**Reactive and Proactive Response Inhibition in Neurodevelopmental Stuttering**

by

Anna Tendera

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**Abstract**

The present doctoral thesis focused on understanding the potential imbalance of inhibitory control in neurodevelopmental stuttering. Inhibitory control is defined as an ability to suppress behaviours that are no longer needed. Two types of inhibitory control were of particular interest - reactive inhibition, the ability to rapidly cancel an ongoing motor behaviour that is no longer required in reaction to a particular external cue; and proactive inhibition, the ability to anticipate the potential necessity of a withhold response and to make an intrinsically-generated decision to stop.

Using a behavioural reactive inhibition task (Study 1), we found that AWS showed a similar point of subjective equality, a psychometric measure of stopping effectiveness when compared to AWNS. The probability of stopping for AWS was also similar to AWNS. Similar probability of stopping for AWS and AWNS was evident in both speech and manual response conditions. Response times (RTs) were comparable across conditions. In the behavioural proactive inhibition task (Study 2), we found some subtle dysregulation in proactive stopping processes in AWS, which influenced the overall accuracy of stopping and decreased its probability in both speech and manual response conditions. However, PSE was similar in AWS and AWNS. Additionally, AWS tended to respond faster in failed STOP trials and in correct GO trials in manual and speech conditions. Finally, a faster RT of GO trials after a failed STOP trials (adjRT) was present in AWS, indicating faster RT adjustments after an error, but only when a manual response was required. In the electroencephalographic (EEG) reactive inhibition task (Study 3), we found that AWS had a shallower P3 amplitude in trials when a stop signal was presented compared to AWNS. AWS also showed an earlier P3 peak than AWNS. The N2

component, however, was not sensitive to group differences. The EEG results demonstrate the utility of P3 as a temporally precise neural marker of stuttering.

Taken together, these findings suggest that behavioural measurements in proactive inhibition were sensitive to stuttering, while reactive behavioural measurements showed that stopping in AWS was as effective as in AWNS. However, the ERP findings of stopping in AWS showed important latency and amplitude differences, consistent with the idea that the neural correlates of inhibition are dysregulated in AWS.

*Keywords*: stuttering, speech motor control, inhibitory control, stop-signal task, EEG/ERP

## Preface

This thesis is an original work by Anna Tendera. The research projects, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "The relationship between executive function and stuttering therapy outcome", Project ID Pro00080236, and from the Max Planck Institute (Germany), Project Name "EEG-Study on motor control in Adults who Stutter" ("Eine EEG-Studie zur Untersuchung der motorischen Kontrolle bei Erwachsenen, die stottern") Project ID Moko. Some of the research conducted for this thesis forms part of an international research collaboration, led by Dr. Torrey Loucks at the University of Alberta and Dr. Nicole Neef, being the lead collaborator at the Max Planck Institute, Germany. The technical procedures referred to in chapter 2 & 3 were designed by me, with the assistance of Dr. Loucks and Dr. Neef. No part of this thesis has been previously published.

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# CHAPTER 1.

## Introduction

Although speaking might seem like a basic ability, its complexity is particularly revealed when speech breaks down in communication disorders. Moreover, psycholinguistic and neuroimaging research has shown speech relies on an elaborated dynamic network of cognitive, sensorimotor and emotional systems (e.g., Smith & Weber, 2017; Metzger et al., 2017; Neef et al., 2017). During a speech event, speakers must quickly conceptualize a thought, formulate and articulate it in a smooth and cohesive manner. However, in the case of stuttering, speakers fail to produce a fluent narrative as their speech gets disrupted by sound prolongations, syllable repetitions, and silent blocks. Recent and ongoing research on stuttering is based on the assumption that stuttering is caused by a miscommunication in the central nervous system (e.g., Craig-McQuaide, Akram, Zrinzo, & Tripoliti, 2014; Etchell, Johnson, & Sowman, 2014; Fox, Ingham, Ingham, Hirsch, & Downs, 1996; Neumann et al., 2003; Toyomura et al., 2007). The default position of this body of research is that stuttering is a disorder of execution (e.g., Fox et al., 1996; Smith & Weber, 2017). Yet, this is still an open question. The punctuated starts and stops observed in stuttering have alternatively been hypothesized to involve an imbalance between mechanisms of execution and inhibition (Neef et al., 2016). This idea is actually not recent as one early theory posited that the signature of stuttering is "an interruption in the forward flow of speech, a holding back in a situation which calls for going ahead" (Sheehan, 1953, p. 27). Several recent behavioural and neurophysiological studies have followed up on this proposal and suggested that stuttering symptoms are provoked by an imbalance in the neural system that regulates inhibition (Neef et al., 2016, Markett et al., 2016; Ning et al., 2017; Neef et al., 2018). The current project will test whether inhibition is aberrant in adults who stutter (AWS)

