Applying the stop signal task to speech: neural and behavioural investigations of proactive and reactive inhibition

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Thesis abstract

It is interesting to investigate how the brain executes a response such as a spoken word or a manual action but perhaps even more intriguing to study how such responses are deactivated. This thesis focuses on response inhibition with a particular focus on inhibition of vocal responses. There are two types of response inhibition: proactive inhibition refers to withholding a response when a stop signal is imminent; in contrast, reactive inhibition requires countermanding an already initiated response at the appearance of a stop signal. In this thesis I examine the hypotheses (1) that greater level of proactive inhibition enhances reactive inhibition; (2) that manual and vocal responses are controlled by common central generators for response inhibition; (3) and that reactive and proactive inhibitions are less efficacious in the vocal compared to the manual effector system.

In chapter 1 I review the literature on response inhibition, clinical and non-clinical deficiencies in response inhibition and provide evidence for differences in the efficacy of response inhibition across the ocular, vocal and limb effector systems. In chapter 2 I compare both reactive and proactive inhibition across vocal and manual responses, the relationship between proactive and reactive inhibition and the effect of excitatory transcranial direct current stimulation (anodal tDCS) on response inhibition. In chapter 3 I develop a new task to explore proactive inhibition where response time is controlled within a sensorimotor synchronisation task. In chapter 4 I explore magnetoencephalographic (MEG) indices of vocal response inhibition in younger and older adults. In chapter 5 I measure the effect of proactive on reactive inhibition by varying the stop signal probability and explore the relationship between response inhibition and both functional and dysfunctional impulsivity trait measures.

The main findings in this thesis are threefold. First, greater level of proactive inhibition enhanced reactive inhibition. Second, vocal and manual reactive inhibitions are controlled by common central generators. Third, vocal relative to manual responding shows weaker reactive inhibition. These findings contribute to our understanding of vocal response inhibition and response inhibition enhancement, findings that could potentially contribute to the treatment of clinical and non-clinical response inhibition deficiencies. I address the implications of these findings in Chapter 6.

Statement

I certify that the research presented in this thesis has not previously been submitted for a higher degree nor has it been submitted as part of the requirements for a degree to any university or institution other than Macquarie University.

I also certify that this thesis presents my original work. I have appropriately acknowledged any help or assistance I received during the research presented in and the preparation of this thesis, as well as any sources of information I used.

The research presented in this thesis was approved by the Macquarie University Ethics Review Committee (Human Research). The studies in chapter 2 and 3 were approved with the ethics reference number HE29MAY2009-R06600; the study in chapter 4 was approved with the ethics reference number for was 5201300054 and the study in chapter 5 was approved with the ethics reference number 5201200035.

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Author note

All the work presented in this thesis has been performed under the PhD candidature at Macquarie University. This thesis has been prepared in the form of a 'Thesis by publication'. The reference style reflects the APA Publication Manual (6th edition). Chapter 2, 4 and 5 has a slightly different formatting, as they have already been published. Due to the 'Thesis by publication' format, there is a degree of repetition in some of the chapters, particularly in the introduction. I have tried to avoid repetition as much as possible whilst still allowing each chapter to stand on its own. In the general discussion, I added some information about the procedure of the experimental studies, as I wanted the reader to avoid going back to check for this crucial information. I am first author on the work of each experimental chapter.

Chapter 1 – General introduction

1. General introduction

1.1. Response inhibition

Inhibiting an action, thought or emotion because it is judged to be irrelevant, dangerous or inappropriate, is a function that both humans and non-human animals (at least in the case of actions) seem to perform effortlessly. This thesis focuses on studying inhibition via the response inhibition paradigm. Inhibition is important for our everyday lives, and deficiencies in response inhibition are associated with various neuropsychological disorders.

Response inhibition is described as the act of stopping a prepotent response (Aron, 2011; Logan, 1994; Logan & Cowan, 1984). In this thesis the prepotent response is either a spoken word or a button press. The main literature on response inhibition delineates between two types of response inhibition: reactive and proactive. Reactive inhibition refers to outright stopping at the appearance of a stop-signal (Logan, 1994; Logan & Cowan, 1984), whereas proactive inhibition describes the act of withholding a prepotent response when a stop-signal is thought to be imminent (Aron, 2011).

The assessment of response inhibition has employed a variety of experimental tasks that probe inhibitory control mechanisms that are thought to be vital in dealing with stimuli that are irrelevant to, or that interfere with, the task at hand. Among these tasks are the go/no-go task (de Jong, Coles, Logan, & Gratton, 1990; Drewe, 1975; Falkenstein, Hoormann, & Hohnsbein, 1999; Garavan, Ross, & Stein, 1999; Picton et al., 2007; Scangos & Stuphorn, 2010; Schachar et al., 2007; Smith, 2005), the stop-signal task (SST, Logan & Cowan, 1984; Verbruggen & Logan, 2008b), the anti-saccade task (Anderson, Husain, & Sumner, 2008; Butter, Rapcsak, Watson, & M, 1988; Hallett, 1978; Munoz & Everling, 2004; Walker, Husain, Hodgson, Harrison, & Kennard, 1998), the Stroop task (Bush et al., 1999; Jensen & Rohwer Jr, 1966; Potenza et al., 2003; Stroop, 1935), and the Eriksen flanker task (Eriksen & Eriksen, 1974; Heil, Osman, Wiegelmann, Rolke, & Hennighausen, 2000; Kopp, Rist, & Mattler, 1996; Wylie, Ridderinkhof, Eckerle, & Manning, 2007). However, it remains controversial whether the Stroop task or Eriksen flanker task isolate processes of response inhibition as opposed to other processes related cognitive control such as conflict resolution, response selection, attention or working memory (Nigg, 2000). This thesis

investigated response inhibition via the SST (i.e. stopping an ongoing response); I proceed to describe this task in more detail below.

1.1.1. The stop-signal task and the independent horse race model

Response inhibition as it is measured by the SST (Lappin & Eriksen, 1966; Logan & Cowan, 1984), describes the attempted (successful or not) countermanding of an already initiated response such that it does not proceed to completion. The SST classically consists of go and stop trials. There are now many variants of the SST, but in the most common design the go trials usually induced an overt response, which generally consist of simple or choice reaction time (RT) tasks (e.g. Logan & Burkell, 1986; Logan, Cowan, & Davis, 1984; Rieger & Gauggel, 1999). The modality of action most commonly studied in response inhibition experiments is manual, usually via button press responses (e.g. Logan & Burkell, 1986; Logan et al., 1984; Rieger & Gauggel, 1999). Other responses modalities have also been studied, albeit with a more limited coverage such as, speech (Cai, Oldenkamp, & Aron, 2012; Etchell, Sowman, & Johnson, 2012; Ladefoged, Silverstein, & Papçun, 1973; van den Wildenberg & Christoffels, 2010; Xue, Aron, & Poldrack, 2008), ocular movement (Logan & Irwin, 2000) and foot movement (De Jong, Coles, & Logan, 1995). The go-signal within the SST has usually been represented via visual channels (Cai et al., 2012; Etchell et al., 2012; Ladefoged et al., 1973; Logan & Burkell, 1986; Logan et al., 1984; Logan & Irwin, 2000; Rieger & Gauggel, 1999; Stahl & Gibbons, 2007; van den Wildenberg & Christoffels, 2010; Walsh & Haggard, 2010).

The design for the stop trials within the SST usually starts with a go-signal and after a given delay (i.e. the stop signal delay), a stop-signal is presented (Logan & Cowan, 1984). Participants are asked to stop any ongoing response and attempt not to complete their response. The stop-signal can be presented in the same sensory channel as the go-signal or can use a different channel. For example, the go-signal may be visually presented and the stop-signal auditory presented (e.g. Verbruggen & Logan, 2009b) or both go and stop signals could occur visually (e.g. Cai et al., 2012; Etchell et al., 2012; Ray Li, Huang, Constable, & Sinha, 2006; van den Wildenberg & Christoffels, 2010).

In addition to this classic SST design, in which the stop-signal is an imperative to stop a prepotent response, there are other forms of the task which require different forms of alteration to the prepotent response, such as the stop change task and the dual task (Logan

& Burkell, 1986). The stop-change task, for example, requires the subject to change the prepotent response to another overt response or to add a secondary response to the primary response (Donkers & van Boxtel, 2004). The RT difference between go trials and go trials with the stop-change task is usually small (~ 16 ms), suggesting that the inhibition induced in these tasks is smaller than that induced by the SST or that perhaps a no-stop inhibition task is faster than that of a stop-all responses inhibition task.

An additional variant of the SST is the selective inhibition task (Coxon, Stinear, & Byblow, 2007; Logan, 1994; Logan, Kantowitz, & Riegler, 1986; Riegler, 1986; van de Laar, van den Wildenberg, van Boxtel, & van der Molen, 2010; Verbruggen & Logan, 2008b). In this paradigm, there are more than two stop-signals and participants are asked to stop to one of them. The go and stop RTs are usually longer compared to those in the simple version of the SST (i.e. one stop-signal), suggesting that selective inhibition is more cognitively demanding than stop-all responses. Logan (1994) proposed that we have a global mode to stop all responses and a local mode to selectively stop an action within a group of actions. This idea has been further expanded by studies that have shown that when participants have foreknowledge of which response to stop in a selective inhibition task, they employ a selective stopping mechanism (Aron & Verbruggen, 2008). By contrast, recruitment of the global mechanism of inhibitory control halts the action of other irrelevant muscles along with those of the target effector (Badry et al., 2009; Coxon, Stinear, & Byblow, 2006; Sohn, Wiltz, & Hallett, 2002). Aron and Verbruggen (2008) concluded that a selective mechanism is employed when there is the need to control particular responses, whereas the global mechanism is used when stopping quickly is essential.

Finally, the independent race model (Logan, Yamaguchi, Schall, & Palmeri, 2015), proposed initially as the horse race model (Logan & Cowan, 1984) suggests there are two main processes enacted in the SST: a go and a stop process. Go trials within the SST allow a measure of the go process, whilst the relative success of stopping on the stop trials describes the stop process (Logan, 1994; Logan & Cowan, 1984). It is assumed that whichever process finishes first, wins – thus the eponymous analogy to a horse race (Logan & Cowan, 1984). If, following a stop signal, a participant successfully stops a prepotent response, the independent race model claims that the stop process was faster than the go process and thus reached completion first. Therefore, the response was successfully

stopped. Contrarily, following a stop signal, if the participant could not stop i.e. a response was enacted after the stop signal (failed stop), the model claims this occurred because the go process reached completion before the stop process. Therefore, the response was executed.

1.1.1.1. Assumptions and predictions of the independent race model

The independent race model assumes that the going and stopping processes are independent variables (Logan & Cowan, 1984). This assumption was developed when it was noticed that failed stop RTs are generally faster than go RTs, an observation that indicates that stopping fails because the go process completes before the stop process. Logan and Cowan (1984) noted that this assumption was important to simplify the formal development of the model but it does not need to be accepted, as most other types of dual-task show that concurrent processes are not independent (Kantowitz, 1974; Welford, 1952).

Based on the assumption of independence between going and stopping, the independent race model needs to be able to account for two main predictions. First, the go RT and the failed stop RT should not be different from an analogous single-task control (i.e. simple go RT). Second, the failed stop RT should be faster than the go RT and they should increase with the stop-signal delay.

1.1.1.2. Estimating reactive inhibition

As described previously, one type of response inhibition is reactive inhibition, that is, how participants stop a response outright when instructed by a stop-signal. There are three constituent measures within the SST: the stop-signal delay, the go RT and the inhibition function (i.e. the stop-signal RT). These measures are described in the following subsections. Importantly, reactive inhibition is a primary dependent variable in all of the experimental thesis chapters that follow.

1.1.1.2.1. <u>Estimating the stop-signal delay</u>

The stop-signal delay (SSD) refers to the time in a stop trial between the go-signal and the stop-signal. It is measured from the onset of the go-signal to the onset of the stop-signal. There are two approaches for obtaining a distribution of SSDs within the SST: either a set

of fixed-SSDs is employed or a continuous tracking procedure is used (Verbruggen & Logan, 2009a).

The fixed-SSD method uses a set of SSDs of fixed lengths and then, within the SST, these values are randomly assigned across the stop trials. For example, in Logan and Cowan (1984), 10 fixed SSDs were used from 50 to 500 ms with 50 ms increments. They found that the longer the SSD on a given stop trial, the lower the probability of successful stopping was.

In contrast, the tracking approach to setting SSD adjusts the SSD length dynamically according to the participant's performance (Logan, Schachar, & Tannock, 1997; Osman, Kornblum, & Meyer, 1986, 1990; Verbruggen & Logan, 2009a). The increment used to make these adjustments varies across studies; but for a general example: for a given increment of 50 ms the SSD will increase by 50 ms if a participant successfully stops following a stop signal, and will decrease by 50 ms if the participant fails to stop. Thus, the mean SSD can be obtained by averaging all SSDs across the experimental session or by averaging all SSDs within experimental blocks and then averaging across blocks (Verbruggen & Logan, 2009a). The aim of this procedure is to induce the same stopping performance in all subjects: a probability of unsuccessful stopping of 0.5.

1.1.1.2.2. Estimating the go reaction time

Estimating the go RT is a simple matter of measuring the time from the go-signal to the time of each participant's response. Then, either averaging all go RTs obtained across the experiment or, averaging go RTs within blocks and then averaging across blocks (Logan & Cowan, 1984; Verbruggen & Logan, 2008b).

1.1.1.2.3. Estimating stop-signal reaction time

The stop-signal RT (SSRT) is measured from the time to the stop-signal to the time of successful inhibition (i.e. probability of inhibiting: p_inhibit). The time of the stop-signal corresponds to the mean SSD whereas the time of the p_inhibit is unknown as no overt response is obtained on a successful stop trial. Thus, p_inhibit needs to be estimated. There are two methods for estimating the stop-signal RT (SSRT): the mean method and the integration method (Logan & Cowan, 1984).

To estimate the SSRT using the mean method we subtract the mean SSD from the mean of the go RTs. To estimate the SSRT based on the integration method, we calculate the probability of unsuccessful stopping (p_respond) and find the point at which the go RT distribution equals p_respond. This is done by multiplying the go-distribution by p_respond and returns the nth RT, which we assume corresponds to the finishing time of inhibition. Because this finishing time is based on the go RT, we need to subtract the SSD. Therefore, via the integration method, SSRT is estimated by subtracting the mean SSD from the nth RT.

It has been shown that the integration method and the mean method give the same estimation for the SSRT if in both methods the p_respond was 0.5 (Logan & Cowan, 1984; Verbruggen, Chambers, & Logan, 2013). It has also been shown that when the data is skewed or distorted by gradual slowing of go RT, the most robust method of SSRT estimation is the integration method and in particular when the SSRT is estimated for smaller blocks of trials prior to averaging across blocks (Verbruggen et al., 2013).

1.1.1.3. Estimating proactive inhibition

Proactive inhibition denotes the preparation to stop an upcoming prepotent response (Aron, 2011). Proactive inhibition is generated according to the aims of the subject rather than by the qualities of the stop-signal, it is based more on a 'hold-your-horses' hypothesis that puts a 'brake' on the prepotent response. To measure how much participants put a brake on their responses, the measure of proactive inhibition requires a control response, which is usually manifest as a go trial in a context that does not ever require stopping. Go responses can be manipulated on a trial-by-trial (Chikazoe, Jimura, Hirose, et al., 2009; Jahfari, Stinear, Claffey, Verbruggen, & Aron, 2010) or block-by-block basis (Verbruggen & Logan, 2009b), or in a strategic sense when accuracy is emphasized over speed (Bogacz, Wagenmakers, Forstmann, & Nieuwenhuis, 2010). In the case of trial-by-trial manipulation for example, proactive inhibition is estimated from the subtraction of experimental go trials (i.e. trials in which a stop signal may occur) and control go trials (i.e. go trials that are never followed by a stop-signal; Chikazoe, Jimura, Hirose, et al., 2009). Block-by-block manipulation of proactive inhibition refers to the case where there are blocks of only go trials (i.e. control go blocks) counterposed against other blocks that contain both go and stop trials (i.e. experimental go blocks). In this thesis, chapters 2 and 3

calculate proactive inhibition via a block-by-block manipulation whereas chapters 4 and 5 estimate proactive inhibition via a trial-by-trial manipulation.

1.1.2. The neural network for reactive inhibition

In chapters 2 and 3 specifically, we investigated the effect of a node in the inhibitory network on reactive and proactive inhibition. In the next section, I will describe the underlying neural networks that support reactive inhibition. The neural network for reactive inhibition is not well understood. While it is more clear for the oculomotor system (eye), understanding is less advanced for the corticospinal system (Stuphorn, 2015) and even less clear for the corticobulbar system (jaw movements and some speech movements). Converging evidence suggests there are a number of different brain areas involved in reactive inhibition that include: the ventrolateral prefrontal cortex (VLPFC), the medial prefrontal cortex (medial PFC), the basal ganglia and the motor cortex (for reviews see Aron, 2011; Chambers, Garavan, & Bellgrove, 2009; Mostofsky & Simmonds, 2008; Stuphorn, 2015).

1.1.2.1. The ventrolateral prefrontal cortex

The VLPFC is part of the prefrontal cortex, primarily overlapping anatomically with the inferior frontal gyrus (IFG) and being attributed to the anatomical structures of Brodmann's areas (BA) 47, 45 and 44. It is considered to be approximately equivalent to anterior (pars orbitalis), mid (pars triangularis) and posterior (pars opercularis) subregions of the IFG respectively. The VLPFC has been shown to be essential for successful stopping (Aron, Durston, et al., 2007; Aron, Robbins, & Poldrack, 2004). In particular, subjects with lesions to the right pars opercularis exhibit significant lengthening of the SSRT (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003) compared to healthy controls, and increased variability of inhibitory responses (Picton et al., 2007). Moreover, the amount of damage to the right VLPFC has been positively correlated with the length of the SSRT (Aron et al., 2003). The role of VLPFC in response inhibition has further been confirmed by transcranial magnetic stimulation (TMS) studies that show increase SSRT associated with TMS-induced 'virtual lesions' to the right VLPFC (Chambers et al., 2007; Chambers et al., 2006; Verbruggen, Aron, Stevens, & Chambers, 2010) and a reduction of the motor-evoked potential (MEP) 75 ms after the initiation of a reprogramming task, which suggests an inhibitory effect of the VLPFC on a prepotent response change (Buch, Mars, Boorman, & Rushworth, 2010). Direct electrical stimulation of the right VLPFC

generates inhibition of ongoing movements (for a review see Filevich, Kühn, & Haggard, 2012) and excitatory (anodal) transcranial direct current stimulation (tDCS) to the right VLPFC decreases the SSRT of manual responses in control subjects (Ditye, Jacobson, Walsh, & Lavidor, 2012; Jacobson, Javitt, & Lavidor, 2011). Functional magnetic resonance imaging (fMRI) studies have also reported that the right VLPFC is activated when participants successfully stop a manual response (Aron & Poldrack, 2006; Aron et al., 2004; Chikazoe, Jimura, Asari, et al., 2009; Garavan, Hester, Murphy, Fassbender, & Kelly, 2006; Garavan et al., 1999; Rubia, Russell, et al., 2001; Rubia, Smith, Brammer, & Taylor, 2003; Sharp et al., 2010), irrespective of whether the subjects used the left or right hand (Konishi et al., 1999). The right VLPFC is also activated by successful stopping of vocal responses (Xue et al., 2008) and saccadic eye movements (Leung & Cai, 2007). A positron emission tomography (PET) study of the Go/No-Go task found greater activation in the right VLPFC in no-go trials compared to go trials (Kawashima et al., 1996). In macaque monkeys, response inhibition activates the macaque homologue of the ventral prefrontal cortex (Morita, Nakahara, & Hayashi, 2004). The macaque homologue of the ventral PFC induces inhibitory deficits when it is microstimulated or lesioned (Hasegawa, Peterson, & Goldberg, 2004; Iversen & Mishkin, 1970; Lüders et al., 1988; Sakagami et al., 2001; Sasaki, Gemba, & Tsujimoto, 1989). It can be stated therefore that the right VLPFC plays an important role in response inhibition, not only in the manual effector system but also in the vocal and oculomotor systems.

1.1.2.2. The dorsolateral and medial prefrontal cortex

The dorsolateral and medial PFC, parts of the prefrontal cortex, are located in the middle frontal gyrus and subdivided into the dorsolateral prefrontal cortex (DLPFC), supplementary motor area (SMA) and pre-supplementary motor area (pre-SMA). The DLPFC corresponds to the anatomical structures of BA 9 and 46 (Hoshi, 2006); the SMA and pre-SMA correspond to BA 6 (Akkal, Dum, & Strick, 2007). BA 6 also contains the premotor cortex, which will be described in more detail in the subsequent section. For a review of the functional role of the SMA and pre-SMA see Nachev, Kennard, and Husain (2008).

Evidence shows that lesions to the dorsolateral and medial PFC cause inhibitory deficits in actions controlled by the corticospinal system (Décary & Richer, 1995; Floden & Stuss, 2006; Picton et al., 2007). For example, patients who have had excision of the DLPFC,

anterior cingulate and SMA display an increased rate of omission and commission errors in a go/no-go task compared to patients with temporal excisions and controls (Décary & Richer, 1995); damage to the right SMA/pre-SMA causes SSRTs to be longer in patients than in controls (Floden & Stuss, 2006). Damage to the left SMA/pre-SMA has also been observed to be correlated with increased numbers of commission errors (Picton et al., 2007). Interestingly, damage to the pre-SMA but not to the SMA results in longer stopping time in the presence of response conflict (Nachev, Wydell, O'Neill, Husain, & Kennard, 2007). Moreover, TMS applied to the pre-SMA disrupts the ability to stop in response to a stop-signal (C. Y. Chen, Muggleton, Tzeng, Hung, & Juan, 2009; Mars et al., 2009). Electrical stimulation to the pre-SMA causes arrest of manual movements and speech (Fried et al., 1991; Lüders et al., 1988). Moreover, recording of pre-SMA neurons in monkeys (Isoda & Hikosaka, 2007), has shown that they are selectively activated when switching from an automatic to a controlled action, suggesting a role for pre-SMA in controlling a prepotent response in order to change an action. fMRI studies showed that the DLPFC is activated for response inhibition (Garavan et al., 2006). In sum, the DLPFC, SMA and pre-SMA are important areas for response inhibition (Aron, 2007; Chambers et al., 2009).

1.1.2.3. Basal ganglia

The basal ganglia are functionally divided into the striatum (caudate nucleus and putamen), the globus pallidus, the substantia nigra (pars compacta and pars reticulata), the nucleus accumbens and the subthalamic nucleus (Fix, 2008). The striatum receives input from many brain areas and sends inhibitory output to motor-related areas; The globus pallidus sends output to the substantia nigra; In the substantia nigra, the pars compacta serves as input to the basal ganglia circuit and the pars reticulata acts as an output. The subthalamic nucleus (STN) receives input mainly from the striatum and the cerebral cortex (namely the pre-SMA and the right IFG (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Inase, Tokuno, Nambu, Akazawa, & Takada, 1999) and sends output to the globus pallidus.

It has been shown that lesions to the basal ganglia make SSRTs longer (Rieger, Gauggel, & Burmeister, 2003), whereas deep brain stimulation to the subthalamic region enhances reactive inhibition – reducing SSRT (van den Wildenberg et al., 2006), but seems to increase commission errors in no-go trials in patients with Parkinson's disease (Ballanger et al., 2009; Hershey et al., 2004). fMRI performed during the SST reveals activation of

the subthalamic nucleus on successful stop trials (Aron & Poldrack, 2006; Ray Li, Yan, Sinha, & Lee, 2008). In rodents, lesions to the striatum increased the SSRT by up to 60% (Eagle & Robbins, 2003), although the striatum has recently been more related with proactive inhibition. Its role in inhibitory control will therefore be described in more detail in the following section on proactive inhibition.

It has also been shown in rats that neurons of the substantia nigra pars reticulata (SNr) respond to stop cues on successful inhibition trials (Schmidt, Leventhal, Mallet, Chen, & Berke, 2013), reflecting the input of two distinct processes: cue-related excitation from the STN (i.e. the go process) and movement-related inhibition from the striatum (i.e. the stop process).

1.1.2.4. Posterior cingulate gyrus

The posterior cingulate gyrus (PCG) is a subdivision of the cingulate gyrus (CG), which corresponds to BA 31. It has been reported as an area that is more strongly activated by successful compared to failed inhibitions in an fMRI study that tested manual response inhibition via the SST (Ray Li et al., 2006). MEG studies also report that the field distribution for a peak at around 160 ms that is larger in amplitude for successful stop compared to failed stops, was generated in bilateral posterior cingulate gyrus (PCG, Boehler et al., 2009; Luus, Van Snellenberg, & Liotti, 2007).

1.1.2.5. The motor cortex

The motor cortex is divided into the primary motor cortex (M1), the premotor cortex (PMC) and the supplementary motor area (SMA). In this section I focus on M1 and the PMC, as the SMA was discussed as part of the section on the role of medial prefrontal cortex in response inhibition. The M1, corresponding approximately to BA 4, largely contains giant pyramidal neurons known as Betz cells (in layer V) and other cortical neurons that send long axons directly to the spinal cord where they synapse with alpha motor neurons. The PMC shares BA 6 with the SMA and the pre-SMA. As with M1 it sends projections directly to the spinal cord and also to the striatum, the motor thalamus and other brain areas (He, Dum, & Strick, 1995). For reviews see (Stinear, Coxon, and Byblow (2009); Stuphorn (2015)).

The M1 is the final cortical processing area for the execution of motor commands before they descend to the spinal cord. Inhibitory networks in this area are important for the prevention and suppression of movement (Stinear et al., 2009). Corticospinal excitability and intracortical inhibition can be assessed via TMS-based measures such as the motor-evoked potential (MEP) and the cortical silent period (CSP) respectively (Roshan, Paradiso, & Chen, 2003). It has been shown that for the execution of a voluntary movement, intracortical inhibition in the M1 is reduced (Chikazoe, Jimura, Hirose, et al., 2009) followed by increase in corticospinal excitability; whereas, for movement cancelation, intracortical inhibition is increased in the M1 (for a review see Stinear et al., 2009). Even small levels of voluntary activation of a muscle reduce intracortical inhibition (Reynolds & Ashby, 1999; Ridding, Taylor, & Rothwell, 1995) and increase corticospinal excitability (Burle, Bonnet, Vidal, Possamai, & Hasbroucq, 2002; R. Chen, Yaseen, Cohen, & Hallett, 1998; Hoshiyama et al., 1996; Leocani, Cohen, Wassermann, Ikoma, & Hallett, 2000; MacKinnon & Rothwell, 2000; Schneider, Lavoie, Barbeau, & Capaday, 2004). In monkeys, application of a GABA antagonist to the PMC reduces the ability to withhold an arm movement, suggesting that GABA-ergic inhibition in the PMC suppresses movement initiation (Sawaguchi, Yamane, & Kubota, 1996). In short, the motor cortex is one of the final agents of response inhibition and therefore plays an important role in suppressing action. Inhibitiory control mechanisms in the M1 and PMC have been mostly studied in the corticospinal and cortico-ocular system (Stuphorn, 2015) but much less investigation of response inhibition has been done in the corticobulbar system (important for the control of speech).

1.1.2.6. The spinal cord

There is a recent account that contends an important role for spinal circuits in response inhibition (Stuphorn, 2015). Furthermore, two concurrent inhibitory mechanisms have been described during response preparation (Duque, Lew, Mazzocchio, Olivier, & Ivry, 2010), one that acts at the cortical level to determine what response to make by suppressing the excitability of muscles globally as revealed by a decrease in both the MEP and the H-reflex. Another mechanism, possibly acting at the level of the spinal cord, only suppresses the relevant muscles reflected by a suppression of the MEP but not the H-reflex in the selected effector. This spinal inhibitory mechanism has also been described in primates, where inhibitory spinal interneurons have been shown to increase their firing

before movement onset (Cohen, Sherman, Zinger, Perlmutter, & Prut, 2010; Prut & Fetz, 1999; Stuphorn, 2015).

In summary, a right-lateralized canonical network for reactive inhibition has been described that contains the VLPFC, the medial PFC, the PCG and the basal ganglia (for reviews see Aron, 2011; Stuphorn, 2015). The output of this network is expected to influence those cortical areas underlying movement preparation and initiation, i.e., the M1 and the PMC and the spinal cord (as the final agent for spinal inhibition of movement) (Mattia et al., 2012; Stuphorn, 2015). This inhibitory network is structurally and functionally connected (Aron, Behrens, et al., 2007; Aron & Poldrack, 2006; Inase et al., 1999; Johansen-Berg et al., 2004; Magill, Sharott, Bevan, Brown, & Bolam, 2004; Maurice, Deniau, Glowinski, & Thierry, 1998; Nambu, Tokuno, & Takada, 2002) and may be functionally connected via oscillatory activity in the canonical beta band (~16 Hz, Kühn et al., 2004; Swann et al., 2009). As the spinal cord is a final agent for corticospinal inhibition, there should be homologous inhibitory interneurons, which act on the lower motor neurons of other effector systems.

1.1.3. The neural network for proactive inhibition

It has been found that the same network for reactive inhibition (i.e. right VLPFC, pre-SMA and the STN) is activated for proactive inhibition: the greater the amount of proactive inhibition, the more activity in these areas is observed (Jahfari, Stinear, Claffey, Verbruggen, & Aron, 2010). Other areas have also been reported to be involved in proactive inhibition such as the DLPFC and the striatum (X. Chen, Scangos, & Stuphorn, 2010; Chikazoe, Jimura, Hirose, et al., 2009; Hester et al., 2004; Majid, Cai, Corey-Bloom, & Aron, 2013; Stuphorn, Brown, & Schall, 2010; Vink et al., 2005). It has also been found that deep brain stimulation applied to the STN decreases proactive inhibition and concurrently activity in the right VLPFC (Ballanger et al., 2009). People with Huntington's disease who present with striatal and pallidal volume reductions exhibit an absence of proactive motor suppression (Majid et al., 2013). In macaque monkeys, earlier activation of the SMA, as measured by intracranial local field potentials (LFP), predicts successful inhibition of arm movements (X. Chen et al., 2010). In short, it seems that proactive inhibition pre-activates the network for reactive inhibition and therefore, as the behavioural evidence demonstrates, the greater the amount of proactive inhibition, the shorter is the

time needed to reactively stop (Aron, 2011; Chikazoe, Jimura, Hirose, et al., 2009; Jahfari et al., 2010).

1.1.4. Neurophysiological signatures of response inhibition

Understanding the temporal markers of response inhibition is important to better understand how response inhibition is executed in the brain. Most data describing the temporal evolution of neural activations related to response inhibition comes from event-related potential (ERP) studies that have utilised electroencephalography (EEG) mostly extracranially but also intracranially (i.e. Mattia et al., 2012; Swann et al., 2009). A few studies also describe the temporal correlates of response inhibition via magnetoencephalography (MEG). The temporal evolution of response inhibition (mostly reactive inhibition) is characterised in ERP studies with a fronto-central N2/P3 and later error recognition peaks.

In general, the inhibition-associated ERP exhibits larger amplitudes compared to no-stop signal trials (i.e. go trials) (Dimoska & Johnstone, 2008; Etchell et al., 2012; Zordan, Sarlo, & Stablum, 2008). The N2 in ERP studies refers to a negativity that peaks at about 200 ms (ranges described from 175 – 300 ms) after the appearance of the stop signal. Some studies have reported that the N2 amplitude is larger when it is evoked by successful stops compared to failed stops (Liotti, Pliszka, Higgins, Perez Iii, & Semrud-Clikeman, 2010; Schmajuk, Liotti, Busse, & Woldorff, 2006) but other studies have reported exactly the opposite (Dimoska, Johnstone, Barry, & Clarke, 2003; Greenhouse & Wessel, 2013; Kok, Ramautar, De Ruiter, Band, & Ridderinkhof, 2004; Ramautar, Kok, & Ridderinkhof, 2004) whereas other studies have not found it (Bekker, Kenemans, Hoeksma, Talsma, & Verbaten, 2005). It is unclear why such contradictory findings exist.

The stop-related P3 refers to a positive ERP waveform that peaks at about 300 ms (ranges described from 200 – 744 ms) after the stop signal. It has been consistently shown that the P3 is larger for successful stops compared to failed stops (Bekker et al., 2005; Dimoska et al., 2003; Greenhouse & Wessel, 2013; Lansbergen, Böcker, Bekker, & Kenemans, 2007; Liotti et al., 2010; Wessel & Aron, 2014; but see Ramautar et al., 2004). An interesting aspect of the stop-related P3 is that its onset latency is correlated with the behavioural SSRT (Wessel & Aron, 2014).

Later response-inhibition related ERP peaks described as occurring between 370 and 650 ms after the stop signal presentation (so-called 'error recognition peaks') have been reported with various names and scalp topographies. However, all such reports agree on the observation that the amplitude of ERPs evoked by failed stopping are larger than those evoked by successful stopping. One of the first reports of these effects termed them N_e and P_e, -- negative and positive error-related ERPs -- respectively. These ERPs were elicited when people had reaction errors in choice RT tasks (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Falkenstein et al., 1999). At first, it was thought that such ERPs were elicited only for response errors and more recently with error awareness (Murphy, Robertson, Allen, Hester, & O'Connell, 2012) but other studies have reported that they could be elicited for correct reactions albeit with smaller amplitudes (F. Vidal, Hasbroucq, Grapperon, & Bonnet, 2000). In tasks like the SST, later, error-related peaks have been reported as a later P3 called the P3b that occurs mainly in posterior areas of the scalp. The P3b elicited in during the SST is larger for failed stops relative to successful stops and no-stop-signal trials (Greenhouse & Wessel, 2013; Kok et al., 2004; Ramautar et al., 2004; Schmajuk et al., 2006; Squires, Squires, & Hillyard, 1975).

There are still no clear explanations as to why the N2 and P3 amplitude related-ERPs for successful stopping are sometimes larger than for failed stops and in other studies they are smaller. There is only one study that has found a significant relationship between stopping latencies and the onset of the P3 (Wessel & Aron, 2014). They found that the earlier the P3 onset, the shorter the SSRT, which is what would be expected if this ERP reflects reactive inhibition: the independent race model asserts that the cortical command for stopping should be executed before the actual movement occurs milliseconds later.

The event-related fields (ERFs) for MEG studies of response inhibition have reported that an inhibition-ERF waveform, (peaking at around 165 ms), was larger in amplitude for successful stopping compared to failed stopping (Boehler et al., 2009; Luus et al., 2007). An MEG study also reported that theta and alpha frequency oscillations in the right IFG are associated with the stopping process (Jha et al., 2015)

1.1.5. Deficiencies of response inhibition in clinical and non-clinical populations

Deficiencies of response inhibition (i.e. go RT, SSRT) have been reported in neuropsychological disorders and also in non-clinical populations, which suggests these populations may have a common deficit in inhibitory control. These deficiencies are described in turn.

1.1.5.1. Clinical deficiencies and response inhibition

Inhibitory control deficiencies have been found in attention-deficit hyperactivity disorder (ADHD; Aron & Poldrack, 2005; Barkley, 1997; Rubia, Russell, et al., 2001), schizophrenia (Enticott, Ogloff, & Bradshaw, 2008; Kiehl, Smith, Hare, & Liddle, 2000), obsessive-compulsive disorder (OCD) and trichotillomania (Bohne, Savage, Deckersbach, Keuthen, & Wilhelm, 2008; Menzies et al., 2007; Penadés et al., 2007), Tourette syndrome (Ziemann, Paulus, & Rothenberger, 1997), chronic pain (Glass et al., 2011; Veldhuijzen, Sondaal, & Oosterman, 2012), developmental stuttering (Eggers, De Nil, & Van den Bergh, 2013) and illicit drug users and smokers (Hester & Garavan, 2004; Hester, Lubman, & Yücel, 2010; Luijten et al., 2013).

Behaviourally, ADHD populations have longer SSRTs (for reviews see Aron & Poldrack, 2005; M Lijffijt, Kenemans, Verbaten, & Van Engeland, 2005; Nigg, 2005) and exhibit smaller total cerebral volume and smaller prefrontal cortices (for a review see Giedd, Blumenthal, Molloy, & Castellanos, 2001), particularly affected is the volume of the right VLPFC (Aron & Poldrack, 2005). Under-activation of the VLPFC, DLPFC, caudate nucleus and globus pallidus is observed in ADHD relative to control groups during the performance of inhibitory tasks (for a review see Chambers et al., 2009). It has also been reported that response inhibition related to event-related potentials (ERP) are smaller in amplitude in ADHD (Dimoska et al., 2003).

Studies on schizophrenic populations have also noted that SSRTs are significantly longer relative to controls (Enticott et al., 2008) and that schizophrenics are more prone to interference in the Stroop task (Thoma, Wiebel, & Daum, 2007).

OCD research has reported longer SSRTs relative to controls, a smaller percentage of successful stops in a go/no-go task and higher interference in the Stroop task (Menzies et

al., 2007; Penadés et al., 2007). At the structural level, people with OCD and their relatives exhibit reduced grey matter in orbitofrontal and VLPFC and increased grey matter in cingulate, parietal and striatal regions (Menzies et al., 2007).

Research on trichotillomania has reported that in a go/no-go task, this group tended to perform either 'fast and inaccurate' or 'slow and accurate' compared to OCD and healthy control groups (Bohne et al., 2008).
Research in chronic pain has reported that patients with fibromyalgia perform as well as controls on both RT and accuracy in a go/no-go task. However, differences exist in the neural activations that underpin these behaviours; specifically, fibromyalgia patients had lower activation in the right premotor cortex, SMA midcingulate cortex, putamen and VLPFC (Glass et al., 2011). The authors of this study concluded that response inhibition and the development of chronic pain may rely on partially overlapping neural networks.

1.1.5.1.1. Research on speech disorders

TMS research on Tourette syndrome reported that, compared to a control group, the Tourette group had shorter cortical silent periods and reduced intracortical inhibition, suggesting that the deficiencies of inhibitory control that exists behaviourally is the result of inhibitory deficiencies at the cortical level (Ziemann et al., 1997).

Finally, Eggers et al. (2013) found that children who stutter exhibited more false alarms, more premature responses and showed slower reaction times for false alarms compared to age-matched controls in a go/no-go task. Stutters also exhibit larger amplitude error-recognition ERP waveforms (i.e. error-related negativity and error positivity) compared to controls, suggesting that stuttering may be due to over-monitoring the speech plan (Arnstein, Lakey, Compton, & Kleinow, 2011). In a TMS study investigating short-term intracortical inhibition (SICI) and excitability of the tongue M1, Neef, Paulus, Neef, von Gudenberg, and Sommer (2011) showed that adults who stutter exhibit a reduction of SICI and intracortical facilitation compared to controls.

In sum, clinical neuropsychological disorders (i.e. ADHD, schizophrenia, OCD, trichotillomania, Tourette syndrome, chronic pain, developmental stuttering, drug users and smokers) share deficiencies in response inhibition, which not only encompass slower

go and stop RTs but also extend to under-activation of the right VLPFC, DLPFC, SMA and the basal ganglia, and reduced ERP amplitudes evoked by stop signals compared to control conditions. Interestingly, Tourette syndrome and stuttering (both disorders that affect speech) share reduced intracortical inhibition compared to controls. Although, it is still unclear whether inhibitory deficiencies cause the aforementioned neuropsychological disorders or whether these inhibitory deficiencies are a result of other problems, understanding how response inhibition functions may help us to understand and develop methods to treat or even prevent these neuropsychological disorders.

