for Go trials following successful Go and Stop trials, with a one-way RM ANOVA with Preceding Trial Type as factors (GG, SG, GS and SS). A 2 Digit x 4 Preceding Trial Type RM ANOVA tested for differences in LTs on Go trials following successful Go and Stop trials.

A.1 Behavioural effects of preceding trial type

LTA was measured on Go trials (GG). There was a main effect of Preceding Trial Type ($F_{3,36}$ = 12.3, $P < 0.001$). LTA was larger on GG trials preceded by SG trials (10 ± 3 ms) than by GG trials (5 ± 3 ms; $t_{12} = 2.9$, $P = 0.013$), indicating that the left finger lagged the right to a greater extent after stopping on the previous trial (Figure A.1A). Conversely, LTA on GG trials was less when preceded by GS (-1 ± 3 ms) than by GG trials ($t_{12} = 3.8$, $P = 0.003$), indicating that the left finger led the right after the right stopped on the previous trial. There was no difference in LTA following SS compared to GG trials ($t_{12} < 0.1$, $P = 0.978$).

Alterations to LTs on Go trials following successful Partial trials underlie the LTA results. LTs are all reported relative to target. LTs showed a Digit x Preceding Trial Type interaction ($F_{3,36} = 11.6$, $P < 0.001$, Figure A.1 B), a main effect of Preceding Trial Type ($F_{3,36} = 11.8$, $P < 0.001$), and no main effect of Digit ($F_{1,12} = 2.6$, $P = 0.132$). Post hoc tests revealed a faster average Go LT with the left digit immediately after a GS trial (805 ± 3 ms) compared with after a Go trial (821 ± 3 ms; $t_{12} = 6.7$, $P < 0.001$). Similarly, Go LT with the right digit was faster immediately after a SG trial (803 ± 4 ms) compared with after a Go trial (817 ± 2 ms; $t_{12} = 5.4$, $P < 0.001$). Both digits were faster on a subsequent Go trial if they had been previously

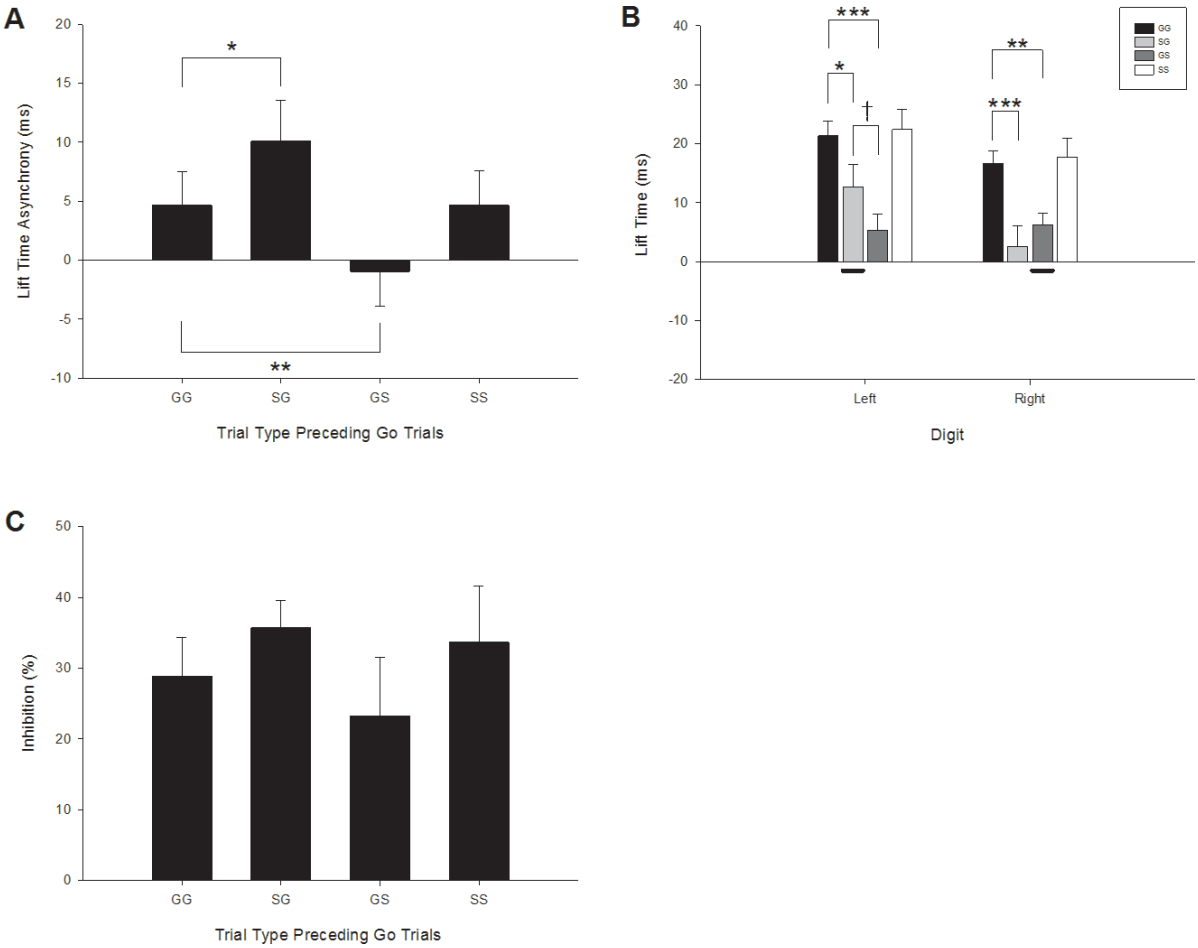

Figure A.1 Lift times and percent inhibition on Go trials following successful Go and Stop trials. Lift time asynchrony (*A*), lift times (*B*) and percent inhibition (C) on Go trials after successful Go and Stop trials. Positive lift time asynchrony indicates the left digit lifted after the right. Lift times in (*B*) are relative to target (0 ms). Stimulation on Go trials was at −600 ms. Thick black horizontal lines in (*B*) denote digit that was cancelled on previous Partial trial. GG: Go trials; SG: Stop Left – Go Right trials; GS: Go Left – Stop Right trials; SS: Stop Both trials. Bars are means ± SE ($N = 13$). $*P < 0.05$; $**P < 0.01$; $***P < 0.001$; $\dagger P = 0.074$.

executed on a Partial trial. The left Go LT was also faster after a SG trial (813 ± 4 ms) and the right Go LT faster after a GS trial (806 ± 2 ms) compared to after a Go trial ($t_{12} = 2.7$, $P = 0.020$ and $t_{12} = 4.3$, $P = 0.001$, respectively). Digits were therefore also faster on a Go trial after they had been cancelled on a Partial trial, although to a lesser extent than when they had been previously executed (especially for the left digit, $P = 0.074$). After a SS trial, there was no difference in left (822 ± 3 ms) or right (818 ± 3 ms) LT compared to after a Go trial (both $P > 0.7$).

A.2 Neurophysiological effects of preceding trial type

To investigate inhibition after response execution and cancellation, we compared %INH on Go trials that were preceded by successful Go trials versus those preceded by successful Stop trials. Percent INH on Go trials showed a pattern consistent with the LTA results (Figure A.1 C), but with no main effect of Preceding Trial Type ($F_{3,27} = 0.6$, $P = 0.611$).

For NC MEP amplitude, there was no main effect of Preceding Trial Type ($F_{3,27} = 2.4$, $P = 0.091$). NC MEP amplitude was no different on Go trials when the preceding trial was a successful Stop or Go trial.

Partial trials caused carryover effects on subsequent Go trials, as reported previously (Coxon et al., 2007; MacDonald et al., 2012 Chapter 5). Go LTs were faster for the component previously executed on the immediately preceding Partial trial (Figure A.1 B), giving rise to LTA results (Figure A.1 A), and demonstrating that the greater facilitatory drive of the initiated response on Partial trials carries over to affect behaviour on the following trial. This would appear to argue against the persistent behavioural effects (lift time asynchronies) from partial RI being caused by lingering GABAergic inhibition. We speculate that generally faster LTs after Partial trials reflect arousal or motor set. NC MEP amplitude was no different on Go trials when the preceding trial was a successful Stop or Go trial, but right M1 sICI on GG trials tended to increase after a SG trial and decrease after a GS trial (Figure A.1 C), although this difference was not statistically significant.

Appendix B

Response Inhibition Task Instructions

Movement task instructions

You will now perform a movement task that measures how accurately you can produce a timed response. This is the display you will see at the beginning of each trial. When you push down with your fingers on both red switches, you will see two black bars begin to rise from the bottom of the white rectangles. The bars will rise at the same rate to always reach the top of the rectangles in 1 second. You will be controlling the bars with the switches. When you lift your finger off a switch, the corresponding black bar will stop rising.