based on current conceptions of inhibition that differentiate between rapid braking of initiated movements versus anticipatory suppression of movements. Behavioural and electrophysiological methods will be employed to identify and quantify inhibition of speech and manual movements. Before discussing these findings and offering hypotheses of inhibitory function in stuttering, we will describe stuttering and summarize recent advances in inhibition research as context.

### 1.1 A brief summary of stuttering

Stuttering is recognized as a genetically transmitted neurodevelopmental disorder (Yairi & Ambrose, 1996; Suresh et al., 2006). The core symptoms of stuttering are prolongations, repetitions and blocks that interrupt the progression of speaking (Yairi & Ambrose, 1996). The definition of stuttering is based on symptoms as the cause of stuttering is still unknown. A widely used definition of stuttering is "the flow of speech is disrupted by involuntary repetitions and prolongations of sounds, syllables, words or phrases as well as involuntary silent pauses or blocks in which the person who stutters is unable to produce sounds" (WHO, 2016). Stuttering almost always refers to the developmental form of stuttering, which is most common, as contrasted with rare stuttering-like symptoms following neurological insults such as stroke. The prevalence of stuttering is approximately 5% in children below the age of 6 years and ~1% in teenagers and adults. The symptoms typically begin between 30-36 months of age after children have already begun to acquire adult-like syntax (Cavenagh, Costelloe, Davis, & Howell, 2015; Yairi & Ambrose, 1999). Recent findings portray most children who stutter (CWS) and AWS experience anxiety and isolation that can limit social and vocational experiences (Alm, 2004; Blood, Blood, Bennett, Simpson, & Susman, 1994; Craig & Craig, 2003). Approximately 70% of children recover from stuttering within 1-2 years while the remainder continues to stutter chronically (Yairi & Ambrose, 1999). While the cure for stuttering is still unknown, many

individuals benefit from current forms of treatment but still experience stuttering symptoms at reduced rates (Yaruss, 2001).

A comprehensive theory of stuttering has not been offered and recent proposals vary from linguistic explanations to motor explanations (Ludlow & Loucks, 2003; Smith & Weber, 2017); although, the most recent explanations are inspired by neuroimaging reports of atypical brain structure and function (see for a review Belyk, Kraft, & Brown, 2015). Stuttering research has mostly focused on how language and speech are produced under the premise that stuttering is a disorder of execution as stated above (Ludlow & Loucks, 2003; Smith, 1989). Previous empirical observations point to a possible root of stuttering in the central nervous system and focus primarily on the disconnection at the level of speech motor planning and/or auditory motor integration (see for review Craig-McQuaide et al., 2014). There is also evidence for both phonological processing anomalies and basic speech production aberrations that have not been reconciled (e.g., Maxfield, 2017).

A large number of production studies showing associations between atypical production and stuttering remains important for building a theory of stuttering, but advancements in knowledge of neurological inhibition have prompted testing of cognitive function in people who stutter (e.g., Bosshardt, 2006; Howell, 2004; Eichorn et al., 2016; Chang et al., 2008). Previous theories propose that stuttering might be associated with an imbalance of attentional resources or of an overall executive function system. Bosshardt (2006) offered a cognitive load framework of stuttering, where he suggested that AWS experience greater attention-demanding processing in speaking. Such abnormally elevated level of executive control demands might create extra effort for AWS. Therefore, a failure to fulfill the demand in executive function resources can cause a breakdown in systems which depend on it and regulate motor, linguistic, cognitive, and socio-

emotional subsystems (e.g., Bosshardt, 2006; Heitman et al., 2004; Eichorn, Marton, Pirunsky, 2018; Doneva, Davis, & Cavenagh, 2018).