1.1.5.2. Non-clinical deficiencies and response inhibition

Response inhibition has also been related to non-clinical deficiencies; namely impulsivity traits in non-clinical adults, and aging. Based on the I7 questionnaire (S. B. Eysenck & Eysenck, 1978) individuals with high impulsivity scores had longer manual SSRTs (Lansbergen et al., 2007) compared to people with low impulsivity scores. In another study, van den Wildenberg and Christoffels (2010) measured impulsivity via the Dickman's impulsivity inventory (Dickman, 1990), which dissociates between functional and dysfunctional impulsivity. Functional impulsivity is defined as rapid responding in situations when impulsivity is optimal and adaptive, whereas dysfunctional impulsivity refers to rapid reactions when impulsivity is less optimal or adaptive. In contrast to Lansbergen et al. (2007) this study found that only dysfunctional impulsivity had a positive relationship with the vocal SSRT (not manual SSRT), indicating that adults with high scores on dysfunctional impulsivity were the slowest on verbal reactive inhibition (van den Wildenberg & Christoffels, 2010). The authors did not explain why their results differ from those of the previous study.

Another interesting relationship of response inhibition occurs in the normal ageing process. Behaviourally, older relative to younger adults have longer SSRTs (Bedard et al., 2002; Coxon et al., 2014; but Williams, Ponesse, Schachar, Logan, & Tannock, 1999) and longer go RTs (Bedard et al., 2002; Kramer, Humphrey, Larish, & Logan, 1994; Williams et al., 1999). Moreover, imaging evidence suggests that, compared to younger adults, older adults not only have longer SSRTs but also exhibit hypoactivity in the pre-SMA and striatum (Coxon et al., 2014). During the go/no-go task, older adults show activation not only in the right VLPFC and right SMA, as younger adults do, but also in the left VLPFC and left SMA (Colcombe, Kramer, Erickson, & Scalf, 2005; Nielson, Langenecker, &

Garavan, 2002). Apart from the SST and go/no-go task, in another task that involves response inhibition (the Stroop task), it has been shown that older adults have bilateral activation of VLPFC and SMA relative to younger adults (Langenecker, Nielson, & Rao, 2004) where such activations are primarily unilateral. It seems to be the case that response inhibition deficiencies in the normal ageing process are related to hypoactivity of the right PFC and hyperactivity of the left PFC.

In general ERPs in older adults are reported to occur later and to be of smaller amplitude relative to ERPs in younger adults (Brown, Marsh, & LaRue, 1983; Dustman et al., 1990; Mullis, Holcomb, Diner, & Dykman, 1985; Pfefferbaum, Ford, Wenegrat, Roth, & Kopell, 1984). An exception to this general rule exists for a number of low-level sensory evoked responses. Visual-evoked potentials (VEP, located occipitally) and somatosensory-evoked potentials (SEP, located at the vertex) are larger in amplitude and have a wider peak in older compared to younger adults (De Sanctis et al., 2008; Díaz & Amenedo, 1998; Dustman et al., 1990) possibly reflecting age-related degeneration of intracortical inhibition (Schmolesky, Wang, Pu, & Leventhal, 2000). Furthermore, across species studies have revealed that mammalian aging results in more spontaneous cortical activity and decreased visual orientation and direction selectivity (Hua et al., 2006; Schmolesky et al., 2000; Zhang et al., 2008). This account has further been confirmed via the application of GABA in the V1 that can reverse age-related decreases in visual orientation selectivity (Leventhal, Wang, Pu, Zhou, & Ma, 2003). In short, normal impulsivity traits and aging are related to longer SSRT.

To sum up, clinical populations (i.e. ADHD, schizophrenia, OCD, trichotillomania, Tourette syndrome, chronic pain, developmental stuttering, drug users and smokers) and normal variations in the neurophysiological/neuropsychological status of non-clinical populations (i.e. impulsivity traits in non-clinical adults and aging) exhibit common deficiencies in response inhibition such as longer SSRT, hypoactivity in the right dorsolateral and medial prefrontal areas as well as basal ganglia and also exhibit smaller ERP amplitudes evoked by stop signals.

1.1.6. The efficacy of response inhibition in different effector systems

As described above, most of the studies investigating human response inhibition have focused on inhibitory control over actions controlled by the corticospinal system (e.g.

button presses) but a few have also assessed response inhibition in the ocular (Leung & Cai, 2007; Logan & Irwin, 2000) and vocal systems (Cai et al., 2012; Etchell et al., 2012; Fried et al., 1991; Ladefoged et al., 1973; Lüders et al., 1988; van den Wildenberg & Christoffels, 2010; Xue et al., 2008). Response inhibition in the oculomotor system of primates has been well-characterised (for a review see Stuphorn, 2015). There is evidence that inhibition acting at the level of the spinal cord modulates MEPs in response-selection relevant muscles (Duque & Ivry, 2009; Duque et al., 2010), therefore, in addition to the VLPFC, medial prefrontal cortex and the motor cortex, the spinal cord may be one of the final agentive sites for response inhibition. If in the corticospinal system, the spinal cord acts as a final agent for response inhibition, other non-spinal effector systems such as the corticobulbar system, which in part controls speech, are likely to have homologous inhibitory mechanisms. Based on the idea that different effector systems may have common central generators for response inhibition e.g. (Xue et al., 2008) but different final agents, we would be able to explain the differences in response inhibition performance across effector systems. For instance, that inhibition of eye movements is faster than that of the hands (measured by countermanding saccades, Leanne Boucher, Stuphorn, Logan, Schall, & Palmeri, 2007; Curtis, Cole, Rao, & D'Esposito, 2005; Logan & Irwin, 2000); that naming part-words is slower than both manual responses and letter naming; and that the SSRT is faster for letter naming than for both manual responding and for naming part-words (Xue et al., 2008). These differences across effector systems may be due to differences in the expression of inhibitory projections at the level of the lower motor neuron.

In fact, physiological differences among the vocal and limb systems have already been described. For example, Kent (2004) describes how speech muscles are unique in their genetic, developmental, functional and phenotypical properties compared to limb muscles. Evidence of these differences is supported by interventions that lead to consistent improvements in limb movements with sometimes neutral or even negative results for speech movements. This discrepant pattern have been reported for levodopa therapy, unilateral or bilateral posteroventral pallidotomy, foetal dopamine transplants and pallidal or thalamic stimulation (for a review see Kent, 2004).

More specifically, Luschei and Goldberg (2011) reported that the neurophysiology of the corticospinal system (i.e. limbs) and the corticobulbar system (i.e. vocal) are different in

regard to their inhibitory control. Unlike the corticospinal system, the corticobulbar system has few or no muscle Golgi tendon organs, few or no muscle spindles in the jaw-opening muscles, no reciprocal Ia-inhibition between antagonists, no Ib or Ia-inhibitory interneurons, and no Renshaw recurrent inhibition of motoneurons (see Türker et al., 2007). One of the functions of the muscle Golgi tendon organ is to mediate the autogenic inhibition reflex, which refers to a reduction in excitability of a contracting muscle. Muscle spindles also play a significant role in regulating the contraction of muscles via the stretch reflex. Reciprocal inhibition controls the contraction of opposing muscle whereas recurrent inhibition inhibits muscle fibers of the same muscle that is contracting. The inhibitory neuron found in the spinal cord is called a Renshaw cell, which regulates the feedback loop for recurrent inhibition. Overall, neurophysiological mechanisms for inhibitory control in general might be considered sparser or less potent for vocalisation than for limb movement which may lead to differences in voluntary countermanding performance even in the presence of a common response inhibition generator (Xue et al., 2008).

More evidence of these differences comes from suprathreshold TMS studies, which have shown that interruption of the muscle activity in the corticobulbar system produces a cortical silent period (CSP) that is shorter than in those studies reporting the CSP of the corticospinal system (Cruccu, Inghilleri, Berardelli, Romaniello, & Manfredi, 1997; Jaberzadeh, Sakuma, Zoghi, Miles, & Nordstrom, 2008; Ortu et al., 2008; Paradiso, Cunic, Gunraj, & Chen, 2005; Sowman, Flavel, McShane, Miles, & Nordstrom, 2008; Werhahn, Classen, & Benecke, 1995). Because the CSP measures the net amount of ($GABA_b$- ergic) inhibition applied to a muscle, the shorter CSP in muscles of the vocal system suggest that inhibitory control may be weaker in the corticobulbar system than the corticospinal system.

In sum, I have presented behavioural evidence that suggests response inhibition is different across effector system, that response inhibition may be controlled by a common central generator (e.g. VLPFC, DLPFC, SMA, pre-SMA and basal ganglia) but that the final agents of response may have different inhibitory mechanisms across effector systems. Particularly, I showed evidence that the spinal cord has a function in inhibitory control and that a homologous area for inhibition of eye and speech presumably is also important; that the corticobulbar relative to the corticospinal system has sparser or less potent autogenic inhibition reflex, stretch reflexes, reciprocal inhibition and recurrent inhibition; and that the CSP of (some) muscles of vocalisation is shorter than those of the limbs suggesting weaker

inhibitory control. Taken together, these lines of evidence suggest that response inhibition of vocal responding may be less efficacious than that of manual responding.

1.1.7. Vocal response inhibition

In this thesis we focus on vocal response inhibition. Above, we have discussed physiological evidence that response inhibition across effector systems is different and that perhaps, the vocal effector system has weaker response inhibition than that of the limb system. We have also described that specific neuropsychological disorders affect mainly speech (i.e. Tourette and stuttering) and that therapeutic interventions to neuropsychological disorders that affect the limb system do not have the same effect in the vocal system. We have also described how high levels of dysfunctional impulsivity are associated with slower vocal response inhibition. This thesis will be the basis for characterising vocal response inhibition in the normal developing brain. It will be the basis not only for the understanding of speech disorders like Tourette and stuttering but also for the understanding of everyday speech and inhibition. Specifically, this thesis will help us better understand why some people may restrain their speech more cautiously while others are less able to halt an impulsive word.

1.2. Transcranial direct current stimulation (tDCS) and response inhibition

1.2.1. The basics of tDCS

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that can facilitate or suppress cortical excitability by applying either anodal (increasing excitability) or cathodal (decreasing excitability) currents extra-cranially over the scalp (for a review see Juan & Muggleton, 2012). To increase and decrease excitability, the neuronal membrane is depolarized and hyperpolarized respectively, through a battery that injects current into the brain through the appropriate pole of an electrode pair placed over the scalp above the targeted brain cortical area (wiki of Neuroelectrics-Software). The anodal electrode in tDCS injects positively charged current whereas the cathodal electrode collects positively charged current.

One of the first descriptions of the usage of tDCS was in Bindman, Lippold, and Redfearn (1964). In this study the authors applied tDCS and measured effects on spontaneous and neuronal evoked activity in the rat cortex. In order to understand the effects of tDCS, they

first described the normal neuronal evoked potential of the rat cortex. The authors explained that the normal neuronal evoked potential of the rat cortex consists of an initial small positive (or diphasic positive-negative) wave occurring at about 5 ms after the stimulus; this is followed by a larger positive wave (latency of 7-9 ms) and a negative wave of variable size and shape (latency of 10-15 ms; duration of up to 25 ms). The positive and negative waves refer to depolarization and hyperpolarization process of post-synaptic origin (Bindman et al., 1964); most neurons in cats and rats are activated by inward positively charged currents (anodal tDCS) and inhibited by outward currents (cathodal tDCS) involving spontaneous and evoked activity and can last for several minutes after the stimulation (Bindman et al., 1964; Creutzfeldt, Fromm, & Kapp, 1962; Purpura & McMurtry, 1965).

1.2.2. tDCS applications

In humans, the effect of anodal and cathodal tDCS has been shown to persist for several minutes after the end of stimulation, which makes tDCS a very appropriate technique for treatment and experiments (Nitsche et al., 2008; Nitsche et al., 2009; Nitsche & Paulus, 2000). The current used in tDCS on humans prior to 2008 varied between 0.029 and 0.08 milliampere (mA) (for a review see Nitsche et al., 2008) but more recent studies have used currents of up to 2mA (Clark et al., 2012; Ditye et al., 2012; Jacobson et al., 2011).

1.2.2.1. Investigations on possible treatments

Investigating possible treatments, tDCS was applied to a group of people diagnosed with ADHD to investigate whether the inhibitory deficits in this disorder could be reduced (Hsu et al., 2011). Inhibitory deficiencies were measured via the SST and tDCS was applied over the pre-SMA. Hsu et al. (2011) reported that anodal tDCS improved successful stopping compared to cathodal tDCS. In healthy adults, it has been shown that anodal tDCS over the right VLPFC increases response inhibition, decreasing the SSRT compared to cathodal tDCS, anodal tDCS over the left VLPFC and anodal tDCS to a control site (the right angular gyrus; Ditye et al., 2012; Jacobson et al., 2011). Effects of tDCS have also been reported in the context of the go/no-go task: cathodal tDCS over the right DLPFC increases the number of commission errors (Beeli, Casutt, Baumgartner, & Jäncke, 2008). While this thesis was being written, a meta-analytic analysis suggest that no reliable effects are found in tDCS (Horvath, Forte, & Carter, 2015). However, one limitation pointed out by the authors is the lack of comparable research, describing that in the meta-analysis

opposite effects were included for an analysis, for example that 1 paper reported enhancement and another reported impairment of a particular function. The authors suggest that future studies should report state-dependency effects to help us understand why some studies report tDCS effects and others not. The state-dependency effects include information concerning the time-of-day, day-of-week, duration of unique stimulation sessions, satiation-levels, energy-levels, amount-of-sleep, etc. The results of this thesis will therefore form part of this debatable issue. Unfortunately, the data was already collected and no state-dependency effects were gathered.

It is important to note that Chhatbar and Feng (2015) points out various methodological problems in Horvath et al. (2015). Furthermore, other meta-analytic articles have reported effects of tDCS on language (A. R. Price & Hamilton, 2015; Amy R. Price, McAdams, Grossman, & Hamilton, 2015).

1.3. Magnetoencephalography (MEG)

Magnetoencephalography (MEG) is a non-invasive technique for recording and localising neuronal activity in the human brain (for a review see Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). Temporal resolution for MEG can be better than 1 ms (the same as for EEG) and its spatial resolution can reach 2-3 mm (under optimal conditions). The tiny magnetic fields produced by electric currents flowing in the neurons are recorded by MEG via superconducting quantum interference devices (SQUID).

1.3.1. The basics of MEG

A stimulus either conducted to the brain or internally generated, activates respective portions of the cortex in charge of its processing. The activation of these cells is associated with a primary current source related to the movement of ions due to gradients of chemical concentrations. Additionally, passive ohmic currents (or electrical resistance) are set up in the surrounding medium to prevent buildup of charge. The magnetic field is generated by both the primary and the ohmic currents (Hämäläinen et al., 1993). The MEG and EEG field distribution are mutually orthogonal. Data from these two techniques complement each other but MEG has better spatial accuracy than EEG because conductive inhomogeneities and anisotropies in the head have a strong influence on electric fields but have no effect on magnetic fields.

Neuromagnetic fields are very small (approx 50-500 femtoTesla (fT)), one part in 10^9 or 10^8 of the earth's magnetic field. The most efficacious detector of these tiny fields is the SQUID (Josephson, 1962; Lounasmaa, Louasmaa, & Lounasmaa, 1974; Ryhänen, Seppä, Ilmoniemi, & Knuutila, 1989; Zimmerman & Silver, 1964), which is coupled to a flux transformer that funnels the magnetic fields to the SQUID. Environmental noise is attenuated by a combination of shielding, primary sensor geometry and synthetic methods such as higher-order gradiometers (Vrba & Robinson, 2001).

1.4. Summary and conclusion

The independent horse model for studying response inhibition via the SST allows us to discriminate between two possible processes when stopping an action: the go and the stop. Firstly, the go process is activated in order to execute a prepotent action; in this thesis that action will be either a spoken word or a button press; secondly, a stopping process gets activated in response to a stop signal in an attempt to stop the execution of the prepotent response. Two types of response inhibition are involved in the go and stop processes. Proactive inhibition is activated in order to withhold the execution of the prepotent response, whereas reactive inhibition executes outright stopping of the prepotent response following the appearance of a stop-signal. The central generators of the neural network for reactive inhibition in manual, vocal and oculomotor response modalities have been commonly described as an interplay between the VLPFC, dorsolateral and medial prefrontal cortex (DLPFC, SMA and pre-SMA) and various areas of the basal ganglia. However, evidence has shown there are other final agentive areas that are important in response suppression such as the motor cortex and the spinal cord (for the spinal system only). In the current study, I applied anodal tDCS to the right PFC to investigate whether this area has a controlling influence over both manual and vocal reactive inhibition.

Neurophysiological evidence suggests that inhibition of vocal responses has sparser or less potent inhibitory mechanisms within these final agentive areas compared to the manual system. The neural network for proactive inhibition has been less studied but the little data that does exist suggests that it may consist of a pre-activation of the same network that controls reactive inhibition. In fact, two out of three experiments examining this reported a positive relationship between proactive and reactive inhibition, that the greater the amount

of proactive inhibition there was, the faster reactive inhibition occurred. It is not clear why one experiment did not show this relationship (Jahfari et al., 2010).

1.5. General aims of this thesis

The objectives of this thesis are threefold: (1) Explore the influence of proactive inhibition on reactive inhibition. I address the question: does a greater level of proactive inhibition enhance reactive inhibition in both manual and vocal responses? (2) Determine if response inhibition is controlled by common central generators for both manual and vocal effector systems. (3) Compare response inhibition of vocal responses versus manual responses. I address the question: are reactive and proactive inhibitions less efficacious in the vocal compared to the manual effector system?

1.5.1. Chapter 2: Vocal response inhibition is enhanced by anodal tDCS over the right prefrontal cortex

In chapter 2, I address three questions: (1) is there a negative relationship between proactive and reactive inhibition, in particular does more proactive inhibition equate to faster reactive inhibition? (2) Is the right VLPFC involved in vocal response inhibition and can reactive inhibition be enhanced in the vocal as well as in the manual effector systems by anodal tDCS? (3) Are reactive and proactive inhibitions less potent in vocal relative to manual responses?

1.5.2. Chapter 3: Proactive inhibition enhances sensorimotor synchronisation

In chapter 3, I address the question: will induced proactive inhibition enhance sensorimotor synchronisation (SMS) in both manual and vocal response modalities? To test this question, we developed a new task that combines the SST with a SMS task.

1.5.3. Chapter 4: Event-related fields related to vocal response inhibition: a comparison of younger and older adults.

In chapter 4, I investigate MEG event-related fields of vocal response inhibition and compared them with the EEG literature on manual response inhibition. I address the main question: do ERFs for vocal response inhibition exhibit similar patterns to those described for manual response inhibition? In particular, I have three predictions: (1) if successful stopping requires early inhibition in order to stop a prepotent response then the inhibition-

related ERFs should show larger amplitudes than the failed stop ERFs prior to the SSRT; (2) if the later peaks in the response inhibition related waveforms are related to error recognition then failed stops should evoke larger amplitudes than successful stops in these later latency ERFs; (3) if aging affects response inhibition, inhibition-related ERF waveforms should be smaller in amplitude in older adults relative to younger adults.

1.5.4. Chapter 5: The effect of proactive inhibition on reactive inhibition and their relationships with impulsivity: evidence from the stop signal task applied to vocal and manual responses

In chapter 5, I address four questions: (1) does proactive inhibition increase and reactive inhibition decrease in a high relative to a low probability stop condition? (2) Do reactive and proactive inhibitions have a positive relationship suggesting that more preparation enhances outright stopping? (3) Is reactive inhibition slower in vocal relative to manual responses? (4) Will slower reactive inhibition be related to higher dysfunctional impulsivity scores? To accomplish these questions and in response to possible limitations observed in the previous chapters, I increased the sample size to obtain more statistical power and added more control to the SST by having warning signals that controlled proactive and reactive inhibition performance.

1.6. References

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Chapter 2 – Vocal response inhibition is enhanced by anodal tDCS over the right prefrontal cortex

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2. Vocal response inhibition is enhanced by anodal tDCS over the right prefrontal cortex

2.1. Abstract

Background: Stopping outright (reactive inhibition) and slowing down (proactive inhibition) are types of response inhibition, which have mainly been investigated in the manual effector system. This study compared reactive inhibition across manual and vocal effector systems, examined the effects of excitatory anodal transcranial direct current stimulation (anodal tDCS) over the right prefrontal cortex (right-PFC) and looked at the relationship between reactive and proactive inhibition.

Hypotheses: We hypothesised (1) that vocal reactive inhibition would be less effective than manual reactive inhibition as evidenced by longer stop signal reaction times; (2) that anodal tDCS would enhance both vocal and manual reactive inhibition and (3) that proactive and reactive inhibition would be positively related.

Methods: We tested 14 participants over two sessions (one session with anodal tDCS and one session with sham stimulation) and applied stimulation protocol in the middle of the session i.e. only during the second of three phases. We used a stop signal task across two stop conditions: relevant and irrelevant stop conditions in which stopping was required or ignored respectively.

Results: We found that reactive inhibition was faster during and immediately after anodal tDCS relative to sham. We also found that greater level of proactive inhibition enhanced reactive inhibition [indexed by shorter stop signal reaction times (SSRTs)].

Conclusions: These results support the hypothesis that the right-PFC is part of a core network for reactive inhibition and supports previous contention that proactive inhibition is possibly modulated via preactivating the reactive inhibition network. The fact that anodal tDCS did not affect proactive inhibition may suggest that proactive and reactive inhibition rely on different brain networks

Keywords:
Anodal tDCS, vocal inhibition, stop signal task, response inhibition, reactive inhibition and proactive inhibition

2.2. Introduction

Response inhibition, the act of stopping or slowing a process or an action, consists of two main types. The first and most studied type is reactive inhibition, which is described as the process that suppresses current emotions, thoughts or behaviours because they are deemed irrelevant, dangerous or no longer appropriate (Aron, 2011; Chambers et al., 2009; Jacobson et al., 2011; Logan, 1994; Logan & Cowan, 1984). For example, reactive inhibition is the process that stops you from stepping out onto the road when you notice a previously undetected car approaching. The second, less studied inhibitory type is proactive inhibition. It slows current emotions, thoughts or behaviours because they may need to be restrained at some point in the future. Slowing your walking speed before stepping out onto the road is an example of proactive inhibition (Aron, 2011; Jaffard et al., 2008).

Understanding response inhibition is important because we not only use it for our everyday activities but also because deficiencies in normal response inhibition are thought to underpin or contribute to disorders such as attention-deficit hyperactivity disorder (ADHD; Aron & Poldrack, 2005; Barkley, 1997; Rubia, Russell, et al., 2001), schizophrenia (Enticott et al., 2008; Kiehl et al., 2000), obsessive-compulsive disorder and trichotillomania (Bohne et al., 2008; Menzies et al., 2007; Penadés et al., 2007), Tourette syndrome (Ziemann et al., 1997), chronic pain (Glass et al., 2011; Jongsma et al., 2011; Veldhuijzen et al., 2012) and developmental stuttering (Eggers et al., 2013).

Despite the fact that response inhibition is thought to be a central process that bears upon all modalities of action, be they manual action, eye movements, vocalisation or even thoughts – the study of reactive inhibition has largely been limited to the manual effector system. However, evidence shows that the efficacy of response inhibition may vary depending on the effector system, for example, some studies have found that manual response inhibition is slower than ocular response inhibition (Leanne Boucher et al., 2007; Curtis et al., 2005; Logan & Irwin, 2000). In addition, other studies have found that manual response inhibition is faster than vocal response inhibition (Castro-Meneses, Johnson, & Sowman, 2015)

There is significant evidence from single- and paired-pulse transcranial magnetic stimulation (TMS) studies (for a review see Stinear et al., 2009) that suggests that the primary motor cortex (M1) is the final cortical processing area for voluntary motor commands before they move downwards to the spinal cord. Inhibitory interneurons within motor cortex are proposed to play the final "agentive" role within the network that supports inhibitory control. Significant differences in the mechanisms that govern inhibition at the motoneuronal level between the corticospinal and corticobulbar systems are known to exist (for review see Luschei & Goldberg, 2011). Specifically, it is thought that cortical inhibitory projections onto the corticobulbar motoneurones (which supply some of the muscles of vocalisation) are sparser or less potent than those that impinge on spinal motoneurones (Jaberzadeh et al., 2008; Ortu et al., 2008; Sowman et al., 2008). This idea is based largely on TMS studies utilising a phenomenon, whereby a suprathreshold TMS pulse causes an interruption of ongoing muscle activity, known as the silent period (SP). The SP duration is generally shorter in muscles of the cranial nerves (CN) than in the limbs (Cruccu et al., 1997; Jaberzadeh et al., 2008; Ortu et al., 2008; Paradiso et al., 2005; Sowman et al., 2008; Werhahn et al., 1995). This may in part explain why some disorders of inhibition like Tic disorders disproportionally affect the outputs of the cranial nerves (Sandler, 2003). A better understanding of voluntary inhibitory control could be gained by extending the study of response inhibition to effector systems beyond the corticospinal system.

The reactive inhibitory network has largely been described for the manual effector system but little is known about the extent to which this network can be considered the inhibitory controller for the vocal effector system. The right prefrontal cortex (right-PFC), in particular the right ventrolateral-PFC and supplementary motor area (SMA) are two areas in the brain that have been associated with manual response inhibition (Aron et al., 2003; Aron et al., 2004; Chambers et al., 2009). Direct electrical stimulation of the right-PFC and SMA generates inhibition of ongoing movements (for a review see Filevich et al., 2012). Moreover, functional magnetic resonance imaging (fMRI) studies utilizing both the stop signal task (SST) and the go/no go task have shown greater activation of the right-PFC when participants successfully inhibit manual responses (Rubia, Russell, et al., 2001; Rubia et al., 2003). Lesion studies show that damage to right ventrolateral-PFC disrupts patients' stopping performance on the SST (Aron et al., 2003) and "virtual lesions" induced in TMS studies have impaired manual response inhibition by transiently

suppressing the excitability of the right ventrolateral PFC (Chambers et al., 2007; Chambers et al., 2006; Verbruggen et al., 2010). In addition, reduced inhibition have been reported in studies that used transcranial direct current stimulation (tDCS) over the right dorso-lateral PFC (Beeli et al., 2008) and pre-SMA (Hsu et al., 2011). Conversely, anodal (excitatory) transcranial direct current stimulation (tDCS) to the PFC enhances manual inhibition (Ditye et al., 2012; Hsu et al., 2011; Jacobson et al., 2011). Jacobson et al., (2011) showed that only anodal stimulation over right ventrolateral-PFC improved manual inhibition. A control condition in which the anode was placed over the right angular gyrus did not affect response inhibition, demonstrating brain-area selectivity of this effect. For a review on brain stimulation and inhibitory control see Juan and Muggleton (2012).

While there are many behavioural studies that have used the SST to study manual response inhibition (for a review see Verbruggen & Logan, 2008b), relatively few studies have examined the control of vocal response inhibition or compared the efficacy of inhibition across modalities (Cai et al., 2012; Etchell et al., 2012; van den Wildenberg & Christoffels, 2010; Wessel & Aron, 2014; Xue et al., 2008). Only one fMRI study has investigated vocal response inhibition (Xue et al., 2008). To date we are not aware of any study that has investigated the effect of right-PFC stimulation on vocal reactive or proactive inhibition.

Although, neurophysiological studies indirectly suggest that reactive vocal inhibitory control might be less efficacious compared to manual inhibition (Luschei & Goldberg, 2011), direct experimental evidence has not yet consistently demonstrated this. While two studies failed to find significant differences in reactive inhibition between the vocal and manual effector systems (Etchell et al., 2012; van den Wildenberg & Christoffels, 2010). Other study found that vocal reactive stopping was slower by 17 ms compared to manual reactive stopping (Castro-Meneses et al., 2015). However, Xue et al., (2008) found that inhibition of word naming (150 ms) was 25 ms faster than inhibition of manual responses (175 ms) – an observation that seems at odds with the neurophysiology. Our first aim was to compare reactive inhibition across manual and vocal effector systems. We hypothesised that vocal reactive inhibition would be slower than manual reactive inhibition.

According to the study of Xue et al. (2008) right ventrolateral-PFC is activated in both manual and vocal reactive inhibition. Therefore, we hypothesized that anodal tDCS over that area would improve inhibition of vocal responses in a similar manner to manual responses (Ditye et al., 2012; Jacobson et al., 2011).

This study had two further aims regarding the characterisation of proactive inhibition. Proactive inhibition is measured as a difference between go reaction times (go-RTs) that occur in a task context where stopping is required and go-RTs that occur in a task context where stopping is not required. Firstly, we examined proactive and reactive inhibition relationship. Two out of three previous experiments have shown that proactive inhibition is positively related with reactive inhibition, as measured by shorter stop signal reaction times (SSRTs, Chikazoe, Jimura, Hirose, et al., 2009; Jahfari et al., 2010). In other words, the greater the level of proactive inhibition, the faster reactive inhibition is. One explanation for this might be that proactive inhibition pre-activates the same inhibitory network (i.e. right ventrolateral-PFC and SMA) that is subsequently used for reactive inhibition. Therefore, when the stop signal appears, the stopping process is faster because the inhibitory network is already primed (Aron, 2011). However, this effect has not been consistently demonstrated across experiments; in fact, this effect was found in experiment 1 but not experiment 3 of Jahfari et al. (2010). In regard to these contradictory findings we had two aims: firstly, we aimed to test whether reactive inhibition is positively correlated with proactive inhibition and; secondly, whether this relationship is maintained across manual and vocal response modalities. Our hypothesis was that, in line with Aron (2011), proactive and reactive inhibition would be positively related and that this relationship would be observed for both manual and vocal response modalities

2.3. Methods

2.3.1. Participants

Fourteen subjects participated in this study (11 females) aged (mean ±SD) of 22 ±3.9 years. All participants were right-handed and reported no history of neurological or psychiatric conditions. They all were naïve to the nature of the tDCS mode within the experiment (i.e. in terms of anodal versus sham stimulations) and gave written informed consent prior to the experiment. Participants received either course credit or cash payment

for their participation. The experiment was approved by the Macquarie University human ethics committee.

2.3.2. Apparatus

The task was implemented in Presentation® software (version 16.1, www.neurobs.com) and delivered via a Samsung monitor (SyncMaster SA950_LS27A950, 27 inches, 1920 x 1080 pixels, 120 Hz refresh rate). Vocal responses were measured (8 bit, 2 channels, 48 kHz) via an external microphone placed 2 cm from each subject's mouth and detected via the sound response device in Presentation software, which detected a vocal response when a sound pass a threshold of 0.1 (range is from 0 to 1, being 0.1 very sensitive to sound that a whisper can be detected as a vocal response). We did not record the utterances so no offline checking of response correctness was performed. Given the simplicity of the task i.e. producing one of 2 vowels, we are confident that the rate of error would be so low as to have negligible effects on the results. Manual-responses were recorded via key press elicited by the index and middle fingers of the right hand. Participants were seated 80 cm from the monitor.

2.3.3. Stop Signal Task

This study used a version of the SST to measure stimulus selective inhibition (Bissett & Logan, 2014; Logan, 1994; Logan & Cowan, 1984). It consisted of two stop conditions (relevant and irrelevant stop condition) that differed only in the instructions that were given to the participants. In the relevant stop condition, go trials consisted of a simple forced choice reaction time task where participants were required to respond as quickly and accurately as possible to the go signal, which was signalled by the visual onset of one of two possible vowels "I" and "O". These vowels were presented in white (2.5 cm height) on a black background. The relevant stop condition had two types of response-modality (manual and vocal) tested in separate blocks. In the manual response modality, participants were instructed to respond with the index and middle fingers of their right hands by pressing keys "I" or "O" respectively. For vocal responses, they were instructed to make the short vowel sounds, as it would occur in the words "hit /hɪt/" for "I" and "hot /hɒt/" for "O".

The stop trials in the relevant stop condition were similar to the go trials in that they started with a go signal initially; however, after a given delay, a stop signal would appear. The

stop signal was comprised of a change in the target vowel font size; it doubled from 2.5 cm to 5.5 cm in height. The time between the onset of the go signal and the onset of the stop signal is termed the stop signal delay (hereafter as SSD; Logan & Cowan, 1984). The current study utilised a dynamic SSD staircase which involved changing the SSD after every stop trial, increasing it by 30 ms if subjects successfully inhibited their response and decreasing it by 30 ms if inhibition was unsuccessful (Logan et al., 1997; Osman et al., 1986, 1990; Verbruggen & Logan, 2009a). In the first five trials of a staircase, SSD was changed by 50 ms, after that it was changed by 30 ms. This method facilitates a probability of successful stopping on stop trials of approximately 50%. The staircases for manual and for vocal responses were independent. The starting SSD in both response modalities was set at 200 ms based on previous studies that have found that inhibition occurs at around 200 ms (Aron & Poldrack, 2005; Leanne Boucher et al., 2007; Etchell et al., 2012; Logan, 1994; Logan & Cowan, 1984; van den Wildenberg & Christoffels, 2010; Wessel & Aron, 2014).

The other condition was the irrelevant stop condition. The irrelevant stop condition looked exactly the same as the relevant stop condition: i.e. there were go and stop trials. The first difference was that participants were instructed to ignore the stop signals and always respond on all trials, i.e. to treat the stop trials as if they were go trials. Another difference was that the SSD on the stop trials did not vary by means of a dynamic staircase because participants were asked to always respond, thus the probability of responding was expected to be 1. Hence, the SSD of stop trials in the irrelevant SST varied randomly between ± 20% of the mean SSD from the previous relevant stop condition staircase. For example, the SSD for the vocal response modality from the irrelevant stop condition was ± 20% of the mean SSD of the previous vocal response modality from the relevant stop condition.

The index of reactive inhibition is the stop signal reaction time (SSRT; Logan & Cowan, 1984) which cannot be measured directly but must rather be estimated based on the assumptions of the independent horse-race model (Logan & Cowan, 1984). We used the integration method to estimate SSRT (Logan & Cowan, 1984; Verbruggen & Logan, 2009a) which is currently considered the most robust approach to estimating SSRT (Verbruggen et al., 2013). Using this method, SSRTs were estimated by subtracting the starting time of the stop process (when participants see a stop signal) from the finishing time of the stop process. The starting time of the stop process is known: the time of SSD.

The finishing time was estimated from go-RT distribution. Go-RTs were rank ordered from the shortest to longest and then the *nth* RT was selected. Where *n* was selected by multiplying the probability of responding (or unsuccessful stopping) on stop trials by the total number of go-RTs. The probability of responding was calculated as the number of unsuccessful stops divided by the total number of stop trials. SSRT was then estimated by subtracting the SSD from the *nth* RT.

The index of proactive inhibition was estimated by subtracting the mean of the go-RTs of the relevant stop condition from the mean of the go-RTs of the irrelevant stop condition in each response-modality (Chikazoe, Jimura, Hirose, et al., 2009; Jahfari et al., 2010).

2.3.4. Experimental design

The study consisted of two sessions, which were counterbalanced. Each session was divided into 4 phases as follows: phase-$0_{SSD\text{-}stabiliser}$, phase-1, phase-2 and phase-3. Phase-$0_{SSD\text{-}stabiliser}$ stabilised subject's SSD by allowing the staircase to adjust itself to a participant's individual stopping performance (probability of 0.5), this phase was not included in any statistical analysis. In phase-2 either anodal tDCS or sham was applied. See figure 1 for an illustration of experimental design. A description of the stimulation protocol can be found later in the text.

The experiment consisted of 16 blocks with a 2 x 2 design: 2 stop conditions: either irrelevant or relevant stop condition by 2 response modalities: either vocal or manual. Conditions and response modalities were pseudo-randomised with the conditions that one type of response modality could only be followed by the other type of response modality of the same condition, and that each stop condition could only be followed by the other stop condition once the first condition was met. This meant that the first 4 blocks had 2 stop conditions and 2 response modalities, for example, if the first block was the relevant stop condition with manual responses then the second block had to be relevant stop condition with vocal responses, subsequently, the third block had to be an irrelevant stop condition with manual responses and the fourth block an irrelevant stop condition with vocal responses. At the beginning of each block, participants read instructions presented on the screen indicating what type of stop condition and response modality was going to be presented. Each phase contained 4 blocks.

Each block had 72 trials: 1/3 were stop trials and 2/3 were go trials. Each phase (or 4 blocks) had 288 trials (~13 minutes in duration). Each trial started with a fixation cross which was presented for 1.9 s, and was then immediately succeeded by a go signal. If the current trial was a stop-trial, a stop-signal occurred after the SSD. Trials ended after 4 s or when a response was given. Participants could rest in between each block for a maximum of 2 min. The whole experiment lasted approximately 1 hour. A schematic representation of each trial type is given in Figure 2A

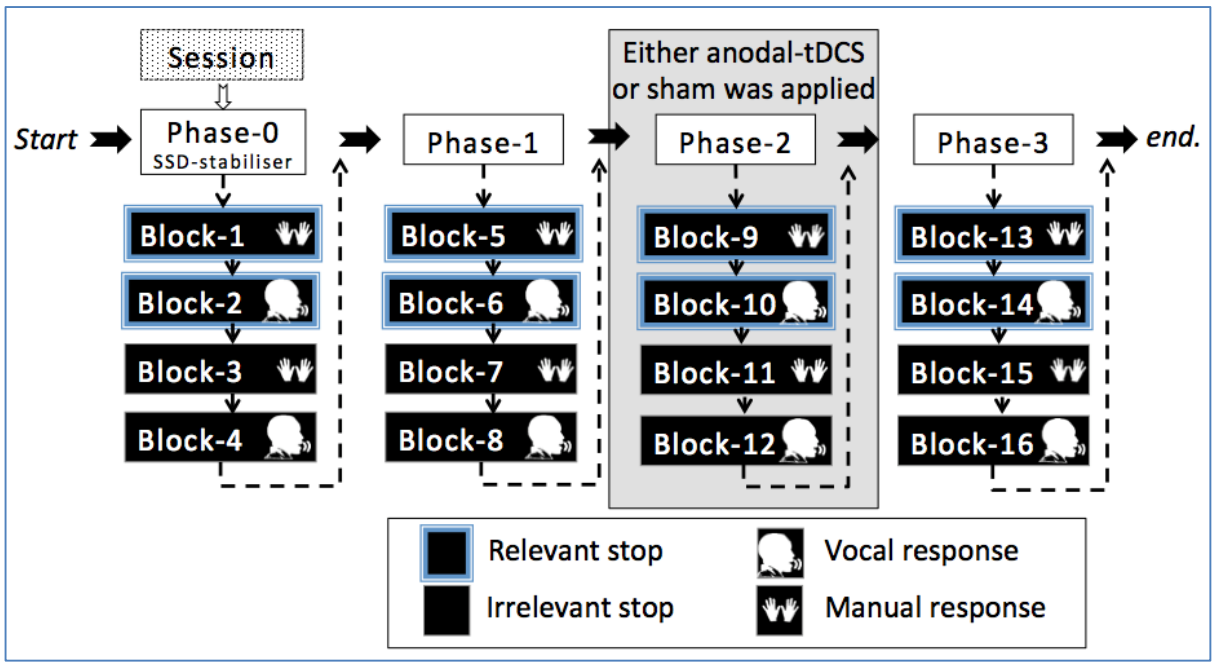

Figure 1 Illustration of the experimental design for a session (chapter 2)

It contained 4 phases, each of which included 4 blocks. Phase-0[SSD-stabiliser] was not included for the statistical analysis but was used to stabilise SSD. The 4-block order (i.e. a phase) was pseudo-randomised by the condition that two blocks were either irrelevant or relevant stop condition for each response modality (manual or vocal). The grey rectangle in phase-2 depicts the time at which anodal transcranial direct current stimulation (anodal-tDCS) or sham stimulation was applied.