For the first couple of blocks, your task is to lift both fingers off the switches to stop the bars as close as you can to the horizontal target line. If you are close, the target bar will go green. For these first two blocks, try and become as accurate as you can. The last trial in the block will show the bars stopping really early. Don't worry about those trials.

After 2 blocks, we will pause and I will give you more instructions. You can pause between trials if you need, the task will wait for you to press down both switches before beginning a trial.

Start when you're ready.

After two blocks of Go only:

Now things are going to get interesting. The majority of trials will be the same as you have just been practicing. You will still stop both bars at the target by lifting both fingers. It is important you stay as accurate as you can on these types of trials.

But now, occasionally one or both bars may stop early automatically, before reaching the target. In this case, you have to cancel your response. If both bars stop early, cancel both responses and keep both fingers on the switches. If only the left bar stops early, you need to cancel your left finger response and keep your left finger down on the switch. The right bar will continue to rise, so you will still need to lift your right finger to stop the right bar at the target. And the opposite thing if the right bar stops early; cancel your right finger response but still lift the left finger to stop the left bar.

Any questions?

Appendix C

Participant Information Sheet

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Participant Information Sheet

Title of Project: How does the brain change its mind?

Researchers:
Associate Professor Winston Byblow
Dr Cathy Stinear
Misss Hayley MacDonald (BScHon)
Mr Fred Noten

You are invited to participate in the above named study. The aim of the study is to investigate motor regions of the brain involved in task switching and the neural pathways between them during a reaction time task in healthy adults. Please take your time to think about the information provided below, and feel free to discuss it with your whanau, family or significant other support people, before deciding whether to take part. Taking part is completely voluntary (your choice).

What is the study about?

The study will include approximately 25 adults, aged between 18 and 45 years. The study will investigate changes in the activity of the brain while switching from one movement to another. The movement is lifting one or two of your fingers from keys on a mouse, in time with moving indicators on computer display.

Am I eligible to participate?

You are eligible to participate in this study if you are aged between 18 and 45 years, are right-handed, and have no history of neurological illness. You are not eligible to participate if you have a cardiac pacemaker or experience seizures. If you volunteer for this study, you will be asked to complete a safety checklist, to ensure that you are eligible to participate. You will also be asked to complete a handedness questionnaire, to determine how right- or left-handed you are. If you aren't eligible to participate, then any materials relating to you, such as the safety checklist and handedness questionnaire, will be immediately destroyed.

What does the study involve?

The study involves having an MRI scan (detailed below) at the Centre for Advanced MRI, Grafton Campus, University of Auckland (lasting up to 30 minutes) and three experimental sessions at the Movement Neuroscience Laboratory, Tamaki Campus, University of Auckland (each session lasting up to 2 hours).

In the experimental sessions you will be asked to perform a reaction time task on the computer. You will be trained in this task prior to starting the experiment. There are no risks associated with this task.

At the beginning of the first session you will be asked to complete a questionnaire that will be used to determine your handedness (about 5 minutes) and to complete two questionnaires that will ensure you can safely participate in the procedures (about 5 minutes).

Transcranial magnetic stimulation

During the experiment we will use a technique called non-repetitive Transcranial Magnetic Stimulation (TMS) to measure changes in movement areas of your brain. Single and dual-pulse TMS is a safe, painless, non-invasive technique. It involves holding a device gently against your scalp, which creates a very brief magnetic field. This activates some of the cells in the movement areas of the brain. This stimulus causes a brief twitch in the muscles of the hand and forearm which we record using electromyography. This electrical activity is recorded using sensors positioned on the skin over the muscles of interest. The skin must first be prepared by shaving hair and mild abrasion of the skin. This can result in a mild and transient irritation of the skin that does not require treatment. Occasionally, some people experience mild, transient scalp discomfort, due to the activation of the scalp muscles by the stimulator. If you feel uncomfortable at any time during the experiment, please notify the experimenter.

Magnetic Resonance Imaging(MRI)

We will need to obtain a structural image of your brain, using magnetic resonance imaging (MRI). MRI is a widely used, safe, non-invasive imaging technique. Some people experience mild anxiety during magnetic resonance imaging, as the scanner is an enclosed space. You will be provided with a safety buzzer in one hand, so that if you want to stop the scanning at any time, you can use this device to alert the radiographers.

In the event that a condition which is assessed to be a clinical abnormality is detected through performing a scan on you, you will be informed of this and will be advised to consult your general practitioner or other health professional of your choice. Because the images are not routinely reviewed by a radiologist we are unable to perform diagnostic scans for medical purposes of areas where you have known abnormalities. You should be aware that once you have been informed that a clinical abnormality has been detected through performing a scan on you this could affect your ability to obtain insurance whether or not you take the matter further.

Brain Polarisation using Transcranial Direct Current Stimulation (TDCS)

TDCS is painless and safe and can transiently increase or decrease activity in the area of the brain beneath the stimulating electrodes. TDCS polarises the brain with a low-intensity direct current, delivered across the scalp using a small, battery-powered device. This normally persists for 30-60 minutes, but has no lasting effects beyond that time. You may receive different types of TDCS stimulation in each session.

TDCS involves putting a small damp sponge on the top of your head and another on your forehead just above your left eye. You will experience a slight tingling sensation under the electrodes for up to 1 - 2 minutes, after which the sensation diminishes and may become imperceptible. There is no need to shave your head and the area under the electrode on your forehead will be cleaned using an alcohol wipe. The current will be set to 1 mA and the duration of stimulation will be up to 20 minutes. If you feel uncomfortable at any time during the stimulation, please notify the experimenter

There are no risks associated with the use of TMS and brain polarisation by TDCS in the same experimental session. Effects of TMS and brain polarisation are transient and will not affect your ability to drive home, or return to study or work after participation.

Participation

Your participation is voluntary and you may withdraw from participating at anytime during the experiment without reason, and at your request we will stop the experiment. You have the right to withdraw your data from this study up to 3 months after you complete the study. Withdrawal or non-participation will not affect your relationship with the University. You will be assigned and identified by a code. The data obtained from this experiment will be stored to disk for a period of up to six years and will be used for publication in a scientific journal. After six years, your data will be deleted from disk and your consent form and all related paperwork put through a shredder. No material that could personally identify you will be used in any reports in this study. The information and data collected from you will be stored securely, in locked cabinets and on secure computer networks. Only the investigators will have access to this information, and your data will be made anonymous by assigning

a unique code to it. You can request a summary of the study's results, which we can send to you once the project is complete.

Summary of Your Rights

- Your participation is entirely voluntary.
- You may withdraw from the project at any time without providing a reason.
- You may have your data withdrawn from the study within three months of your participation.
- The information and data collected from you will be stored securely, in locked cabinets and on secure computer networks. Only the investigators will have access to this information, and your data will be made anonymous by assigning a unique code to it.
- You may obtain results regarding the outcome of the project from the experimenters upon completion of the study.
- Your identity will be kept strictly confidential, and no identification of you or your data will be made at any time during collection of the data or in subsequent publication of the research findings.
- After six years, your data will be deleted from disk and your consent form and all related paperwork put through a shredder
- Discomfort or incapacity have not been reported from any of the procedures that will be used in this project, however, if the procedures cause you concern, you may withdraw from the project at any time.
- You are encouraged to consult with your whanau/family, hapu or iwi regarding participation in this project.

Who should I contact if I have further questions?

If you have any further questions please contact:

Associate Professor Winston Byblow, Department of Sport and Exercise Science
Building 734 Room 316, phone 373-7599 ext 86844
Private Bag 92019, Auckland

or Associate Professor Greg Anson, Head of Department, Sport and Exercise Science, Building 734 Room 319, phone 373-7599 ext 84681
Private Bag 92019, Auckland

or Hayley MacDonald (Honours student)
Building 734, Tamaki Campus
Phone 373-7599 ext 84897
hmac080@aucklanduni.ac.nz

For any queries regarding ethical concerns please contact:

The Chair,
University of Auckland Human Participants Ethics Committee
University of Auckland
Private Bag 92019, Auckland
Tel: 373 7599 ext 87830

APPROVED BY THE UNIVERSITY OF AUCKLAND HUMAN PARTICIPANTS ETHICS COMMITTEE on 09/06/2010 for a period of 3 years, from 09/06/2010 to 09/06/2013. Reference Number 2010/218.

Experiments in Chapters 5 and 6 were covered by my Honours experiment ethics approval and therefore used the same Participant Information Sheet. Participants were informed they would only be receiving TMS and to disregard sections on TDCS and MRI.