The hypothesis of the dysregulation of executive function has been offered in a number of previous theories, including the EXPLAN theory by Howell (2004). Howell (2004) proposed that stuttering is caused by a temporal imbalance between speech motor execution (EX) and speech planning (PLAN). He argued that asynchronous functioning of these processes causes a potential error in planning of linguistic sequences that result in attempts to repeat or blocking of an ongoing speech. Two earlier theoretical works on the stuttering cause proposed an articulatory planning problem. First, the Covert Repair Hypothesis by Postma and Kolk (1993) suggests that stuttering symptoms manifest a correction of a speech planning error caused by a delay at phonological preparation stage, also known as phonological encoding. Second, the Neuropsycholinguistic theory by Perkins, Kent, and Curlee (1991) also emphasize a possible error in planning of linguistic (lexical and phonological) and supralinguistic (e.g., speech rate and syllabic stress) processes and a factor of time pressure as important causal mechanisms in stuttering. Recent neurological studies have prompted testing of one of the core processes of executive function - inhibitory control in persons who stutter (Neef et al., 2011; Neef et al., 2016; Ning, Peng, Liu, & Yang, 2017; Neef et al., 2017; Metzger et al., 2017).

### 1.2 Inhibition

The intact function of the nervous system involves facilitating desired behaviours and thoughts while preventing undesired or intrusive behaviours. Most research in psychology and neuroscience has focused on actions that are carried out or the engagement of a given cognitive process, but balancing, preventing or terminating intrusive/competitive behaviours and thoughts is now recognized as having an essential contribution to brain health (Jahanshahi, Obeso,

Rothwell, & Obeso, 2015; Noorani, 2017; Noorani & Carpenter, 2017). Ideas of inhibition have been discussed since the origin of psychology, but systematic experimental studies are relatively recent (Bari & Robins, 2013). A general definition of inhibition is the ability to refrain, restrain or limit thoughts and behaviours, and broadly refers to the executive function mechanism that allows for prevention and braking as well as the neural system that mediates these outcomes. There is a general consensus that inhibition involves several active and constant brain processes mediated by more than one pathway originating in the prefrontal cortex (Aron, 2011; Jahanshahi et al., 2015). In this section, inhibition will be reviewed in terms of 1) how inhibition is classified; 2) the neural system of inhibition; 3) impaired inhibition; and, 4) inhibition of speech production.

Inhibition as an ability (or system) is differentiated from synaptic inhibition, which is the cellular process that limits the likelihood of action potentials and/or reflexes operating throughout the nervous system. Inhibition must incorporate synaptic inhibition, but it operates as a large-scale active brain system governing ongoing behaviours and cognition (Bari & Robbins, 2013). A discussion of physiological inhibition at the level of neurons, reflexes, and saccades is important for regulating behaviour but is beyond the scope of this review. Even though a complete and elaborated theory of inhibition has not been offered yet, classification systems have been proposed and several quantitative models are being tested and compared (e.g., Bari & Robbins, 2013; Noorani & Carpenter, 2017; Verbruggen & Logan, 2008).

**1.2.1 Classification of Inhibition.** The broadest classification of inhibition comes from the systematic review by Bari and Robbins (2013), who offer a dual map of inhibitory control that distinguishes behavioural inhibition and cognitive inhibition. Behavioural inhibition encompasses inhibition of impulsive choices (i.e. impulsive choice as an urge to obtain