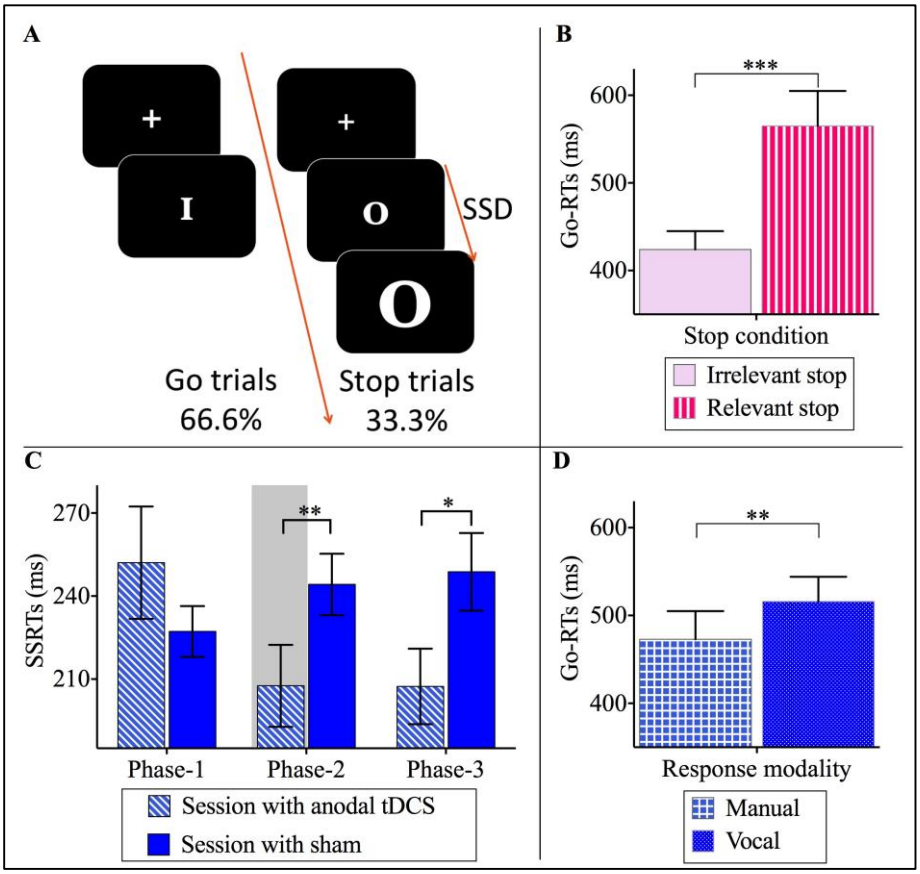

Figure 2 Trial structure of stop signal task (SST) and mean of stop signal reaction time (SSRT) and go reaction time (Go-RT) values (chapter 2)

A) Go trials had either the letter "I" or "O" interleaved in equal numbers. Stop trials started in the same way as a go trial but after the stop signal delay (SSD) a stop signal, which consisted of an increase in font size, was presented. Go and stop trials were presented in exactly the same way in both stop conditions (irrelevant and relevant stop) but the only difference was that in the irrelevant stop condition, participants were instructed to ignore the stop signal and always respond. **B)** Go reaction times (go-RTs) for irrelevant and relevant stop conditions. It was observed that the go-RT in the relevant relative to the irrelevant stop condition were longer. **C)** Reactive inhibition as measured by the SSRT across three phases: phase-1, phase-2 and phase-3 for each session. The grey rectangle in phase-2 (session with anodal tDCS) depicts the time at which anodal tDCS was applied. Sham was applied in phase-2 of the session with sham. Graph C shows that the SSRTs were faster in phases 2 and 3 of the session with anodal tDCS. **D)** Go-RTs for manual and vocal responses. Graph D shows that vocal go-RTs were slower than those of manual RTs. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$. Error bars indicate standard error of the mean (SEM).

2.3.5. Transcranial direct current stimulation

Anodal tDCS of 1.5 mA (ramped up and down over 5 seconds) was applied for 15 min via two saline-soaked surface sponge electrodes (25 cm^2) (Ditye et al., 2012) and delivered by a battery-driven device (Neuroelectrics, Barcelona, Spain). The session with sham used the same protocol but electric current was only applied for the first 30 s. Based on the 10-20

EEG system (Jasper, 1958), the anodal electrode was placed over the intersection point of a line between T4-Fz and a line between F8-Cz. The cathodal electrode was placed on the left cheek (Jacobson et al., 2011; Stinear et al., 2009).

2.3.6. Procedure

Participants completed two sessions in counterbalanced order at an interval of between 1 and 7 days. Prior to the start of each session and before the electrodes were placed, the experimental procedure was explained to ensure participants understood the task. The participant then completed a short practice block of the irrelevant stop condition; this task had 12 trials in each condition (1/3 stop-signals). After this, we described the sensations participants were likely to experience with the stimulation. We then placed the electrodes and ran tDCS for 10 s. This was to allow the participants to give informed consent for the full stimulation protocol. Immediately after this consent was obtained, the experimental blocks started.

2.4. Results

2.4.1. Reactive inhibition (SSRTs)

SSRTs were calculated for the relevant stop condition in phase-1, phase-2 and phase-3. A 2 x 3 x 2 ANOVA of SSRTs was carried out with within subject factors of two response modalities (manual, vocal), three phases (phase-1, phase-2 and phase-3) and two sessions (session with anodal tDCS, session with sham). None of the main effects were statistically significant: response-modality ($F(1, 13)= 2.36$, $p= 0.15$, $\eta p^2= 0.15$), phases ($F(1.2, 15.3)= 1.02$, $p= 0.38$ (Greenhouse-Geisser correction), $\eta p^2= 0.07$) and sessions ($F(1, 13)= 3$, $p= 0.11$, $\eta p^2= 0.19$). The interaction between phases and sessions was statistically significant ($F(2,26)= 9$, $p< 0.001$, $\eta p^2= 0.41$) See figure 2C. Post hoc comparisons (Bonferroni adjusted for multiple comparisons) showed that SSRTs in phase-$1_{[\text{session with anodal tDCS}]}$ (M = 252 ms, SD = 83) were not significantly different from those in phase-$1_{[\text{session with sham}]}$ (M = 227 ms, SD = 42, p = 0.16). In contrast, SSRTs from phase-2 and phase-3 were significantly shorter in the session with anodal tDCS compared to the session with sham. Thus, SSRTs of phase-$2_{[\text{session with anodal tDCS}]}$ (M = 207 ms, SD = 58) were 37 ms shorter compared to SSRTs of phase-$2_{[\text{session with sham}]}$, (M = 244 ms, SD = 49, $p < 0.01$). Similarly, SSRTs from phase-$3_{[\text{session with anodal tDCS}]}$ (M = 207 ms, SD = 55) were 41 ms shorter compared to SSRTs from phase-$3_{[\text{session with sham}]}$ (M = 248 ms, SD = 62, $p < 0.05$). All other

interactions were non-significant: response-modality by phase ($F(2, 26)= 0.13$, $p= 0.88$, $\eta p^2= 0.01$), response-modality by session ($F(1,13)= 0.56$, $p= 0.47$, $\eta p^2= 0.04$) and response-modality by phase by session ($F(2,26)$, $p= 0.67$, $\eta p^2= 0.03$). Means and standard errors of the means for SSDs and SSRTs can be found in appendix A.

2.4.2. Go-RTs and the slowing effect

A repeated measures 2 x 2 x 3 x 2 ANOVA for go-RTs with the within-subject factors of 2 response-modalities (manual, vocal), 2 stop conditions (irrelevant and relevant stop conditions), 3 phases (phase-1, phase-2 and phase-3) and 2 sessions (session with anodal tDCS and session with sham) was carried out. Two main effects were statistically significant: response-modality ($F(1,13) = 9.32$, $p < 0.01$, $\eta p^2= 0.42$) and stop condition ($F(1,13) = 27.54$, $p < 0.001$, $\eta p^2= 0.68$). The other two factors were not statistically significant: phases ($F(2,26) = 2.53$, $p = 0.10$, $\eta p^2 = 0.16$) and sessions ($F(1,13) = 0.54$, $p = 0.48$, $\eta p^2 = 0.04$). All interactions were non-significant, the results of these can be found in appendix B and means in appendix A.

The analysis of the main effect of response modality revealed that go-RTs from manual responses ($M = 473$ ms, $SD = 32$) were 43 ms shorter than go-RTs in vocal responses ($M = 516$ ms, $SD = 28$, $p < 0.01$), see figure 2D. On the other hand, the main effect of stop condition showed that go-RTs from the irrelevant stop condition ($M = 424$ ms, $SD = 21$) were 141 ms shorter compared to the go-RTs from the relevant stop condition ($M = 565$ ms, $SD = 40$, $p < 0.001$), see figure 2B.

2.4.3. Relationship between proactive and reactive inhibition

Spearman correlations (2-tailed) were carried out between the index of proactive inhibition and the index of reactive inhibition (i.e. the SSRTs). We calculated 12 correlations across the 2 response modalities (vocal and manual), the 2 sessions (either anodal tDCS or sham involved) and the 3 phases (phase-1, phase-2 and phase-3). All of these correlations are described in appendix C and depicted in figure 3. The correlation coefficient across all of these 12 correlations showed a negative relationship between the SSRT and proactive inhibition but only reached statistically significant difference for a 2-tailed test in phase-$2_{[\text{session with sham}]}$ of manual responses ($r_s(13) = - 0.67$, $p < 0.05$) and in phase-$3_{[\text{session with anodal tDCS}]}$ of both response modalities: manual ($r_s(13) = - 0.58$, $p < 0.05$) and vocal ($r_s(13) = - 0.56$, $p < 0.05$). These results revealed that indeed, when more proactive inhibition is

implemented, SSRTs get shorter (reactive inhibition is enhanced). In fact, the highest proactive inhibition occurred in phase-3$_{[\text{session with anodal tDCS}]}$, which was 141 and 184 ms for vocal and manual response modalities respectively; interestingly, this phase had the shortest SSRT (213 and 201 ms for vocal and manual respectively). Because of these significant relationships in the session with anodal tDCS, we wondered whether the stimulation protocol affected proactive inhibition. To test this idea, we performed a separate 2 x 3 x 2 repeated measures ANOVA for proactive inhibition with the within subject factors of 2 sessions (session with anodal tDCS and session with sham), 3 phases (phase-1, phase-2 and phase-3) and 2 response modalities (manual and vocal). We did not find an effect of session or any interaction; the non-significant result of session suggests that anodal tDCS had not effect on proactive inhibition. The results of this ANOVA are in appendix D.

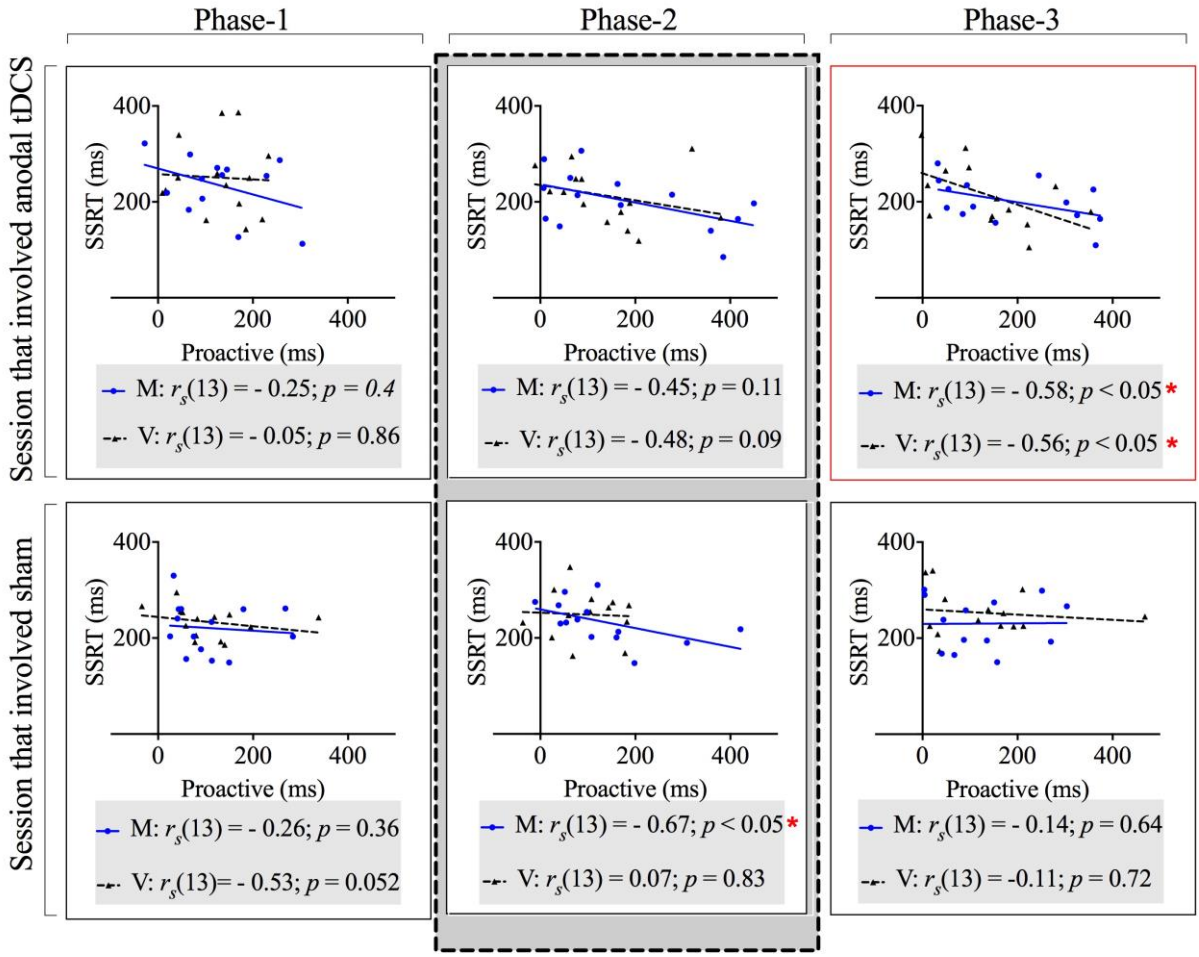

Figure 3 Spearman correlations for reactive and proactive inhibition (chapter 2)

Reactive inhibition was measured by the stop signal reaction times (SSRTs) of the relevant stop condition only. Proactive inhibition index was obtained by the subtraction of go-RTs from the relevant stop condition from the go-RTs of the irrelevant stop condition. There are three columns each representing a phase of the experiment. The top panel depicts the analysis from the session that involved anodal tDCS and the bottom panel represents the session that involved sham. The gray rectangle around phase-2 represents the time in which either anodal tDCS or sham was applied. Significant negative correlations were obtained in phase-3 of the session that involved anodal tDCS and phase-2 of the session that involved sham.

2.5. Discussion

The first aim of this study was to compare reactive inhibition across vocal and manual effector systems. It was hypothesised that vocal reactive inhibition would be weaker than manual reactive inhibition. Secondly, we aimed to investigate whether the well-known role that right-PFC plays in manual inhibition extends to the vocal domain. We hypothesised that anodal tDCS would enhance reactive inhibition of vocal responses as it does for manual responses. Finally, we investigated the putative relationship between proactive and reactive inhibition by testing the hypothesis that reactive inhibition would be positively related with proactive inhibition in both manual and vocal responses. Our data provide evidence to support the second and third hypotheses. All hypotheses are discussed in turn.

2.5.1. Reactive inhibition

We predicted that reactive inhibition (as measured by the SSRTs) from vocal responses would be longer than SSRTs from manual responses. Although a statistical difference was not found there was a trend toward this being the case. Indeed, SSRTs under vocal responding were longer than SSRTs under manual responding across all phases and sessions (mean difference = 11 ms). A similar difference was found by Wessel and Aron (2014) but they did not statistically compare the two effector systems. They found that vocal SSRTs were on average 20 ms longer than manual SSRTs with visual stop-signals and 63 ms longer with auditory stop-signals. It could be that this difference is so subtle (i.e. the effect size is small) that we would require a more sensitive task to find such a difference. For example, a recent study (Castro-Meneses et al., 2015) that did find that vocal responses were slower compared to manual responses by 17 ms, used a simpler stop signal task in which the go task was a one-choice task compared to this study in which we used a two-choice go task.

The second aim of the current study was to test whether anodal tDCS would enhance reactive inhibition in vocal and manual effector systems. We found that reactive inhibition was significantly shortened (by 37 ms) during anodal tDCS (phase-$2_{[\text{session with anodal tDCS}]}$) compared to sham (phase-$2_{[\text{session with sham}]}$) across both response modalities (manual and vocal). Furthermore, it was also found that this effect was maintained immediately after stimulation; that is, the SSRT in phase-$3_{[\text{session with anodal tDCS}]}$ was on average 41 ms shorter relative to phase-$3_{[\text{session with sham}]}$. These results are comparable to the study by Jacobson et

al. (2011) which found anodal tDCS decreased the SSRTs of manual responses by 33 ms as compared to sham stimulation. We further extended those findings to the vocal effector system and showed that anodal tDCS enhanced reactive inhibition compared to a sham session, not only after stimulation (phase-3), but also during stimulation (phase-2).

2.5.2. Proactive inhibition and its relationship with reactive inhibition

The third aim was to test whether there was a statistically significant positive relationship between proactive and reactive inhibition. Our data showed a positive relationship existed in phase-$3_{[\text{session with anodal tDCS}]}$ in both response modalities (manual and vocal) and in phase-$2_{[\text{session with sham}]}$ for manual responses. These relationships revealed that greater level of proactive inhibition was related to faster reactive inhibition (as measured by shorter SSRTs). This finding is consistent with two out of three experiments (Chikazoe, Jimura, Hirose, et al., 2009; Exp 1, Jahfari et al., 2010). The question that remains is why we did not found this relationship in all phases? The answer may lie in the third experiment of Jahfari et al. (2010), which did not find a significant relationship between reactive and proactive inhibition. In their study proactive inhibition was minimal in their third experiment (55 ms) compared to their first experiment in which proactive inhibition was 111.4 ms. Moreover, in a very recent study (Castro-Meneses et al., 2015) it was found that reactive inhibition was related to proactive inhibition only in the high compared to the low probability stops. Interestingly, proactive inhibition was 142 and 51 ms in the high and low probability stops respectively. In our study, phase-3 had the highest proactive inhibition and the shortest SSRTs. Therefore, it seems reasonable to conclude that proactive inhibition has a measurable effect on reactive inhibition only when proactive inhibition is stronger. However, there still remains the question as to what the threshold needed for proactive inhibition to affect reactive is.

Anodal tDCS had no effect on go-RTs and therefore, no effect on proactive inhibition. This finding is consistent with a previous tDCS study (Jacobson et al., 2011), previous TMS studies (Chambers et al., 2006; Verbruggen et al., 2010) of manual responses and a study investigating high and low response selection load tasks (Filmer, Mattingley, Marois, & Dux, 2013). We extended these findings to the vocal effector system. It is interesting to observe that, unlike SSRTs, go-RTs are not affected by anodal stimulation over the right-PFC. This suggests that the effect of anodal tDCS is not due to enhanced attention or arousal caused by stimulation, and that our findings are in line with previous fMRI

experiments that have shown that the right-PFC is more activated during a stop signal task compared to baseline (Rubia, Russell, et al., 2001; Rubia et al., 2003; Xue et al., 2008) and that lesions to this region result in inhibitory deficits (Aron et al., 2003). Taken together with these previous findings, the current results provide more evidence to support the theory that the right-PFC is a core region for the reactive inhibitory network (Aron et al., 2004; Chambers et al., 2009).

One limitation of this study is that we only conducted two sessions, one that involve anodal-tDCS and other with sham session. It would have been optimal to carry out a third session with either cathodal tDCS or stimulation a different scalp site such as the left PFC. However, Jacobson et al. (2011) conducted her study with these two control conditions and found an effect in only the anodal tDCS in the right-PFC. Therefore, we decided to extend the results to the vocal domain by following the same protocol of stimulation as Jacobson et al. (2011) and here we replicate Jacobson's findings for manual responding. Furthermore, we used a control phase (phase-1) that was not included in Jacobson's study and it was present in both sessions (anodal tDCS and sham) before any stimulation protocol was applied. This phase was important to tease apart whether the effect we found could have been attributed to a general session effect. Interestingly, we found no differences in the SSRT in phase-1 and therefore, the faster SSRT in phase-2 and phase-3 can only be attributed to anodal tDCS. In addition, other studies that have applied anodal tDCS to the right-PFC and other control areas such as the left-PFC have found that only anodal tDCS applied over the right-PFC has an effect, for example, in spatial working memory tasks (Giglia et al., 2014). TMS studies also have shown that disruption only to the right-PFC impairs inhibition compared to other control sites (Chambers et al., 2006).

In conclusion, this study showed that anodal tDCS over the right-PFC enhanced rapid stopping in both manual and vocal response modalities. These results agree with the contention that reactive inhibition network is in part mediated by the right-PFC (Aron, 2011; Aron, Behrens, et al., 2007). We also showed that anodal tDCS only affected reactive inhibition and not proactive inhibition. This suggests these two forms of response inhibition may be modulated independently of each other. Although, it has been suggested that proactive inhibition activates the network that mediates reactive inhibition (Aron, 2011), our results suggest that the right-PFC does not strongly modulate proactive inhibition.

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Appendix A

Table 1: Go reaction times (go-RTs), stop-signal delay (SSD), stop-signal reaction times (SSRTs) and p_inhibit (chapter 2)

	Phase-1		Phase-2		Phase-3	
	Vocal	Manual	Vocal	Manual	Vocal	Manual
SSRT: session with anodal tDCS + relevant stop block	253 ± 20	250 ± 24	212 ± 15	203 ± 16	213 ± 17	201 ± 12
SSRT: session with sham + relevant stop block	233 ± 8	220 ± 14	254 ± 14	234 ± 11	252 ± 12	244 ± 20
Go-RT: session with anodal tDCS + irrelevant stop condition	439 ± 21	388 ± 25	446 ± 23	401 ± 32	450 ± 23	388 ± 28
Go-RT: session with sham + irrelevant stop condition	466 ± 20	398 ± 24	456 ± 19	405 ± 25	450 ± 21	399 ± 26
Go-RT: session with anodal tDCS + relevant stop condition	558 ± 32	511 ± 29	560 ± 38	557 ± 41	565 ± 37	561 ± 43
Go-RT: session with sham + relevant stop condition	580 ± 36	543 ± 51	600 ± 52	560 ± 51	594 ± 51	571 ± 64
SSD: session with anodal tDCS + relevant stop block	303 ± 39	266 ± 35	343 ± 46	337 ± 47	345 ± 44	344 ± 52
SSD: session with sham + relevant stop block	333 ± 39	288 ± 42	339 ± 54	327 ± 62	340 ± 63	330 ± 65
p_inhibit: session with anodal tDCS + relevant stop block	.47 ± .01	.50 ± .03	.50 ± .02	.53 ± .03	.53 ± .02	0.49 ± .02
p_inhibit: session with sham + relevant stop block	.46 ± .03	.47 ± .03	.51 ± .02	.53 ± .03	.51 ± .02	0.49 ± .04

Mean reaction times (RT) and standard error of the mean (SEM) in milliseconds go-RTs across three phases (phase-1, phase-2 and phase-3) for each session (session with anodal tDCS and session with sham). Note that SSDs, p_inhibit and SSRTs were calculated in the relevant stop condition only, whereas go-RTs were estimated in both the relevant and irrelevant stop condition. p_inhibit refers to the probability of successful stopping. Black rectangle around phase-2 highlights that only in this phase either anodal tDCS or sham was applied.

Appendix B

Table 2: Non-significant interactions for the 2 x 2 x 3 x 2 ANOVA of go-RTs (chapter 2)

Interactions	F value (degrees of freedom)	p-value	Partial eta-square
Sessions * response modalities	F(1,13) = 0.34	0.57	0.03
Sessions * stop conditions	F(1,13) = 0.08	0.80	0.01
Response modalities * stop conditions	F(1,13) = 3.18	0.10	0.02
Sessions * response modalities * stop conditions	F(1,13) = 0.13	0.73	0.01
Session * phases	F(2,26) = 0.60	0.57	0.05
Response modality * phases	F(2,26) = 1.45	0.25	0.1
Session * response modality * phases	F(2,26) = 0.84	0.44	0.07
Stop conditions * phases	F(2,16.3) = 3.9	0.06	0.23
Session * stop conditions * phases	F(2,26) = 0.08	0.93	0.01
Response modalities * stop conditions * phases	F(2,26) = 0.37	0.70	0.03
Sessions * response modality * stop conditions * phases	F(2,26) = 1.23	0.31	0.09

Appendix C

Analyses of Spearman correlations between proactive and reactive inhibition

Table 3: Spearman correlations between proactive and reactive inhibition (2-tailed) (chapter 2)

	Phase-1	**Phase-2**	**Phase-3**
Session that involved anodal tDCS - manual responses	$r_s(13) = -0.25$, $p = 0.40$	$r_s(13) = -0.45$, $p = 0.11$	$r_s(13) = -0.58$, $p = 0.03$ *
Session that involved anodal tDCS - vocal responses	$r_s(13) = -0.05$, $p = 0.86$	$r_s(13) = -0.48$, $p = 0.09$	$r_s(13) = -0.56$, $p = 0.04$ *
Session that involved sham - manual responses	$r_s(13) = -0.26$, $p = 0.36$	$r_s(13) = -0.67$, $p = 0.011$ *	$r_s(13) = -0.14$, $p = 0.64$
Session that involved sham - vocal responses	$r_s(13) = -0.53$, $p = 0.052$	$r_s(12) = 0.07$, $p = 0.83$	$r_s(13) = -0.11$, $p = 0.72$

r_s = Spearman correlation

* = Significant difference

Black rectangle around phase-2 highlights that only in this phase either anodal tDCS or sham was applied, (M ± SEM).

Appendix D

Results for the 2 x 3 x 2 repeated measures ANOVA for proactive inhibition. This ANOVA was done for the effects of 2 sessions (session with anodal tDCS and session with sham), 3 phases (phase-1, phase-2 and phase-3) and 2 response modalities (manual and vocal). The results showed that session had no effect on proactive inhibition.

Table 4: 2 x 3 x 2 repeated measures ANOVA for proactive inhibition (chapter 2)

Effects and interactions	F value (degrees of freedom)	p-value	Partial eta-square
Session	$F(1,13) = 1.36$	0.26	0.1
Phases	$F(1.3,16.4) = 3.87$	0.06	0.23
Response modalities	$F(1,13) = 3.18$	0.10	0.2
Session * phases	$F(2,26) = 0.38$	0.70	0.03
Session * response modalities	$F(1,13) = 2.49$	0.14	0.17
Phases * response modalities	$F(2,26) = 0.37$	0.70	0.03
Session * phases * response modalities	$F(2,26) = 0.09$	0.92	0.01

Chapter 3 – Proactive inhibition enhances sensorimotor synchronisation for manual but not for vocal responding

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3. Proactive inhibition enhances sensorimotor synchronisation for manual but not vocal responding

3.1. Abstract

There is evidence suggesting that sensorimotor synchronisation (SMS) requires proactive inhibitory mechanisms that control a prepotent response until its release. In this study, we induced proactive inhibition and measure the effect on SMS. We developed a new task that combined the SST and the tapping task with two stop block types: relevant and irrelevant. We hypothesised that in the relevant stop block, the increment in proactive inhibition would make manual and vocal responses closer to the beat. We found that the appearance of stop signals for the relevant stop block induced proactive inhibition in both manual and vocal systems. Specifically, for the relevant stop block manual synchronisation responses (SR) were shifted closer to the beat onset, in contrast to vocal SR that were shifted away from the beat onset. These results support the interpretation that proactive inhibitory mechanisms enhanced SMS for manual responses. Although proactive inhibition shifted vocal SR, its effect was smaller in size compared to manual SR because vocal SR were already very accurate (i.e. in the irrelevant stop block, vocal SR were very accurate with respect to the beat onset).

Keywords:
Proactive inhibition, sensorimotor synchronisation, stop signal task, speech, response inhibition, reactive inhibition and anodal tDCS.

3.2. Introduction

Sensorimotor synchronisation (SMS) is the coordination of movement with an external rhythm. It measures how accurate responses are with respect to an external beat. Normally, when tapping in time to a beat humans tend to make their responses not at the point of absolute temporal coincidence with the beat, but at about 20 to 80 ms prior to the beat (referred to negative mean asynchrony (NMA), Aschersleben, 2002). Interestingly, trained musicians generally have less NMA than novices (Aschersleben, 2002; Repp, 2005). How might this reduction in NMA be achieved? One clue comes from experiments that have used explicit performance feedback to train non-musician subjects to tap closer to the beat. In such studies (i.e. Aschersleben & Prinz, 1995) subjects have been shown to be able to significantly reduce their NMA by learning to "hold themselves back" in order to delay the tap. Such self-reports suggest that in order to tap closer to a beat (as musicians do) one must learn to overcome a natural tendency (i.e. prepotent response) to anticipate the beat. However, this experience of holding a response has not been experimentally measured. Firstly, we would need to understand why mechanism/s are involved in the control of a prepotent response.

There is evidence that shows the control of a prepotent response seems to be associated with inhibitory mechanisms. For example, Duque and Ivry (2009) described how an action is accompanied by corticospinal (CS) suppression of the muscle to be used, suggesting that CS suppression arises from impulse control mechanisms that ensure responses associated with potentially selected actions are not initiated prematurely. From the response inhibition paradigm, the control of a prepotent response at the presence of stop signals is associated with proactive inhibition (Chambers et al., 2009; Logan, 1994; Logan & Cowan, 1984). Proactive inhibition withholds a response until on time release. Thus, this study was designed to experimentally reduced the NMA by inducing proactive inhibition.

We devised a novel task that combined a stop-signal task (SST) and a finger-tapping task [called the stop signal synchronisation task (SS synch task)]. The SS-synch task consisted of go trials, represented by taps or vocalisations in time with an isochronous beat, as in the classic sensorimotor synchronisation (SMS) paradigm –e.g. finger tapping task (for a review see Repp, 2005; Repp & Su, 2013) and intermittent stop trials presented before a beat, as in the SST (Logan & Cowan, 1984). We also included two types of stop blocks:

irrelevant and relevant. In the irrelevant stop block, participants were instructed to ignore the stop signal and just respond in time with the beat like in the classical SMS whereas in the relevant stop block participants were instructed to stop responding at the presence of a stop signal (thus inducing proactive inhibition).

We predicted that proactive inhibition would increase by introducing intermittent stop signals for the relevant stop block. We hypothesised that synchronisation responses (SR) of both manual and vocal response modalities would shift closer to the beat (i.e. reduce the NMA). Finally, in chapter 2 we found that anodal transcranial direct current stimulation (anodal-tDCS) over the right prefrontal cortex (PFC) enhanced reactive inhibition (i.e. SSRT) in both response modalities but did not affect proactive inhibition. We predicted that if enhanced synchronisation is mediated by proactive inhibitory mechanisms, we would expect that anodal-tDCS of the right PFC would enhance reactive inhibition but have no effect on synchronisation.

3.3. Methods

3.3.1. Participants

Twelve participants completed this study (8 females) aged (mean ±SD) 20 ±2.45 years. All participants were right-handed and reported no history of neurological or psychiatric conditions. They all were naïve to the nature of the experiment and gave written informed consent prior to the experiment. Participants received either course credit or cash payment for their participation. The experiment was approved by Macquarie University human ethics committee.

3.3.2. Apparatus

The experimental task was implemented in Presentation® software (version 16.1, www.neurobs.com) and delivered via a Samsung monitor (SyncMaster SA950_LS27A950, 27 inches, 1920 x 1080 pixels, 120 Hz refresh rate). A beep (750 Hz, 75 ms) was synthesised in Audacity (version 1.34-beta [computer program] http://audacity.sourceforge.net/). Vocal-responses were sampled at (8 bit, 2 channels, 48 kHz) via an external microphone placed 2 cm from each subject's mouth and detected via the sound response device in Presentation software, which detected a vocal response when a sound passed a preset threshold. Manual-responses were recorded via key press elicited

by the index finger of the right hand. Participants were seated approximately at 80 cm from the monitor.

3.3.3. Stop signal synchronisation task

This study combined two paradigms: the stop-signal task (SST; Logan, 1994; Logan & Cowan, 1984) and the sensorimotor synchronisation (SMS) task, (Stevens, 1886; Wing, 2002) to develop a task we called the stop-signal synchronisation task (SS-Synch task, see Figure 4 B). It consisted of two blocks: relevant and irrelevant stopping, which varied only in the instructions given to the participants. The relevant stop block contained both go and stop trials. Go trials were represented by an isochronous beat in which subjects were required to synchronise to the beat by making either a manual or vocal response. If it was a manual-response, participants were asked to tap in time with the beat whereas in vocal-responses, participants were asked to synchronise with the beat by producing the vowel sound "ɪ" as it would occur in the word "hit /hɪt/". The stimulus onset asynchrony (SOA) between beats was constant at 1250 ms. Go trials (80 trials in a block or, 4/5 of total trials) were more frequent than stop trials (20 trials in a block or, 1/5 of total trials) thus inducing a prepotent 'go' response trend (see figure 4 C).

In the classic SST (Logan, 1994; Logan & Cowan, 1984), go trials contain a signal, which initiates the go process. Conversely, in this version of the SST, go trials contained a synchronisation signal, which represented a temporal target for the end of the go process. Because we could not measure the start of the go process, we assigned a 'virtual-go signal' to a point 400 ms before the beep in order that the stopping process could be presented as an SSRT as per the classical SST. The timing of the virtual go signal and the initial stop-signal (400 and 200 ms respectively) were based on previous findings (Aron & Poldrack, 2005; Leanne Boucher et al., 2007; Castro-Meneses, Johnson, & Sowman; Etchell et al., 2012; Logan, 1994; Logan & Cowan, 1984; van den Wildenberg & Christoffels, 2010). Refer to figure. 4 A and B for an illustration of the classical SST model and the SS-Synch task.

The stop trials in the relevant stop blocks were visually presented with a red 'X' on the screen (400 font size, 12 cm in height and 10.5 cm width, 8.5° visual angle, 200 ms in duration) on a black background. Subjects were asked to halt their response when they saw this signal. There was a minimum of 4 and a maximum of 16 go trials after any stop trial in

order that participants could re-synchronise with the beat before having to stop again. The stop-signal was initially located at 200 ms before the beep (or 200 ms after the beginning of the virtual-go signal) and adjusted according to a dynamic stop-signal delay (SSD) staircase (Logan & Cowan, 1984).

In the SST, the SSD is typically the time between the onset of the go signal and the onset of the stop-signal (Logan & Cowan, 1984). In this SS-Synch task, the SSD occurred between the time of the virtual-go (400 ms prior to a beep) and the onset of the stop-signal. A staircase procedure changed the SSD after every stop trial, increasing it by 30ms if participants successfully inhibited their previous response and decreasing it by 30ms if previous inhibition was unsuccessful (Logan et al., 1997; Osman et al., 1986, 1990; Verbruggen & Logan, 2009a). This method facilitates a percentage of successful stopping on stop trials of approximately 50%. The staircases for manual and vocal-responses were adjusted independently.

The other stop block was the irrelevant stop block. The irrelevant stop block looked exactly the same as the relevant stop block in terms of go and stop trials. However, subjects were asked to ignore the stop-signals and always respond as if all trials were go trials. Thus, SSD did not adjust according to previous response performance because the percentage of successful inhibition was expected to be 0%; rather, it varied randomly between ± 20% of the mean SSD from the previous relevant stop block.

The index of proactive inhibition is typically estimated based on the go-RT distribution and measured as the increment in RT in the presence of intermittent stop signals (Aron, 2011). In the present study we estimated proactive inhibition based on the go-synchronisation response distribution. The synchronisation response was estimated as the time from the virtual-go signal to the onset of the button press and compared across the irrelevant stop block against the relevant stop block (i.e. block-by-block basis, see Verbruggen & Logan, 2009b). The synchronisation response data is statistically equivalent to the typical measure in SMS studies: **a**synchrony (Repp, 2005; Repp & Su, 2013) and therefore, the statistical results presented here are equivalent to response onset asynchrony. To convert synchronisation response data to asynchrony data we would subtract the onset of the beat in the trial (i.e. 400 ms). For example, if I am presenting a response at 380 ms,

we need to subtract 380 - 400 = - 20 ms. Then, we can say that the response asynchrony occurs 20 ms prior to the beat onset.

The index of reactive inhibition was measured as the stop-signal reaction time (SSRT) based on the independent horse-race model (Logan & Cowan, 1984). We used the integration method to estimate SSRT, which is currently considered the most robust approach for estimating SSRT (Verbruggen et al., 2013; Verbruggen & Logan, 2009a). Using this method, SSRTs were estimated by subtracting the starting time of the stop process (when participants see a stop-signal) from the finishing time of the stop process. The starting time of the stop-process is known, which is the time of SSD; however, the finishing time needs to be estimated. The finishing time is usually estimated by integrating the go reaction time (go-RT) distribution. The go distribution in the SS-Synch task did not contain RTs but rather synchronisation responses (SR), thus we calculated the go-SR distribution, which was estimated as the time from the virtual-go signal to the onset of the button press (end of go process). We used this method to make the SSD here comparable to the SSD as described in the classic SST. The go-SR were rank ordered from the shortest to the longest SR time then, the *nth* SR time was selected. Where *n* was selected by multiplying the probability of responding on stop trials (or unsuccessful stopping) by the total number of go-SR. The probability of responding was calculated as the number of unsuccessful stops divided by the total number of stop trials. SSRT was estimated by subtracting the SSD from *nth* SR time. SSRT was estimated only in the relevant stop blocks.

As a measure of response variability, standard deviations of the inter-response interval (IRI) were also calculated. These results are described in the supplementary material.

3.3.4. Experimental design

This study involved 2 sessions counterbalanced in order across subjects (session with anodal tDCS and session with sham); each session was administered at an interval of between 1 and 7 days. Each session had three phases: phase-1, phase-2 and phase-3. Each phase consisted of four blocks (in total 12 blocks per session) in which two blocks were relevant stop blocks (one manual and the other vocal) and two blocks were irrelevant stop blocks (one manual and the other vocal). The 4-block order (i.e. a phase) was pseudo-randomised by condition such that firstly, a response-modality could only be followed by

the other response-modality of the same stop block (either irrelevant or relevant stop). Secondly, a stop block could only be followed by the other stop block once the first condition was met. For example, if the first block was a relevant stop block with manual-responses then the second block had to be relevant stop block with vocal-responses, subsequently, the third block was an irrelevant stop block with manual-responses and the fourth block was an irrelevant stop block with vocal-responses. At the beginning of each block, instructions were presented on the screen indicating what type of stop block and response-modality was to follow, see figure 5.

3.3.5. Transcranial direct current stimulation

Anodal-tDCS of 1 mA (ramped up and down over 5 sec) was applied for 10 minutes (about a phase length) via two saline-soaked surface sponge electrodes (25 cm^2) (same current intensity and duration as in Ditye et al., 2012; and Jacobson et al., 2011) and delivered by a battery-driven device (Neuroelectrics, Barcelona, Spain). Anodal-tDCS was administered in phase-2 of the session with anodal tDCS. Phase-2 of the session with sham involved sham stimulation, which used the same protocol but electric current was only applied for the first 10 sec. Based on the 10-20 EEG system (Jasper, 1958), the anodal electrode was placed over the intersection point of a line between T4-Fz and a line from F8-Cz. The return electrode was placed on the left cheek as per Jacobson et al. (2011).