Appendix D

Consent Form

DEPARTMENT OF SPORT AND EXERCISE SCIENCE

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Consent Form

THIS CONSENT FORM WILL BE HELD FOR A PERIOD OF SIX YEARS

Title of Project: How does the brain change its mind?

Researchers: Associate Professor Winston Byblow, Dr Cathy Stinear, Miss Hayley MacDonald, Mr Fred Noten

I have been given and understood the explanation of this research project and my role as a participant. I have had the opportunity to consult my whanau, hapu or iwi, or a family member/friend to help me ask questions. I have had time to consider whether to take part. I am satisfied with the answers I have been given. I know who to contact if I have any further questions about the study.

I have been informed that:

- the total time required for the study is 6.5 hours, spread over four sessions
- for the MRI scan, the session will last up to 30 minutes
- the three experimental sessions may each last up to 2 hours
- my participation is voluntary
- I may withdraw myself from the experiment at any time without giving a reason
- I can withdraw any information traceable to me, from this study, up until three months after I have completed this study
- I may obtain results regarding the outcome of this experiment from the named researcher upon completion of the study
- after six years, my data will be deleted from disk and this consent form and all associated paperwork put through a shredder
- my anonymity will be maintained in any reporting of this research
- any incidental findings and an appropriate course of action will be explained to me by the researchers
- if I do not wish to be informed of incidental findings I will be excluded from participating

If for some reason I am not eligible to participate in this research, I understand that all material relating to me will be immediately destroyed.

I agree to take part in this research during which I may be asked to:

- complete questionnaires to determine my handedness and ensure I can safely participate in the project
- perform a computer-based task where I prepare to make a movement, and at some times may need to stop myself from making the prepared movement and possibly switch to another movement
- have the activity of forearm muscles recorded by sensors placed on my skin
- have single-pulse and dual-pulse (not repetitive) Transcranial Magnetic Stimulation
- have an MRI for an anatomical brain scan
- have a weak current applied to the scalp that temporarily polarizes the brain

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I would like the researchers to send me a summary of the study results YES NO
If YES: my address is _____

Signed:_____
Name:_____
(Please print name in full)

Date:_____
APPROVED BY THE UNIVERSITY OF AUCKLAND HUMAN PARTICIPANTS ETHICS COMMITTEE on 09/06/2010 for a period of 3 years, from 09/06/2010 to 09/06/2013 Reference Number 2010/218

Experiments in Chapters 5 and 6 were covered by my Honours experiment ethics approval and therefore used the same Consent Form. Participants were informed they would only be receiving TMS and to disregard sections on TDCS and MRI.

Appendix E

Edinburgh Handedness Inventory

EDINBURGH HANDEDNESS INVENTORY

Last name: _____

First names: _____

Date of birth: _____ Gender: _____

Please indicate your preference for the use of the left or right hand in the following tasks by placing a "+" in the appropriate column. If you have such a strong preference for one hand that you would never try to use the other unless forced to, place a "++" in the column. If you would perform the task with either hand place a "+" in both columns.

Some of the tasks require both hands. In these cases the part of the task, or object, for which hand preference is wanted is indicated in the brackets.

Please try to answer all of the questions. Only leave a blank if you have no experience of the task or object.

		LEFT	RIGHT
1	Writing		
2	Drawing		
3	Throwing		
4	Scissors		
5	Toothbrush		
6	Knife (without fork)		
7	Spoon		
8	Broom (upper hand)		
9	Striking match (match)		
10	Opening box (lid)		
I	Which foot do you prefer to kick with?		
II	Which eye do you use when only using one?		

Appendix F

TMS Safety Checklist

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CENTRE FOR BRAIN RESEARCH
THE UNIVERSITY OF AUCKLAND
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Appendix G