3.3.6. Procedure

Prior to the start of each session, and before the electrodes were placed, the experimental procedure was explained. Participants were told that they had to synchronise to the beat and stop responding when a stop-signal was presented. We explained that synchronising and stopping were equally important and that they would fail to stop in about 50% of the stop trials because the experiment adjusted itself to give them easy and hard stop-signals according to their performance. Each participant completed two practice blocks. The first practice block contained only go-trials (40 trials). This was used to familiarise subjects with the beep and the rhythm. The second practice block was a version of the relevant stop block with 12 trials (3 were stop trials). After this, we administered the experimental blocks. The first 10 trials in each block were always go-trials (for the purpose of familiarization with the rhythm). These trials were not included in any statistical analyses.

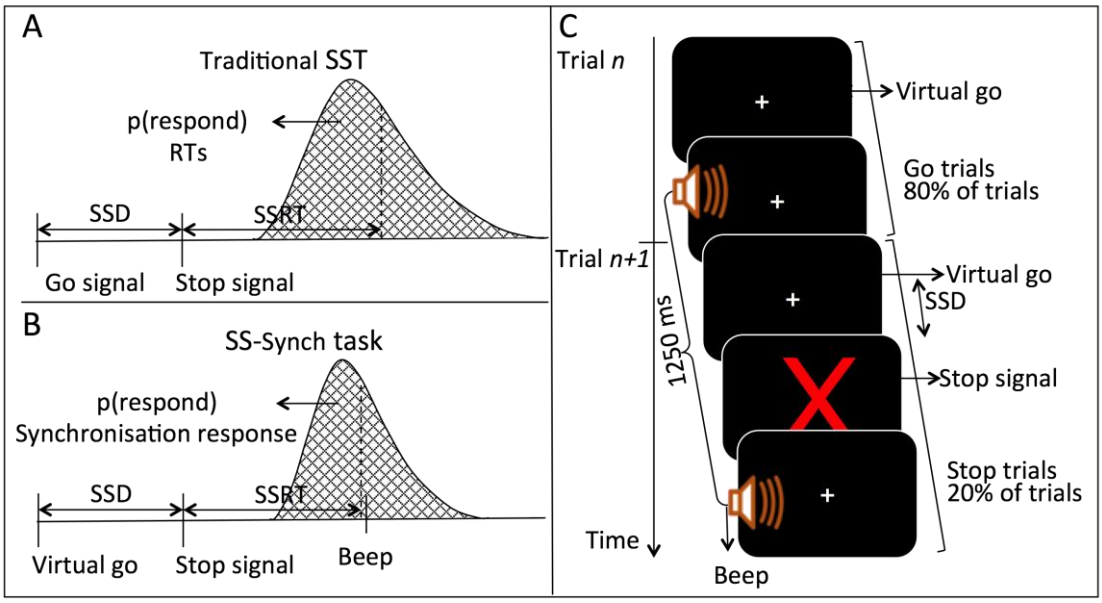

Figure 4 Graphical representation of the independent horse-race model and trial structure (chapter 3)

A) Traditional stop-signal task (SST) taken from (Logan & Cowan, 1984) **B)** Stop-signal synchronisation task (SS-Synch task). The area under the curve to the left of the dashed line represents probability of responding in stop trials [p(respond)]. **C)** Trial structure of SS-Synch task. Each trial lasted for 1,250 ms. Go trials consisted of a visual fixation cross (continuously presented) and a tone (750 Hz, 75 ms in duration) emitted at the time of the beat, 400 ms into the trial. Stop trials started as per go trials but after the stop-signal delay (SSD), a stop-signal, consisting of a red X, was presented.

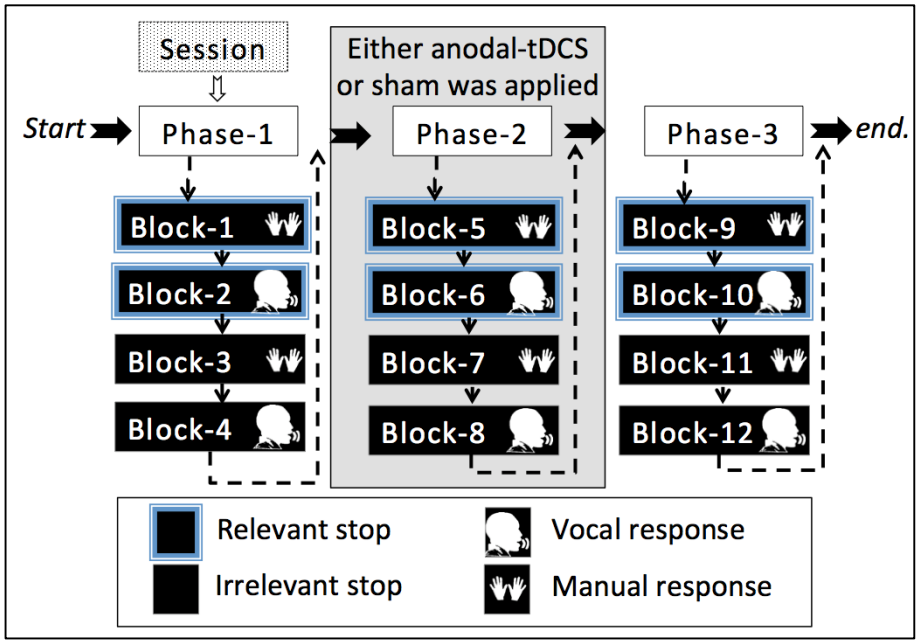

Figure 5 Illustration of experimental design for a session (chapter 3)

Illustration of experimental design for a session. It contained 3 phases and each phase included 4 blocks. The 4-block order (i.e. a phase) was pseudo-randomised by the condition that two blocks were either irrelevant or relevant stop blocks for each response modality (manual or vocal). The grey square in phase-2 depicts the time at which either anodal transcranial direct current stimulation (anodal-tDCS) or sham was applied.

3.4. Results

3.4.1. Synchronisation response time and proactive inhibition

A repeated measures 2 x 2 x 3 x 2 ANOVA was carried out with within-subject factors of 2 stop blocks (irrelevant stop, relevant stop), 2 response-modalities (manual, vocal), 3 phases (phase-1, phase-2 and phase-3) and 2 sessions (session with anodal tDCS and session with sham). Phase factor ($F(2,22) = 19$, $p < 0.001$, $\eta^2_p = 0.64$) and the interaction between stop block and response-modality ($F(1,11) = 41.43$, $p < 0.001$, $\eta^2_p = 0.8$) were statistically significant. All other factors and interactions are reported in Table 5 (supplementary material).

Analysis of the phase factor showed that the go synchronisation response (SR) in phase-1 ($M = 396$ ms, $SE = 7$) were statistically later compared to those in phase-2 by 20 ms ($M = 376$ ms, $SE = 7$, $p < 0.001$) and phase-3 by 22 ms ($M = 374$ ms, $SE = 7$, $p < 0.001$). There were no significant differences across SR between phase-2 and phase-3 ($p = 1.00$). Figure 6 A represents the phase factor.

Post hoc analysis following up on the stop blocks by response-modality interaction (Bonferroni corrected), revealed that across stop blocks, the irrelevant stop block had shorter go-SR compared to the relevant stop block across response modalities; go-SR of the manual irrelevant stop block (M = 318 ms, SE = 13) occurred 75 ms significantly earlier compared to go-SR of the manual relevant stop block (M = 393 ms, SE = 8, p < 0.001). Likewise, go-SR of the vocal irrelevant stop block (M = 402 ms, SE = 8) occurred 13 ms earlier compared to those from the vocal relevant stop block (M = 415 ms, SE = 7, p < 0.05). Moreover, manual SR occurred earlier than vocal SR by 84 and 22 ms for the irrelevant (p < 0.001) and relevant stop blocks respectively (p < 0.05). Figure 6 B depicts this interaction.

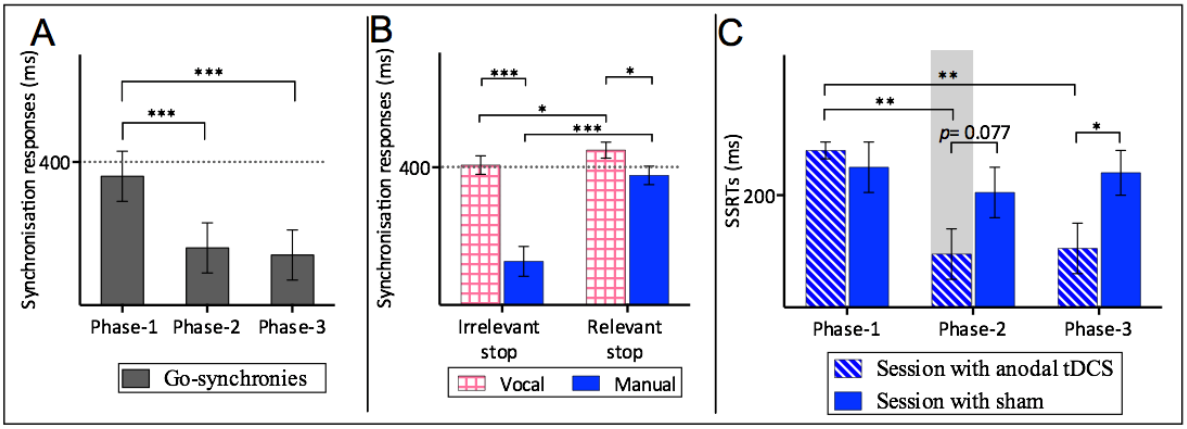

Figure 6 Go-synchronisation response (go-SR) and stop signal reaction time (SSRT) (chapter 2)

Go-synchronisation response (go-SR) and stop signal reaction time (SSRT). **A)** Phase factor for go-SR. Horizontal dashed line indicates time of perfect synchronisation (beat onset). **B)** Go-SR: stop block by response-modality interaction. Horizontal dashed line indicates time of perfect synchronisation (beat onset). **C)** SSRTs: phase by session interaction. Grey bar under phase-2 indicates the time when anodal transcranial direct current stimulation (anodal tDCS) was applied. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$. Error bars indicate standard error of the mean (SEM).

3.4.2. Reactive inhibition – stop signal reaction times (SSRTs)

We aimed to examine the effect of anodal-tDCS on SR and the response cost from the irrelevant to the relevant stop blocks. SSRTs were calculated for the relevant stop block across phase-1, phase-2 and phase-3. A repeated measures 2 x 3 x 2 ANOVA was carried out on the SSRTs with the within-subject factors of 2 response-modalities (manual, vocal), 3 phases (phase-1, phase-2 and phase-3) and 2 sessions (session with anodal tDCS and session with sham). The results revealed two significant interactions: response-modality by session ($F(1,11) = 7.4$, $p = 0.02$, $\eta^2_p = 0.4$) and phase by session ($F(2,22) = 3.6$, $p = 0.05$,

η^2_p = 0.24). All other non-significant main factors and interactions are reported in Table 5 (supplementary material).

Post hoc analyses of the phase by session interaction (Bonferroni corrected) revealed that SSRTs were 27 ms significantly shorter in the phase-3 of session with anodal tDCS [immediately after anodal-tDCS] (*M* = 181 ms, *SE* = 9) compared to phase-3 of session with sham (*M* = 208 ms, *SE* = 8, $p < 0.05$). Phase-2 of the session with anodal tDCS (*M* = 179 ms, *SE* = 9) was not statistically different compared to the phase-2 of the session with sham (*M* = 201 ms, *SE* = 9, p = 0.077). Likewise, SSRTs from phase-1 of session with anodal tDCS (*M* = 216 ms, *SE* = 3) were not significantly different compared to phase-1 of session with sham (*M* = 210 ms, *SE* = 7, $p = 0.31$). Figure 6 C depicts this interaction. Furthermore, in the session with anodal tDCS, SSRTs of phase-1 were significantly different from those in phase-2 ($p < 0.01$) and phase-3 ($p < 0.01$). There were no differences between phase-2 and phase-3 ($p = 1.00$). Go-SR between phases in the session with sham were not different: phase-1 was not different from phase-2 ($p = 0.812$) or phase-3 ($p = 1.00$) and phase-2 was not different from phase-3 ($p= 1.00$).

On the other hand, post hoc analyses following up on the response-modality by session interaction (Bonferroni corrected) showed that across response-modalities there were no significant differences in SSRTs: the manual-responses were not different from vocal-responses during session with anodal-tDCS ($p = 0.544$) or the session with sham ($p = 0.393$).

3.5. Discussion

This study measured whether proactive inhibition increase SR in both manual and vocal responses. We devised a version of the SST in which go trials consisted of a SR to a beat. We included two stop blocks: relevant and irrelevant stop. We hypothesised that induced proactive inhibition via the introduction of stop signals in the relevant stop block would reduce the NMA (i.e. enhance synchronisation). Our data provide evidence to support this hypothesis for the manual system only. This is discussed in turn.

3.5.1. Proactive inhibition on synchronisation

We induced proactive inhibition by presenting intermittent stop signals in the relevant stop block. The increment in proactive inhibition shifted the SR positively. The augmentation in proactive inhibition on the relevant stop blocks made manual SR very accurate with respect to the beat (-7 ms prior to the beat on average, $p = 0.12$ one sample t-test) whereas vocal SR occur significantly later with respect to the beat (+15 ms, $p = 0.001$ one sample t-test).

Our results support previous evidence that suggest proactive inhibitory mechanisms are involved in withholding a prepotent response. For instance, during cued reaction time tasks, reduced activity in the electromyogram (EMG) suggests that the early period of the delay between the warning and the imperative signal is characterised by corticospinal suppression of the limb to be used (Boulinguez, Jaffard, Granjon, & Benraiss, 2008; Duque & Ivry, 2009). It has also been found that single-pulse transcranial magnetic stimulation (TMS) elicits smaller motor evoked potentials (MEPs) over the course of a short foreperiod where faster RTs were obtained compared to a long foreperiod, revealing that temporal preparation involves inhibition of the cortical-spinal pathway (Davranche et al., 2007; Duque et al., 2010). This could be interpreted as a mechanism by which on-time responses are withheld until the appropriate interval has passed, favouring the notion that corticospinal suppression may reflect proactive inhibitory mechanisms that suppress a prepotent response until the time at which it should be released (Jaffard et al., 2008).

Interestingly, the vocal effector system used less proactive inhibition relative to the manual effector system. In other words, the appearance of stop signals for the relevant compared to the irrelevant stop block delayed SR much less in the vocal compared to the manual system (delayed SR by 13 and 75 ms for vocal and manual respectively). More surprisingly, while the manual SR for the irrelevant stop block depicted the standard pattern of earlier responses (i.e. NMA of -82 ms prior to beat, $p < 0.001$ one sample t-test), vocal SR were almost on time with the beat onset (only + 2 ms asynchrony with the actual tone onset, $p = 0.7$ one sample t-test). The fact that vocal SR were very accurate in the irrelevant stop block may explain why the effect of proactive inhibition was diminished: proactive inhibition was not necessary for synchronisation as the system was already very accurate.

However, it remains the question of why vocal compared to the manual system had less NMA in the irrelevant stop block. We suggest that vocalisation was still using some kind of inhibitory control to release the prepotent responses more accurately for the irrelevant stop block. This inhibitory mechanism may be the one described as impulse control (Duque & Ivry, 2009). However, further testing would be required to support this mechanism. We further suggest that an active impulse control mechanism may explain why vocal RTs are usually slower compared to manual RTs: it could be that the system is more 'cautious' at responding or uses more impulse control.

Contrarily, it could be argued that the differences between manual and vocal responses were due to different measurements (i.e. key-presses vs. voice) and the instruments (i.e. response box vs. microphone) but then, why did the ratio of differences between response modalities not persist in both irrelevant and relevant stop blocks?

The final aim of the current study was to enhance reactive inhibition without affecting synchronisation, which would show that synchronisation might not rely on reactive inhibition. We found that SSRTs got significantly shorter (by 27 ms) in phase-3 for both response-modalities (i.e. manual, vocal) in session with anodal tDCS [immediately after the phase that anodal-tDCS was applied] compared to session with sham [immediately after the phase of sham stimulation]. These findings are comparable to our previous study (chapter 2) in which SSRTs in phase-3 decreased by 41 ms. In contrast, in chapter 2 we also found significant differences in phase-2 (by 37 ms, during simultaneous anodal-tDCS). These differences may be explained by the differences in tDCS exposure time and current intensity used between the two chapters. While in the present study we applied 1 mA for 10 min, in the previous chapter we applied 1.5 mA for 15 min. Jacobson et al.,'s 2011 study also found that anodal-tDCS over the right PFC (using the same localisation procedure, exposure time and current intensity as the present study) reduced SSRTs of manual-responses by 33 ms as compared to a sham session immediately after. Additionally, the analogue of the SSRT we use in the current study had very similar latencies to previous studies, showing that this task is comparable to the traditional SST (Aron & Poldrack, 2005; Leanne Boucher et al., 2007; Etchell et al., 2012; Logan, 1994; Logan & Cowan, 1984; Logan & Irwin, 2000; van den Wildenberg & Christoffels, 2010; Verbruggen & Logan, 2008b; Wessel & Aron, 2014).

3.5.2. Summary

We suggest that enhanced sensorimotor synchronisation for manual responding can be induced via proactive inhibition.

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Appendix E. Supplementary material

Synchronisation response time and stop-signal

We firstly investigated whether the appearance of a stop-signal altered rhythmic synchronisation in the go trials. To do this we compared the synchronisation response (SR) of the first and second go trial after each stop-signal (1st-go and 2nd-go respectively) with all other go trials (other-go). A 3 x 2 x 2 x 3 x 2 ANOVA was carried out with within-subject factors of 3 go-types (1st-go, 2nd-go, other-go), 2 stop block types (irrelevant stop, relevant stop), 2 response-modalities (manual, vocal), 3 phases (phase-1, phase-2 and phase-3) and 2 sessions (session with anodal tDCS, session with sham). The results showed that there was no significant main effect of go-types ($F(2,22) = 2.14$, $p = 0.14$, $\eta^2_p = 0.16$) but there was a significant interaction between go-type and phase ($F(4,44) = 2.56$, $p = 0.05$, $\eta^2_p = 0.19$). Because this ANOVA was done to explore the effect of stop-signals on SR, we followed to describe this interaction. Main factors and significant interactions are reported in Table 5.

Post hoc comparisons following up on the go-type* phase interaction (Bonferroni corrected) showed that go-SR in phase-1 were significantly different from those in phase-2 and phase-3, this pattern was observed in all three go-types. This is 1st-go in phase-1 (M = 400 ms, SE = 7) was statistically different from 1st-go in phase-2 (M = 374 ms, SE = 8, p = 0.003) and phase-3 (M = 373 ms, SE = 9, p = 0.002). Furthermore, the 2nd-go in phase-1 (M = 391 ms, SE = 7) was significantly different from the 2nd-go in phase-2 (M = 367 ms, SE = 7, p = 0.0001) and phase-3 (M = 366 ms, SE = 7, p = 0.001). Lastly, other-go in phase-1 (M = 396 ms, SE = 7) was significantly different from both other-go in phase-2 (M = 380 ms, SE = 7, p = 0.002) and phase-3 (M = 377 ms, SE = 8, p = 0.005). There were no significant differences between go-types when comparing phase-2 to phase-3 (p = 1.00). In sum, this interaction showed that there were no statistically significant differences between the 1st-go, 2nd-go and other-go, this means that the appearance of the stop signal did not alter rhythmic synchronisation.

Standard deviation of inter-response-interval

On the standard deviation (SD) of the inter-response interval (IRI) we conducted a repeated measures 2 x 2 x 3 x 2 ANOVA with within-factors of 2 stop block type (irrelevant stop, relevant stop), 2 response-modalities (manual, vocal), 3 phases (phase-1,

phase-2 and phase-3) and 2 sessions (session with anodal tDCS, session with sham). The results revealed a three-way significant interaction: stop block type * response-modalities * phases ($F(2,22) = 4.73$, $p = 0.02$, $\eta^2_p = 0.3$). Main factors and other interactions are reported in Table 5.

Post hoc analyses following stop block type* response-modality* phase interaction (Bonferroni corrected), revealed that SD of IRI in the irrelevant stop condition with vocal-responses in phase-2 was statistically less variable ($M = 76$ ms, $SE = 4$) compared to relevant stop condition with vocal-responses in phase-2 ($M = 98$ ms, $SE = 5$; $p < 0.01$). Likewise, there was a statistically significant difference in phase-3: the irrelevant stop condition with vocal-responses ($M = 81$ ms, $SE = 5$) was less variable compared to relevant stop condition with vocal-responses ($M = 97$ ms, $SE = 5$, $p < 0.05$). There were no differences in phase-1 ($p = 0.2$). On the other hand, SD of ITI for manual-responses did not differ statistically from irrelevant stop condition compared to relevant stop block across any phases ($p = 0.06$, 0.8, 0.56 for phase-1, phase-2 and phase-3 respectively). Across response-modalities, this interaction showed that irrelevant stop block with manual-responses in phase-2 had significantly more variability ($M = 120$ ms, $SE = 16$) than irrelevant stop block with vocal-responses in the same phase ($M = 76$ ms, $SE = 4$, $p < 0.05$). Likewise in phase-2, relevant stop block with manual-responses ($M = 116$ ms, $SE = 5$) was statistically more variable than relevant stop block with vocal-responses ($M = 98$ ms, $SE = 5$, $p = 0.023$). There was a statistically significant difference in phase-3, in which irrelevant stop block of manual-responses ($M = 103$ ms, $SE = 8.4$) was more variable than those of vocal-responses ($M = 81$ ms, $SE = 5$, $p < 0.05$). The last significant paired wise comparison was between irrelevant stop block of vocal-responses between phase-1 ($M = 90$ ms, $SE = 5$) and phase-2 ($M = 76$ ms, $SE = 3.66$, $p < 0.05$).

Table 5: Results of all ANOVA that were not included in main text (chapter 3)

ANOVA	Factor and interaction	F value (degrees of freedom)	p-value	Partial eta-square
3 x 2 x 2 x 3 x 2 DV: go-SR	Sessions	F(1,11) = 2	0.17	0.2
	Stop block types	F(1,11) = 111	0.001	0.9
	Response-modalities	*F*(1,11) = 22	0.001	0.7
	Phases	*F*(2,22) = 20	0.001	0.6
	Stop block type*response-modality	*F*(1,11) = 35	0.001	0.8
2 x 2 x 3 x 2 DV: go-SR	Stop block types	*F*(1,11) = 140	0.001	0.9
	Response-modality	*F*(1,11) = 23	0.006	0.7
	Sessions	*F*(1,11) = 2	0.15	0.2
	Stop block type*phases	*F*(2,22) = 0.42	0.7	0.04
	Response-modality*phases	*F*(2,22) = 0.6	0.5	0.05
	Stop block type*response-modality*phases	*F*(2,22) = 1	0.4	0.1
	Stop block type*sessions	*F*(1,11) = 0.01	1.0	0.01
	Response-modality*sessions	*F*(1,11) = 0.08	0.8	0.01
	Stop block type*response-modality*sessions	*F*(1,11) = 3	0.11	0.2
	Phases*sessions	*F*(2,22) = 0.01	1.0	0.001
	Stop block type *phases*sessions	*F*(2,22) = 0.07	0.92	0.01
	Response-modality*phases*sessions	*F*(2,22) = 0.95	0.4	0.08
	Stop block type*response-modality*phases*sessions	*F*(2,22) = 0.21	0.8	0.02
2 x 3 x 2 DV: SSRT	Sessions	*F*(1,11) = 9.8	0.01	0.5
	Phase	*F*(2,22) = 7.7	0.003	0.4
	Response-modality	*F*(1,11) = 0.02	0.9	0.001
	Response-modality*phase	*F*(2,22) = 0.3	0.7	0.03
	Response-modality*phase*sessions	*F*(2,22) = 0.07	0.93	0.01
2 x 2 x 3 x 2 DV: SD of IRI	Stop block type	*F*(1,11) = 4.2	0.06	0.3
	Response-modality	*F*(1,11) = 7.7	0.02	0.41
	Phases	*F*(2,22) = 1.1	0.35	0.09
	Sessions	*F*(1,11) = 0.01	0.92	0.001
	Response-modality*phases	*F*(2,22) = 3.65	0.042	0.3

ANOVA	Factor and interaction	F value (degrees of freedom)	p-value	Partial eta-square
	Stop block type*response-modality	$F(1,11) = 1.5$	0.25	0.1
	Stop block type*phases	$F(2,22) = 0.17$	0.84	0.02
	Stop block type*sessions	$F(1,11) = 0.2$	0.7	0.02
	Response-modality*sessions	$F(1,11) = 0.42$	0.53	0.04
	Stop block type* response-modality*sessions	$F(1,11)=1.5$	0.25	0.12
	Phases*sessions	$F(2,22) = 2.2$	0.13	0.16
	Response-modalities*phases*sessions	$F(2,22) = 2.77$	0.09	0.2
	Stop block type* phases*sessions	$F(2,22) = 0.02$	1.00	0.001
	Stop block type* response-modality* phases* sessions	$F(2,22) = 0.6$	0.6	0.05

This table contains all the results of the ANOVA performed during the analyses and were not included in the main text. The first column indicates the amount of factors included in the ANOVA and the dependent variable (DV) measured. The second column contained the factors and interactions, third column describes the p-values and the last column the effect size as measured by partial eta-squared.

SR = synchronisation response

SSRT = stop signal reaction time

IRI = inter-response interval

Table 6: Go reaction times (go-RTs), stop-signal delay (SSD), stop-signal reaction times (SSRTs) and p_inhibit (chapter 3)

	Phase-1		Phase-2		Phase-3	
	Vocal	Manual	Vocal	Manual	Vocal	Manual
SSRT: session with anodal tDCS + relevant stop block	221 ± 6	211 ± 5	180 ± 10	178 ± 12	181 ± 8	180 ± 11
SSRT: session with sham + relevant stop block	209 ± 8	211 ± 10	200 ± 10	204 ± 12	202 ± 9	213 ± 10
Go-RT: session with anodal tDCS + irrelevant stop condition	405 ± 12	336 ± 13	338 ± 13	306 ± 17	388 ± 13	303 ± 18
Go-RT: session with sham + irrelevant stop condition	422 ± 6	342 ± 16	407 ± 7	310 ± 16	401 ± 13	309 ± 13
Go-RT: session with anodal tDCS + relevant stop condition	421 ± 8	400 ± 10	406 ± 8	382 ± 11	406 ± 12	377 ± 11
Go-RT: session with sham + relevant stop condition	434 ± 9	411 ± 10	416 ± 11	390 ± 10	415 ± 13	398 ± 13
SSD: session with anodal tDCS + relevant stop block	203 ± 7	189 ± 13	209 ± 11	179 ± 13	212 ± 15	191 ± 16
SSD: session with sham + relevant stop block	232 ± 10	192 ± 15	230 ± 15	205 ± 13	230 ± 11	200 ± 13
p_inhibit: session with anodal tDCS + relevant stop block	.51 ± .02	.48 ± .04	.51 ± .02	.48 ± .03	.50 ± .01	0.54 ± .01
p_inhibit: session with sham + relevant stop block	.55 ± .01	.51 ± .02	.49 ± .01	.49 ± .02	.52 ± .02	0.54 ± .02

Mean reaction times (RT) and standard error of the mean (SEM) in milliseconds go-RTs across three phases (phase-1, phase-2 and phase-3) for each session (session with anodal tDCS and session with sham). Note that SSDs, p_inhibit and SSRTs were calculated in the relevant stop condition only, whereas go-RTs were estimated in both the relevant and irrelevant stop condition. p_inhibit refers to the probability of successful stopping. Black rectangle around phase-2 highlights that only in this phase either anodal tDCS or sham was applied.

Chapter 4 – Event related fields evoked by vocal response inhibition: a comparison of younger and older adults

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4. Event related fields evoked by vocal response inhibition: a comparison of younger and older adults

4.1. Abstract

The current study examined event-related fields (ERFs) evoked by vocal response inhibition in a stimulus selective stop signal task. We compared inhibition-related ERFs across a younger and an older group of adults. Behavioural results revealed that stop-signal reaction times (RTs), go RTs, ignore-stop RTs and failed stop RTs were longer in the older, relative to the younger group by 38, 123, 149 and 116 ms respectively. The amplitude of the ERF M2 peak (approximately 200 ms after the stop signal) evoked on successful stop trials, was larger compared to that evoked on both failed stop and ignore-stop trials. The M4 peak (approximately 450 ms post stop signal) was of larger amplitude in both successful and failed stops compared to ignore-stop trials. In the older group, the M2, M3 and M4 peaks were smaller in amplitude and peaked later in time (by 24, 50 and 76 ms respectively). We demonstrate that vocal response inhibition-related ERFs exhibit a similar temporal evolution to those previously described for manual response inhibition: an early peak at 200 ms (i.e. M2) that differentiates successful from failed stopping, and a later peak (i.e. M4) that is consistent with a neural marker of response-checking and error-processing. Across groups, our data supports a more general decline of stimulus processing speed with age.

Keywords: response inhibition, speech, magnetoencephalography, event-related fields, aging and stop signal task

4.2. Introduction

Response inhibition is defined as either preparing in advance to withhold a response before a stop signal has occurred (proactive inhibition) or stopping an action in response to a stop signal (reactive inhibition; Aron, 2011; Logan, 1994; Logan & Cowan, 1984). The main aim of the current study was to investigate magnetoencephalography (MEG) -based neurophysiological markers of response inhibition in a less studied effector system: that of vocalisation. Because this thesis is intended to be the basis for investigating vocal inhibition, we studied the neurophysiological markers of younger and older adults.

Studying vocal response inhibition is important because this study may help us to understand specific neuropsychological disorders that affect speech such as stuttering and Tourette syndrome. For example, it is interesting to observe that these two disorders share a common reduced intracortical inhibition (Eggers et al., 2013; Neef et al., 2011).

Characterisation of the temporal cortical signature of response inhibition is based on results largely derived from button press studies using electroencephalography (EEG). However, behavioural results show that response inhibition performance is different across effector systems. For example, the stop signal reaction time (SSRT) for hand movements is longer than that for eye movements (Leanne Boucher et al., 2007; Curtis et al., 2005) or letter naming (Xue et al., 2008) and shorter than that for vowel-sound production (Castro-Meneses et al., 2015). Such results suggest that the temporal signature of inhibition in other effector domains should not be assumed to mirror that of manual response inhibition.

Few studies of response inhibition in vocalisation exist (Cai et al., 2012; Castro-Meneses et al., 2015, 2016; Etchell et al., 2012; van den Wildenberg & Christoffels, 2010; Xue et al., 2008) and, to our knowledge, only one of these studies has previously investigated the neurophysiological temporal evolution of vocal response inhibition. Using EEG Etchell et al. (2012) reported three event-related potential (ERP) peaks after a stop signal: a P2, an N2 and a P3. However, these peaks did not differ in amplitude between successful and failed stopping, a finding that conflicts with most of the previous ERP literature on manual response inhibition (e.g. Dimoska et al., 2003; Greenhouse & Wessel, 2013; Huster, Enriquez-Geppert, Lavallee, Falkenstein, & Herrmann, 2013; Kok et al., 2004; Lansbergen et al., 2007; Liotti et al., 2010; Schmajuk et al., 2006; Wessel & Aron, 2014). Although

there are MEG studies that have investigated manual response inhibition with the go/no-go task (e.g. Hege, Preissl, & Stingl, 2014; Hughes, Rittman, Regenthal, Robbins, & Rowe, 2015; Mazaheri, Nieuwenhuis, van Dijk, & Jensen, 2009; Nakata, Inui, Wasaka, Akatsuka, & Kakigi, 2005; Nakata, Sakamoto, Otsuka, Yumoto, & Kakigi, 2013; J. Vidal, Mills, Pang, & Taylor, 2012), only one previous MEG study has investigated (manual) response inhibition via the stop signal task. In that study, ERFs locked to the stop signal yielded a magnetic peak at around 160 ms (range 140 and 160 ms) which was of larger amplitude for successful stops relative to failed stops (Boehler et al., 2009).

Like Boehler et al. (2009), most previous neurophysiological investigations of response inhibition have reported mainly early peaks (e.g. pre-400 ms). However, a notable few studies have reported a later peak occurring between ~ 370 and 650 ms after the stop signal, the so-called 'error-processing' peak (Falkenstein et al., 2000; Ramautar et al., 2004). The amplitude of this later peak is larger for failed stops relative to successful stops (Kok et al., 2004; Ramautar et al., 2004; Schmajuk et al., 2006; Squires et al., 1975) and is similarly reported to occur in response to erroneous responses in choice RT tasks (Falkenstein et al., 2000; Falkenstein et al., 1999). One of the aims of the current study was to characterise this later 'error-processing' peak in the context of vocal response inhibition. Given that disordered response monitoring is thought to contribute to disorders of speech like stuttering (see Hartsuiker, Bastiaanse, Postma, & Wijnen, 2005 for an overview of this theory), a neurophysiological index of error-monitoring for vocal responses could provide an important measure for testing such a hypothesis in future.

Behaviourally, manual response inhibition becomes less effective with age, and older compared to younger adults have significantly longer stopping times (as measured by SSRT, Bedard et al., 2002; Coxon et al., 2014; Williams et al., 1999). Neurophysiological indices of inhibition also exhibit age-related changes, e.g. in the Oddball task, the latency of the P3 occurs later for older compared to younger adults (Brown et al., 1983; Dustman et al., 1990; Pfefferbaum et al., 1984). Several other studies have reported that the P3 in inhibitory tasks[1] not only occurs later but is also smaller in amplitude in posterior areas in

[1] The task used by Mullis et al., (1985) consisted of three trial types that each presented a letter sequence: a low probability target (16.7%), a high probability non-target (67%) and an unexpected category (16.9%). Participants had to press a button at the appearance of the low probability target. The task used by Podlesney et al., (1984) was a so-called "respond-

older adults compared to younger adults (Mullis et al., 1985). While the source of this inhibitory decline could be inhibition specific, it could also reflect a global slowing of neural processing like that ascribed to slowing differences for go-RTs in older adults (Bedard et al., 2002; Kramer et al., 1994; Williams et al., 1999). No study has yet investigated age-related differences in vocal response inhibition.

In sum, little research has been performed on the temporal neurophysiological evolution for vocal response inhibition especially in the ageing brain, despite there being behavioural and neurophysiological evidence to suggest that the strength of inhibitory control might be different for vocalisation. Furthermore, the single study that does exist failed to report the usual pattern of significant differences in cortical response amplitude between successful and failed stopping.

The current study investigated vocal response inhibition by means of high-resolution MEG. Using a stimulus selective stop signal task (SST, Bissett & Logan, 2014), we investigated latency and amplitude differences for three types of trials (i.e. successful stop, failed stop and ignore-stop trials). Our study explored ERFs for vocal response inhibition across an older and a younger group of adults. We hypothesised that, in contrast to Etchell et al. (2012), the amplitude of successful stopping would be larger compared to both failed stops and ignore-stop trials in an early peak at around 160 ms (based on the MEG findings of Boehler et al. (2009)). Secondly, we hypothesised that amplitude modulations by trial type in a later peak (~350 to 700), would support an error-processing account i.e. this peak would be larger in amplitude for failed compared to both successful stops and ignore-stop trials. Finally, we hypothesised that if older relative to younger adults have slower SSRTs because of a specific stopping deficiency, then the ERF peak most related to successful stopping would have an amplitude reduction and/or a latency delay.

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withhold" task, which contained two conditions. One condition was very similar to the go/no-go task and another condition was similar to a selective SST.

4.3. Methods

4.3.1. Participants

Forty-one participants completed this study. Participants were grouped by age. 20 were assigned to a younger group (age range= 18-27; mean age= 22.25 years; *SD*= 3.2; 13 females) and 21 to an older group (age range= 43-83; mean age= 58 years; *SD*= 11; 8 females). No participant had a history of neurological impairment or psychiatric illness. The study was approved by Macquarie University Human Research Ethics Committee. All participants provided written informed consent.

4.3.2. Stimuli and apparatus

This study used a stimulus selective SST to measure response inhibition (Bissett & Logan, 2014; Logan, 1994; Logan & Cowan, 1984). The task is similar to the one described in Etchell et al. (2012). It contained three types of trials: go, ignore-stop and stop trials. Go trials consisted of a simple forced choice reaction time task where participants were required to respond as quickly and accurately as possible to the go-signal, which was the visual onset of one of two possible vowels "I" and "O" (5.5 cm in height). Go trials began with a white fixation cross appearing in the centre of a black background. Following the fixation cross, at a random interval between 1.5 and 3.5 s, a black letter (either an I or an O) appeared on a white square (7 cm each side) in the centre of the screen surrounded by a green border (12.5 cm each side). Each letter was presented in half of the trials and the order of their appearance was randomised. Participants were instructed to make a short vowel sound, as would occur in the words hit and hot for the letters "I /hɪt/" and "O /hɒt/" respectively. Vocalisations were recorded by a directional microphone positioned on the ceiling of the magnetically shielded room above the subject's head.

The stop trials were similar to the go trials in that they started with a fixation cross which was followed by a go-signal; however, after the stop-signal delay (SSD), a stop-signal appeared. The imperative to stop was signalled by a change of the border colour from green to red, which instructed participants to withhold their response. The SSD changed dynamically throughout the experiment depending on stopping performance. If a participant inhibited successfully on a stop trial, then successful response inhibition was made less likely on the subsequent stop trial by increasing the SSD by 50 ms. If however, the participant failed to stop on a stop trial, successful response inhibition was made more

likely for the next stop trial by decreasing the SSD by 50 ms. After 20 direction reversals, the staircase step size was reduced to 17 ms. Four staircases were employed that started at arbitrarily selected time points (50, 83, 117 and 150 ms). Each staircase was independently adjusted but randomly interleaved.

Ignore-stop trials functioned as go trials but were similar to stop trials in that, after a given delay, the green border changed colour to blue. The ignore-stop signal delay (ISD) chased the SSD of the stop trials (i.e. the SSD for any given ignore-stop trial was the same as that for the most recent stop trial). Participants were instructed to respond on ignore-stop trials as if they were go trials.

Importantly, go, stop and ignore-stop trials all occurred within the same block of trials. A graphical representation of the stimulus design is illustrated in figure 7. Overall, there were 864 trials divided into 9 blocks, with 96 trials in each block; of these, 24 trials were stop trials (25%), 24 trials were ignore-stop trials (25%) and 48 trials were go trials (50%).

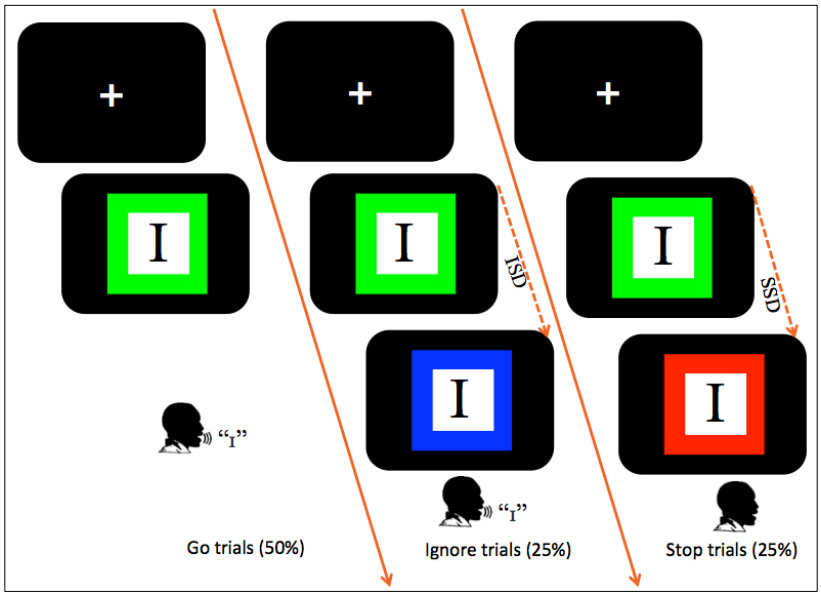

Figure 7 Trial structure for the selective stop-signal task (chapter 4)

Trial structure for the selective stop-signal task (selective SST). Trials had either the letter "I" or "O" presented as a forced choice reaction cue. Stop and ignore-stop trials started in the same way as a go trial but after a given delay, the colour of the border around the response cue changed. In stop trials, the border changed from green to red after the stop signal delay (SSD), which was adjusted throughout the task according to the participant's stopping performance. In ignore-stop trials the border colour changed from green to blue after the ignore-stop delay (ISD), which was the same as the previous SSD. Participants were instructed to respond verbally as quickly and accurately as possible to the go and ignore-stop trials and to refrain from responding on the stop trials.

4.3.3. MEG data acquisition and pre-processing

Prior to MEG recordings the locations of 3 cardinal landmarks (the nasion and bilateral preauricular points), 5 marker coil positions and the subject's head shape were recorded with a pen digitizer (Polhemus Fastrack, Colchester, VT). Each subject's head position in relation to the sensors was measured at the start of each recording block by energizing the 5 marker coils briefly. MEG recordings were obtained using the KIT-Macquarie MEG160 (Model PQ1160R-N2, KIT, Kanazawa, Japan) with participants supine in a magnetically shielded room (Fujihara Co. Ltd., Tokyo, Japan). Data were recorded using 160 coaxial first-order gradiometers with a 50 mm baseline (Kado et al., 1999; Uehara et al., 2003). MEG data were acquired with a sampling rate of 1000 Hz and an online bandpass filter of 0.03-200 Hz. Subsequent offline data processing was performed with Statistical Parametric Mapping software for MEG and EEG (SPM 8; http://www.fil.ion.ucl.ac.uk/spm) running on Matlab R2014 (The MathsWorks Inc, Natick, USA).

Offline, data were bandpass butterworth-filtered with: high-pass filter at 0.5 Hz to attenuate low frequencies (e.g. scanner drifts, coil interference, slow vascular/metabolic oscillations (~<0.01 Hz) or breathing (~0.3 Hz) (Teplan, 2002) and low-pass filtered at 90 Hz to attenuate high frequencies because desired biosignals lie below 90 Hz. The data was also stopband butterworth-filtered from 49 to 51 Hz to remove alternating current power line noise (Teplan, 2002). Data were downsampled to 200 Hz and then epoched from -1000 to 1000 ms relative to the go, stop and ignore-stop signals as well as the speech onsets. Data thus epoched were assigned to 5 conditions: go, ignore-stop, successful stop, failed stop and speech-onset. After epoching, data were baseline corrected using an epoch -1000 to -800 ms prior to the relative stimulus presentation. This early baseline was implemented to avoid other overlapping process (i.e. prepotent response preparation). To remove mouth movement artefacts, the field pattern of mouth muscle activity was identified from the MEG signals averaged with respect to the speech-onset, and then was projected out of the MEG epoched data using an approach similar to that used in (Salmelin, Schnitzler, Schmitz, & Freund, 2000; Sörös, Cornelissen, Laine, & Salmelin, 2003; Uusitalo & Ilmoniemi, 1997; Vihla, Laine, & Salmelin, 2006) and implemented here with the spatial confound procedure in SPM8. Data were then re-filtered with a 30 Hz low-pass filter. After this step, the positions of the sensors across blocks were transformed to a common sensor space using the method of single-space projection to correct for head movements (Knösche, 2002). To do this, sensors were realigned from each block's

recordings into a standardized space containing 160 sensors using the ft_megrealign script implemented in the FieldTrip toolbox (Fieldtrip Toolbox for MEG/EEG Analysis; F. C. Donders Centre, Radboud University Nijmegen, Nijmegen, The Netherlands; product of MathWorks). Finally, all trials were averaged with respect to each condition. For display purposes the averaged files were cropped to display the epoch between −100 and 700 ms.

4.4. Data Analysis and statistical tests

4.4.1. Behavioural data

Independent sample t-tests were carried out for go-RT, ignore-stop RT, failed stop RTs and SSRTs across the younger and older groups. Go, failed stop and ignore-stop RTs were estimated from the time of a go-signal to a response. Missed trials (1.25% and 0.9% in go and ignore-stop trials respectively) were excluded.

Based on the integration method (Verbruggen et al., 2013), SSRTs were estimated by subtracting the starting time from the finishing time of the stop process. The starting time occurs when participants see the stop signal, a process that is modulated by the time of the SSD. Thus, the initial stop signal time was the mean of the SSDs. The finishing time is unknown because a successful stop cannot be measured directly, so it was estimated based on the go-RT distribution. Go-RTs were rank ordered from the shortest to longest and then the *nth* RT was selected. Where *n* was selected by multiplying the probability of responding or p_respond (i.e. failed stop) on stop trials by the total number of go-RTs. The p_respond was calculated as the number of failed stops divided by the total number of stop trials. SSRT was then estimated by subtracting the SSD from the *nth* RT.

4.4.2. Sensor space analysis of MEG data - Amplitude

The peaks we report were named according to the peak's ordinal position as per Box 1.2 in Luck (2005). The event-related field (ERF) polarity is not constant across the scalp topography; the measured magnetic field produced by neural activity has both a source and a sink. Therefore, ERFs are often positive on one side of the scalp and negative on the other. Hence, for description of comparison between conditions we use the term 'larger' to describe amplitudes of peaks that are either more positive or more negative between conditions. We present the peaks with the prefix "M" (for magnetic), which returns no information in regard to the sign of the peak, followed by the peak's ordinal position. For example the "M2" refers to the second peak in the evoked magnetic field.

The averaged ERF data were converted to 2D images (space x time dimensions); this procedure generates a separate image for each sample in time for each condition. These images were then taken to the second level of the classical SPM analysis. Because we were interested in testing whether there were significant differences across groups and conditions (ignore-stop, successful stop and failed stops), we firstly conducted a 2 x 3 flexible ANOVA (Gläscher & Gitelman, 2008) with a two-level between-subjects factor of group (younger, older) and three-level within-subject factor of condition (ignore-stop, successful stops and failed stops). From this, we analysed the main effect of condition and the interaction of group by condition, which are statistically valid measures for the SPM flexible ANOVA (McLaren, 2014). A height threshold of $p < 0.001$ was first applied to the whole sensor space topography and clusters above this threshold were deemed significant if they survived family wise error correction (FWE-corr) at an alpha of $p < 0.05$ unless stated otherwise. For the group by condition interaction, we conducted four t-contrasts comparing the amplitude difference between successful stop and ignore-stop, failed stops and ignore-stop and their respective reverse weights (e.g. ignore-stop - successful stop). For the differences in condition, six t-contrasts were conducted on the differences between successful stops and ignore-stops, failed stops and ignore-stops, successful stops and failed stops, and the respective reverse contrasts.

The main effect of group in the flexible factorial ANOVA in SPM uses the within-subject error term and incorrect degrees of freedom, which makes the main effect of group a statistically invalid measure (McLaren, 2014). Because of this, we conducted an independent sample t-test to get a valid effect of group by averaging across the 3 conditions: ignore-stops, successful stops and failed stops. We also conducted independent sample t-tests for each condition separately across groups to understand better any significant interactions, as well as the main effect of group. The reader is referred to supplementary information for full details of the t-contrasts carried out on the 2 X 3 ANOVA and further details on amplitude and latency analyses (e.g. cluster size and peak coordinates). Here we present the main findings.

4.4.3. Sensor space analysis of MEG data - Latencies

From the analysis of the flexible factorial, we obtained the sensors that had a significant difference in amplitude and created two regions of interests (ROIs) over central sensors. The two central ROIs corresponded to left and right sides of the scalp (likely reflecting a

central source) for the peaks M2, M3 and M4. Each ROI was averaged across eight electrodes for each condition (i.e. ignore-stops, successful stops and failed stops) within each subject. We then obtained the latency at the maximum within predefined time-windows. The time-window for the M2 was between 165 and 300 ms, for the M3 was between 250 and 410 ms and for the M4 between 350 and 700 ms. We conducted a 2 x 3 x 2 repeated measures ANOVA with the within-subject factor of 2 ROIs (left and right) and 3 conditions (ignore-stops, successful stops and failed stops) and the between-subject factor of 2 groups (younger and older).

4.5. Results

4.5.1. Behavioural results

Go-RTs in the older group were 123 ms slower (M = 701 ms, SD = 153) compared to the younger group (M = 578 ms, SD = 121, $t(39)$= -2.85, $p < 0.01$). Likewise, ignore-stop RTs in the older group were 149 ms slower (M = 761 ms, SD = 183) relative to those of the younger group (M = 612 ms, SD = 130, $t(36.1)$= -3.01, $p < 0.01$). Finally, failed stop RTs for the older group were 116 ms slower (M = 655 ms, SD = 132) compared to the younger group (M = 539 ms, SD = 98, $t(39)$= -3.2, $p < 0.01$).

SSRTs in the older group were 38 ms slower (M = 327 ms, SD = 76) compared to those of the younger group (M = 289 ms, SD = 44, $t(32.133)$= -2.028, $p < 0.05$).

Table 7: Behavioural data (chapter 4)

	Younger group	Older group
Go-RTs	578 ms ± 121	701 ms ± 153
Ignore-stop RTs	612 ms ± 130	761 ms ± 183
SSRT	289 ms ± 44	327 ms ±76
Failed stop RT	539 ms ± 98	655 ms ± 132
SSD	283 ms ± 102	377 ms ± 185
Accuracy of successful stop	0.49 ± 0.043	0.51 ± 0.065
Missed go trials	3 ± 3	8 ± 13
Missed ignore trials	2.4 ± 4	5 ± 8

Mean ± SD; SSRT= stop signal RT; SSD= stop signal delay;

4.5.2. MEG sensor space results

ERFs locked to the stop signal were characterised by between-condition significant differences in the M2, M3 and M4 peaks over central and centro-lateral sensors. The differences between these ERF peaks as a function of condition (i.e. successful stops, failed stops and ignore-stop trials) and group (i.e. younger and older groups) are presented below.

4.5.2.1. The M2 peak

Centro-lateral sensors revealed that the amplitudes for both successful and failed stops were significantly larger than the amplitude for ignore-stop trials in the M2 peak (time range 190 - 300 ms, $p < 0.001$ FWE-corr, see Figure 8A). In addition, the M2 peak for successful stops peaked 15 ms earlier compared to the M2 peak for the ignore-stop trials (average M2 peak latencies 215 and 230 ms respectively, $p < 0.001$). At more central locations, we found that the M2 amplitude for the successful stops was statistically larger than the amplitude for failed stops (time range 100 - 195 ms, $p < 0.001$ FWE-corr, see Figure. 8A).

At the group level, between 170 and 200 ms, the M2 amplitude was reduced for the older compared to the younger group ($p < 0.0001$ uncorr at peak level). Independent sample t-tests revealed that the M2 amplitude was reduced in the older relative to the younger group for both the successful stops (time range = 165 to 205 ms, $p < 0.0001$) and the failed stops (time range= 205 to 250 ms, $p < 0.01$). No differences were found in the M2 amplitude for the ignore-stop trials across the older and younger group, suggesting that the difference in the M2 amplitude at the group level was mainly driven by differences between both successful and failed stops rather than ignore-stops. Moreover, analysis of the M2 latency at the group level revealed a significant difference ($F(1,39)= 10.88$, $p < 0.01$, $\eta^2_p = 0.23$) across all conditions (i.e. successful stops, failed stops and ignore-stop trials). This difference showed that the M2 peaked 24 ms later in the older group ($M = 234$ ms, $SE = 5$) compared to the younger group ($M = 210$ ms, $SE = 6$).

4.5.2.2. The M3 peak

Between 285 and 390 ms, we observed that the M3 amplitude was significantly larger for both successful and failed stops compared to the ignore-stop trials ($p < 0.001$ FWE-corr);

there were no latency differences between successful stops, failed stops or ignore-stops for the M3 peak (see Figure. 8B).

At the group level, between 280 and 317 ms, the M3 amplitude was significantly different across groups ($p < 0.01$ FWE-corr) when carrying out the t-contrast [H0: (Successful stop - ignore-stop)$_{younger}$ = (successful stop - ignore-stop)$_{older}$] and between 265 and 280 ms when comparing the amplitude of successful stops via independent sample t-test ($p < 0.05$). The M3 latency analysis revealed a significant group effect ($F(1,39)= 43.77$, $p < 0.001$, $\eta^2_p = 0.53$), which showed that the M3 peaked 50 ms later in the older group (M = 362 ms, SE = 6) relative to the younger group (M = 312 ms, SE = 6).

4.5.2.3. The M4 peak

Between 445 and 700 ms, we found that the M4 amplitude was significantly larger for both stop trials (successful and failed stops) compared to the ignore-stop trials ($p < 0.001$ FWE-corr). M4 amplitude was significantly larger for the failed stops compared to successful stops ($p < 0.001$ FWE-corr, see figure 8C). Additionally, the M4 peaked 61 ms earlier for the successful stops (521 ms) compared to ignore-stop (582 ms, $p < 0.001$) and 53 ms earlier for the successful stops relative to failed stops (574 ms, $p < 0.001$).

Across groups, there was a significant difference in the M4 amplitude between 370 and 470 ms ($p < 0.05$ FWE-corr). Independent samples t-test across groups for the difference between successful and failed stops between 430 to 530 ms revealed a significant group difference ($p < 0.05$). For both the main effect of group and the independent sample t-tests, the amplitude of the M4 was reduced in the older compared to the younger adults. M4 latency analysis revealed a significant difference at the group level ($F(1,39)= 24.57$, $p < 0.001$, $\eta^2_p = 0.4$), which shows that the M4 peaked 76 ms later for the older group (M = 597 ms, SE = 11) compared to the younger group (M = 521 ms, SE = 11).

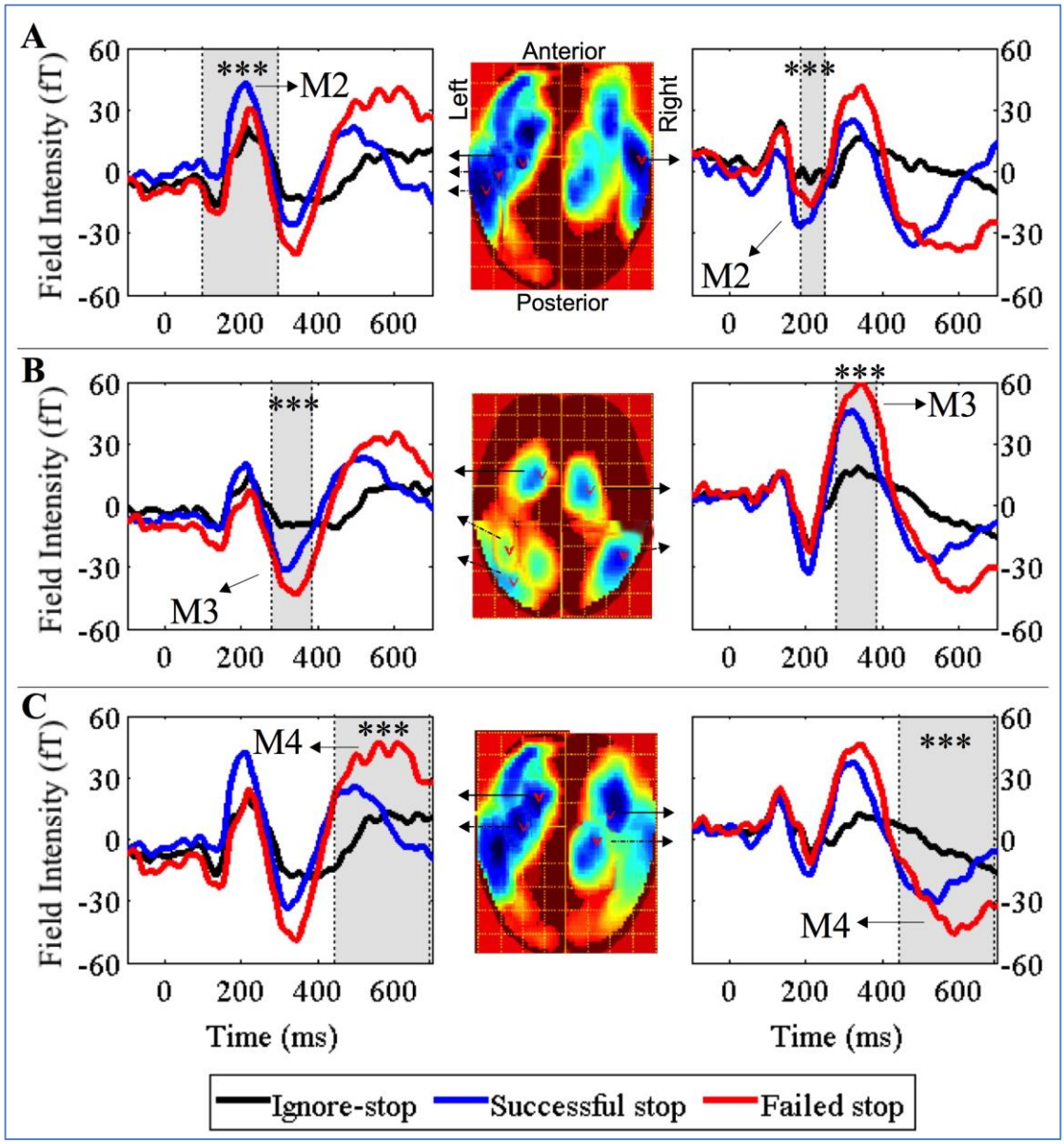

Figure 8 M2, M3 and M4 peaks across ignore-stops, successful stops and failed stops (chapter 4)

A) The M2 amplitude for both failed and successful stops was significantly larger compared to the ignore-stop trials between 190 and 300 ms in centro-lateral locations. At central sensors between 100 and 195 ms, the M2 amplitude for the successful stops was significantly larger compared to the failed stops, and peaked 15 ms earlier relative to ignore-stop trials. **B)** Between 285 and 390 ms in central locations, we found that the M3 amplitude for both successful and failed stops was significantly larger compared to that in the ignore-stop trials. **C)** Between 445 and 700 ms, the M4 amplitude for both the successful and failed stops was significantly larger compared to the ignore-stop trials. Furthermore, between 620 and 700 ms the M4 amplitude for the failed stops was significantly larger relative to the successful stops. Solid lines represent the location of ERF depicted in the scalp topography. Dashed lines represent scalp locations of other significant differences in amplitude. The right hand column depicts the same time range of activation as the left side but with the reverse contrast weights. Time 0 ms represents the time of stop signal. The central column depicts sensor space topographical difference SPMs. All significant amplitude differences are at *** $p < 0.001$ FWE-corr.

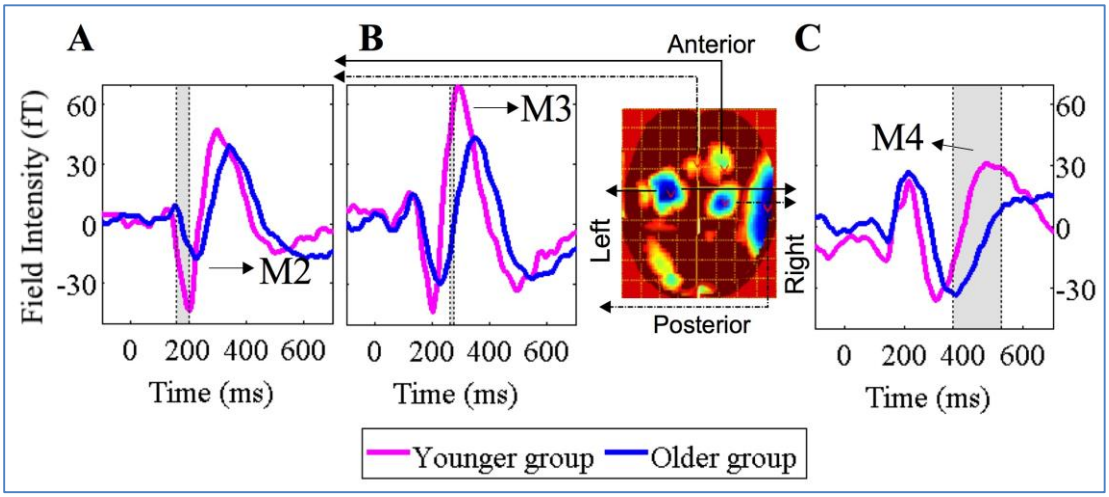

Figure 9 M2, M3 and M4 ERF waveforms for the older and the younger groups (chapter 4)

A) The M2 waveform peaked 24 ms later and had an amplitude reduction in the older relative to the younger group. **B)** The M3 waveform peaked 50 ms later and had an amplitude reduction in the older compared to the younger group. **C)** The M4 waveform peaked 76 ms later and had an amplitude reduction in the older relative to the younger group. The solid arrow represents the ERF location in the scalp topography; the dashed arrow portrays locations of significant amplitude differences for the reverse t-contrast weights; Graphs A and C represent the group main effect (i.e. the average over the three conditions: successful stops, failed stops and ignore-stop trials) whereas graph B depicts the group effect for successful stops only. *** p< 0.001 FWE-corr; * $p < 0.05$ FWE-corr.

4.6. Discussion

The current study investigated response inhibition-related sensor space ERF topographies in the infrequently studied vocal effector system and compared these between older and younger adults. Firstly, we hypothesised that there would be an ERF peak with larger amplitude for successful stops relative to failed stops and ignore-stop trials that occurred at about 160 ms. Secondly, we hypothesised that across successful stops, failed stops and ignore-stops, a later peak would be evident that was modulated in a manner consistent with error-processing. Finally, between groups we hypothesised that if the older relative to the younger group had longer SSRTs because of a selective decline in inhibitory mechanisms, then only the peak occurring before the SSRT would have an amplitude reduction and/or latency delay. The results support the first and second hypotheses.

4.6.1. The M2 peak

Our first hypothesis predicted that an early peak, at about 160 ms, would be larger for successful stops compared to both failed stops and ignore-stop trials. We found that the M2 amplitude (peaking at around 200 ms) for the successful stops was significantly larger relative to the failed stops between 100 and 200 ms, an epoch spanning the onset to the zenith of the peak. This finding is consistent with a previous ERP study on vocal response inhibition (Etchell et al., 2012) that reported the P2 (~190 ms) was larger amplitude for successful stops compared to ignore-stop trials. The peak time of the M2 (200 ms) is also consistent with an MEG study of manual response inhibition (Boehler et al., 2009), which reported a peak at around 160 ms which was larger in amplitude for successful stops relative to failed stops. It is interesting to observe that our M2 peaked about 40 ms later (~200 ms) compared to a previous MEG study (Boehler et al., 2009). The exact source of this difference might become apparent in a study that compared the two modalities directly.

In addition, we found that both stop trials (successful and failed stops) had larger amplitude M2 and M3 peaks compared to ignore-stop trials, replicating the findings of Etchell et al. (2012) . This is a very important finding because it shows that the amplitude of these peaks represents the temporal evolution of response inhibition and is not just an effect of stimulus novelty. One of the criticisms of ERP findings in regards to response inhibition is that the comparison between stop and go trials is inappropriate, as go trials are usually presented more often and therefore the go ERP amplitude is smaller because of habituation and, conversely, the stop ERP amplitude is larger because of novelty (Nieuwenhuis, Yeung, van den Wildenberg, & Ridderinkhof, 2003). In particular, Wessel and Aron (2013) showed that the ERP amplitude is larger for novel compared to standard trials and that, even between blocks, the first block usually evokes larger amplitudes in both novel and standard trials compared to the last block. For this reason, in the current study, stop trials were compared to no-stop trials (i.e. ignore-stop trials), which were matched for frequency to the stop trials, thus eliminating the relative novelty effect. Our variant of the SST had three types of trials: go (50%), stop (25%) and ignore-stop (25%) (similar to Bedard et al., 2002; Boulinguez, Ballanger, Granjon, & Benraiss, 2009; Dimoska & Johnstone, 2008; Etchell et al., 2012). With this design we have shown that the ERF difference between stop and ignore-stop trials was not only due to the stimulus novelty of the stop trials but rather to inhibitory processes.

4.6.2. Later peak (the M4)

Our second hypothesis predicted that the amplitude of the later peak (the M4, from 350 to 700 ms) would reflect error-processing i.e. be larger in amplitude for failed stops compared to successful stops. Whilst this pattern was confirmed, the M4, which started to rise at about 400 ms, was larger in amplitude for both stop trials (successful and failed) relative to the ignore-stop trials between 445 to 700 ms, suggesting that the peak is representative of more than just error processing – rather it also represents some form of response checking as previously described in Falkenstein et al. (2000), who reported this later peak to be enhanced for both correct and incorrect responses. Because failed stops evoked even larger amplitude ERF relative to both the successful stops and ignore-stop trials between 620 and 700 ms, we suggest there is still an aspect of error processing represented. Indeed, Falkenstein et al. (2000) concluded that this late peak after correct responses reflects response checking, and on error trials reflects response checking plus an overlaid error processing. This contention is in line with previous ERP studies of manual responses that reported failed stops evoking larger amplitudes in the later peak compared to successful stops (Kok et al., 2004; Ramautar et al., 2004; Schmajuk et al., 2006; Squires et al., 1975) and incorrect responses evoking larger amplitudes compared to correct responses (Falkenstein et al., 2000; Falkenstein et al., 1999; Schmajuk et al., 2006).

4.6.3. Differences across groups

Our third hypothesis predicted that if the older relative to the younger group have longer SSRTs due to a specific decline in inhibitory processing, the peak index of successful stopping (i.e. the M2) would be of smaller amplitude and longer latency. Whilst this was the case, the fact that all significant ERF peaks were smaller in amplitude and later in time suggests that the existence of a deficit in inhibitory processing that is distinct from a general processing speed decline cannot be supported. MEG sensor space analyses showed that the M2, M3 and M4 were of smaller amplitude and occurred later (by 24, 50 and 76 ms respectively; see figure 9) in older compared to younger adults. These findings are in line with results reported in previous ERP-studies in which the P3 occurred later and was of smaller amplitude in an older group compared to younger adults (Mullis et al., 1985; Podlesny, Dustman, & Shearer, 1984).

We found that SSRTs in older compared to younger adults were longer by 38 ms, go-RTs were longer by 123 ms and ignore-stop RTs longer by 149 ms. The SSRT difference

between older and younger adults in our study (38 ms) was very consistent with previous studies that have used a stimulus selective SST, in which the SSRT difference between groups was 41 ms (Bedard et al., 2002) and 32 ms (Coxon et al., 2014). Importantly, the SSRT difference in simple SSTs between older and younger adults is much smaller - only about 12 ms (Williams et al., 1999). In general, SSRTs for a simple SST are shorter compared to those of a stimulus selective SST (e.g. Etchell et al., 2012; Lavallee, Herrmann, Weerda, & Huster, 2014). The differences in go-RT (123 ms) and ignore-stop RT (149 ms) are also very consistent with previous studies that have compared RTs in older adults to those in younger adults (go-RT difference of 158 ms in a stimulus selective SST (Bedard et al., 2002); go-RT difference of 107 ms in a simple SST (Williams et al., 1999)).

4.6.4. Conclusions

In conclusion, we found that the temporal neurophysiological evolution of vocal response inhibition is largely consistent with that reported for manual response inhibition. We found an M2 peak that was of larger amplitude for successful stops and a M4 peak that was of larger amplitude for both failed and successful stop trials compared to ignore-stop trials. Moreover, the behavioural results combined with the ERFs indicate that stopping performance declines with age, but that this decline fits within a general age-related decline in processing speed. This study contributes to the understanding of vocal response inhibition in healthy younger and older adults. Our present study could be the basis for investigating neuropsychological disorders which primarily manifest themselves in the domain of vocalisation e.g. Tourette syndrome and stuttering.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix F. Supplementary material

This material contains the results for the 2 x 3 factorial ANOVA with 2 between-group factor (younger and older group) and 3 within-subject factors (ignore-stop, successful stops and failed stops). It also contains the results for the independent samples t-test across groups for ignore-stop, successful stops and failed stops.

Amplitude analyses: main effect of condition (2 x 3 flexible factorial ANOVA)

This material contains significant clusters found in the analysis of the main effect of condition in the 2 x 3 factorial ANOVA.

Table 8: Amplitude analyses: main effect of condition (2 x 3 flexible factorial ANOVA) (chapter 4)

T-contrast of conditions							
Null hypothesis (H_0)	Cluster-level			Peak-level			
	p-value	Cluster size*	T	Peaks	Peak coordinates**		Time (ms)
	FWE-correction				X	Y	
Failed stops = Ignore-stop	< 0.001	4,174	5.9	3	-51, -66	-62,8	240-300
	< 0.001	18,769	5.2	16	-21 to -40	-11 to 50	445-615
	< 0.001	7,712	5.1	5	21 to 51	-68 to -6	350-390
Ignore-stop = Failed stops	< 0.001	6,348	7	5	47 to 60	-34 to 34	190-255
	< 0.001	23,656	6.3	14	15 to 47	-19 to 67	450-615
	< 0.001	7,723	5.3	9	-51 to -17	-65 to 5	285-390
Successful stops = Ignore-stop	< 0.001	13,643	6	14	-42 to -19	5 to 50	445-500
	< 0.001	8,555	6	4	-62 to -49	-30 to 24	200-270
	< 0.001	7,268	5.6	4	45 to 19	-57 to -11	285-335
Ignore-stop = Successful stops	< 0.001	17,947	9	4	23 to 40	-21 to 21	450-540
	< 0.001	10,245	7	12	-57 to -19	-76 to -6	285-460

T-contrast of conditions							
Null hypothesis (H_0)	Cluster-level			Peak-level			
	p-value	Cluster size*	T	Peaks	Peak coordinates**		Time (ms)
	FWE-correction				X	Y	
Failed stops = Successful stops	< 0.001	8,152	7	3	-32 to -34	-6 to -1	620-700
Successful stops = Failed stops	<0.001	5,030	5.8	11	-55 to -11	-36 to 26	100-195
	<0.001	5,868	5	5	26 to 34	-11 to 10	620-700

* Comma indicates thousands

** Peak coordinates refer to spatial locations in the 2D topographic sensor-space SPM

Amplitude analyses: interaction of group by condition (2 x 3 flexible factorial ANOVA)

Table 9: Amplitude analyses: interaction of group by condition (2 x 3 flexible factorial ANOVA) (chapter 4)

T-contrast of main effect of conditions							
Null hypothesis (H_0)	Cluster-level			Peak-level			
	p-value	Cluster size*	T	Peaks	Peak coordinates**		Time (ms)
	FWE-correction				X	Y	
(Successful stops - Ignore-stop)$_{younger}$ = (Successful stops - Ignore-stop)$_{older}$	< 0.01	2,931	5	4	55 to 68	-60 to-6	280-317
	< 0.05	1,849	5	2	-21,-36	-81,-62	135-145
(Failed stops - Successful stops)$_{younger}$ = (Failed stops - Successful stops)$_{older}$	< 0.05	20	5	1	32	40	100-105

* Comma indicates thousands

** Peak coordinates refer to spatial locations in the 2D topographic sensor-space SPM

Amplitude analyses: main effect of group

Because the main effect of group is statistically invalid in the flexible factorial ANOVA in SPM, we conducted an independent sample t-test of the two groups by averaging together the 3 conditions (i.e. ignore-stop trials, successful stops and failed stops) for each group.

Table 10: Amplitude analyses: main effect of group (chapter 4)

T-contrast of conditions							
Null hypothesis (H_0)	Cluster-level			Peak-level			
	p-value	Cluster size*	T	Peaks	Peak coordinates**		Time (ms)
	FWE-correction				X	Y	
Younger group = older group	<0.05	1,850	4.6	5	-28 to -42	-11 to 8	370-475
Older group = younger group	<0.05	2,386	6.1	3	30 to 38	-62 to 60	130-150
	0.053	1,545	4.8	1	23	-14	430
	<0.001 uncorr at peak level			2	15	21	270-200

* Comma indicates thousands

** Peak coordinates refer to spatial locations in the 2D topographic sensor-space SPM

Independent sample t-test for each condition across groups

We conducted an independent sample t-test for each condition because the main effect of group gave significant differences across groups but we could not know what condition was driving the differences between younger and older group.

Table 11: Independent sample t-test for each condition across groups (chapter 4)

Independent sample t-test of conditions (t-contrast)							
Null hypothesis (H_0)	Cluster-level			Peak-level			
	p-value	Cluster size*	T*	Peaks	Peak coordinates**		Time (ms)
	FWE-correction				X	Y	
$(\text{Ignore-stop})_{\text{older}} = (\text{Ignore-stop})_{\text{younger}}$	< 0.05	1,924	5.5	1	23	-68	135
$(\text{Successful stops})_{\text{younger}} = (\text{Successful stops})_{\text{older}}$	< 0.05	1,477	5.2	1	-28	-9	440
	< 0.05 unc	1,001	4.4	2	21, 23	-17, -6	265-280
$(\text{Successful stops})_{\text{older}} = (\text{Successful stops})_{\text{younger}}$	< 0.05	2,086	5.6	3	30 to 40	-62 to 60	130-155
$(\text{Failed stops})_{\text{younger}} = (\text{Failed stops})_{\text{older}}$	< 0.05	2,231	5.3	2	-26, -34	-9, 2	455-470
$(\text{Failed stops})_{\text{older}} = (\text{Failed stops})_{\text{younger}}$	< 0.01	2,547	5.5	3	19 to 21	-14 to -22	430-530
	< 0.05 unc	1,247	4.8	1	38	-60	155
	< 0.01 uncorr at the peak level			3	-2 to 15	18	205-250

* Comma indicates thousands

** Peak coordinates refer to spatial locations in the 2D topographic sensor-space SPM

Latency analyses: 2 x 3 x 2 mixed ANOVA

We conducted four 2 x 3 x 2 mixed ANOVA with the within subject factors of two region of interests (ROI, left and right) and 3 peaks (Ignore-stop, Successful stops and Failed stops) and with the between subject factor of groups (younger and older). Each mixed ANOVA was done separately for the dependent variables of M2 peak, M3 peak and M4 peak.

Table 12: Latency analyses: 2 x 3 x 2 mixed ANOVA (chapter 4)

DV	Factor and interaction	F(df)	p-value	η^2p
M2	ROI	F(1,39) = 2.8	0.1	0.07
	ROI * group	F(1,39) = 0.5	0.5	0.01
	Peaks	F(2,78) = 9.4	< 0.001 ***	0.2
	Peaks * group	F(2,78) = 1.9	0.7	0.05
	ROI * peaks	F(2,78) = 0.05	0.9	0.01
	ROI * peaks * group	F(2,78) = 0.7	0.5	0.02
	Group	F(1,39) = 10.9	< 0.01 **	0.23
M3	ROI	F(1,39) = 2.7	0.11	0.06
	ROI * group	F(1,39) = 0.3	0.6	0.01
	Peaks	F(2,78) = 2.2	0.12	0.05
	Peaks * group	F(2,78) = 1.7	0.19	0.04
	ROI * peaks	F(2,78) = 1.7	0.18	0.04
	ROI * peaks * group	F(2,78) = 1.9	0.15	0.05
	Group	F(1,39) = 43.8	< 0.001 ***	0.53
M4	ROI	F(1,39) = 3.43	0.07	0.08
	ROI * group	F(1,39) = 0.01	0.9	0.01
	Peaks	F(2,78) = 17.2	< 0.001 ***	0.31
	Peaks * group	F(2,78) = 0.44	0.65	0.01
	ROI * peaks	F(2,78) = 0.17	0.84	0.01
	ROI * peaks * group	F(2,78) = 1.77	0.18	0.04
	Group	F(1,39) = 24.6	< 0.001 ***	0.39

DV = dependent variable
df = degrees of freedom
η^2p = Partial eta-square
ROI = region of interest

Chapter 5 – The effect of proactive inhibition on reactive inhibition and the go process: insights from the stop signal task of vocal and manual responses

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5. The effect of proactive inhibition on reactive inhibition and the go process: insights from the stop signal task of vocal and manual responses

5.1. Abstract

This study measured proactive and reactive response inhibition and their relationships with self-reported impulsivity. We examined the domains of both vocal and manual responding using a stop signal task (SST) with two stop probabilities: high and low probability stop (1/3 and 1/6 stops respectively). Our aim was to evaluate the effect stop probability would have on reactive and proactive inhibition. We tested 44 subjects and found that for the high compared to low probability stop signal condition, more proactive inhibition was evident and this was correlated with a reduction in the stop signal reaction time (SSRT). We found that reactive inhibition had a positive relationship with dysfunctional but not functional impulsivity in both vocal and manual domains of responding. These findings support the hypothesis that proactive inhibition may pre-activate the network for reactive inhibition.

Keywords:
Vocal inhibition, stop signal task, response inhibition, reactive inhibition, proactive inhibition and selective inhibition.

5.2. Introduction

This study measured response inhibition via the stop signal paradigm (Lappin & Eriksen, 1966; Logan & Cowan, 1984; Vince, 1948) in two effector systems: vocal and manual. Response inhibition is described as the ability to stop a prepotent response (Logan, 1994; Logan & Cowan, 1984), which, in our study was either a spoken word or a button press. We measured two types of response inhibition: proactive and reactive inhibition. Proactive inhibition is defined as the advanced preparation to halt action in the anticipation of an imminent stop signal. Reactive inhibition is defined as the performance of outright stopping in response to the appearance of a stop signal (Aron, 2011; Chambers et al., 2009).

The analysis of the stop signal task (SST) is based on the horse race model proposed by Logan and Cowan (1984). The model assumes that the stop and the go processes are independent of each other in the sense that whichever finishes first, wins. This assumption is based on the fact that failed stop trials always have faster mean reaction times (RTs) compared to go trials, suggesting that participants fail to stop because the go process finishes before the stop process. For a model that proposes the go and stop processes interact, see L. Boucher, Palmeri, Logan, and Schall (2007). The horse race model was mainly developed by testing reactive inhibition (measured by the stop signal RT or SSRT) but has been little tested in the context of proactive inhibition manipulations (measured by the increment of go RTs in the context of possible stop signal appearance). Some evidence suggests that the complexity of go and stop tasks affect the latency of go and stop RTs. For example, regarding the complexity of the go task: go RTs are always slower in two or more choice-RT tasks than in simple RT tasks. Likewise the SSRT is longer when the go imperative consists of a choice RT task compared to a simple RT task (Logan et al., 1984; Riegler, 1986). Such observations suggest that the complexity of the go task interferes with both go and stop processes. Regarding the complexity of the stop task, some studies have increased the stop signal from one to two and asked participants to stop to one but to ignore the other stop signal (this refers to selective inhibition; Logan et al., 1986; Riegler, 1986). These studies find that go RTs are slower and SSRTs longer in selective inhibition tasks compared to simple inhibition tasks, suggesting that the complexity of the stop task interacts with both go and stop processes. In sum, the complexity of the go and the stop

task interfere with each other. When either the go or stop task is complex, go RTs become slower and SSRTs become longer.

We interpreted these results to indicate that the complexity of the go and stop tasks added an additional variable: a slowing effect, which would probably help to perform either task more effectively. In particular, selective inhibition creates the need to hold the prepotent response more strongly because the stopping process is more complicated, requiring an increase in proactive inhibition. In other words, our idea was that in selective inhibition, proactive inhibition is increased to help reactive inhibition. In fact, this idea has already been supported by Chikazoe, Jimura, Hirose, et al. (2009) and in the first experiment of Jahfari et al. (2010) who reported a significant negative relationship between proactive inhibition and the SSRT, a result which suggests that a greater level of preparation is related to faster reactive stopping. It has also been suggested that, proactive inhibition pre-activates the same inhibitory network for reactive inhibition and this is why participants are able to stop quickly, because the inhibitory network has been primed.