Python Code for Activation Threshold Model

```
"""
Created on Thu Oct 16 10:48:19 2014

@author: Hayley
Code for activation threshold model. Using ARI task experimental data.

To run Go and GS trials with a single facilitation curve: 'python
 ↪  ARI_task.py first'
To run GS trials with an additional facilitation curve using manual
 ↪  input
for optimized parameters from single facilitation curve: 'python
 ↪  ARI_task.py second'

"""

import numpy as np
from scipy import stats
import scipy.optimize as opt
import sys


#%%
def get_trials(params, n_rep=100000):
    '''
    Generates n_rep Guassian facilitation curves

    Parameters
    -------------
    params : sequence (8,) of float
```

```
        mean and sd for a_facGo, b_facGo, c_facGo, inhib
    n_rep : flat
        number of simulated trials

    Returns
    --------
    fac_i : array (t, n_rep)
        facilitation curves for all simulated trials
    inhib_tonic : array (t, n_rep)
        horizontal lines denoting tonic inhibition for all simulated
↪   trials
    t : array (600,)
        sequence of time index
    '''
    a_facGo_mean, a_facGo_sd, b_facGo_mean, b_facGo_sd, c_facGo_mean,
↪   c_facGo_sd, inhib_mean, inhib_sd = params
    t = np.linspace(-.4, .2, 600, endpoint=False)
    a_facGo = np.random.normal(a_facGo_mean, a_facGo_sd, size=n_rep)
    b_facGo = np.random.normal(b_facGo_mean, b_facGo_sd, size=n_rep)
    c_facGo = np.random.normal(c_facGo_mean, c_facGo_sd, size=n_rep)
    fac_i = np.zeros((n_rep, t.size))
    inhib_tonic = np.zeros((n_rep, t.size))
    inhib = np.random.normal(inhib_mean, inhib_sd, size=n_rep)
    inhib_tonic += inhib[:,np.newaxis]

    for i in range(n_rep):
        myparams_fac = a_facGo[i], b_facGo[i], c_facGo[i]
        fac_i[i] = get_fac(t, myparams_fac)
    return fac_i, inhib_tonic, t

#%%
def get_fac(t, params):
    '''
    Generates a single Gaussian facilitation curve

    Parameters
    -------------
    params : sequence (3,) of float
        values for a_facGo, b_facGo, c_facGo

    Returns
    -------
    fac : array (t,)
```

```
        facilitation curve values at times `t`
    '''
    a_facGo, b_facGo, c_facGo = params
    fac = a_facGo * np.exp(-(t - b_facGo)**2 /(2 * c_facGo**2))
    return fac

#%%
def get_activation_thresholds(t, inhib_tonic, params_GS, n_rep=100000):
    '''
    Generates n_rep inhibition curves i.e. activation thresholds

    Parameters
    -------------
    params : sequence (4,) of float
        values for k_inhib, tau_inhib, mean and sd for step_t

    Returns
    --------
    thresholds : array (t, n_rep)
        inhibition curves for all simulated trials
    '''
    k_inhib, tau_inhib, step_t_mean, step_t_sd = params_GS
    thresholds = np.zeros((n_rep, t.size))
    for i in range(n_rep):
        thresholds[i] = get_inhib_increase(t, inhib_tonic[i], params_GS)
    return thresholds

#%%
def get_inhib_increase(t, inhib_tonic, params_GS):
    '''
    Generates a single inhibition curve

    Returns
    ----------
    inhib : array (t,)
        inhibition curve values at times `t`
    '''
    k_inhib, tau_inhib, step_t_mean, step_t_sd = params_GS
    step_t = np.random.normal(step_t_mean, step_t_sd)
    inhib = k_inhib * (1 - np.exp(-(t+step_t)/tau_inhib)) + inhib_tonic
    inhib = np.maximum(inhib, inhib_tonic)
    return inhib
```

```
#%%
def get_trials_facNew(params_facNew, facBimanual, t, n_rep=100000):
    '''
    Generates n_rep facilitation curves from additive Gaussian functions

    Parameters
    ----------
    params_facNew : sequence (2,) of float
        b_facGo_mean, b_facGo_sd for second facilitation curve
    facBimanual : array (t, n_rep)
        original facilitation curves

    Returns
    --------
    fac_i_new : array (t, n_rep)
        combined facilitation curves for all simulated trials
    '''
    a_facGo_mean = 2.6
    a_facGo_sd = 0.03
    b_facGo_mean, b_facGo_sd = params_facNew
    c_facGo_mean = 0.06
    c_facGo_sd = 0.01
    a_facGo = np.random.normal(a_facGo_mean, a_facGo_sd, size=n_rep)
    b_facGo = np.random.normal(b_facGo_mean, b_facGo_sd, size=n_rep)
    c_facGo = np.random.normal(c_facGo_mean, c_facGo_sd, size=n_rep)
    fac_i_new = np.zeros((n_rep, t.size))

    for i in range(n_rep):
        myparams_fac = a_facGo[i], b_facGo[i], c_facGo[i]
        fac_i_new[i] = get_facNew(t, myparams_fac, facBimanual[i])
    return fac_i_new

#%%
def get_facNew(t, params_new, facBimanual):
    '''
    Generates a single facilitation curve from additive Gaussian
 ↪  functions

    Parameters
    ----------
    params_new : sequence (3,) of float
        values for a_facGo, b_facGo, c_facGo
```

```
    Returns
    -------
    fac2 : array (t,)
        combined facilitation curve values at times `t`
    '''
    fac1 = facBimanual
    a_facGo, b_facGo, c_facGo = params_new
    fac2 = np.add(fac1, (a_facGo * np.exp(-(t - b_facGo)**2 /(2 *
 ↪  c_facGo**2))))
    return fac2

#%%
def get_fac_tms_vals(t, fac_i, pts=(-.15, -.125, -.1)):
    '''
    Gets values at pre-defined time points on all simulated facilitation
 ↪  curves

    Parameters
    -------------
    pts : sequence of floats
        time points for comparison to MEP amplitude values from
 ↪  experimental data

    Returns
    -------------
    valsXX : arrays, each of (n_rep,)
        value on all simulated facilitation curves at time point (in ms)
 ↪  requested
    '''
    idx150 = np.flatnonzero(np.isclose(t, pts[0]))
    vals150 = fac_i[:,idx150]
    idx125 = np.flatnonzero(np.isclose(t, pts[1]))
    vals125 = fac_i[:,idx125]
    idx100 = np.flatnonzero(np.isclose(t, pts[2]))
    vals100 = fac_i[:,idx100]
    return (vals150, vals125, vals100)

#%%
def get_GS_tms_vals(t, fac_i, activation_thresholds, inhib_tonic,
 ↪  pts=(-0.075, -0.05, -0.025)):
    '''
    Gets values at pre-defined time points as difference between
 ↪  facilitation
```

```
    curves and rise in inhibition curve above baseline

    Returns
    -------------
    predsXX : arrays, each of (n_rep,)
        values for difference at time point (in ms) requested
    '''
    index75 = np.flatnonzero(np.isclose(t, pts[0]))
    fac_values75 = fac_i[:, index75]
    inhib_step_values75 = activation_thresholds[:, index75]
    diff_inhib75 = inhib_step_values75 - inhib_tonic
    pred75 = fac_values75 - diff_inhib75
    index50 = np.flatnonzero(np.isclose(t, pts[1]))
    fac_values50 = fac_i[:, index50]
    inhib_step_values50 = activation_thresholds[:, index50]
    diff_inhib50 = inhib_step_values50 - inhib_tonic
    pred50 = fac_values50 - diff_inhib50
    index25 = np.flatnonzero(np.isclose(t, pts[2]))
    fac_values25 = fac_i[:, index25]
    inhib_step_values25 = activation_thresholds[:, index25]
    diff_inhib25 = inhib_step_values25 - inhib_tonic
    pred25 = fac_values25 - diff_inhib25
    return pred75, pred50, pred25

#%%
def get_emg_onsets_offsets(t, fac_i, inhib):
    '''
    Gets times when inhibition and facilitaiton curves intersect and
 ↪  slope of
    facilitation curve at first point of intersection. If facilitation
 ↪  curve
    doesn't cross inhibition curve twice (onset & offset), generates
 ↪  large error.

    Parameters
    -------------
    inhib : array (t,n_rep)
        inhibition curves for all simulated trials

    Returns
    -------------
    emg_onsets : array (n_rep,)
        time point when facilitation curves first rise above inhibition
```

```
    gradient : array (n_rep,)
        slope of facilitation curves at first intersection
    emg_offsets : array (n_rep,)
        time point when facilitation curves drop below inhibition
    '''
    ntrials = fac_i.shape[0]
    gradient = np.zeros(ntrials) + np.nan
    getinhib = fac_i < inhib
    switches = getinhib.astype(int)
    switches_diff = np.diff(switches)
    index_trials_onsets = np.nonzero(switches_diff == -1)
    index_trials_offset = np.nonzero(switches_diff == 1)
    emg_onsets = t[index_trials_onsets[1]]
    emg_offsets= t[index_trials_offset[1]]
    for i in range(ntrials):
        if np.all(switches[i] == 1):
            emg_onsets = np.append(emg_onsets, (1000 * (inhib[i,1] -
 ↪  fac_i[i].max()) + t[np.argmax(fac_i[i])]))
            emg_offsets = np.append(emg_offsets, (1000 * (inhib[i,1] -
 ↪  fac_i[i].max()) + t[np.argmax(fac_i[i])]))
        elif switches[i, -1] == 0:
            emg_offsets = np.append(emg_offsets, (1000 * (fac_i[i, -1] -
 ↪  inhib[i, -1]) + t[-1]))

    for trial, time_pt in zip(index_trials_onsets[0],
 ↪  index_trials_onsets[1]):
        rise = fac_i[trial, time_pt + 1] - fac_i[trial, time_pt - 1]
        run  = t[time_pt + 1] - t[time_pt - 1]
        gradient[trial] = rise / run
    return emg_onsets, gradient, emg_offsets

#%%
def get_emg_onsets_facNew(t, fac_i, inhib):
    '''
    Gets time when inhibition and facilitaiton curves first intersect
 ↪  and
    slope of facilitation curve at point of intersection. If
 ↪  facilitation curve
    doesn't cross inhibition curve, generates large error.
    '''

    ntrials = fac_i.shape[0]
    gradient = np.zeros(ntrials) + np.nan
```

```
    getinhib = fac_i < inhib
    switches = getinhib.astype(int)
    switches_diff = np.diff(switches)
    index_trials_onsets = np.nonzero(switches_diff == -1)
    emg_onsets = t[index_trials_onsets[1]]
    for i in range(ntrials):
        if np.all(switches[i] == 1):
            emg_onsets = np.append(emg_onsets, (1000 * (inhib[i,1] -
 ↪  fac_i[i].max()) + t[np.argmax(fac_i[i])]))

    for trial, time_pt in zip(index_trials_onsets[0],
 ↪  index_trials_onsets[1]):
        rise = fac_i[trial, time_pt + 1] - fac_i[trial, time_pt - 1]
        run  = t[time_pt + 1] - t[time_pt - 1]
        gradient[trial] = rise / run
    return emg_onsets, gradient

#%%
def get_chisquare(obs_data, obs_model, nbins=3):
    '''
    Calculates histograms for experimental and predicted data.
    Compares frequencies in each bin. Calculates one-way Chi-square
 ↪  test.

    Parameters
    --------------
    obs_data : array, 1-D, length of number of data points
        experimental data values
    obs_model : array (n_rep,)
        predicted values from simulated trials

    Returns
    ---------------
    Chi-square :  float
        Chi-square statistic for how well predicted data matches
 ↪  experimental data
    '''
    percentile_bins = np.linspace(0, 100, nbins + 1)
    bin_edges = np.percentile(obs_data, list(percentile_bins))
    hist_data, bin_edges  = np.histogram(obs_data,  bins=bin_edges)