However, studies of the relationship between proactive and reactive inhibition have had mixed results: a third experiment reported in Jahfari et al. (2010) showed this relationship did not exist. The authors did not offer an explanation. We propose that the lack of a relationship could have been due to the amount of proactive inhibition that was used in these tasks: while in their first experiment proactive inhibition was measured as a slowing of go RT of 111.3 ms for the relevant compared to an irrelevant stop condition, in the third experiment this difference was only 55 ms. To investigate this idea, this study was designed to manipulate the level of proactive inhibition and assess the relationship between proactive and reactive inhibition. One way to manipulate the level of proactive inhibition is to manipulate stop probabilities. However, previous studies that have manipulated stop probability have shown that either there were no differences in the SSRT (Lansbergen et al., 2007; Ramautar et al., 2004) or they did not analyse the SSRT (Logan & Burkell, 1986). The lack of difference in SSRT could have been because the high probability stop in Ramautar et al. (2004) contained 1/2 stop and 1/2 go trials, which may not have been enough to induce significant proactive inhibition; on the other hand, Lansbergen et al. (2007) recruited participants with the lowest and highest scores on impulsivity, which may have influenced the lack of differences across stop probabilities.

Deficiencies in reactive inhibition have been related to speech disorders such as developmental stuttering (Eggers et al., 2013), Tourette syndrome (Ziemann et al., 1997), attention-deficit hyperactivity disorder (ADHD; Aron & Poldrack, 2005; Barkley, 1997; Rubia, Russell, et al., 2001), schizophrenia (Enticott et al., 2008; Kiehl et al., 2000), obsessive-compulsive disorder (OCD) and trichotillomania (Bohne et al., 2008; Menzies et al., 2007; Penadés et al., 2007) and adolescents at risk of alcoholism and other substance use (Nigg et al., 2006). Interestingly, studies have shown that differences in response inhibition can be related to the level of self-reported impulsivity in control subjects (Logan et al., 1997; van den Wildenberg & Christoffels, 2010).

As described in the first introductory paragraph, response inhibition is characterised by the ability someone has for holding a prepotent response and either releasing or stopping it when it is appropriate to do so. Interestingly, response inhibition has been associated with self-reported impulsivity. For example, slower manual reactive inhibition (i.e. SSRT from manual responses) in individuals with high relative to low impulsivity scores (Farr, Hu, Zhang, & Li, 2012; Logan et al., 1997; Marsh, Dougherty, Mathias, Moeller, & Hicks, 2002) but others have failed to find such differences (Avila & Parcet, 2001; Lansbergen et al., 2007; M. Lijffijt et al., 2004; Rodríguez-Fornells, Lorenzo-Seva, & Andrés-Pueyo, 2002). Moreover, evidence suggests a positive relationship existed between reactive inhibition and impulsivity, which in turn suggests that longer SSRTs are associated with higher impulsivity scores. This positive relationship has been described in the manual effector system only (Logan et al., 1997). In a more recent study, van den Wildenberg and Christoffels (2010) found that longer SSRT were related with dysfunctional impulsivity (not functional impulsivity) for vocal responses (not manual responses). This study is very interesting because it teased apart two types of impulsivity: dysfunctional impulsivity, described as rapid reactions with a less adaptive approach (Dickman, 1990) and functional impulsivity, characterised as rapid responses in situations where this is more optimal (a more adaptive approach). Having a relationship between reactive inhibition and dysfunctional impulsivity is consistent with neuropsychological disorders where impulsive behaviours are inappropriate and less adaptive (Aron & Poldrack, 2005; Barkley, 1997; Bohne et al., 2008; Enticott et al., 2008; Kiehl et al., 2000; Menzies et al., 2007; Penadés et al., 2007; Rubia, Russell, et al., 2001). Although, the evidence from manual response inhibition studies suggests that impulsivity is also related to longer SSRTs (Logan et al., 1997), van den Wildenberg and Christoffels (2010) only found that dysfunctional

impulsivity was related with vocal responses (not manual responses), possibly because of the relatively small sample size (14 participants).

In sum, there is evidence that suggests a greater level of proactive inhibition enhanced reactive inhibition, but one out of three experiments did not show this relationship. It is not clear why. Second, two studies have shown that manual response inhibition is related to impulsivity but two other studies fail to confirm this. More recent evidence has used a impulsivity scale that distinguishes between dysfunctional and functional impulsivity and found that high score in dysfunctional impulsivity is related to slower SSRTs with vocal not manual responses, finding that would contradict a previous study that have shown manual responses are related to impulsivity. In other to clarify these inconsistencies, our aims were to investigate across two response modalities (vocal and manual) the relationship between proactive and reactive inhibition, and the relationship between dysfunctional impulsivity and reactive inhibition in both manual and vocal responses. We developed an SST with two certainty conditions (certain and uncertain, similar to Chikazoe, Jimura, Hirose, et al., 2009). While the certain conditions only had go trials, the uncertain conditions contained both go and stop trials. We manipulated proactive inhibition in the uncertain conditions by implementing two stop probability conditions: high and low (similar to Lansbergen et al., 2007; Logan & Burkell, 1986; Ramautar et al., 2004). The high probability stop condition consisted of 1/3 stops and 2/3 go trials; the opposite was the case for the low probability stop condition, which was comprised of 1/6 stops and 5/6 go trials. We predicted that the high probability stop condition would induce more proactive inhibition relative to the low probability stop condition. We also predicted that the high level of proactive inhibition in the high probability stop would make SSRTs shorter. We hypothesised that if high, relative to low probability stops required more proactive inhibition, then the SSRT would be reduced for the high probability stopping. Further, we hypothesised that there would be a positive relationship between proactive and reactive inhibition. Our final aim was to re-investigate the relationship between dysfunctional impulsivity and reactive inhibition in both effector systems; our prediction was that manual responses would also be related to dysfunctional impulsivity. We hypothesised that the SSRT of both vocal and manual responses would be positively correlated with dysfunctional impulsivity.

5.3. Methods

5.3.1. Participants

Forty-six participants completed this study. Two participants were excluded because they did not meet the SST performance criteria of successfully stopping on ~50% of stop trials; one of these subjects progressively slowed throughout the experiment on the uncertain go trials and thus, this person was able to stop on 96% of the stops (p_inhibit = 0.96). The second person did the opposite and did not stop appropriately at the stop-signal, returning a percentage of unsuccessful stopping of 23% (p_respond = 0.23). Data analysis was performed on the remaining 44 participants (age range= 18-29; mean age= 20.5 years; SD= 2.73; 8 males, p_inhibit range = 0.4 to 0.6). All participants had normal or corrected-to-normal vision, and reported no history of neurological impairment or psychiatric illness. All participants provided written informed consent. The study was approved by Macquarie University Human Research Ethics Committee.

5.3.2. Apparatus

The experimental task was controlled in Presentation® software (version 16.1, www.neurobs.com) and was delivered via Samsung monitor (SyncMaster SA950_LS27A950, 27 inches, 1920 x 1080 pixels, 120 Hz refresh rate). Vocal-responses were sample at 48 kHz via an external microphone placed within 2 cm from each subject's mouth. Manual-responses involved a key press on a button box; Participants were seated approximately at 80 cm from the monitor.

5.3.3. Stop signal task

This study implemented a variant of the stop-signal task or SST (Logan, 1994; Logan & Cowan, 1984). It contained three types of trials (certain go, uncertain go, and stop) that all occurred within every block. All trials began with a black fixation cross appearing in the centre of a white background; the duration of fixation randomly varied between 1 and 2.5 s. Certain go trials consisted of a simple reaction time task where participants were required to respond as quickly as possible to the certain go-signal, which was indicated by the onset of a blue circle, 10.5 cm in diameter (see figure 10) in the centre of the monitor. Certain go trials made up 50% of the total trial number. For manual responses, participants were asked to press a response button as quickly as possible whereas for vocal responses, participants were asked to make the short vowel sound “ɪ” as it would occur in the word

“hit /hɪt/”. The other half of the trials was uncertain go trials in which the onset of yellow circle was the signal to initiate a response. The uncertainty in this trial type was created by the possibility of a stop signal following the go signal (yellow circle). The stop signal could appear with a probability of either one third or two thirds of all uncertain go trials. Hereafter we refer to these as low probability and high probability stop signals respectively. Participants were required to respond to the yellow circle as if this was a blue circle unless the stop-signal appeared.

Stop trials appeared only after uncertain go signals and were represented by a purple circle. In response to the stop signal, participants were instructed to attempt to withhold any response they might have initiated. The time at which the stop-signal was presented is referred to as the stop-signal delay (SSD). The SSD changed dynamically throughout the experiment via a staircase method that depended on each participant’s performance. If a participant inhibited successfully on a stop trial, then successful response inhibition was made less likely on the subsequent stop trial by increasing the SSD by 30 ms. Contrarily, if the participant failed to stop, successful response inhibition was made more likely for the following stop trial by decreasing the SSD by 30 ms. Two independently adjusted staircases were employed that started with a SSD of 200 ms. One staircase was for the low probability stop and the other for the high. The task also contained a warning buzz that sounded when a go response was given after 700 ms or when the SSD dropped to 130 ms.

Overall, there were 900 trials in each response modality (either manual or vocal), which were divided into 6 blocks of 150 trials. In each block, 75 trials were certain go trials (50%) and 75 were uncertain go trials (50%). For the high probability stop blocks, 50 of the uncertain go trials were stop trials whereas for the low probability stop blocks, 25 were stop trials. Each response modality was tested in separate blocks counterbalanced for order across subjects. We also counterbalanced the high and low probability stop blocks. To make these probability blocks comparable, we needed to have an equal number of stop trials for each probability of stopping, thus, out of the 6 blocks, two blocks corresponded to the high probability stop condition (50 stop trials * 2 blocks = 100 stops) and four blocks were for the low probability stops (25 stop trials * 4 blocks = 100 stops). Because the number of blocks for the low probability stops was double that of the high probability stops, we implemented the condition that there would always be two low probability stop blocks between each high probability stop block. Based on this, we implemented two types

of overall block presentation order, which were the only possible permutations that meet the condition of having two low probability blocks between high probability blocks and which also allowed counterbalancing of the order of the first probability block type over subjects. The first order started with a high probability stop block, therefore, block 1 and 4 were high probability stops and blocks 2, 3, 5 and 6 were low probability stops. The second order started with a low probability stop block (blocks 1, 2, 4 and 5) and blocks 3 and 6 were high probability stops. There were instructions at the beginning of each block which communicated the probability of stopping that would follow, it could either say that a stop signal would occur on either one third or two thirds of the uncertain trials, for example, for the low probability stop block the instruction said: “Take a break! During the next block, stop trials will occur on one third of the uncertain go trials (yellow circle)” All instructions were in black text except for the words “one third” which were coloured red and the word "yellow" which was coloured yellow. Participants pressed the space bar to start the block at which point the block number was presented for 1 s e.g. “Block 1 out of 6.” In total there were 12 blocks, 6 were assigned to vocal and 6 to manual responses. All 6 blocks per response modality were administered sequentially. After that, the other 6 blocks of other response modality were given.

The index of reactive inhibition was measured with the stop-signal reaction time or SSRT (Logan & Cowan, 1984) and calculated using the integration method (Verbruggen et al., 2013; Verbruggen & Logan, 2009a). This method estimates SSRTs by subtracting the starting time of the stop process (when participants see a stop-signal) from the finishing time of the stop process. The starting time is known, which is equivalent to the SSD; however, the finishing time needs to be estimated. The finishing time was estimated by integrating the go reaction time (go RT) distribution. The go RTs of the uncertain go conditions were rank ordered from the shortest to the longest then, the *nth* RT was selected. Where *n* was obtained by multiplying the probability of responding on stop trials (or unsuccessful stopping, known as the p_respond) by the total number of go RTs. The probability of responding was calculated as the number of unsuccessful stops divided by the total number of stop trials. SSRT was estimated by subtracting the SSD from *nth* go RT. We calculated the SSRT separately for each block and then the average of the blocks was taken as the final SSRT.

The index of proactive inhibition was based on two previous studies (Chikazoe, Jimura, Hirose, et al., 2009; Jahfari et al., 2010) where it was respectively termed preparation cost and response delay effect. This index is estimated from the go RT by subtracting the mean of the uncertain go RTs from the mean of the certain go RTs. A positive value indicates the amount of slowing the participants applied to their go responses when stop signals were imminent.

All correlations were obtained from a Pearson's linear correlation (1-tailed as the proposed hypotheses were unidirectional).

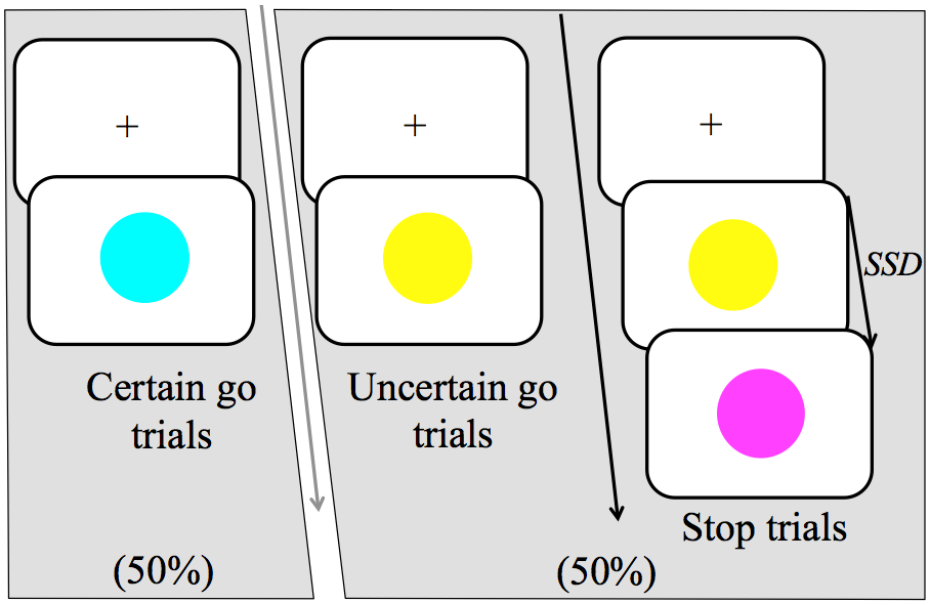

Figure 10 Trial structure of the stop-signal task (chapter 5)

There were three main trial types: certain go, uncertain go and stop trials. Certain go trials were signalled by a blue circle and always required to either press a response button (manual-responses) or produce the short vowel sound "ɪ" as it would occur in the word "hit /hɪt/"(vocal-responses). Uncertain go trials were signalled by a yellow circle and required a response as in the certain go trials. Finally, stop trials started as uncertain go trials but after the stop signal delay (SSD), a stop-signal was presented, which was signalled by a purple circle. Participants were instructed to attempt to withhold their responses on seeing the stop signal. In the high probability stop condition, stop signals occurred following 2/3 of the uncertain go signals whereas in the low probability stop condition stop signals occurred following 1/3 of the uncertain go signals.

5.3.4. Impulsivity inventory

We administered a version of the Dickman's impulsivity inventory (Dickman, 1990) which measures functional and dysfunctional impulsivity. Dysfunctional impulsivity is defined as the tendency to act with less forethought than most people of same ability when this

inclination is a source of difficulty. In contrast, functional impulsivity is the tendency to act with relatively little forethought when such a style is optimal. This inventory has 46 questions: 11 about functional impulsivity, 12 for dysfunctional impulsivity and 23 fillers, which were not included in any statistical analysis (see Appendix G, table 13). The internal consistency reliability of the Functional Impulsivity scale (Cronbach's alpha) was .74 and that of the Dysfunctional Impulsivity scale was .85 (Dickman, 1990).

5.4. Procedure

We first introduced the task verbally by explaining the three types of trials and the types of responses subjects should give. Then, the experimenter read a coloured photocopy with a diagram of the trials and response types. We explained that the time between the stop-signal and the uncertain go signal (i.e. SSD) changed according to the participant's performance and that if they successfully stopped, the next stop trial would be harder because the SSD was going to be longer. We also explained that if they failed to stop, next stop trial would be easier because the SSD was going to be shorter and it would be easier for them to stop. We told them that they would fail on about 50% of stop trials because the experimental program was designed to find the balance between the ability to stop and not and therefore, they should not feel frustrated if they were not able to successfully stop on all trials. We explained that both tasks (i.e. going and stopping) were equally important and they should learn a trade-off between them. After this, we proceeded to do a practice task, which contained 6 blocks with 18 trials in each block. Once again the experimenter read the instructions out from the computer screen and additionally included information about the warning buzz; the experimenter explained that this would help them to gauge their performance and to guide them if any of their main tasks required more attention. They would hear a buzz when a response was too slow indicating that they needed to react faster on the next trial. We explained that this buzz could occur after certain or uncertain go trials. We also explained that they may hear a buzz after a stop trial and this would mean that they had failed to stop too many times and therefore needed to put extra effort into stopping successfully.

5.5. Results

5.5.1. Testing the assumptions of the horse race model

As described in the horse race model (Logan & Cowan, 1984), independence of go and stop processes is assumed because failed stop RTs are faster than the no signal RT. In this experiment we had two RTs, one RT from the uncertain go and the other from the certain go, therefore, we included these two go RTs in the analysis of independence. We conducted a repeated-measures 2 x 2 x 3 ANOVA with within-subject factors of 2 response modalities (manual, vocal), 2 stop probabilities (high and low) and 3 RT types (certain go, uncertain go and failed stop). The results revealed that all three factors were significant: response modality ($F(1,43) = 46$, $p < 0.0001$, $\eta^2_p = 0.52$), stop probability ($F(1,43) = 192$, $p < 0.0001$, $\eta^2_p = 0.82$) and RT type ($F(2,86) = 83$, $p < 0.0001$, $\eta^2_p = 0.66$). The interaction between stop probability and RT was also statistically significant ($F(2,86) = 142$, $p < 0.0001$, $\eta^2_p = 0.77$). All other interactions were non-significant. Because the significant interaction of stop probability and RT type confounds the main effect of these two factors we proceed to describe only this interaction and the response modality main effect.

The response modality factor showed that RTs of the manual responses ($M = 411$ ms, $SE = 10$) were 54 ms earlier compared to those of the vocal responses ($M = 465$ ms, $SE = 10$). The interaction of stop probability and RT showed that all RTs from the high probability stop were statistically longer compared to those of the low probability stop ($p < 0.001$ Bonferroni corrected, see appendix I, table 15 for mean and *SE*) by 20, 112 and 44 ms in the certain go, uncertain go and failed stop trials respectively. Across RTs, this interaction showed that failed stop RTs were significantly shorter than for uncertain go trials ($p < 0.001$) by 128 and 60 ms in the high and low probability stop conditions respectively. This result confirmed the assumption of the horse race model in which failed stop RTs should be faster than no stop signal RTs, suggesting the go process won the race against the stop process in the failed stop condition. Interestingly, failed stopping was not different from certain go, $p = 0.42$ and 0.67 in the high and low probability stops respectively. This finding also supports the assumptions of the horse race model in which failed stop RTs are not different from simple RT (described in more detail in the discussion).

5.5.2. Go reaction times

A repeated measures 2 x 4 ANOVA was conducted for go RTs that contained the within-subject factors of two response modalities (manual, vocal) and four go-certainty types (certain $go_{\text{-Low-probability-stop}}$, certain $go_{\text{-High-probability-stop}}$, uncertain $go_{\text{-Low-probability-stop}}$ and uncertain $go_{\text{-High-probability-stop}}$). Both factors, response modality ($F(1,43) = 44$, $p < 0.0001$, $\eta^2_p = 0.5$) and go-certainty type ($F(3,129) = 102$, $p < 0.0001$, $\eta^2_p = 0.7$) were statistically significant with a large effect size. The response modality by go-certainty type interaction was not significant ($F(3,129) = 0.3$, $p = 0.8$, $\eta^2_p = 0.006$).

The factor of response modality (see figure 11C) showed that go RTs from the manual responses ($M = 428$ ms, $SE = 9$) were shorter compared to vocal responses by 51 ms ($M = 479$ ms, $SE = 10$). Furthermore, the factor of go- certainty type (see figure 11A) revealed that go RTs from the certain $go_{\text{-Low-probability-stop}}$ ($M = 395$ ms, $SE = 6.6$) were significantly shorter: by 20 ms relative to certain $go_{\text{-High-probability-stop}}$ ($M = 415$ ms, $SE = 6$, $p < 0.001$), by 51 ms compared to uncertain $go_{\text{-Low-probability-stop}}$ ($M = 446$ ms, $SE = 12$, $p < 0.001$) and by 163 ms compared to uncertain $go_{\text{-High-probability-stop}}$ ($M = 558$ ms, $SE = 16$, $p < 0.001$). The go RTs from the certain $go_{\text{-High-probability-stop}}$ were also significantly shorter by 31 ms compared to uncertain $go_{\text{-Low-probability-stop}}$ ($p < 0.05$) and by 143 ms compared to uncertain $go_{\text{-High-probability-stop}}$ ($p < 0.001$). Finally, the uncertain $go_{\text{-Low-probability-stop}}$ was significantly shorter compared to the uncertain $go_{\text{-High-probability-stop}}$ by 112 ms.

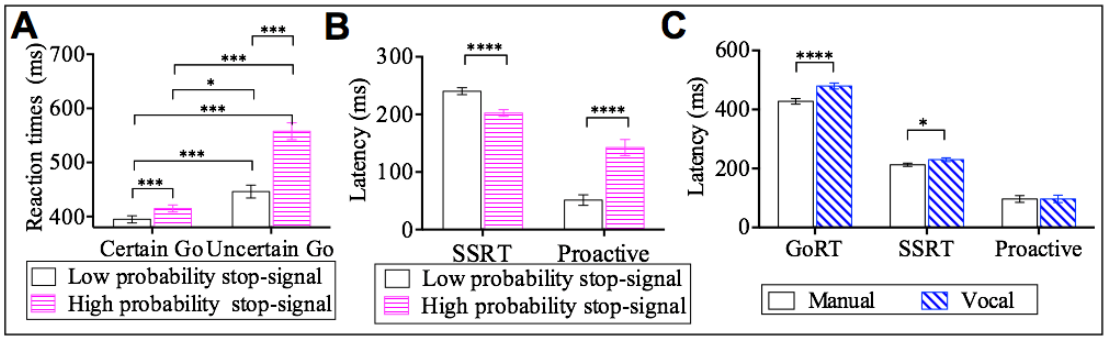

Figure 11 Results for go reaction times (go RT), stop signal reaction time (SSRT) and proactive inhibition across response modalities (manual and vocal) and stop signal probabilities: high and low [2/3 stop and 1/3 stop trials following the uncertain go] (chapter 5) **A)** Go reaction times for the two types of go RT (certain go and uncertain go) across the two stop probabilities (low and high stop probabilities). **B)** SSRT and proactive inhibition as a function of stop signal probability. **C)** Latencies for go-RT, SSRT and proactive inhibition across response modalities. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$. Error bars indicate standard error of the mean (SEM).

5.5.3. Reactive inhibition (SSRT)

A repeated measures 2 x 2 ANOVA was carried out for SSRTs with the within-subject factors of two response modalities (manual, vocal) and two stop probabilities (high and low probability stop). Both factors, response modality ($F(1,43) = 7$, $p < 0.05$, $\eta^2_p = 0.14$) and stop probability ($F(1,43) = 34$, $p < 0.0001$, $\eta^2_p = 0.4$), were statistically significant. The response modality main effect exhibited a medium effect size and the stop probability main effect, a large effect size. The interaction of response modality and stop probability was not statistically significant ($F(1,43) = 0.003$, $p = 0.96$, $\eta^2_p = 0.001$).

Post hoc analysis within the response modality factor revealed that the SSRT of manual responses (M = 213 ms, SE = 6) was shorter by 17 ms relative to the SSRT of vocal responses (M = 230 ms, SE = 6); see figure 11C. Further, the factor of stop probability showed that $SSRT_{\text{-Low-probability-stop}}$ (M = 240 ms, SE = 6) was 38 ms longer compared to the $SSRT_{\text{-High-probability-stop}}$ (M = 202 ms, SE = 6); see figure 11B.

5.5.4. Analyses of SSD and accuracy of stopping

Because we obtained a significant difference in SSRT between vocal and manual responses, we wanted to make sure this difference was not driven by the difference in go RTs: vocal responses compared to manual responses had longer go RTs. We conducted repeated measures 2 x 2 ANOVA separately for SSD and accuracy of stopping. We included the within-subject factors of 2 response modalities (manual, vocal) and 2 stop probabilities (high and low probability stop).

The results for the SSD revealed a significant difference in the factors of response modality ($F(1,43) = 7.05$, $p < 0.05$, $\eta^2_p = 0.15$) and stop probability ($F(1,43) = 136$, $p < 0.01$, $\eta^2_p = 0.76$). The interaction of response modality by stop probability was not significant ($F(1,43) = 1.49$, $p = 0.23$, $\eta^2_p = 0.04$). The response modality factor showed that SSD of the vocal responses (M = 265 ms, SE = 16) were shorter by 38 ms compared to those of the manual responses (M = 303 ms, SE = 18). In addition, the stop probability factor revealed that the SSD of the high probability stops (M = 333 ms, SE = 17.3) were 99 ms longer than those of the low probability stops (M = 234 ms, SE = 14).

As for the results of accuracy of stopping, with the staircase procedure, we expected a probability of successful stops and failed stops of about 50% each (p_inhibit = 0.5;

p_respond = 0.5). The ANOVA revealed a significant factor of stop probability ($F(1,43) = 79.71$, $p < 0.01$, $\eta^2_p = 0.65$), which revealed that participants stopped slightly more successfully in the high probability stop (p_inhibit = 0.52, $SE = 0.005$) relative to the low probability stop (p_inhibit = 0.49, $SE = 0.005$). There were no statistically significant effects of response modality ($F(1,43) = 0.93$, $p = 0.35$, $\eta^2_p = 0.03$) or significant interaction between response modality and stop probability ($F(1,43) = 1.49$, $p = 0.23$, $\eta^2_p = 0.04$). For the response modality factor, both manual and vocal responses had a p_inhibit of 0.51.

In sum, the results of the SSD and accuracy of stopping analyses suggest that the differences in SSRT between response modalities are not driven by the longer go RT as across response modalities the SSDs were also significantly different and the accuracy of stopping was statistically the same.

5.5.5. Proactive inhibition

A repeated measures 2 x 2 ANOVA was conducted for proactive inhibition with within-subject factors of 2 response modalities (manual, vocal) and 2 stop probabilities (high and low probability stop). The results revealed a significant effect of stop probability ($F(1,43) = 199$, $p < 0.0001$, $\eta^2_p = 0.8$). No significant effects of response modality ($F(1,43) = 0.001$, $p = 0.97$, $\eta^2_p = 0.0001$) or significant interaction between response modality and stop probability ($F(1,43) = 1.4$, $p = 0.25$, $\eta^2_p = 0.03$) were found.

The significant effect of stop probability showed that proactive inhibition for low probability stops ($M = 51$ ms, $SE = 9$) was 91 ms significantly shorter compared to the high probability stops ($M = 142$ ms, $SE = 14$); see figure 11B.

5.5.6. Correlations between reactive and proactive inhibitions

We carried out four correlation analyses between reactive (measured by the SSRT) and proactive inhibition across both response modalities and stop probabilities. The results showed there were moderate negative, statistically significant relationships between $\text{proactive}_{\text{-High-probability-stop}}$ and $\text{SSRT}_{\text{-High-probability-stop}}$ in both response modalities: vocal ($r(42) = -0.35$, $p < 0.01$) and manual ($r(42) = -0.27$, $p < 0.05$). These relationships revealed that more advanced preparation for stopping in the high probability stop condition was related to faster reactive stopping. See appendix H for the non-significant correlations in the low

probability stop conditions. Figure 12 depicts the correlation between the SSRT and proactive inhibition.

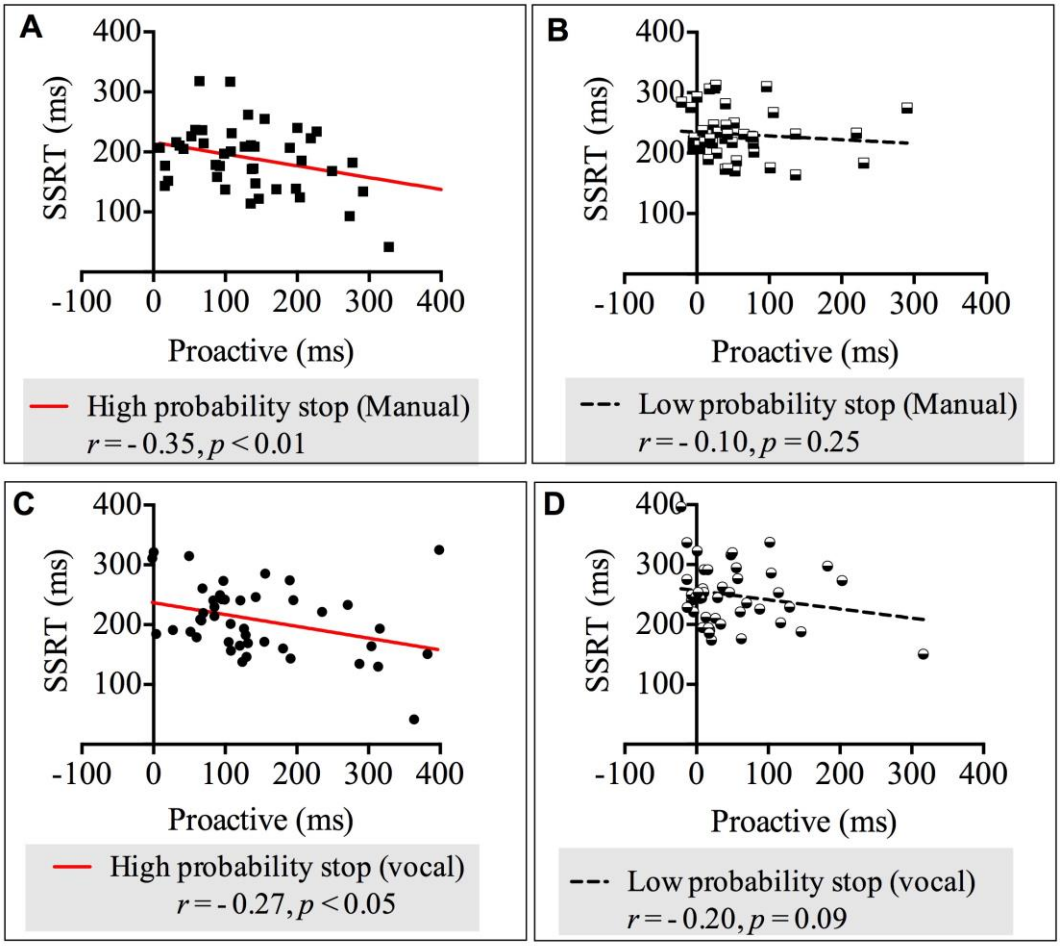

Figure 12 Correlations between proactive and reactive inhibition across response modalities (manual and vocal) and stop probabilities: high and low [2/3 and 1/3 stop trials following the uncertain go] (chapter 5)

A) Correlation between proactive inhibition and SSRT in the high probability stop condition for manual responses. **B)** Correlation between proactive inhibition and SSRT in the low probability stop condition for manual responses. **C)** Correlation between proactive inhibition and SSRT in the high probability stop condition for vocal responses. **D)** Correlation between proactive inhibition and SSRT in the low probability stop condition for vocal responses. Because our alternative hypothesis was in one direction, all Pearson's correlations tested significance with a 1-tailed test.

5.5.7. Correlation between reactive inhibition and impulsivity

We carried out four correlation analyses between reactive inhibition (measured by the SSRT) and impulsivity scores (both dysfunctional and functional impulsivity scores) across both response modalities and stop probabilities. The results showed there was a positive, statistically significant relationship between dysfunctional impulsivity and the

$SSRT_{\text{-High-probability-stop}}$ for manual responses ($r(42) = 0.34$, $p < 0.05$). Likewise, there were positive, statistically significant relationships between dysfunctional impulsivity and the $SSRT_{\text{-Low-probability-stop}}$ for manual responses ($r(42) = 0.29$, $p < 0.05$) and for vocal respones ($r(42) = 0.27$, $p < 0.05$). These relationships revealed that higher scores of dysfunctional impulsivity are related to slower reactive inhibition. See appendix H for the non-significant correlations between the $SSRT_{\text{-High-probability-stop}}$ and dysfunctional impulsivity; and between the SSRTs (both high and low probability stops) and functional impulsivity. See figure 13 for a graphical representation of the correlations between the SSRT and impulsivity.

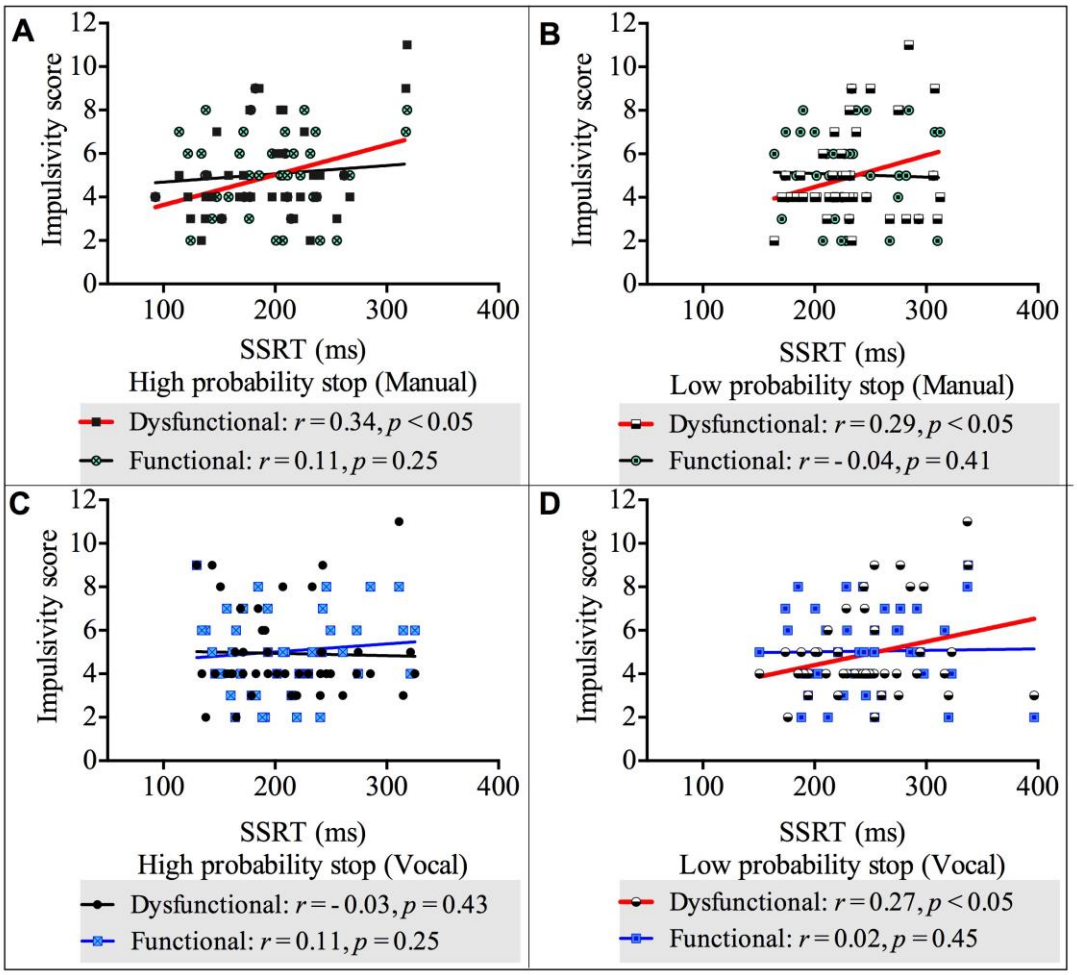

Figure 13 Correlations between impulsivity score and reactive inhibition across response modalities (vocal and manual) and stop probabilities: high and low [2/3 and 1/3 stop trials followed the uncertain go] (chapter 5)

A) Correlation between impulsivity score and SSRT in the high probability stop condition for manual responses. **B)** Correlation between impulsivity score and SSRT in the low probability stop condition for manual responses. **C)** Correlation between impulsivity score and SSRT in the high probability stop condition for vocal responses. **D)** Correlation between impulsivity score and SSRT in the low probability stop condition for vocal responses. Because our alternative hypothesis was in one direction, all Pearson's correlations tested significance with a 1 tailed test. Significant correlations are pointed out with red arrows.

5.5.8. Correlation between proactive inhibition and impulsivity

We carried out 4 correlations in each response modality. These correlations compared the index of proactive inhibition across stop probabilities (high and low probability stops) with scores on impulsivity scales (functional and dysfunctional scores). All correlations were non-significant, the results of these correlations can be found in Appendix H.

5.5.9. Correlation between manual and vocal responses

We conducted correlations between manual and vocal responses across both go RT types (certain go and uncertain go) and both inhibition types (reactive and proactive). The results revealed strong, positive, statistically significant relationships between manual and vocal responses in: certain go RT-$_{\text{High probability stop}}$ ($r(42) = 0.79$, $p < 0.0001$); uncertain go RT-$_{\text{High probability stop}}$ ($r(42) = 0.70$, $p < 0.0001$); proactive-$_{\text{High probability stop}}$ ($r(42) = 0.75$, $p < 0.0001$); certain go RT-$_{\text{Low probability stop}}$ ($r(42) = 0.62$, $p < 0.0001$); uncertain go RT-$_{\text{Low probability stop}}$ ($r(42) = 0.60$, $p < 0.0001$); proactive-$_{\text{Low probability stop}}$ ($r(42) = 0.68$, $p < 0.0001$) and SSRT-$_{\text{Low probability stop}}$ ($r(42) = 0.58$, $p < 0.0001$). These relationships suggested that when one index in vocal responses increased, the counterpart index in manual responses increased too. There was only the correlation of SSRT-$_{\text{High probability stop}}$ between response modalities that was not statistically significant ($r(42) = 0.14$, $p = 0.19$). These results are depicted in figure 14. Interestingly, the SSRT-$_{\text{High probability stop}}$ was the only index that did not correlate with dysfunctional impulsivity.

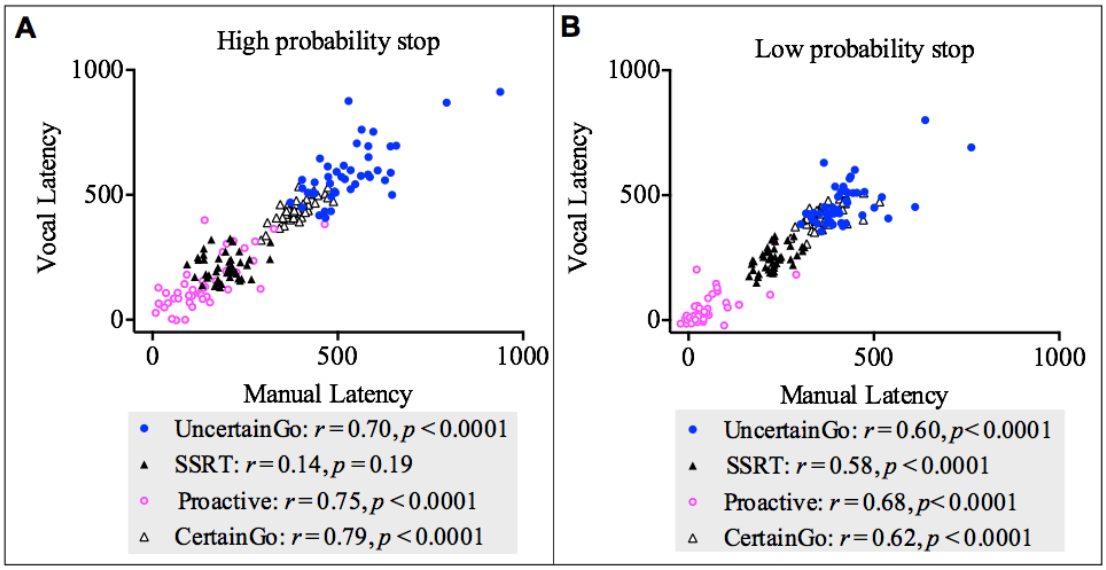

Figure 14 Correlations between vocal and manual responses for both go RT types (certain and uncertain) and both inhibition types (proactive and reactive) (chapter 5)

A) Correlations for the high probability stop [2/3 stop trials followed the uncertain go]. **B)** Correlations for the low probability stop [1/3 stop trials followed the uncertain go].