    hist_data = hist_data / float(obs_data.size)
    hist_model, bin_edges = np.histogram(obs_model, bins=bin_edges)
    hist_model = hist_model / float(obs_model.size)
```

```
    return stats.chisquare(hist_data, hist_model)

#%%
def error_function_Go(params, data150, data125, data100, data_onsets,
 ↪  data_offsets):
    '''
    Compares experimental Go trial MEP and EMG data to values predicted
 ↪  from
    simulated Go trials. Calculates summed Chi-square.

    Parameters
    --------------
    params : sequence (8,) of float
        current mean and sd values for a_facGo, b_facGo, c_facGo, inhib
    dataXX : arrays, 1-D, each length of number of data points
        experimental Go trial MEP amplitudes and EMG onsets & offsets

    Returns
    ---------------
    X2_summed_Go : float
        statistic for how well predicted data matches experimental Go
 ↪  trial data
    '''
    print "Trying with values: " + str(params)
    fac_i, inhib_tonic, t = get_trials(params)
    pred150, pred125, pred100 = get_fac_tms_vals(t, fac_i)
    pred_onsets, pred_rates, pred_offsets = get_emg_onsets_offsets(t,
 ↪  fac_i, inhib_tonic)
    X2_onsets = get_chisquare(data_onsets, pred_onsets, nbins=2)[0]
    print "X2_onsets: ", X2_onsets
    X2_offsets = get_chisquare(data_offsets, pred_offsets, nbins=2)[0]
    print "X2_offsets: ", X2_offsets
    X2_150 = get_chisquare(data150, pred150, nbins=2)[0]
    print "X2_150: ", X2_150
    X2_125 = get_chisquare(data125, pred125, nbins=2)[0]
    print "X2_125: ", X2_125
    X2_100 = get_chisquare(data100, pred100, nbins=2)[0]
    print "X2_100: ", X2_100
    X2_summed_Go = X2_150 + X2_125 + X2_100 + X2_onsets + X2_offsets
    print "X2 summed: ", X2_summed_Go
    return X2_summed_Go

#%%
```

```
def error_function_GS(params_GS, params_Go, data75, data50, data25):
    '''
    Compares experimental GS trial MEP data to values predicted from
    simulated GS trials with single facilitaiton curve and raised
 ↪  threshold.
    Calculates summed Chi-square.

    Parameters
    --------------
    params_GS : sequence (4,) of float
        current values for k_inhib and tau_inhib, mean & sd for step_t
    params_Go : tuple (3,) of arrays, each of shape (t, nreps)
        fac_i, inhib_tonic, t generated from optimized Go parameters
    dataXX : arrays, 1-D, each length of number of data points
        experimental GS trial MEP amplitudes

    Returns
    -------
    X2_summed_GS : float
        statistic for how well predicted MEP data matches experimental
 ↪  GS trial data
    '''
    print "Trying with values: " + str(params_GS)
    fac_i, inhib_tonic, t = params_Go
    activation_thresholds = get_activation_thresholds(t, inhib_tonic,
 ↪  params_GS)
    pred75, pred50, pred25 = get_GS_tms_vals(t, fac_i,
 ↪  activation_thresholds, inhib_tonic)
    X2_75 = get_chisquare(data75, pred75, nbins=2)[0]
    print "X2_75: ", X2_75
    X2_50 = get_chisquare(data50, pred50, nbins=2)[0]
    print "X2_50: ", X2_50
    X2_25 = get_chisquare(data25, pred25, nbins=2)[0]
    print "X2_25: ", X2_25
    X2_summed_GS = X2_75 + X2_50 + X2_25
    print "X2_summed: ", X2_summed_GS
    return X2_summed_GS

#%%
def error_function_GS_facNew(params_facNew, activation_thresholds,
 ↪  components_Go, data_onsets, data_rates):
    '''
```

```
    Compares experimental GS trial EMG onset time and rate of onset data
 ↪  to
    values predicted from simulated GS trials with additive facilitaiton
 ↪  curves.
    Calculates summed Chi-square.

    Parameters
    --------------
    components_Go : tuple (3,) of arrays, each (t,n_rep)
        fac_i, inhib_tonic, t generated from optimized Go parameters
    dataXX : arrays, 1D, each length of data points
        experimental GS trial EMG onset times and rates

    Returns
    ---------------
    X2_summed_facNew : float
        statistic for how well predicted EMG data matches experimental
 ↪  GS trial
        data with combined facilitatory input
    '''
    print "Trying with value: " + str(params_facNew)
    fac_i, inhib_tonic, t = components_Go
    fac_i_new = get_trials_facNew(params_facNew, components_Go[0], t)
    pred_onsets, pred_rates = get_emg_onsets_facNew(t, fac_i_new,
 ↪  activation_thresholds)
    X2_onsets = get_chisquare(data_onsets, pred_onsets, nbins=2)[0]
    print "X2_onsets: ", X2_onsets
    X2_rates = get_chisquare(data_rates, pred_rates, nbins=2)[0]
    print "X2_rates: ", X2_rates
    X2_summed_facNew = X2_onsets + X2_rates
    print "X2_summed: ", X2_summed_facNew
    return X2_summed_facNew

#%%
def load_exp_data(fname):
    '''
    Gets data values from .csv file and removes NaNs

    Parameters
    --------------
    fname : string
        file path for experimental data
```

```
    Returns
    ---------------
    no_nan_data : array, 1-D, length of data points
        experimental data values with NaNs removed
    '''
    file_contents = np.genfromtxt(fname, dtype=float, delimiter=",")
    data  = file_contents.flatten()
    no_nan_data = data[~np.isnan(data)]
    return no_nan_data

#%%
# Loads experimental data
data_dir = ''

# Go trials
fname150 = data_dir + 'Go_MEP_amplitudes_150ms.csv'
fname125 = data_dir + 'Go_MEP_amplitudes_125ms.csv'
fname100 = data_dir + 'Go_MEP_amplitudes_100ms.csv'
exp_MEPs_150 = load_exp_data(fname150)
exp_MEPs_125 = load_exp_data(fname125)
exp_MEPs_100 = load_exp_data(fname100)
fnameGoThreeStimOnly = data_dir + 'Go_EMG_onsets.csv'
exp_EMG_onsets_three_stim = load_exp_data(fnameGoThreeStimOnly) / 1000 -
 ↪  .8  # /1000 to convert onset times into seconds, -0.8 to set
 ↪  relative to target line at 0ms
sim_data_Go_EMG_offsets = np.add(exp_EMG_onsets_three_stim, 0.107)  #
 ↪  sets EMG offset times based on empirical average burst duration of
 ↪  107 ms

# GS trials
fnameGS75 = data_dir + 'GS_MEP_amplitudes_75ms.csv'
fnameGS50 = data_dir + 'GS_MEP_amplitudes_50ms.csv'
fnameGS25 = data_dir + 'GS_MEP_amplitudes_25ms.csv'
exp_GS_MEPs_75 = load_exp_data(fnameGS75)
exp_GS_MEPs_50 = load_exp_data(fnameGS50)
exp_GS_MEPs_25 = load_exp_data(fnameGS25)
fnameGSStimOnsets = data_dir + 'GS_EMG_onsets.csv'
exp_GS_EMG_onsets_three_stim = load_exp_data(fnameGSStimOnsets) / 1000 -
 ↪  .8

#%%
def build_Go_GS():
    '''
```

```
    Optimizes parameters for facilitation and inhibtiion curves on Go
↪   and
    GS trials (with single facilitation curve)

    params_Go : sequence (8,) of float
        a_facGo_mean - average amplitude of Gaussian curve
        a_facGo_sd - standard deviation for amplitude of Gaussian curve
        b_facGo_mean - average time to peak of Gaussian curve
        b_facGo_sd - standard deviation for time to peak of Gaussian
↪   curve
        c_facGo_mean - average curvature of Gaussian curve
        c_facGo_sd - standard deviation for curvature of Gaussian curve
        inhib_mean - average value for tonic inhibition
        inhib_sd - standard deviation for tonic inhibition
    params_GS : sequence (4,) of float
        k_inhib - amplitude of step function
        tau_inhib - time constant of step function
        step_t_mean - 't' at step function onset
        step_t_sd - variation in step function onset
    '''
    # Example initial guess for Go parameters
    a_facGo_mean = 2
    a_facGo_sd = 0.2
    b_facGo_mean = 0.06
    b_facGo_sd = 0.02
    c_facGo_mean = 0.12
    c_facGo_sd = 0.01
    inhib_mean = 1.5
    inhib_sd = 0.3
    # Example initial guess for GS parameters
    k_inhib = 1.2
    tau_inhib = 0.8
    step_t_mean = 0.1
    step_t_sd = 0.02

    params_Go = [a_facGo_mean, a_facGo_sd, b_facGo_mean, b_facGo_sd,
↪   c_facGo_mean, c_facGo_sd, inhib_mean, inhib_sd]
    optGo = opt.minimize(error_function_Go, params_Go,
↪   args=(exp_MEPs_150, exp_MEPs_125, exp_MEPs_100,
↪   exp_EMG_onsets_three_stim, sim_data_Go_EMG_offsets),
↪   method='Nelder-Mead', tol=0.01)
    print "ParamsOptimizedGo", optGo
```

```
    params_Go = optGo.x # optimized parameter output from Go
↪   optimization function
    fac_i, inhib_tonic, t = get_trials(params_Go)
    components_Go = (fac_i, inhib_tonic, t)
    params_GS = [k_inhib, tau_inhib, step_t_mean, step_t_sd]
    optGS  = opt.minimize(error_function_GS, params_GS,
↪   args=(components_Go, exp_GS_MEPs_75, exp_GS_MEPs_50, exp_GS_MEPs_25),
↪   method='Nelder-Mead', tol=0.01)
    print "ParamsOptimizedGS", optGS

#%%
def build_GS_facNew():
    '''
    Generates original facilitation and inhibition curves from
↪   previously optimized
    parameters (input manually). Sets EMG rate of onset for GS trials at
↪   120% of Go trial values,
    as observed experimentally. Optimizes b_facGoNew mean and sd values
↪   for
    second facilitation curve on GS trials.

    params_facNew : sequence (2,) of float
        b_facGS_new_mean - average time to peak of second Gaussian curve
        b_facGS_new_sd - standard deviation for time to peak of second
↪   Gaussian curve
    '''
    # Optimized Go parameters
    a_facGo_mean = 2.57619299
    a_facGo_sd = 0.05308114
    b_facGo_mean = 0.00640317
    b_facGo_sd = 0.00782825
    c_facGo_mean = 0.06399041
    c_facGo_sd = 0.01087128
    inhib_mean = 1.79788944
    inhib_sd = 0.24566962
    # Optimized GS parameters
    k_inhib = 1.88698162
    tau_inhib = 0.05998707
    step_t_mean = 0.13339161
    step_t_sd = 0.01796852
    # Example initial guess for GS second facilitation curve
↪   (params_facNew)
    b_facGS_new_mean = 0.2
```

```
    b_facGS_new_sd = 0.05

    params_Go = [a_facGo_mean, a_facGo_sd, b_facGo_mean, b_facGo_sd,
 ↪  c_facGo_mean, c_facGo_sd, inhib_mean, inhib_sd]
    fac_i, inhib_tonic, t = get_trials(params_Go)
    components_Go = (fac_i, inhib_tonic, t)
    pred_onsets, pred_rates, pred_offsets = get_emg_onsets_offsets(t,
 ↪  fac_i, inhib_tonic)
    sim_data_GS_rates = np.multiply(pred_rates, 1.2)
    params_GS = [k_inhib, tau_inhib, step_t_mean, step_t_sd]
    activation_thresholds = get_activation_thresholds(t, inhib_tonic,
 ↪  params_GS)
    params_facNew = [b_facGS_new_mean, b_facGS_new_sd]
    optFacNew = opt.minimize(error_function_GS_facNew, params_facNew,
 ↪  args=(activation_thresholds, components_Go,
 ↪  exp_GS_EMG_onsets_three_stim, sim_data_GS_rates),
 ↪  method='Nelder-Mead', tol=0.01)
    print "ParamsOptimizedGSFacNew", optFacNew

#%%
if __name__ == "__main__":
    if sys.argv[1] == "first":
        build_Go_GS()
    elif sys.argv[1] == "second":
        build_GS_facNew()
    else:
        print "Unrecognized argument"
#%%
```