5.6. Discussion

This study investigated reactive and proactive response inhibition in two effector systems: vocal and manual. We also examined the relationship between these two types of response inhibition and self-reported functional and dysfunctional impulsivity. We hypothesised that conditions where stopping was required with a high probability (1/3 stops) compared to low probability (1/6 stops) stops would enhance both proactive and reactive response inhibition. Secondly, we hypothesised that reactive and proactive response inhibition would be positively related (a negative slope in the correlation between SSRT and proactive inhibition). Last, that SSRT and dysfunctional impulsivity would be positively correlated i.e. as dysfunctional impulsivity increased, SSRTs would be slower. Our results provide evidence to support all of these hypotheses, which are discussed in turn below.

5.6.1. High compared to low probability stop condition have increased proactive and enhanced reactive response inhibition

As predicted, we found that in the high relative to the low probability stops, proactive inhibition was longer (by 91 ms) and SSRT was shorter (by 38 ms). The results suggest that a greater level of preparation for the impending stop signal was implemented when there was a higher probability of stopping; this preparation was also transferred to the go RT of the certain go (only go) and the uncertain go (includes go and stop trials) conditions, as go RTs were longer in the high compared to the low probability stops. These findings are consistent with the previous literature showing that go RTs are affected by stop probability e.g. go RTs are longer in the most frequent stop signal conditions (Lansbergen et al., 2007; Ramautar et al., 2004) and even after a stop-signal e.g. go RTs are slower after a stop trial (Emeric et al., 2007; Rieger & Gauggel, 1999; Verbruggen & Logan, 2008a; Verbruggen, Logan, Liefooghe, & Vandierendonck, 2008). These findings are also consistent with the proactive adjustment hypothesis (Verbruggen & Logan, 2009b) that assumes subjects balance stop and go processes by increasing the response threshold in the go task when they expect more stop signals.

Supporting our hypothesis, apart from increased proactive response inhibition, SSRTs were shorter in the high probability stop condition. Interestingly, SSRT has also been observed to be shorter in conditions in which participants are informed of the position of the stop signal compared to an uninformed condition (Smittenaar, Guitart-Masip, Lutti, &

Dolan, 2013). This means, that more preparation induced either by a high probability stop or an informed condition enhances reactive inhibition. We also found that in the high probability stops, participants stopped successfully more often (p_inhibit 0.52 compared to 0.49 in the low probability), a finding which is in line with Ramautar et al. (2004) and suggests, participants are slightly biased toward successful inhibition over fast responding. This finding is also consistent with more recent studies that have shown that higher probability of stopping is associated with prolonged go RTs, indicative of increased proactive inhibition (Hu, Ide, Zhang, & Li, 2015).

Contrary to the finding that the high probability stop enhances reactive inhibition, other studies have found that changing the stop probability has no effect on the SSRT (Lansbergen et al., 2007; Logan & Burkell, 1986; Ramautar et al., 2004). The reasons could be the small sample size in these previous studies (~13 participants) whereas our data comes from 44 participants. Another reason could be the percentage of the high probability stops, for example, the high probability stop condition in Ramautar et al. (2004) was 50% of stops and 50% of go, whereas in our study the stops in the high probability were 66.66% of uncertain go, potentially eliciting more preparation. Another reason for the differences could be the amount of stops, while we had 100 stops for each stop probability, Logan and Burkell (1986) had 48 stops in the low probability stop against 192 stops in the high probability stop. Finally, Lansbergen et al. (2007) study was comparing differences in impulsivity, thus, the participants recruited were 14 with the lowest scores in impulsivity and 15 with the highest scores in impulsivity. This could have made the results different to our study. In short, the different findings we present in this study compared to those previous studies (Lansbergen et al., 2007; Logan & Burkell, 1986; Ramautar et al., 2004) could be related to the differences in stop probability distributions, sample size, stop trial size and the particular characteristics of the sample.

The assumption of the horse race model, in which failed stop RTs should be faster than go RTs, was met in both stop probability conditions, in line with previous studies (Chikazoe, Jimura, Hirose, et al., 2009; Logan, 1994; Logan & Cowan, 1984; Ramautar et al., 2004). On the other hand, the finding that SSRTs are different across stop probabilities suggests that the stopping process is not constant, an assumption that agrees with the independent horse race model. It is worth noting that the independent horse race model estimates the SSRT assuming '*the finishing time of the stopping process (stop signal reaction time) is*

constant' (Logan, 1994); '*... the assumption about stop signal reaction time makes mathematics easier, but more importantly, it allows a graphic representation of the underlying processes that illustrates the relationships very clearly*' (Logan, 1994); '*the correctness of the assumption is not very important. Logan and Cowan (1984) (mostly Cowan) analysed the formal consequences of the assumption, and found that it introduced very small measurement errors*' (Logan, 1994).

We conclude that greater levels of preparation, represented by increased proactive inhibition in the high stop probability, reduced the time of reactively stopping a prepotent response. We further supported this idea with our second hypothesis, which is described next.

5.6.2. Reactive and proactive response inhibition have a positive relationship

Our second hypothesis measured the relationship between reactive and proactive inhibition. We found that a greater level of preparation was related to reduced SSRT. This was only observed for the high probability stops in both response modalities. These findings support two out of three experiments in (Chikazoe, Jimura, Hirose, et al. (2009); and Jahfari et al. (2010)). Although the amount of stops was very similar in these two studies (20% of stops in the uncertain go condition and 25% of stops respectively) to our low probability stop condition (33.33% of stops in the uncertain go), we did not find that reactive and proactive were negatively related in the low probability stops, like one experiment in Jahfari et al. (2010). We suggest that this could have been because participants, in the two previous experiments that found a relationship, applied more proactive inhibition compared to the low probability stops. In fact, Jahfari et al. (2010) carried out two experiments and only found that reactive and proactive inhibition were related in experiment 1 where proactive inhibition was larger (111.3 ms in all trials) compared to experiment 3 in which proactive inhibition was much smaller (55 ms). Similarly, Chikazoe, Jimura, Hirose, et al. (2009) found that reactive and proactive inhibition were related when proactive inhibition was 105.5 ms. In our study, the high probability stop condition elicited proactive slowing of 142 ms compared to the low probability stop condition where proactive slowing was only 51 ms. These results suggest that when participants used greater level of preparation to hold the prepotent response (proactive inhibition), they could stop faster, but that when they did not withhold the

prepotent response strongly, reactive inhibition was executed by other process not related to the amount of proactive inhibition.

Taken together (hypotheses one and two), we conclude that our findings are consistent with the proactive adjustment account (Verbruggen & Logan, 2009b) in which participants balance stop and go processes by increasing the go RT when the stop probability increases. These results also support the account that greater level of proactive inhibition enhances reactive inhibition. It could be that this alert to hold the prepotent response pre-activates some of the same neural circuitry responsible for reactive inhibition but only when it is very likely that stopping will occur, as described in Aron (2011). In short, it seems that both the go process and reactive inhibitory control interact with proactive inhibition (L. Boucher et al., 2007; Verbruggen & Logan, 2008b).

5.6.3. Relationship between reactive inhibition and dysfunctional impulsivity

Our last hypothesis predicted that there would be a positive relationship between the SSRT and dysfunctional impulsivity. This is what we found, that slower SSRT (weaker reactive stopping) was related with a higher score on dysfunctional impulsivity (not functional impulsivity). This is consistent with a previous study that used the same Dickman impulsivity inventory (Dickman, 1990) and found this relationship existed for vocal responses only (van den Wildenberg & Christoffels, 2010). We extended this relationship to manual responses, which is consistent with other studies that have tested this effector system and found that SSRTs were related to impulsivity scores (Farr et al., 2012; Logan et al., 1997; Marsh et al., 2002). This relationship between reactive inhibition and self-reported impulsivity is consistent with pathological studies that have found slower SSRTs in neuropsychological disorders where impulsive behaviour is a major characteristic (Aron & Poldrack, 2005; Bohne et al., 2008; Enticott et al., 2008; Menzies et al., 2007; Nigg et al., 2006; Penadés et al., 2007; Rubia, Taylor, et al., 2001). Interestingly, this relationship was only seen for reactive inhibition and not for proactive inhibition, suggesting that self-reported impulsivity is more related with overt inhibitory responses.

However, some studies have found that no relationship existed between SSRTs and impulsivity (Avila & Parcet, 2001; Lansbergen et al., 2007; M. Lijffijt et al., 2004; Rodríguez-Fornells et al., 2002). One of the reasons these studies did not find a relationship could be that they used a different impulsivity inventory; these studies used

the 54 item Eysenck impulsivity scale (I7, S. B. G. Eysenck, Pearson, Easting, & Allsopp, 1985). Studies that found a relationship between SSRTs and impulsivity have used a different impulsivity inventory, for example, Logan et al. (1997) used a previous version of the Eysenck Personality Inventory (H. J. Eysenck & Eysenck, 1969) which contained 22 true-false questions; the other two studies (Farr et al., 2012; Marsh et al., 2002) used the Barratt impulsiveness scale, version 11 (Barratt & Patton, 1983). It is very likely that these different impulsivity inventories are measuring distinctive dimensions of impulsivity. For example, the subscales measured in the Eysenck Personality Inventory (H. J. Eysenck & Eysenck, 1969) are impulsivity and sociability whereas the subscales measured in I7 are impulsivity, venturesomeness and empathy. Another reason could lie in the characteristics of the participants. While Logan et al. (1997) recruited students, some of the studies that did not find a relationship recruited high and low impulsive participants (Lansbergen et al., 2007; M. Lijffijt et al., 2004; Rodríguez-Fornells et al., 2002). In short, the instruments to assess impulsive characteristics and the characteristics of the participants may explain why the SSRTs were not related with impulsivity scores in some previous studies.

5.6.4. Additional findings across response modalities

Across response modalities we found that the go RTs for vocal responses were slower compared to those of manual responses. This is consistent with previous studies (van den Wildenberg & Christoffels, 2010). Another study also found that naming part words was slower compared to both manual and naming letters (Xue et al., 2008). Other studies that have tested vocal responses but not compared them directly with manual responses showed that go RT of vocal responses is slower compared to those of manual responses (Wessel & Aron, 2014).

We also found that the SSRT were slower in vocal compared to manual responses but proactive inhibition was the same across these two response modalities. These results cannot really be explained with the proactive adjustment account that suggests larger proactive inhibition enhances reactive inhibition. Moreover, the SSDs were shorter in vocal compared to manual responses. We explained this with the hypothesis that vocal responses have less efficacious reactive inhibition. For example, neurophysiological studies have suggested that corticobulbar motoneurons (which supply some of the vocal muscles) are sparser or less potent than the spinal motoneurons (limb muscles) (Jaberzadeh et al., 2008; Ortu et al., 2008; Sowman et al., 2008), for a review see (Luschei & Goldberg,

2011). These findings are based on suprathreshold TMS pulse that causes interruption of the muscle activity, known as the cortical silent period (CSP). Studies investigating the CSP on the muscles of the vocalisation system (cranial nerve V) describe shorter CSP compared to studies investigating the CSP in the limb system (Cruccu et al., 1997; Jaberzadeh et al., 2008; Ortu et al., 2008; Paradiso et al., 2005; Sowman et al., 2008; Werhahn et al., 1995).

Finally, we found that both go RT (certain and uncertain go), and both reactive and proactive inhibitions were positively correlated between manual and vocal responses across both stop probabilities. The only relationship across response modalities that was not significant was between the SSRT in the high probability stops. Surprisingly, the SSRT of vocal responses in the high probability stops was not related with dysfunctional impulsivity either. These results suggest that the SSRTs of the high probability stops for vocal responses behave differently to those of manual responses and does not relate with impulsivity. The only reason we could think to explain this finding is via the already described hypothesis that the vocal system has less efficacious reactive stopping. Based on this account, SSRTs of the vocal system might dissociate from those of the manual responses in the high probability stop condition where reactive stopping mechanisms are under the highest performance demand. However, further studies would be required to investigate this hypothesis directly.

Conclusions

This study investigated response inhibition in two response modalities (i.e. manual and vocal) and related them to self-reported functional and dysfunctional impulsivity. We found that high compared to low probability stops required more proactive inhibition and produced faster reactive stopping. This was further confirmed in a correlation analysis that showed greater levels of preparation for stopping reduced the SSRT. We also showed that SSRTs were related to dysfunctional impulsivity. The implications of these findings extend the horse race model by studying proactive response inhibition, which currently encompasses only go RT and the SSRT variables. Our results show that proactive inhibition can enhance reactive inhibition by reducing the SSRT only when proactive inhibition is applied strongly. From a therapeutic point of view, these findings can help to reduce impulsive behaviours by for example, cognitive reinforcement on functional instead

of dysfunctional impulsivity; in addition, cognitive training that favours increment of proactive inhibition could potentially reduce impulsive behaviours.

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Appendix G

Table 13: Dickman's impulsivity inventory (Dickman, 1990) (chapter 5)

Filler_Q1	I would travel a great deal if I had the chance.
F_Q1	I don't like to make decisions quickly, even simple decisions, such as choosing what to wear, or what to have for dinner
Filler_Q2	I seldom tell lies.
D_Q1	I will often say whatever comes into my head without thinking first.
Filler_Q3	I have many hobbies.
F_Q2	I am good at taking advantage of unexpected opportunities, where you have to do something immediately or loose your chance.
Filler_Q4	I would rather read fiction than non-fiction.
D_Q2	I enjoy working out problems slowly and carefully.
Filler_Q5	I would not drive over the speed limit even if I knew I would not be caught.
F_Q3	I am uncomfortable when I have to make up my mind rapidly.
Filler_Q6	I consider myself a sympathetic person.
D_Q3	I frequently make appointments without thinking about whether I will be able to keep them.
Filler_Q7	I enjoy exercising.
F_Q4	I like to take part in really fast-paced conversations, where you don't have much time to think before you speak.
Filler_Q8	I like most of the people I meet.
D_Q4	I frequently buy things without thinking about whether or not I can really afford them.
Filler_Q9	I watch television as much as most people do.
F_Q5	Most of the time, I can put my thoughts into words very rapidly.
Filler_Q10	I enjoy outdoor activities.
D_Q5	I often make up my mind without taking the time to consider the situation from all angles.
Filler_Q11	I have read more books than most of my friends.
F_Q6	I don't like to do things quickly, even when I am doing something that is not very difficult.

Filler_Q12	I am more alert than most people late at night.
D_Q6	Often, I don't spend enough time thinking over a situation before I act.
Filler_Q13	I like to read about scientific research.
F_Q7	I would enjoy working at a job that required me to make a lot of split-second decisions.
Filler_Q14	Religion is very important in my life.
D_Q7	I often get into trouble because I don't think before I act.
Filler_Q15	I have more curiosity than most people.
F_Q8	I like sports and games in which you have to choose your next move very quickly.
Filler_Q16	I read the newspaper almost every day.
D_Q8	Many times the plans I make don't work out because I haven't gone over them carefully enough in advance.
Filler_Q17	I sometimes get depressed for no good reason.
F_Q9	People have admired me because I can think quickly
Filler_Q18	I enjoy it when I get a chance to visit a city I've never seen before.
D_Q9	I rarely get involved in projects without first considering the potential problems.
Filler_Q19	I am easily embarrassed.
F_Q10	I have often missed out on opportunities because I couldn't make up my mind fast enough
Filler_Q20	I am more alert than most people in the morning.
D_Q10	Before making any important decisions, I carefully weigh the pros and cons.
Filler_Q21	I make an effort to take care of my health.
F_Q11	I try to avoid activities where you have to act without much time to think first
Filler_Q22	I generally go to bed at a later hour than most people do.
D_Q11	I am good at careful reasoning.
Filler_Q23	I think that I am more creative than most of my friends.
D_Q12	I often say and do things without considering the consequences.

F= Functional impulsivity; D= Dysfunctional impulsivity. Q= question

Appendix H

Table 14: Pearson's correlations between proactive and reactive inhibition and, between both impulsivity scales (functional and dysfunctional) and both inhibition types (proactive and reactive inhibition) (chapter 5)

Variables	(*r*)	(*p*)
Proactive-High-probability-stop (Manual) & SSRT-High-probability-stop (Manual)	- 0.16	0.15
Proactive-Low-probability-stop (Manual) & SSRT-Low-probability-stop (Manual)	- 0.10	0.25
Proactive-High-probability-stop (Vocal) & SSRT-High-probability-stop (Vocal)	- 0.27	< 0.05
Proactive-Low-probability-stop (Vocal) & SSRT-Low-probability-stop (Vocal)	- 0.20	0.09
Dysfunctional impulsivity & SSRT-High-probability-stop (Manual)	0.34	< 0.05
Dysfunctional impulsivity & SSRT-Low-probability-stop (Manual)	0.29	< 0.05
Dysfunctional impulsivity & SSRT-High-probability-stop (Vocal)	- 0.03	0.43
Dysfunctional impulsivity & SSRT-Low-probability-stop (Vocal)	0.27	< 0.05
Functional impulsivity & SSRT-High-probability-stop (Manual)	0.11	0.25
Functional impulsivity & SSRT-Low-probability-stop (Manual)	-0.04	0.41
Functional impulsivity & SSRT-High-probability-stop (Vocal)	0.11	0.25
Functional impulsivity & SSRT-Low-probability-stop (Vocal)	0.02	0.45
Dysfunctional impulsivity & Proactive-High-probability-stop (Manual)	0.12	0.22
Dysfunctional impulsivity & Proactive -Low-probability-stop (Manual)	0.11	0.25
Dysfunctional impulsivity & Proactive -High-probability-stop (Vocal)	0.07	0.33
Dysfunctional impulsivity & Proactive -Low-probability-stop (Vocal)	0.08	0.32
Functional impulsivity & Proactive -High-probability-stop (Manual)	0.05	0.39
Functional impulsivity & Proactive -Low-probability-stop (Manual)	-0.01	0.48
Functional impulsivity & Proactive -High-probability-stop (Vocal)	0.04	0.40
Functional impulsivity & Proactive -Low-probability-stop (Vocal)	-0.03	0.44

* Note that the SSRT were calculated from only the uncertain condition (uncertain go + stop trials). All degrees of freedom are 42. *r* = correlation coefficient; *p* = significance level, 1 tailed.

Appendix I

Table 15: Reaction times of certain go, uncertain go and failed stops (chapter 5)

Variable	Mean (SE)
HP-Certain Go	415 (7)
HP-Uncertain Go	558 (16)
HP-Failed stop	430 (13)
LP-Certain Go	395 (7)
LP-Uncertain Go	446 (12)
LP-Failed stop	386 (10)

Variables of the interaction stop probability by RT during 2 x 2 x 3 ANOVA. HP = high probability stop; LP = low probability stop.

Appendix J

Correlations across the high and low probability stop between uncertain go with SSD and SSRT. M = manual; V = vocal

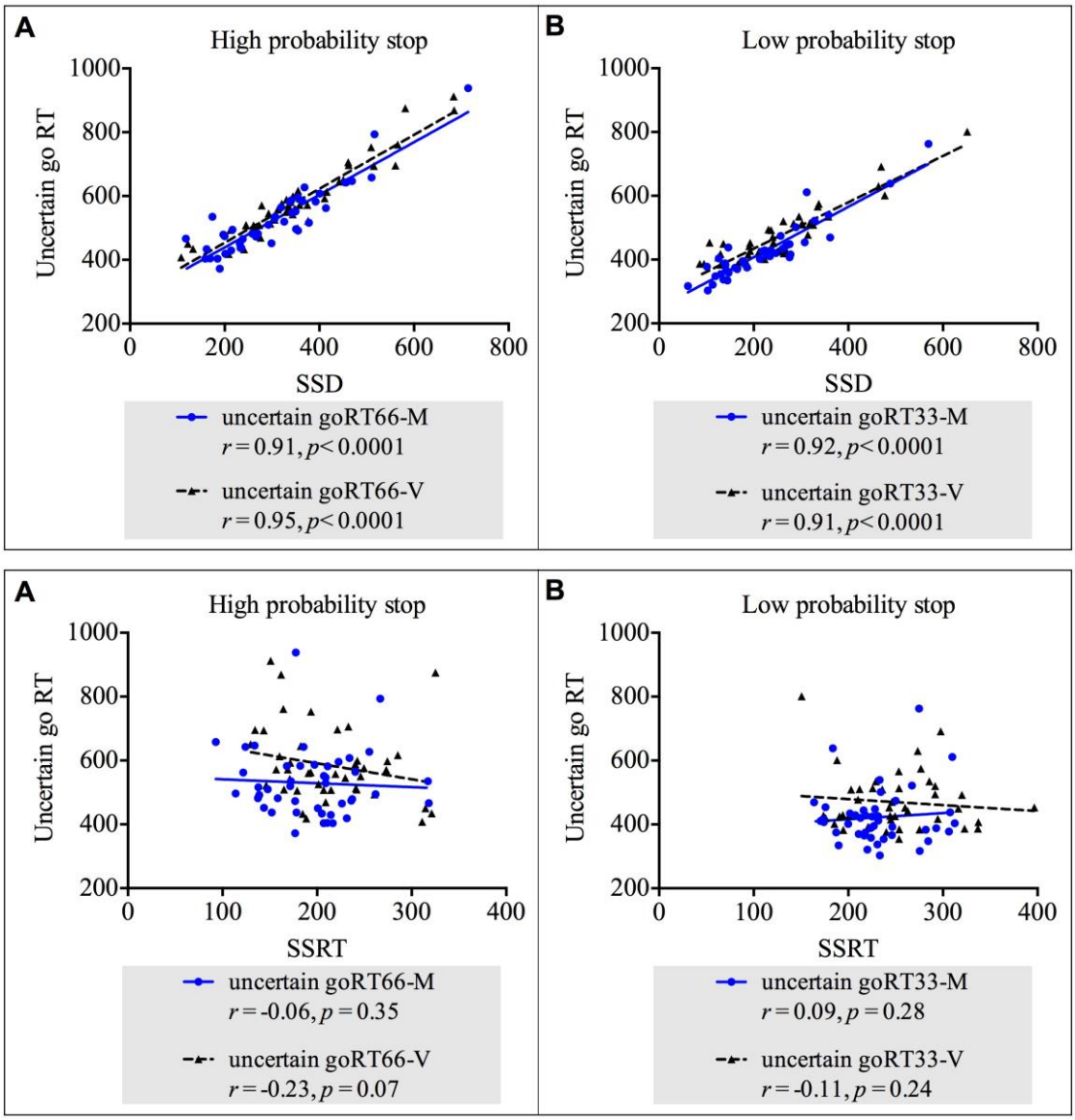

Figure 15 Correlations across the high and low probability stop between uncertain go with SSD and SSRT (chapter 5)

Chapter 6 – General discussion

6. General discussion

6.1. Overview of thesis

In this thesis I investigated the influence that proactive inhibition exerts on reactive inhibition. I particularly focused on whether enhancing proactive inhibition is associated with enhanced reactive inhibition in both manual and vocal response modalities. I also attempted to determine whether response inhibition is controlled by common central generators for both manual and vocal effector system. Lastly, I compared and contrasted vocal and manual reactive and proactive inhibition. Specifically, I explored whether vocal relative to manual response inhibition is less efficacious. In four experiments, I explored the effect of the right VLPFC on both reactive and proactive response inhibition; the effect of proactive inhibition on reactive inhibition, two response inhibition indexes (i.e. reactive and proactive) across response modalities (i.e. vocal and manual) and the neurophysiological markers of vocal response inhibition in younger and older adults. I also investigated the relationship between response inhibition and measures of impulsivity in healthy adults. In this chapter I will review the specific findings of each chapter. I will discuss how these contribute to the main research questions and the implications of the findings in a broader context. Finally, I will discuss a number of outstanding issues that will inspire future research.

6.2. Overview of studies and the implications of their findings

6.2.1. Chapter 2

In chapter 2 "*Vocal response inhibition is enhanced by anodal tDCS over the right prefrontal cortex*" I addressed three questions: (1) is there a negative relationship between proactive and reactive inhibition, in particular does more proactive inhibition equate to faster reactive inhibition? (2) Is the right VLPFC involved in vocal response inhibition, and can reactive inhibition be enhanced in the vocal as well as in the manual effector systems by anodal tDCS? (3) Is reactive inhibition less potent in vocal relative to manual responses?

A SST was designed with two main conditions: relevant stop and irrelevant stop conditions that were tested in separate blocks. The relevant stop condition contained visual go and stop trials (2/3 and 1/3 of total trials respectively), participants had to respond to the go

either with a vocal or a manual response and stop that response at the appearance of a stop-signal. The irrelevant stop condition was made up of exactly the same trials as the relevant stop condition but in this condition, participants were asked to ignore the stop-signal and always respond. We had 16 blocks, 8 were for the relevant stop condition and 8 for the irrelevant stop condition. From these 8 blocks in each stop condition, 4 were for manual and 4 for vocal responses. We had 2 sessions and applied either anodal tDCS or sham in the middle of the session to each stop condition type (relevant and irrelevant stop) and each response modality (vocal and manual). In each session, 4 out of the 16 blocks received the stimulation protocol. I addressed three questions that will be described next.

The first question was: is there a positive relationship between proactive and reactive inhibition; in particular, does more proactive inhibition equate to faster reactive inhibition? The behavioural findings in this experiment revealed significant correlations existed between proactive and reactive inhibition for phase-$3_{[\text{session with anodal tDCS}]}$ in both response modalities (manual and vocal) and in phase-$2_{[\text{session with sham}]}$ for manual responses. These relationship showed that greater level of proactive inhibition can reduce reactive inhibition, which is consistent with two out of three previous experiments (Chikazoe, Jimura, Hirose, et al., 2009; Jahfari et al., 2010). I found out that session had no effect on these significant relationships but the size of proactive inhibition seems to be involved. I found out that the third experiment of Jahfari et al. (2010), that did not find a relationship between proactive and reactive inhibition, had 55 ms for proactive inhibition, compared to the first experiment in which proactive inhibition was 111.4 ms. In the current results, the significant relationships had also the greatest size in proactive inhibition.

The second question was: Is the right VLPFC involved in vocal response inhibition, and can reactive inhibition be enhanced in the vocal as well as in the manual effector systems by anodal tDCS? I found that anodal tDCS enhanced reactive inhibition in both response modalities by an average of 39 ms. These findings showed that the right VLPFC is also an important area for optimal reactive inhibition in vocal responses, which is consistent with fMRI research that shows the right VLPFC is a common neural substrate for response inhibition in the vocal and manual effector systems (Xue et al., 2008). Importantly, stimulation of the right VLPFC did not have an effect on proactive inhibition, suggesting it may only be important for reactive inhibition. The contention that proactive inhibition pre-activates the reactive inhibition network (Aron, 2011) should be understood cautiously

because it could still be possible that proactive inhibition pre-activates the reactive inhibitory network but it may be possible that proactive inhibition relies on other brain substrates to operate.

The third question was: Is reactive inhibition less potent in vocal relative to manual responses? Findings showed that vocal reactive inhibition was not statistically different from manual reactive inhibition. Although I found a trend towards this being the case, this study may not have had the statistical power to detect a small difference. Certainly, the SSRT of vocal responses were, on average, 11 ms longer than those from the manual condition. In previous studies that have measured both vocal and manual responses, some have not directly compared the two response modalities (Etchell et al., 2012; Wessel & Aron, 2014) but the trend toward SSRT in vocal responding being slower existed. For instance, vocal SSRTs were on average 20 and 29 ms longer compared to manual SSRT with visual stop-signals (Etchell et al., 2012; Wessel & Aron, 2014 respectively) and 63 ms longer with auditory stop-signals (Wessel & Aron, 2014). There are two studies that have directly compared these two response modalities. While one study (Xue et al., 2008) reported that the SSRTs were faster for letter naming than both part-word naming and manual responses, which is the opposite to the trend that vocal SSRT are slower than manual SSRT; the other study found that there were no differences in the SSRT for word naming compared to button pressing (van den Wildenberg & Christoffels, 2010). The opposite trend found in Xue et al. (2008) study, could be due to the procedure to estimate vocal responses and remove scanner noise, the authors clarified that because it was a fMRI study, the procedure to detect vocal responses and remove background scanner noise did not allow them to accurately estimate the go RT and therefore the SSRT. The differences with van den Wildenberg and Christoffels (2010) could lie in that participants had to name words, compared to my study in which they only had to make a short vowel sound. In the last study of this thesis (chapter 5) I address the same question but used a mixed block design as in Chikazoe, Jimura, Hirose, et al. (2009) and increase the sample size.

Moreover, the differences between vocal and manual responses could just lie in the fact that vocal responses are slower perhaps because of different measurement procedures (key press vs. microphone) but then, why this difference was not constant across stop conditions? While in the irrelevant stop condition, the difference in go RT between vocal

and manual was of 70 ms, in the relevant stop condition this difference was 35 ms. We address this possible measurement account in the next study (chapter 3).

In summary, this study provides more evidence that the right VLPFC is a common neural generator for response inhibition in both manual and vocal effector systems. Importantly, it is the first study to use non-invasive brain stimulation to investigate vocal response inhibition which in turn strengthens the conclusions from fMRI studies (Xue et al., 2008). I learned that a block design to estimate proactive inhibition may not have been the optimal method to measure proactive inhibition as the differences in RT between irrelevant and relevant stop conditions may not measure pure proactive inhibition as in the irrelevant stop blocks stop signals were never imminent. I improved my design for the last study of this thesis (chapter 5) where I carried out a mixed block design in which I included three types of trials: certain go, uncertain go and stop trials. This allowed me to subtract proactive inhibition from two go response types that were presented within the same block. I also increased the sample size in my last chapter (5) to overcome possible sample-size limitations in the previous chapters. The mixed block design and increased sample-size addressed step-wise the main research question: in anticipation of discussion of this chapter, the results support the predictions that greater proactive inhibition enhances reactive inhibition and that reactive inhibition is less efficacious in vocal compared to manual responding. Moreover, a particular issue in this study (chapter 2) that puzzled me was that go RTs were always slower in vocal responses relative to manual responses even in the irrelevant stop condition. This made me wonder whether participants were using more proactive inhibition during vocalisation even when stopping was not required. I investigated this idea in the next chapter.

6.2.2. Chapter 3

In chapter 3 "*Proactive inhibition enhances sensorimotor synchronisation*" I addressed the question: will induced proactive inhibition enhance synchronisation response (SR) in both the manual and the vocal system.

To address this question, a novel task was designed that allowed manipulating proactive inhibition without affecting RTs *per se*. This task combined the SST with a sensorimotor synchronisation (SMS) task. This new task, the stop-signal synchronisation task (SS-Synch task), contained go and stop trials (4/5 and 1/5 of total trials respectively). The go trials

were represented by an isochronous beat and subjects were required to synchronise to the beat by either giving a button press or producing the letter sound “ɪ” as it would occur in the word “hit /hɪt/”. The stop-signal was the visual presentation of a red letter "X" in the centre of the screen. As in the previous chapter, this task had two stop conditions: a relevant and an irrelevant stop condition. In the relevant stop condition, participants had to respond to the go trials by synchronising to the beat and stopping their ongoing responding at the appearance of a stop-signal. The irrelevant stop condition was made up of exactly the same trials as the relevant stop condition but in this condition, participants were told to ignore the stop-signal and always respond as if it were a go trial. We had 12 blocks, 6 were for the relevant stop condition and 6 for the irrelevant stop condition. From these 6 blocks in each stop condition, 3 were for manual and 3 for vocal responses. There were 2 sessions in which we applied either anodal tDCS or sham in the middle of the session to each stop condition (relevant and irrelevant stop) and each response modality (vocal and manual). In each session, 4 out of the 12 blocks received the stimulation protocol.

We found that the increament in proactive inhibition shifted the SR positively in both manual and vocal responding. However, while the augmentation in proactive inhibition on the relevant stop blocks made manual SR very accurate to the beat onset, vocal SR occurred significantly later with respect to the beat onset. The results of this study show that proactive inhibition enhanced SMS for the manual effector system. The increment of proactive inhibition was less in the vocal system because the system was already very accurate to the beat onset in the irrelevant stop block.

6.2.3. Chapter 4

In chapter 4 "*Event-related fields evoked by vocal response inhibition: a comparison of younger and older adults*" I addressed the question: do ERFs for vocal response inhibition exhibit similar patterns to those described for manual response inhibition? Specifically, I had three predictions: (1) the amplitude of successful stopping would be larger compared to both failed stops and ignore-stop trials in an early peak at around 160 ms; (2) if the later peaks in the response inhibition related waveforms are related to error recognition, then failed stops should evoke larger amplitude ERFs than successful stops in these later latency ERFs; (3) if aging affects response inhibition (slower SSRT), then the ERF peak most related to successful stopping would have an amplitude reduction and/or a latency delay.

To address this main question and its predictions, a selective inhibition SST was designed with three types of trials intermixed within the same block: go, stop and ignore_stop trials (2/4, 1/4 and 1/4 of total trials respectively). All signals were visual; participants had to make either of two vowel sounds when there was a go or an ignore_stop trial and to try to refrain from responding at the stop-signal occurrence. The ignore_stop trials contained a second stop-signal but participants were told to ignore it and respond as per the go trials. There were 9 blocks in which ERFs were recorded throughout.

Prediction 1: *the amplitude of successful stopping would be larger compared to both failed stops and ignore-stop trials in an early peak at around 160 ms*. The M2 peak showed that the successful stop-related ERF amplitude was larger relative to the failed stop-related ERF amplitude between 100 and 195 ms. Moreover, the M2 reached its maximum amplitude at 200 ms. This finding was consistent with ERP studies reporting an N2 that reached maximum amplitude at approximately 200 ms (Liotti et al., 2010; Schmajuk et al., 2006), the N1 (Bekker et al., 2005) and the magnetic N1 from a MEG study (Boehler et al., 2009) that peaked at 160 ms. Our M2, peaking at 200 ms for vocal responding, reached its highest amplitude a bit later compared to the magnetic N1 described in (Boehler et al., 2009), which may suggest slower inhibition for vocal. However, because I did not directly compared vocal and manual responses, it is difficult to conclude that the M2 is slower for vocal compared to manual responses.

Prediction 2: *if the later peaks in the response inhibition related waveforms are related to error recognition then failed stops should evoke larger amplitude ERFs than successful stops in these later latency ERFs*. The findings showed that in the later latency-related ERFs (ranging from 360 to 650 ms) an M4 peak occurred. This peak showed that the amplitude for the failed stop-related ERFs was larger relative to the ERF amplitude for both successful stopping (between 620 to 700 ms) and ignore_stop related ERFs (between 445 to 700 ms). This finding is consistent with the ERP evidence for manual response inhibition that suggests this later peak is related to error processing (Greenhouse & Wessel, 2013; Kok et al., 2004; Ramautar et al., 2004; Schmajuk et al., 2006; Squires et al., 1975). However, the error-processing hypothesis was challenged because the M4 amplitude of the successful stop-related ERF was significantly larger compared to the ignore_stop-related ERF. It was also larger for correct responses in a previous study (Falkenstein et al., 2000). Falkenstein et al. (2000) suggested that this late peak after correct responses reflects

response checking and after error trials reflects response checking plus an overlaid error processing.

Prediction 3: *if aging affects response inhibition, inhibition-related ERF waveforms should be smaller in amplitude in older adults relative to younger adults.* Evidence was found for both a general processing delay and an inhibitory decline as we found that the M2, M3 and M4 were of smaller amplitude and occurred later in the older compared to the younger group. This was consistent with previous ERP studies that have shown manual response inhibition in older relative to younger adults exhibits a smaller, delayed P3 (Mullis et al., 1985).

In summary, vocal response inhibition exhibits similar neurophysiological signatures as the ERP literature has reported for manual response inhibition. The ERF evoked by the response inhibition process is proposed to consist of: (1) an M2 ERF that is larger for successful stop; (2) an M4 signalling response inhibition checking and error-detection; (3) and both amplitude and latency reduction in all ERF peaks for the ageing brain.

6.2.4. Chapter 5

In chapter 5 "*The effect of proactive inhibition on reactive inhibition and their relationship with impulsivity: evidence from the stop signal task applied to vocal and manual responses*" I addressed four questions: (1) does proactive inhibition increase and reactive inhibition decrease in a high relative to a low probability stop condition? (2) Do reactive and proactive inhibition have a positive relationship which would support the contention that more preparation enhances outright stopping? (3) Is reactive inhibition weaker in vocal relative to manual responses? (4) Will weaker reactive inhibition be related to higher dysfunctional impulsivity scores?

Based on my previous studies, the design of the SST was improved. This SST contained a mixed trial design in which each block contained three types of trials: certain go (1/2 of the total trials), uncertain go and stop trials. The certain go trials contained a go-signal that was never followed by a stop-signal, hence they were referred to in name as 'certain'. The uncertain go and stop trials were manipulated based on two stop probability conditions: high and low. In the high probability stop condition, the proportion of uncertain go and stop trials was 1/3 and 2/3 respectively, whereas in the low probability stop condition, the

relative proportion of uncertain go and stop trials was reversed; 2/3 and 1/3 respectively. Participants were told to respond to the certain and uncertain go either with a button press (for manual responses) or by producing the sound "ɪ" as it would occur in the word "hit /hɪt/" (for vocal responses). At the presence of the stop-signal, participants had to attempt to stop responding. There were 12 blocks, 6 were assigned to manual responses and 6 to vocal responses. The order of response modalities was randomised but the 6 blocks of each response were presented sequentially. From this 6 block-sequence, 4 blocks corresponded to the low stop probability condition (100 stops) and 2 blocks corresponded to the high stop probability condition (100 stops).

For the first question: *will proactive inhibition increase and reactive inhibition decrease in a high relative to a low probability stop condition?* The results revealed that this was the case: in the high relative to the low probability stop condition across both response modalities, proactive inhibition was 91 ms longer and reactive inhibition 38 ms shorter. In other words, a greater level of preparation was enacted in the high probability stop condition, which decreased the time needed to reactively stop. The results for proactive inhibition are consistent with previous studies that have reported that go RTs required more proactive inhibition in a high probability stop condition (Lansbergen et al., 2007; Ramautar et al., 2004) or applied more proactive inhibition after a stop trial (Emeric et al., 2007; Rieger & Gauggel, 1999; Verbruggen & Logan, 2008a; Verbruggen et al., 2008). Furthermore, such results support the proactive adjustment hypothesis (Verbruggen & Logan, 2009b), which suggests participants balance stop and go processes by increasing the response threshold in the go task when stop signals are expected. The results for reactive inhibition are also consistent with another study in which the SSRT was found to be shorter in pre-cuing informed conditions compared to uninformed conditions (Smittenaar et al., 2013). This suggests that greater information about when a stop-signal will occur enhances reactive inhibition, possibly because the pre-cuing information increases proactive inhibition.