.

Appendix H

Participant Information Sheet

DEPARTMENT OF SPORT AND EXERCISE SCIENCE

THE UNIVERSITY OF AUCKLAND
NEW ZEALAND

Building 731, Tamaki Campus
Morrin Road, Glen Innes
Auckland, New Zealand
Telephone 64 9 373 7599 ext. 83766
Facsimile 64 9 373 7043

Head of Department Associate Professor
Greg Anson
Telephone 64 9 3737599 ext. 84681

The University of Auckland
Private Bag 92019
Auckland New Zealand

Participant Information Sheet

Title of Project: Falling off the curve - the link between impulsivity and dopamine

Researchers:
Ms Hayley MacDonald (PhD candidate)
Professor Winston Byblow
Dr Cathy Stinear
Ms April Ren
Ms Jennifer Chin
Dr Justin Kao
Ms Lorraine Macdonald
Dr Barry Snow
Dr James Coxon

You are invited to participate in the above named study. Please take your time to think about the information provided below, and feel free to discuss it with your whanau, family or significant other support people, before deciding whether to take part.

What is the study about?

The aim of the study is to understand how common Parkinson's disease medications may contribute to impulsivity in some individuals. The study will investigate impulsivity after the administration of the dopamine medication ropinirole, and its relation to genes affecting dopamine in the brain. This involves taking a blood sample for genetic analysis. Impulsivity will be investigated with two computerized tasks. The risk-reward task involves incrementally pumping up an on-screen balloon with the potential of earning a monetary reward in vouchers. The movement task involves lifting or cancelling the movement of one or two of your fingers from custom-made switches, in time with moving indicators on a computer display.

Am I eligible to participate?

You are eligible to participate in this study if you:

- are between the ages of 40 and 75
- have normal or corrected-to-normal vision
- have no neurological disorders
- are a non-smoker

If you volunteer for this study, you will be asked to complete questionnaires about handedness, impulsiveness and depression, and your motor and cognitive skills will be assessed. If you aren't eligible to participate, then any materials relating to you, such as the questionnaires, will be immediately destroyed.

What does the study involve?

The study will take 11 hours of your time and be completed over a one month period. An initial screening session (1 hour) will take place at the neurology day-stay unit in Auckland Hospital. Three testing sessions will each occur a week apart at the Clinical Neuroscience Laboratory at Auckland Hospital or Movement Neuroscience Laboratory at the University of Auckland Tamaki campus. The first session will last 4 hours and the next two will take 3 hours each. Taxi vouchers will be provided for your travel to the experimental sessions.

During the screening session you will undergo medical screening, assessments of cognitive and motor function, and provide a blood sample. A neurological registrar will screen your medical history and any current medications to ensure it is safe for you to participate. A research nurse will assess your motor and cognitive function and take a blood sample for analysis of genes which influence dopamine levels within the brain.

You will be asked to refrain from caffeine and alcohol on days of testing. During the first experimental session, you will complete a questionnaire to determine your handedness. You will be asked to complete questionnaires about impulsiveness and depression.

Each experimental session will proceed as follows. First, you will take 20 mg of domperidone followed an hour later by ropinirole. Then your body weight will be recorded. After another hour you will perform the computerized tasks. These tasks are designed to test your reaction time, risk-reward behaviour and cognitive skills. During the reaction time task we will record hand muscle activity using electromyography. This electrical activity is recorded using sensors positioned on the skin over the muscles of interest. The skin over the hand muscle must first be prepared by shaving hair and mild abrasion of the skin. This can result in a mild and transient irritation of the skin that does not require treatment.

Medication Side Effects

After the first time you take domperidone and each time you take ropinirole, there will be a one hour observational period. You are welcome to read during this time. Ropinirole is a dopamine medication commonly given to Parkinson's disease patients. It increases dopamine levels within the brain. It is known to be tolerated well by healthy participants, although some people may experience short-lasting side effects including nausea and drowsiness. Taking domperidone will reduce the risk of nausea. Side-effects from domperidone are rare, however some people may experience a dry mouth, dizziness, a headache or an irregular heartbeat. If at any stage you experience any of these side effects or feel unwell, please advise one of the researchers or medical professionals. You shouldn't drive or operate heavy machinery for up to 6 hours after taking ropinirole. The researchers will arrange taxis for your travel to and from experimental sessions if you require.

Blood Sample

You will be asked to provide a single blood sample for analysis of genes known to affect dopamine levels within the brain. Blood samples will be sent to the Liggins Institute (Faculty of Medical and Health Science, University of Auckland) for storage and analysis. Blood samples will be destroyed following analysis. You will not be informed of the results of your blood test as the gene variations that are being studied are all normal variations and not associated with any disease. Your sample will only be used for this purpose. We cannot test your blood for any other medical disorders or other abnormalities. All blood tests carry the usual small risk of bruising and subsequent infection. To minimize this risk, you will be advised to keep the sampling site covered with the dressing provided for at least 24 hours.

Some cultures may hold beliefs about a sacred and shared value of all or any tissue samples removed. There are a range of views held by Maori around these issues; some iwi disagree with storage of samples and genetic testing, citing whakapapa, and advise their people to consult prior to

participation in research where this occurs. However it is acknowledged that individuals have the right to choose. You will be provided with the option of having a blessing or karakia said when your tissues are disposed of.

Participation

Your agreement to participate in this project will be obtained in writing on a Consent Form. Your eligibility will be based on information gathered during the screening session, and whether it identifies the presence of any factors that may affect your ability to take part in the investigation. In the event that a condition which is assessed to be a clinical abnormality is detected, you will be informed of this and will be advised to consult your general practitioner or other health professional of your choice. If you do not wish to be informed of any abnormalities detected, then you should not participate in this study. If you have medical insurance, you are advised to consult your insurance company prior to participating. Your agreement to participate in the project will include your permission for the researchers to obtain the information that will allow your eligibility to be assessed.

Your participation is voluntary and you may withdraw from participating at anytime during the experiment without reason, and at your request we will stop the experiment. Researchers also reserve the right to withdraw participants from the study if, in the opinion of the researcher, participation is not in the best interests of the individual. You have the right to withdraw your data from this study up to 3 months after you complete the study. Withdrawal or non-participation will not affect your relationship with the researchers, the University or Auckland Hospital.

You will be assigned and identified by a code. The data obtained from this experiment will be stored securely in locked cabinets and on secure computer networks for a period of up to six years and will be used for publication in a scientific journal. After six years, your data will be deleted and your consent form and all related paperwork put through a shredder. No material that could personally identify you will be used in any reports in this study. Only the investigators will have access to this information, and your data will be made anonymous by assigning a unique code to it.

You may have your friend, family or whanau support help you understand the risks and/or benefits of this study and any other explanation you may require. You are also welcome to have a friend, family or whanau support with you during every session.You can request a summary of the study's results, which we can send to you once the project is complete.

Summary of Your Rights

- Your participation is entirely voluntary.
- You may withdraw from the project at any time without providing a reason.
- You may have your data withdrawn from the study within three months of your participation.
- The information and data collected from you will be stored securely, in locked cabinets and on secure computer networks. Only the investigators will have access to this information, and your data will be made anonymous by assigning a unique code to it.
- You may obtain results regarding the outcome of the project from the experimenters upon completion of the study.
- Your identity will be kept strictly confidential, and no identification of you or your data will be made at any time during collection of the data or in subsequent publication of the research findings.
- After six years, your data will be deleted from disk and your consent form and all related paperwork put through a shredder
- You are encouraged to consult with your whanau/family, hapu or iwi regarding participation in this project.

Compensation

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation, and Compensation Act 2001. ACC cover is not automatic, and your case will need to be assessed by ACC according to the provisions of the Injury Prevention, Rehabilitation, and Compensation Act 2001. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors, such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses, and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators. If you have any questions about ACC, contact your nearest ACC office or the investigators.

Who should I contact if I have further questions?

If you have any further questions about the study, or would like to participate in this study, please contact one of the following people:

Hayley MacDonald (PhD candidate)
Building 731, Tamaki Campus
Phone 373-7599 ext 84897
hayley.macdonald@auckland.ac.nz

or Professor Winston Byblow, Department of Sport and Exercise Science
Building 731 Room 342, phone 373-7599 ext 86844
Private Bag 92019, Auckland
w.byblow@auckland.ac.nz

or Associate Professor Greg Anson, Head of Department, Sport and Exercise Science
Building 731 Room 343, phone 373-7599 ext 84681
Private Bag 92019, Auckland
g.anson@auckland.ac.nz

If you have any questions or complaints about the study you may contact:

-
- The Auckland District Health Board by telephoning 09 367 000
- The Health and Disability Ethics Committee by telephoning 0800 4438 442 or via email at hdecs@moh.govt.nz
- The Auckland District Health Board Maori Research Committee or Maori Research Advisor by telephoning 09 4868920 ext 3204

If you require Māori cultural support, talk to your whānau in the first instance. Alternatively you may contact the administrator for He Kamaka Waiora (Māori Health Team) by telephoning 09 486 8324 ext 2324.

APPROVED BY THE NORTHERN A HEALTH AND DISABILITY ETHICS COMMITTEE on 18/12/2013 for a period of 2 years. Reference Number 13/NTA/215.

Appendix I

Consent Form

DEPARTMENT OF SPORT AND EXERCISE SCIENCE

THE UNIVERSITY OF AUCKLAND
NEW ZEALAND

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Telephone 64 9 373 7599 ext. 86887
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Head of Department Associate Professor
Greg Anson
Telephone 64 9 3737599 ext. 84681
g.anson@auckland.ac.nz

The University of Auckland
Private Bag 92019
Auckland New Zealand

Consent Form

THIS CONSENT FORM WILL BE HELD FOR A PERIOD OF SIX YEARS

Title of Project: Falling off the curve - the link between impulsivity and dopamine

Researchers:
Ms Hayley MacDonald (PhD candidate)
Professor Winston Byblow
Dr Cathy Stinear
Ms April Ren
Dr Justin Kao
Ms Lorraine Macdonald
Dr Barry Snow
Dr James Coxon

I have been given and understood the explanation of this research project and my role as a participant. I have had the opportunity to consult my whanau, hapu or iwi, or a family member/friend to help me ask questions. I have had time to consider whether to take part. I am satisfied with the answers I have been given. I know who to contact if I have any further questions about the study.

I have been informed that:

- the total time required for the study is approximately 11 hours, spread over 4 sessions
- the screening session may last up to 1 hour
- the first experimental session may last up to 4 hours, the second and third may each last up to 3 hours
- medical information will be obtained to determine my eligibility to participate
- any incidental findings and an appropriate course of action will be explained to me by the researchers. If I do not wish to be informed of incidental findings I will be excluded from participating
- I will be asked to provide a blood sample for genetic testing, which will be destroyed after analysis
- I will be asked to take domperidone and the dopamine medication ropinirole
- if I experience side effects from the medications, I am to to inform a researcher or medical professional
- I will be asked to complete cognitive and motor assessments, and computer-based cognitive and motor tasks
- my body weight will be recorded during each experimental session
- I will be asked to refrain from drinking caffeine or alcohol on the days of testing
- driving or operating heavy machinery for up to 6 hours after taking ropinirole is not advised
- compensation will be offered in the form of petrol or taxi vouchers for experimental sessions
- my participation is voluntary
- I may withdraw myself from the experiment at any time without giving a reason and it will not affect my relationship with the researchers, the University of Auckland or Auckland Hospital

DEPARTMENT OF SPORT AND EXERCISE SCIENCE

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The University of Auckland
Private Bag 92019
Auckland New Zealand

- researchers reserve the right to withdraw participants from the study if, in the opinion of the researcher, participation is not in the best interests of the individual
- I can withdraw any information traceable to me, from this study, up until three months after I have completed this study
- I may obtain results regarding the outcome of this experiment from the named researchers upon completion of the study
- after six years, my data will be deleted from disk and this consent form and all associated paperwork put through a shredder
- my anonymity will be maintained in any reporting of this research

If for some reason I am not eligible to participate in this research, I understand that all material relating to me will be immediately destroyed.

I agree to take part in this research during which I may be asked to:

- provide medical information to determine my eligibility to participate
- complete motor and cognitive assessments
- provide a blood sample for genetic testing
- complete questionnaires about handedness, impulsiveness, and depression
- take domperidone and the dopamine medication ropinirole
- perform computerized motor and cognitive tasks designed to test my reaction time, risk-reward behavior, and cognitive skills
- have the activity of hand muscles recorded by sensors placed on my skin

I give consent for a blood sample to be taken for genetic testing YES NO

I would like a blessing or karakia said when my tissues are disposed of YES NO

Which ethnic group do you belong to? _____

I would like the researchers to send me a summary of the study results YES NO
If YES: my email address is _____

I hereby consent to take part in this study

Signed:_____
Name:_____
(Please print name in full)

Date:_____

APPROVED BY THE NORTHERN A HEALTH AND DISABILITY ETHICS COMMITTEE on 18/12/2013 for a period of 2 years. Reference Number 13/NTA/215.

Appendix J

Barratt Impulsiveness Scale

DIRECTIONS: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and put an X on the appropriate circle on the right side of this page. Do not spend too much time on any statement. Answer quickly and honestly.

① Rarely/Never ② Occasionally ③ Often ④ Almost Always/Always

1	I plan tasks carefully.	①	②	③	④
2	I do things without thinking.	①	②	③	④
3	I make-up my mind quickly.	①	②	③	④
4	I am happy-go-lucky.	①	②	③	④
5	I don't "pay attention."	①	②	③	④
6	I have "racing" thoughts.	①	②	③	④
7	I plan trips well ahead of time.	①	②	③	④
8	I am self controlled.	①	②	③	④
9	I concentrate easily.	①	②	③	④
10	I save regularly.	①	②	③	④
11	I "squirm" at plays or lectures.	①	②	③	④
12	I am a careful thinker.	①	②	③	④
13	I plan for job security.	①	②	③	④
14	I say things without thinking.	①	②	③	④
15	I like to think about complex problems.	①	②	③	④
16	I change jobs.	①	②	③	④
17	I act "on impulse."	①	②	③	④
18	I get easily bored when solving thought problems.	①	②	③	④
19	I act on the spur of the moment.	①	②	③	④
20	I am a steady thinker.	①	②	③	④
21	I change residences.	①	②	③	④
22	I buy things on impulse.	①	②	③	④
23	I can only think about one thing at a time.	①	②	③	④
24	I change hobbies.	①	②	③	④
25	I spend or charge more than I earn.	①	②	③	④
26	I often have extraneous thoughts when thinking.	①	②	③	④
27	I am more interested in the present than the future.	①	②	③	④
28	I am restless at the theater or lectures.	①	②	③	④
29	I like puzzles.	①	②	③	④
30	I am future oriented.	①	②	③	④

Patton, Stanford, Barratt (1995). *J Clin Psy*, vol. 51, pp. 768-774

Appendix K

Beck Depression Inventory

BDI-II

Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying

0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

_____ Subtotal Page 1

Continued on Back

11. Agitation

0 I am no more restless or wound up than usual.

1 I feel more restless or wound up than usual.

2 I am so restless or agitated that it's hard to stay still.

3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.

1 I am less interested in other people or things than before.

2 I have lost most of my interest in other people or things.

3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.

1 I find it more difficult to make decisions than usual.

2 I have much greater difficulty in making decisions than I used to.

3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.

1 I don't consider myself as worthwhile and useful as I used to.

2 I feel more worthless as compared to other people.

3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.