For the second question: *Do reactive and proactive inhibition have a positive relationship suggesting that more preparation reduces outright stopping?* The results showed that a positive relationship existed between reactive and proactive inhibition but only for the high probability stop condition. This is consistent with two out of three previous experiments (Chikazoe, Jimura, Hirose, et al., 2009; Jahfari et al., 2010). In contrast, in the low

probability stop condition no relationship existed between proactive and reactive inhibition. I posit that in the low probability stop condition, the smaller amount of proactive inhibition elicited (51 ms for low probability vs. 142 ms in the high probability stop) meant that a relationship between proactive and reactive was not manifest. The lack of this relationship in the low probability stop is consistent with the third experiment presented in Jahfari et al. (2010) where proactive inhibition was only 55 ms; and no relationship existed between proactive and reactive inhibition. Contrarily, in the high probability stop condition, proactive inhibition was 142 ms longer, a finding in close agreement with Chikazoe, Jimura, Hirose, et al. (2009) who found a proactive lengthening in RT of 105.5 ms and the first experiment reported in Jahfari et al. (2010) where proactive inhibition resulted in slowing in of 111.3 ms. In short, my findings in regard this second question suggest that when a greater level of proactive inhibition is elicited by conditions that require more caution, reactive inhibition is more powerful. Whereas when the prepotent response is not strongly proactively held, reactive inhibition is slower. Finally, these results provide more evidence to support the hypothesis that proactive inhibition pre-activates the neural circuitry for reactive inhibition, making reactive inhibition faster (Aron, 2011).

For the third question: *Is reactive inhibition weaker in vocal relative to manual responses?* The results showed that the SSRT was slower in vocal compared to manual responses but proactive inhibition was not different, which suggest slower SSRTs were not related to a difference in proactive inhibition for vocalisation. This result was interpreted with the hypothesis that vocal relative to manual responses had weaker reactive inhibition, which is consistent with neurophysiological studies that reported that the cortical silent period (CSP) is shorter in vocal responses compared to those studies that reported the CSP in the limbs (Jaberzadeh et al., 2008; Luschei & Goldberg, 2011; Ortu et al., 2008; Sowman et al., 2008). It is also consistent with Luschei and Goldberg (2011) who showed that the corticobulbar relative to the corticospinal system has sparser or less potent autogenic inhibition reflexes, stretch reflexes, reciprocal inhibition and recurrent inhibition.

For the fourth question: *Will weaker reactive inhibition be related to higher dysfunctional impulsivity scores?* The results showed that indeed slower SSRT was positively related with higher scores on dysfunctional impulsivity (not functional impulsivity). These findings are consistent with previous studies that correlated self-report impulsivity in

healthy participants with manual SSRT (Avila & Parcet, 2001; M. Lijffijt et al., 2004; Logan et al., 1997) and dysfunctional impulsivity with vocal SSRT (van den Wildenberg & Christoffels, 2010). Impulsivity has also been related to neuropsychological disorders (Aron & Poldrack, 2005; Bohne et al., 2008; Enticott et al., 2008; Menzies et al., 2007; Nigg et al., 2006; Penadés et al., 2007; Rubia, Taylor, et al., 2001).

In summary, this study showed that greater amount of proactive inhibition made reactive inhibition faster, possibly because it operates by pre-activating the reactive inhibitory network. Secondly, reactive inhibition was slower in vocal compared to manual responses, possibly reflecting less efficacious reactive inhibition with vocal responses. Finally, the slower SSRT was positively related to higher scores on dysfunctional impulsivity.

6.3. Discussion and outstanding questions

6.3.1. The influence of proactive inhibition on reactive inhibition

In two experiments I showed that the greater the level of proactive inhibition is, reactive inhibition can be reduced (chapters 2 and 5). For example, in chapter 5 when I manipulated the amount of stop-signals (1/3 and 2/3 for low and high stop probability) proactive inhibition was enhanced in the high probability stop condition by 91 ms relative to the low probability stop condition, a finding consistent with previous studies (Emeric et al., 2007; Lansbergen et al., 2007; Ramautar et al., 2004; Rieger & Gauggel, 1999; Verbruggen & Logan, 2008a; Verbruggen et al., 2008). I also found that this increment in proactive inhibition was related to enhanced reactive inhibition, as the SSRT was 38 ms faster in the high compared to the low stop probability, consistent with Smittenaar et al. (2013). This positive relationship is consistent with two out of three previous experiments (Chikazoe, Jimura, Hirose, et al., 2009; Jahfari et al., 2010) but at odds with the third experiment in Jahfari et al. (2010) which did not show this correlation.

Moreover, this positive relationship that relates higher level of proactive with enhanced reactive inhibition was only observed in the high not in the low probability stop condition. I interpreted this results in comparison to a third experiment in Jahfari et al. (2010). I found that in these situations, participants did not utilise much proactive inhibition, for instance in my low probability stop the index of proactive inhibition was 51 ms compared to 55 ms in the third experiment of Jahfari et al. Contrarily, in my high probability stop condition

and in the two previous experiments that found this relationship (Chikazoe, Jimura, Hirose, et al., 2009; Jahfari et al., 2010) proactive inhibition index was much higher being 142, 105.5 and 111.3 ms respectively.

In short, these findings showed that when proactive inhibition is strongly recruited (larger size), it can have an effect on reactive inhibition by making the SSRT shorter. This supports the account that proactive inhibition pre-activates the same neural network for reactive inhibition and then, reactive inhibition is faster because the network has been primed (Aron, 2011). However, this contention needs to be understoond cautiously as in the next section I showed that anodal tDCS to the right PFC can enhance reactive but not proactive, suggesting proactive inhibition may rely in other neural networks.

6.3.2. The right VLPFC as a common central generator of reactive inhibition in both manual and vocal effector systems

The findings of this thesis support the hypothesis that the right VLPFC is part of a common central generator of response inhibition, in particular for reactive inhibition (not proactive inhibition) in both the manual and vocal effector systems. Its role of reactive inhibition is consistent with fMRI research in humans (Aron & Poldrack, 2006; Aron et al., 2004; Chikazoe, Jimura, Asari, et al., 2009; Garavan et al., 1999; Konishi et al., 1999; Rubia, Russell, et al., 2001; Rubia et al., 2003; Xue et al., 2008) and other mammals (Morita et al., 2004), lesion studies in humans (Aron et al., 2003; Picton et al., 2007) and other mammals (Hasegawa et al., 2004; Iversen & Mishkin, 1970; Lüders et al., 1988; Sakagami et al., 2001; Sasaki et al., 1989), TMS-induced virtual lesions (Buch et al., 2010; Chambers et al., 2007; Chambers et al., 2006; Verbruggen et al., 2010) and anodal tDCS with manual responses (Ditye et al., 2012; Jacobson et al., 2011).

6.3.3. Neuromagnetic markers of vocal response inhibition in younger and older adults

We found that the neuromagnetic markers of vocal response inhibition exhibit similar neurophysiological temporal evolution to those described for manual response inhibition. Particularly, I found that the M2 peak exhibited larger amplitudes for the successful stop-related ERF compared to both failed stop and ignore_stop related ERFs between 100 and 195 ms. This finding is consistent with previous ERP research reporting larger amplitudes for successful stop at the N2 (Liotti et al., 2010; Schmajuk et al., 2006), the N1 (Bekker et

al., 2005) and the magnetic N1 from a MEG study (Boehler et al., 2009), all of which converge on a similar latency; all of these peaks occurred at about 200 ms. The magnetic N1 reported in Boehler et al. (2009) peaked at 160 ms for manual responding, which may further support the contention that vocal stopping may be slower than manual because the M2 I found peaked at 200 ms. However, future studies making a direct comparison within the same experimental context will be needed to further elucidate such a difference if it occurs. In addition, I also found that the M4 peak of vocal responding, which occurred from about 400 ms to 700 ms supported the error-recognition hypothesis, as the ERFs exhibited larger amplitudes for failed stops relative to successful and ignore_stop. The M4 peak also supported a proposed hypothesis that it represents the post hoc analysis of response inhibition. The M4 for both successful and failed stop related ERFs was different from ignore_stop-related ERFs at the beginning of the peak, consistent with a previous study on choice RT of manual responding (Falkenstein et al., 2000). Therefore, I concluded that the M4 ERF waveform represented both processes already reported in manual responding: an initial process for response inhibition checking and the last part as an error-detection process. Finally, I compared the neuromagnetic ERFs of vocal responding for younger adults relative to an older group. The findings revealed that the older relative to the younger group exhibited both a general processing delay and an inhibitory decline, as the M2, M3 and M4 peaks all occurred later and were of smaller amplitude. These findings are consistent with previous findings on manual response inhibition (Mullis et al., 1985).

In short, the ERFs of the vocal effector system revealed very similar peaks to those previously described for the manual effector system.

6.3.4. Reactive inhibition is positively related to higher scores on dysfunctional impulsivity

We re-investigated whether reactive inhibition of vocal and manual responding was related to dysfunctional impulsivity as a previous study had shown this correlation only existed in the vocal domain (van den Wildenberg & Christoffels, 2010). I found that across both response modalities reactive inhibition was related to dysfunctional impulsivity but not with functional impulsivity in healthy participants. These results suggest that high scores on dysfunctional impulsivity measures are related to a decrease in the strength of reactive inhibition, consistent with previous studies of manual responding (Avila & Parcet, 2001;

M. Lijffijt et al., 2004; Logan et al., 1997) and vocal responding (van den Wildenberg & Christoffels, 2010). Interestingly, reactive inhibition is not related to functional impulsivity, which may explain why there are many studies reporting reactive inhibition to be impaired in various neuropsychological disorders in which high levels of impulsive behaviour are characteristic (Aron & Poldrack, 2005; Bohne et al., 2008; Enticott et al., 2008; Menzies et al., 2007; Nigg et al., 2006; Penadés et al., 2007; Rubia, Taylor, et al., 2001).

However, vocal reactive inhibition in the high probability stop condition was not related to dysfunctional impulsivity. In the next sections I reported that the SSRTs of vocal responding were statistically longer and not positive correlated with those of manual responding. All together such results suggest that vocal reactive inhibition is different from manual reactive inhibition. I will go in more detail of what this difference could be later in this chapter.

6.3.5. Proactive inhibition, reactive inhibition (only low probability stop condition) and go reaction times (certain and uncertain go RT) are positively related to the vocal and manual effector systems

In my last experiment (chapter 5), I found that proactive inhibition, reactive inhibition in the low probability stop condition, go RTs of the certain and uncertain go trials were positively related between vocal and manual effector systems. This means that when one index of inhibition increased in one effector system, the equivalent index in the other effector system increased too, and vice versa. This finding was very interesting because it once more added evidence to the hypothesis that a similar generator controls these two response modalities. Interestingly, I did not find that reactive inhibition was positively related between manual and vocal responding in the high probability stop condition. It is very likely that this correlation did not exist for differences in the vocal reactive inhibition, as the vocal SSRT was not related to dysfunctional impulsivity either (described above). The correlation did not exist because, as I described later in this section, the SSRT of vocal responses are slower compared to manual responses. Based on the idea that response inhibition is controlled by the same central generator, it is likely that one of the final and more specific agents of the vocal effector system is the one making reactive inhibition slower. This means, that at some point in the inhibitory network, vocal reactive inhibition loses power.

6.3.6. Vocal reactive inhibition is less efficacious than manual reactive inhibition

The findings of the last experiment revealed this was possibly the case (chapter 5). Reactive inhibition was slower by 17 ms in vocal compared to manual responding, this difference only constituted a medium effect size. Possibly I did not obtain a statistical difference between effectors for SSRT in my first two experiments (chapter 2 and 3) because there was not enough statistical power. Having weaker reactive inhibition is consistent with TMS studies that report vocal relative to manual responding exhibit shorter CSPs (Jaberzadeh et al., 2008; Luschei & Goldberg, 2011; Ortu et al., 2008; Sowman et al., 2008) and with those studies that found the corticobulbar motoneurons (vocal muscles) have sparser or less potent autogenic inhibition reflex, stretch reflex, reciprocal inhibition and recurrent inhibition than the spinal motoneurons (for a review see Luschei & Goldberg, 2011).

It is more likely that reactive inhibition is less efficacious in the vocal relative to the manual system because of relatively fewer inhibitory interneurons in the final areas that control inhibition. As we described in introduction, it has been demonstrated that the final agent for manual response inhibition is located in the spinal cord (Stuphorn, 2015), it is very plausible that this final agent for vocal response inhibition is the one causing vocal reactive inhibition to be weaker than for the limb system. An evolutionary reason why this could be the case is that reactive inhibition in the limb system was important for avoiding injuries (e.g. such as falling a cliff) whereas the consequences for outright stop vocalisation may not have been a survival skill and vocal linguistic communication also evolved later. There may also be a case for the difference in control being related to the fact that the vocal apparatus shares a large proportion of its machinery with the masticatory system, a system that operates in a largely automatic manner. This could mean that higher cognitive control over the shared operations e.g. jaw excursion, is less well developed.

6.3.7. Go responses and proactive inhibition

Go responses for the vocal effector system are longer compared to manual responses, consistent with my findings (chapters 2 and 5) and with previous research (van den Wildenberg & Christoffels, 2010; Xue et al., 2008). Regarding proactive inhibition, I did not find significant differences in proactive inhibition across the vocal and manual effector systems in chapters 2 and 5. However, the results in chapter 3 showed that vocal SR used

less proactive inhibition compared to manual SR but were much more accurate with respect to the beat onset (vocal SR were +2 and +15 ms compared to manual SR (-82 and -7 ms). I interpreted that vocal responses rely more on impulse-control mechanisms that slow down the execution of the prepotent response(Duque & Ivry, 2009). However, further testings will be required to support this argument.

6.3.8. Limitations

One of the limitations I flag in this thesis is that the first two studies had a relatively small sample size. I improved this in my fourth and last study and found the statistics were very clear. This possibly prevented false negative findings by avoiding marginal significance (e.g. 0.07).

Another limitation is that we only investigated vocal responses for two simple utterances "I" and "O" which have predefined phonetic articulation. To generalise these results to the general patterns of vocal response inhibition, it would be very useful to investigate other phonetic sounds.

The tDCS experiment in chapter 1 only included two sessions: an anodal tDCS and sham. It would have been even more convincing to carry out a third session with a control site for example. However, we did have a pre-stimulation section, in which all conditions were investigated before any stimulation protocol was given, which was the control condition within session.

6.3.9. Implications and future directions

The finding that when a greater level of proactive inhibition is applied, reactive inhibition is enhanced is important because the results may provide insights into possible treatments of neuropsychological disorders such as ADHD and OCD where impulsive behaviours such as stopping an urge is sometimes too difficult. For example, it could be possible to train individuals in learning how to balance the trade-off between going and stopping using the SST. We could also train individual on increasing proactive inhibition, which may also be related to reduce impulsive behaviours.

We also present the finding that anodal tDCS enhanced reactive inhibition. This is also a potential tool to improve deficiencies in response inhibition and could be used by itself or

in combination with cognitive training. Given that tDCS is a non-invasive brain stimulation technique, its potential uses for young and older people are promising. For instance, it has been shown that anodal tDCS accelerates learning to identify concealed objects (Clark et al., 2012), improves language learning (Floel, Rosser, Michka, Knecht, & Breitenstein, 2008), word production in conductive aphasia (Dominguez et al., 2014; Fiori et al., 2010) and picture naming (Sparing, Dafotakis, Meister, Thirugnanasambandam, & Fink, 2008). However, it is encouraging to measure state-dependency effects to understand the effects of anodal tDCS (Horvath et al., 2015) such as time-of-day, day-of-week, duration of unique stimulation sessions, satiation-levels, energy-levels, amount-of-sleep, etc.

Disentangling functional and dysfunctional impulsivity could also potentially play a role in cognitive training on people with inhibitory deficiencies. Training focusing on understanding and implementing the more adaptive approach of impulsivity (functional impulsivity), favouring functional over dysfunctional impulsivity may help to reduce inhibitory deficiencies which in turn could help to reduce impulsive behaviours.

Finally, there are some intriguing findings about when and why participants used more proactive inhibition in some situations and in others not, irrespective of the number of stop-signals. For example, in two previous studies the distribution of stop-signals was 20% and 25% in Chikazoe, Jimura, Hirose, et al. (2009) and the first experiment of Jahfari et al. (2010) respectively, and proactive inhibition was 105.5 ms and 111.3 ms respectively. In my low probability stop condition, the distribution of stop-signals was 33.33% and proactive inhibition was 51 ms, similar to the third experiment in Jahfari et al. (2010) where it was 55 ms. Thus irrespective of the absolute probability of stop-signals, it seems that participants adopt more or less proactive inhibition. Further investigations should try to understand what are the cognitive processes that favour more or less proactive inhibition. One study has already provided some insight into this (Greenhouse & Wessel, 2013). The authors found that reactive inhibition was 39 ms faster when successful stopping was rewarded over responding. This difference was thought to be caused by enhanced preparation for stopping. From a therapeutic point of view, this could potentially help us to understand impulsive behaviours in which going may be weighted as more important and rewarding perhaps, than stopping.

6.4. Summary and conclusions

In this thesis, I focused on three main questions: (1) does a greater level of proactive inhibition enhance reactive inhibition in both manual and vocal responses? (2) Is response inhibition controlled by common central generators for both manual and vocal effector systems? (3) Are reactive and proactive inhibition less efficacious in the vocal compared to the manual effector system?

For the first question I found that indeed greater level of proactive inhibition, in both vocal and manual response modalities, enhanced reactive inhibition and that when proactive inhibition was not strongly evoked it did not have an effect on reactive inhibition.

For the second question, I found that vocal responding is controlled, at least in part, by a common central generators that control manual responding as I found the right VLPFC enhanced reactive inhibition in these two effector systems to the same degree; I also found that neuromagnetic markers of vocal response inhibition were characterised by similar ERF patterns as those that have been described for the manual effector system in younger and in older adults; that reactive inhibition was related to dysfunctional impulsivity in the low probability stop condition for both response modalities but that for the high probability stop condition, dysfunctional impulsivity was related with only manual reactive inhibition and not vocal; finally, I found that manual and vocal responding indexes were statistically correlated, that is, it was found that proactive inhibition, uncertain go RTs and certain go RTs were positively related between manual and vocal responding. This means than when one index increased in manual responses, it also increased for vocal responding. The only relationship that did not exist was between the two modalities for reactive inhibition, as the SSRT in manual responses did not relate with the SSRT in vocal responses.

For the final question, I found that reactive inhibition was less efficacious in the vocal relative to the manual effector system. For proactive inhibition, results showed that the vocal effector system uses less proactive inhibition than the manual system when stopping and synchronisation is required (chapter 3) but in the traditional SST, both manual and vocal effector system have comparable usage of proactive inhibition (chapters 2 and 5).

In summary, I have shown that greater levels of preparation enhance reactive inhibition. That response inhibition of both vocal and manual effector systems seems to be controlled by a common central generator but that the final agent in vocal responding, possibly weaker inhibitory interneuronal projections onto the motor neurons, may be the cause of slower reactive inhibition for the vocal system. Finally, that proactive inhibition is less used in vocal relative to manual responses when both response inhibition and synchronisation are measured.

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Appendix K: Ethics clearance for chapter 2 and chapter 3

MACQUARIE University

Leidy Castro-Meneses <leidy.castro-meneses@mq.edu.au>

Fwd: Ethics Application REF HE29MAY2009-R06600 - Amendment Approved

1 message

Paul Sowman <paul.sowman@mq.edu.au> 14 May 2013 at 13:41
To: Leidy Castro-Meneses <leidy.castro-meneses@mq.edu.au>

Hi Leidy. Please remove the highlighting. This was just to show what the amendments were. P

---------- Forwarded message ----------
From: **Paul Sowman** <paul.sowman@mq.edu.au>
Date: Thu, Mar 21, 2013 at 9:53 AM
Subject: Fwd: Ethics Application REF HE29MAY2009-R06600 - Amendment Approved
To: Ana Maiques <ana.maiques@starlab.es>

Hi Ana, below is the acceptance of my Human Ethics amendment to use TDCS. I have included the amendment app and our info and consent forms. Not sure if they're useful for you but...P

---------- Forwarded message ----------
From: **Ethics Secretariat** <ethics.secretariat@mq.edu.au>
Date: Fri, Feb 22, 2013 at 5:01 PM
Subject: Ethics Application REF HE29MAY2009-R06600 - Amendment Approved
To: paul.sowman@mq.edu.au

Dear Paul

RE: "Combined transcranial magnetic stimulation (TMS) and electroencephalography (EEG) studies of attention and cognitive control in the human brain" (REF: HE29MAY2009-R06600)

Thank you for submitting an amendment to the above application for review. The following amendment to this project, which was submitted on 4 February 2013, was approved by the Macquarie University Human Research Ethics Committee (Medical Sciences) (HREC (Medical Sciences)) at its meeting held on 21 February 2013.

1. To use a Transcranial current stimulator (tCS) which allows safe transcranial stimulation in the form of direct current stimulation (tDCS) transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS) and sham stimulation.

The following documents have been approved:

1. Participant information and Consent form, Version 9, February 2013.

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007).

The HREC (Medical Sciences) wishes you every success in your research.

Regards

Nicola Myton
Human Research Ethics Officer (Health)

--

Office of the Deputy Vice Chancellor (Research)

Ethics Secretariat

Research Office
Level 3, Research HUB, Building C5C
Macquarie University
NSW 2109

Ph: +61 2 9850 6848
Fax: +61 2 9850 4465

Email: ethics.secretariat@mq.edu.au

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Paul F Sowman
NHMRC Postdoctoral Training Fellow
ARC Centre of Excellence for Cognition and its Disorders (CCD)
MACQUARIE UNIVERSITY NSW 2109

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Paul F Sowman
NHMRC Postdoctoral Training Fellow
ARC Centre of Excellence for Cognition and its Disorders (CCD)
MACQUARIE UNIVERSITY NSW 2109

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2 attachments

TMS Amendment Request Jan2013.docx
40K

Info and Consent TMS_Feb13.docx
54K

Appendix L: Ethics clearance for chapter 4

MACQUARIE University

Leidy Castro-Meneses <leidy.castro-meneses@mq.edu.au>

Fwd: Approved- Ethics application- Johnson (Ref No: 5201300054)

1 message

Paul Sowman <paul.sowman@mq.edu.au> 19 July 2015 at 13:31
To: Leidy Castro-Meneses <leidy.castro-meneses@mq.edu.au>

I think you appended yourself to this one too. P
---------- Forwarded message ----------
From: **Ethics Secretariat** <ethics.secretariat@mq.edu.au>
Date: Thu, Mar 28, 2013 at 8:37 AM
Subject: Approved- Ethics application- Johnson (Ref No: 5201300054)
To: Dr Blake Johnson <blake.johnson@mq.edu.au>
Cc: Prof Stephen Crain <stephen.crain@mq.edu.au>, Dr Graciela Tesan <graciela.tesan@mq.edu.au>, Dr Jon Brock <jon.brock@mq.edu.au>, Dr Paul Sowman <paul.sowman@mq.edu.au>, Mr Fabrice Bardy <fabrice.bardy@students.mq.edu.au>, Mr Mehdi Parviz <mehdi.parviz@students.mq.edu.au>, Miss Wei He <wei.he5@students.mq.edu.au>, Mrs Joann Tang <huizhen.tang@students.mq.edu.au>

Dear Dr Johnson

Re: "MEG, EEG and fMRI Studies of adult cognition" (Ethics Ref: 5201300054)

Thank you for your recent correspondence. Your response has addressed the issues raised by the Human Research Ethics Committee and you may now commence your research.

This research meets the requirements of the National Statement on Ethical Conduct in Human Research (2007). The National Statement is available at the following web site:

http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/e72.pdf.

The following personnel are authorised to conduct this research:

Dr Blake Johnson
Dr Graciela Tesan
Dr Jon Brock
Dr Paul Sowman
Miss Wei He
Mr Fabrice Bardy
Mr Mehdi Parviz
Mrs Joann Tang
Prof Stephen Crain

NB. STUDENTS: IT IS YOUR RESPONSIBILITY TO KEEP A COPY OF THIS APPROVAL EMAIL TO SUBMIT WITH YOUR THESIS.

Please note the following standard requirements of approval:

1. The approval of this project is conditional upon your continuing compliance with the National Statement on Ethical Conduct in Human Research (2007).

2. Approval will be for a period of five (5) years subject to the provision of annual reports.

Progress Report 1 Due: 28 March 2014
Progress Report 2 Due: 28 March 2015
Progress Report 3 Due: 28 March 2016

Progress Report 4 Due: 28 March 2017
Final Report Due: 28 March 2018

NB. If you complete the work earlier than you had planned you must submit a Final Report as soon as the work is completed. If the project has been discontinued or not commenced for any reason, you are also required to submit a Final Report for the project.

Progress reports and Final Reports are available at the following website:

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics/forms

3. If the project has run for more than five (5) years you cannot renew approval for the project. You will need to complete and submit a Final Report and submit a new application for the project. (The five year limit on renewal of approvals allows the Committee to fully re-review research in an environment where legislation, guidelines and requirements are continually changing, for example, new child protection and privacy laws).

4. All amendments to the project must be reviewed and approved by the Committee before implementation. Please complete and submit a Request for Amendment Form available at the following website:

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics/forms

5. Please notify the Committee immediately in the event of any adverse effects on participants or of any unforeseen events that affect the continued ethical acceptability of the project.

6. At all times you are responsible for the ethical conduct of your research in accordance with the guidelines established by the University. This information is available at the following websites:

http://www.mq.edu.au/policy/

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics/policy

If you will be applying for or have applied for internal or external funding for the above project it is your responsibility to provide the Macquarie University's Research Grants Management Assistant with a copy of this email as soon as possible. Internal and External funding agencies will not be informed that you have final approval for your project and funds will not be released until the Research Grants Management Assistant has received a copy of this email.

Please retain a copy of this email as this is your official notification of final ethics approval.

Yours sincerely
Dr Karolyn White
Director of Research Ethics
Chair, Human Research Ethics Committee

--

Paul F Sowman

ARC DECRA Fellow

Department of Cognitive Science

Level 3, Room 3.824

Australian Hearing Hub
16 University Drive
Macquarie University, NSW 2109, Australia

T: +61 2 9850 6732 | **F:** +61 2 9850 6059
W: **Profile Page**
W: **MQU Stuttering Research Facebook Page**

MACQUARIE UNIVERSITY

Leidy Castro-Meneses <leidy.castro-meneses@mq.edu.au>

Fwd: New Personnel Approved - Johnson (Ref: 5201300054)

1 message

Paul Sowman <paul.sowman@mq.edu.au> 4 June 2014 16:26
To: Leidy Castro-Meneses <leidy.castro-meneses@mq.edu.au>

---------- Forwarded message ----------
From: **Blake Johnson** <blake.johnson@mq.edu.au>
Date: Wed, Jun 4, 2014 at 4:25 PM
Subject: Fwd: New Personnel Approved - Johnson (Ref: 5201300054)
To: Paul Sowman <paul.sowman@mq.edu.au>, Rebecca Gelding <rebecca.gelding@students.mq.edu.au>, Elena Pagliarini <e.pagliarini@campus.unimib.it>

---------- Forwarded message ----------
From: **Ethics Secretariat** <ethics.secretariat@mq.edu.au>
Date: Wed, Jun 4, 2014 at 4:24 PM
Subject: New Personnel Approved - Johnson (Ref: 5201300054)
To: Dr Blake Johnson <blake.Johnson@mq.edu.au>

Dear Associate Professor Blake,

Re: MEG, EEG and fMRI Studies of adult cognition

Thank you for your Amendment Request for the above project (received
28/5/2014). The following has been approved:

1. The removal of Dr Graciela Tesan and Ms Julia Shibaylo from the project.

2. The addition of the following personnel to the project:

Ms Leidy Castro-Meneses
Mr Andrew Etchell
Ms Rebecca Gelding
Ms Erin Martin
Ms Elena Pagliarini
Ms Margaret Ryan
Ms Yanan Sun
Dr Stan Tarnavskii

Please don't hesitate to contact the Ethics Secretariat if you have any
concerns.

Kind regards,

Michelle Thorpe

--
Blake Johnson
Associate Professor
Department of Cognitive Science
Level 3, S2.6 Australian Hearing Hub
Macquarie University
NSW 2109 Australia
T: +61 2 9850 6879
F: +61 2 9850 6059
blake.johnson@mq.edu.au

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Paul F Sowman
ARC DECRA Postdoctoral Fellow
Department of Cognitive Science
ARC Centre of Excellence for Cognition and its Disorders (CCD)
MACQUARIE UNIVERSITY NSW 2109

Appendix M: Ethics clearance for chapter 5

MACQUARIE University

Leidy Castro-Meneses <leidy.castro-meneses@mq.edu.au>

Approved- Ethics application Castles (Ref: 5201200035)

4 messages

Ethics Secretariat <ethics.secretariat@mq.edu.au> 27 February 2012 at 11:34
To: Prof Anne Castles <anne.castles@mq.edu.au>
Cc: Dr Britta Biedermann <britta.biedermann@mq.edu.au>, A/Prof Genevieve McArthur <genevieve.mcarthur@mq.edu.au>, A/Prof Sachiko Kinoshita <sachiko.kinoshita@mq.edu.au>, A/Prof Veronika Coltheart <veronika.coltheart@mq.edu.au>, A/Prof Robyn Langdon <robyn.langdon@mq.edu.au>, Prof Lyndsey Nickels <lyndsey.nickels@mq.edu.au>, Dr Melanie Porter <melanie.porter@mq.edu.au>, Dr Jon Brock <jon.brock@mq.edu.au>, Dr Lisa Yen <lisa.yen@mq.edu.au>, Dr Anina Rich <anina.rich@mq.edu.au>, A/Prof Mark Williams <mark.williams@mq.edu.au>, Dr Blake Johnson <blake.johnson@mq.edu.au>, Dr Kevin Brooks <kevin.brooks@mq.edu.au>, Ms Samantha Baggott <samantha.baggott@mq.edu.au>, Dr Paul Sowman <paul.sowman@mq.edu.au>, Mr Peter De Lissa <peter.delissa@mq.edu.au>, Miss Nora Fieder <nora.fieder@students.mq.edu.au>, Miss Tracey Anne Shaw <tracey.shaw@mq.edu.au>, Miss Regine Zopf <regine.zopf@students.mq.edu.au>, Mr Lars Marstaller <lars.marstaller@mq.edu.au>, Ms Bianca De Wit <bianca.de-wit@students.mq.edu.au>, Dr Eva Marinus <eva.marinus@mq.edu.au>, Ms Astrid Annemarie Zeman <astrid.zeman@students.mq.edu.au>, Mr Andy Christopher Etchell <andrew.etchell@students.mq.edu.au>, Mr Yao-Ching Chiu <yao-ching.chiu@students.mq.edu.au>, Mr Nathan Caruana <nathan.caruana@students.mq.edu.au>, Dr Serje Robidoux <serje.robidoux@mq.edu.au>, Mr Robert Malcolm Ross <robert.ross@students.mq.edu.au>, Mrs Leidy Janeth Castro Meneses <leidy-janeth.castro-meneses@students.mq.edu.au>, Ms Xenia Schmalz <xenia.schmalz@students.mq.edu.au>, Miss Trudy Geertruida Krajenbrink <trudy.krajenbrink@students.mq.edu.au>, Miss Anastasiya Romanova <anastasiia.romanova@students.mq.edu.au>, Dr Nicholas Badcock <nicholas.badcock@mq.edu.au>, Mrs Joann Tang <huizhen.tang@students.mq.edu.au>, Ms Mivsim Sinmaz <mevsim.sinmaz@students.mq.edu.au>, Miss Ivana Kihas <ivana.kihas@students.mq.edu.au>, Ms Jasmina Vrankovic <jasmina.vrankovic@students.mq.edu.au>, Ms Jennifer Zaman <jennifer.zaman@students.mq.edu.au>

Dear Prof Castles

Re: "Recognising, naming, classifying and understanding visually and/or auditorily presented stimuli (Student)" (Ethics Ref: 5201200035)

The above application was reviewed by the Human Research Ethics Committee at its meeting on 24-Feb-12 . Final Approval of the above application is granted, effective 27 February 2012, and you may now commence your research.

The following personnel are authorised to conduct this research:

Chief Investigator- Prof Anne Castles

Co-Investigators- A/Prof Genevieve McArthur, A/Prof Mark Williams, A/Prof Robyn Langdon
A/Prof Sachiko Kinoshita, A/Prof Veronika Coltheart, Dr Anina Rich, Dr Blake Johnson
Dr Britta Biedermann, Dr Eva Marinus, Dr Jon Brock, Dr Kevin Brooks, Dr Lisa Yen
Dr Melanie Porter, Dr Nicholas Badcock, Dr Paul Sowman, Dr Serje Robidoux
Miss Anastasiya Romanova, Miss Ivana Kihas, Miss Nora Fieder, Miss Regine Zopf
Miss Tracey Shaw, Miss Trudy Geertruida Krajenbrink, Mr Andy Christopher Etchell
Mr Lars Marstaller, Mr Nathan Caruana, Mr Peter De Lissa, Mr Robert Malcolm Ross
Mr Yao-Ching Chiu, Mrs Joann Tang, Mrs Leidy Janeth Castro Meneses, Ms Astrid Annemarie Zeman, Ms Bianca De Wit, Ms Jasmina Vrankovic, Ms Jennifer Zaman
Ms Mivsim Sinmaz, Ms Samantha Baggott, Ms Xenia Schmalz & Prof Lyndsey Nickels

NB. STUDENTS: IT IS YOUR RESPONSIBILITY TO KEEP A COPY OF THIS APPROVAL EMAIL TO SUBMIT WITH YOUR THESIS.

Please note the following standard requirements of approval:

1. The approval of this project is conditional upon your continuing compliance with the National Statement on Ethical Conduct in Human Research (2007).

2. Approval will be for a period of five (5) years subject to the provision of annual reports. Your first progress report is due on 27 February 2013.

If you complete the work earlier than you had planned you must submit a Final Report as soon as the work is completed. If the project has been discontinued or not commenced for any reason, you are also required to submit a Final Report for the project.

Progress reports and Final Reports are available at the following website:

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics/forms

3. If the project has run for more than five (5) years you cannot renew approval for the project. You will need to complete and submit a Final Report and submit a new application for the project. (The five year limit on renewal of approvals allows the Committee to fully re-review research in an environment where legislation, guidelines and requirements are continually changing, for example, new child protection and privacy laws).

4. All amendments to the project must be reviewed and approved by the Committee before implementation. Please complete and submit a Request for Amendment Form available at the following website:

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics/forms

5. Please notify the Committee immediately in the event of any adverse effects on participants or of any unforeseen events that affect the continued ethical acceptability of the project.

6. At all times you are responsible for the ethical conduct of your research in accordance with the guidelines established by the University. This information is available at the following websites:

http://www.mq.edu.au/policy/

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics/policy

If you will be applying for or have applied for internal or external funding for the above project it is your responsibility to provide the Macquarie University's Research Grants Management Assistant with a copy of this email as soon as possible. Internal and External funding agencies will not be informed that you have final approval for your project and funds will not be released until the Research Grants Management Assistant has received a copy of this email.

If you need to provide a hard copy letter of Final Approval to an external organisation as evidence that you have Final Approval, please do not hesitate to contact the Ethics Secretariat at the address below.

Please retain a copy of this email as this is your official notification of final ethics approval.

Yours sincerely

Dr Karolyn White
Director of Research Ethics
Chair, Human Research Ethics Committee

Samantha Baggott <samantha.baggott@mq.edu.au> 12 March 2012 at 13:44
To: Prof Anne Castles <anne.castles@mq.edu.au>, Dr Britta Biedermann <britta.biedermann@mq.edu.au>, A/Prof Genevieve McArthur <genevieve.mcarthur@mq.edu.au>, A/Prof Sachiko Kinoshita <sachiko.kinoshita@mq.edu.au>, A/Prof Veronika Coltheart <veronika.coltheart@mq.edu.au>, A/Prof Robyn Langdon <robyn.langdon@mq.edu.au>, Prof Lyndsey Nickels <lyndsey.nickels@mq.edu.au>, Dr Melanie Porter <melanie.porter@mq.edu.au>, Dr Jon Brock <jon.brock@mq.edu.au>, Dr Lisa Yen <lisa.yen@mq.edu.au>, Dr Anina Rich <anina.rich@mq.edu.au>, A/Prof Mark Williams <mark.williams@mq.edu.au>, Dr Blake Johnson <blake.johnson@mq.edu.au>, Dr Kevin Brooks <kevin.brooks@mq.edu.au>, Dr Paul Sowman <paul.sowman@mq.edu.au>, Mr Peter De Lissa <peter.delissa@mq.edu.au>, Miss Nora Fieder <nora.fieder@students.mq.edu.au>, Miss Tracey Anne Shaw <tracey.shaw@mq.edu.au>, Miss Regine Zopf <regine.zopf@students.mq.edu.au>, Mr Lars Marstaller <lars.marstaller@mq.edu.au>, Ms Bianca De Wit <bianca.de-wit@students.mq.edu.au>, Dr Eva Marinus <eva.marinus@mq.edu.au>, Ms Astrid Annemarie Zeman <astrid.zeman@students.mq.edu.au>, Mr Andy Christopher Etchell <andrew.etchell@students.mq.edu.au>, Mr Yao-Ching Chiu <yao-ching.chiu@students.mq.edu.au>, Mr Nathan Caruana <nathan.caruana@students.mq.edu.au>, Dr Serje Robidoux <serje.robidoux@mq.edu.au>, Mr Robert Malcolm Ross <robert.ross@students.mq.edu.au>, Mrs Leidy Janeth Castro Meneses <leidy-janeth.castro-meneses@students.mq.edu.au>, Ms Xenia Schmalz <xenia.schmalz@students.mq.edu.au>, Miss Trudy Geertruida Krajenbrink <trudy.krajenbrink@students.mq.edu.au>, Miss Anastasiya Romanova <anastasiia.romanova@students.mq.edu.au>, Dr Nicholas Badcock <nicholas.badcock@mq.edu.au>, Mrs Joann Tang <huizhen.tang@students.mq.edu.au>, Ms Mivsim Sinmaz <mevsim.sinmaz@students.mq.edu.au>, Miss Ivana Kihas <ivana.kihas@students.mq.edu.au>, Ms Jasmina Vrankovic <jasmina.vrankovic@students.mq.edu.au>, Ms Jennifer Zaman <jennifer.zaman@students.mq.edu.au>

Dear all,

As you can see from the email below, approval for this ethics application has been granted effective February 27, 2012. The ethics approval number for this application is 5201200035.

A requirement of this ethics approval is that an annual progress report is submitted each February. To complete this report, some information will be required from you regarding the studies you have run through the course of the year. Consequently, could you please advise me via email whenever you plan to commence testing for a study. I will then contact you before the progress report is due to collect the required information.

Finally, I have attached to this email:
1. A pdf copy of the ethics application that was submitted. Please ensure you are familiar with the details of this application. Note: in place of the contact details section, a list of named researchers has been included. These people are authorised to conduct research under this ethics clearance.
2. A word file of the approved Information and Consent form - the relevant sections marked in ***bold/italic*** must be completed before use. Please also send a copy of this completed consent form to me before you commence testing for a study.

If you have any questions or concerns, please contact me.

Thanks,
Sam

[Quoted text hidden]

[Quoted text hidden]

http://www.research.mq.edu.au/for/researchers/how_to_obtain_ethics_approval/human_research_ethics/forms

3. If the project has run for more than five (5) years you cannot renew approval for the project. You will need to complete and submit a Final Report and submit a new application for the project. (The five year limit on renewal of approvals allows the Committee to fully re-review research in an environment where legislation, guidelines and requirements are continually changing, for example, new child protection and privacy laws).