1 I have less energy than I used to have.

2 I don't have enough energy to do very much.

3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.

1a I sleep somewhat more than usual.

1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.

2b I sleep a lot less than usual.

3a I sleep most of the day.

3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.

1 I am more irritable than usual.

2 I am much more irritable than usual.

3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.

1a My appetite is somewhat less than usual.

1b My appetite is somewhat greater than usual.

2a My appetite is much less than before.

2b My appetite is much greater than usual.

3a I have no appetite at all.

3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.

1 I can't concentrate as well as usual.

2 It's hard to keep my mind on anything for very long.

3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.

1 I get more tired or fatigued more easily than usual.

2 I am too tired or fatigued to do a lot of the things I used to do.

3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I am much less interested in sex now.

3 I have lost interest in sex completely.

3 4 5 6 7 8 9 10 11 12 A B C D E

Subtotal Page 2

Subtotal Page 1

Total Score

Scoring the Beck Depression Inventory

After you have completed the questionnaire, add up the score for each of the 21 questions. The following table indicates the relationship between total score and level of depression according to the Beck Depression Inventory.

Classification	Total Score	Level of Depression
Low	**1-10**	**Normal ups and downs**
	11-16	**Mild mood disturbance**
Moderate	**17-20**	**Borderline clinical depression**
	21-30	**Moderate depression**
Significant	**31-40**	**Severe depression**
	Over 40	**Extreme depression**

Appendix L

Ropinirole and Domperidone Safety Checklist

Title of Project: Falling off the curve - the link between impulsivity and dopamine

PARTICIPANT CHECKLIST FOR DOMPERIDONE AND ROPINIROLE PRESCRIPTION

Last name:_____

First names:_____

DOB:_____ dd/mm/yy

Sex: M/F

Please take a moment to carefully answer all questions

	Question:	**Yes/No**
1	Do you suffer from any neurological or psychiatric disorder?	
2	Do you have any other medical conditions such as heart, liver or kidney problems, diabetes, high or low blood pressure?	
3	Do you have a history of dizziness or fainting?	
4	Do you have any allergies or food intolerances?	
5	Is there any chance you could be pregnant or are you currently breast feeding?	
6	Do you currently smoke or have a nicotine patch?	
7	Do you take any prescription or non-prescription medication or drugs?	

Participant

Signature: _____

Date: _____

Title of Project: Falling off the curve - the link between impulsivity and dopamine

Comments:

Outcome ☐ Include ☐ Exclude

Consultation with neurology registrar

Name: Justin Kao

Signature: _____

Date: _____

Appendix M

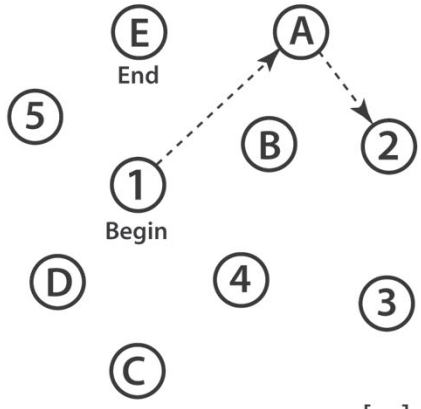
Montreal Cognitive Assessment

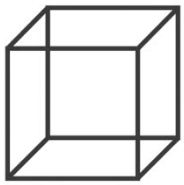
MONTREAL COGNITIVE ASSESSMENT (MOCA)

Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE





Copy cube

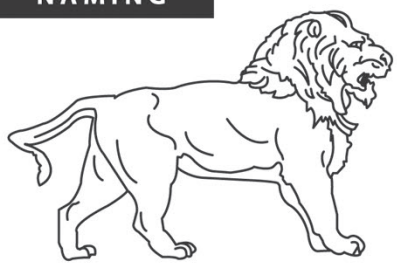
[ ] [ ]

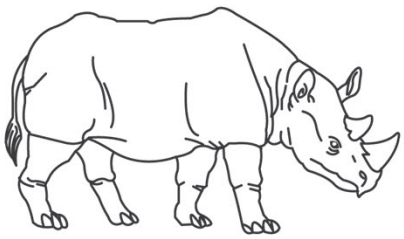
Draw CLOCK (Ten past eleven)
(3 points)

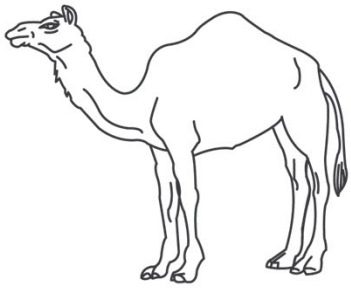
[ ] Contour [ ] Numbers [ ] Hands

POINTS ___/5

NAMING







[ ] [ ] [ ]

___/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

___/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

___/3

LANGUAGE

Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

___/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

___/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

___/2

DELAYED RECALL

	Has to recall words **WITH NO CUE**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

___/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

___/6

www.mocatest.org

Normal ≥ 26 / 30

TOTAL ___/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

Appendix N

Unified Parkinson's Disease Rating Scale Motor Section

Title of Project: Falling off the curve - the link between impulsivity and dopamine

UNIFIED PARKINSON'S DISEASE RATING SCALE

Participant code:_____

DOB:_____ dd/mm/yy

Sex: M/F

	MOTOR EXAMINATION	SCORE
18	**Speech** 0 = Normal. 1 = Slight loss of expression, diction and/or volume. 2 = Monotone, slurred but understandable; moderately impaired. 3 = Marked impairment, difficult to understand. 4 = Unintelligible.	
19	**Facial Expression** 0 = Normal. 1 = Minimal hypomimia, could be normal "Poker Face". 2 = Slight but definitely abnormal diminution of facial expression. 3 = Moderate hypomimia; lips parted some of the time. 4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.	
20	**Tremor at rest** (head, upper and lower extremities) 0 = Absent. 1 = Slight and infrequently present. 2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present. 3 = Moderate in amplitude and present most of the time. 4 = Marked in amplitude and present most of the time.	Face R Arm L Arm R Leg L Leg
21	**Action or Postural Tremor of hands** 0 = Absent. 1 = Slight; present with action. 2 = Moderate in amplitude, present with action. 3 = Moderate in amplitude with posture holding as well as action. 4 = Marked in amplitude; interferes with feeding.	R Hand L Hand
22	**Rigidity** (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.) 0 = Absent. 1 = Slight or detectable only when activated by mirror or other movements. 2 = Mild to moderate. 3 = Marked, but full range of motion easily achieved. 4 = Severe, range of motion achieved with difficulty.	Neck R Arm L Arm R Leg L Leg

23	**Finger Taps** (Patient taps thumb with index finger in rapid succession.) 0 = Normal. 1 = Mild slowing and/or reduction in amplitude. 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement. 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement. 4 = Can barely perform the task.	R Hand L Hand
24	**Hand Movements** (Patient opens and closes hands in rapid succession.) 0 = Normal. 1 = Mild slowing and/or reduction in amplitude. 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement. 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement. 4 = Can barely perform the task.	R Hand L Hand
25	**Rapid Alternating Movements of Hands** (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.) 0 = Normal. 1 = Mild slowing and/or reduction in amplitude. 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement. 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement. 4 = Can barely perform the task.	R Hand L Hand
26	**Leg Agility** (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.) 0 = Normal. 1 = Mild slowing and/or reduction in amplitude. 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement. 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement. 4 = Can barely perform the task.	R Leg L Leg
27	**Arising from Chair** (Patient attempts to rise from a straightbacked chair, with arms folded across chest.) 0 = Normal. 1 = Slow; or may need more than one attempt. 2 = Pushes self up from arms of seat. 3 = Tends to fall back and may have to try more than one time, but can get up without help. 4 = Unable to arise without help.	

28	**Posture** 0 = Normal erect. 1 = Not quite erect, slightly stooped posture; could be normal for older person. 2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side. 3 = Severely stooped posture with kyphosis; can be moderately leaning to one side. 4 = Marked flexion with extreme abnormality of posture.	
29	**Gait** 0 = Normal. 1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion. 2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion. 3 = Severe disturbance of gait, requiring assistance. 4 = Cannot walk at all, even with assistance.	
30	**Postural Stability** (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared) 0 = Normal. 1 = Retropulsion, but recovers unaided. 2 = Absence of postural response; would fall if not caught by examiner. 3 = Very unstable, tends to lose balance spontaneously. 4 = Unable to stand without assistance.	
31	**Body Bradykinesia and Hypokinesia** (Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.) 0 = None. 1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude. 2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude. 3 = Moderate slowness, poverty or small amplitude of movement. 4 = Marked slowness, poverty or small amplitude of movement.	

Appendix O

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