immediate reward), flexibility/compulsivity (i.e. ability to re-learn a strong association between an action and its consequence), and response inhibition (Bari & Robbins, 2013). For example, behavioural inhibition helps to postpone immediate gratification in order to obtain a larger reward later (Kühn, Haggard, & Brass, 2009) and assists in changing plans and being flexible. The second type of inhibitory control is cognitive inhibition that strictly encompasses termination or suppression of mental processes (MacLeod, 2007). It facilitates a mental withholding that suppresses the execution of unwanted behaviours. An example of cognitive inhibition includes suppression of unpleasant, traumatic, or just irrelevant memories. Owing to its internal operation, cognitive inhibition is less tangible and more difficult to test, so it has received less attention than behavioural inhibition. However, the neural mechanisms that mediate cognitive inhibition are considered highly similar to the mechanisms of behavioural inhibition; therefore, theories and data related to behavioural inhibition apply to the cognitive context. Nonetheless, distinctions between behavioural and cognitive inhibition are pertinent particularly in cases of impaired inhibition. Poor impulse control or the inability to suppress urges reveals deficient behavioural inhibition while high distractibility typifies deficient cognitive inhibition. Although cognitive inhibition is usually studied separately from behavioural inhibition, most of the following discussion applies to both forms.

The next distinction is between volitional versus automatic inhibition (Jahanshahi et al., 2015; Verbruggen & Logan, 2008). Volitional inhibition is a slow, goal-directed, top-down process that uses cognitive resources to actively prevent unwanted behaviours. Volitional inhibition is highly interconnected with working memory and attention and is a sub-component of cognitive control (Kühn et al., 2009; Bari & Robbins, 2013). Automatic inhibition is a habitual process that begins as volitional inhibition but becomes automatic through repetition.

Minimal attentional resources are required for automatic inhibition and, thus, it is considered fast, inflexible and difficult to override. According to Verbruggen and Logan (2008), volitional inhibition is transformed into automatic inhibition through repetitive learning allowing faster but more stereotyped suppression. Volitional inhibition encompasses behavioural and cognitive inhibition while automatic inhibition is only defined for overt behaviour.

While the volitional/automatic inhibition distinction is conceptually appealing, it does not readily map onto the neural pathways of inhibition. A related but nuanced classification that can be related to neurophysiological mechanisms involves reactive and proactive inhibition. Reactive inhibition is defined as an ability to "suppress behaviours that are inappropriate, unsafe or no longer required" in reaction to a particular cue or signal (Chambers, Garavan, & Bellgrove, 2009, p. 632). A pertinent example is when a pedestrian starts crossing the road when the traffic light suddenly turns red. He/she needs to immediately inhibit entry into the intersection. Reactive inhibition thus helps us make a corrective 'braking' response to a rapidly changing environment. The short latency of this inhibition is considered to be mediated by a fast pathway, which is described in the section on the neurology of inhibition.

A number of researchers emphasize that reactive inhibition is relevant only to impulse control (e.g., Chambers et al., 2009; Aron, 2011). However, inhibition in the real world includes not only braking responses to a signal but also anticipating when stopping might be needed. This preventive/suppression mechanism has recently been called "proactive inhibition" (e.g., Aron, 2011; Bartholdy, Dalton, O'Daly, Campbell, & Schmidt, 2016; Jaffard et al., 2008) and enables us to tune inhibition to our goals and plans rather than reacting to an unexpected event. Proactive inhibition involves a preparatory step before the actual response because it includes the

possibility of both completing a response or withholding it (Aron, 2011). This form of inhibition has also been related to a distinct neural pathway described below.

### 1.2.2 Overview of neural mechanisms

**1.2.2.2 The fronto-basal ganglia model.** The neural systems regulating response inhibition depend on a complex cortical-subcortical circuit that appears to be predominantly localized within the right-hemisphere (Garavan, Hester, Murphy, Fassbender, & Kelly, 2006; Rubia et al., 2001). According to recent studies, the reactive and proactive systems have distinct cortical origins but converge on the same subcortical structures. Essentially, both forms of inhibition are initiated in the prefrontal cortex (PFC) and then project to subcortical structures, which in turn, project back to the cortex to brake or prevent actions and thoughts (Chambers et al., 2009; Aron, 2011). The subcortical structures are the nuclei of the basal ganglia forming the center for action facilitation and action cancellation in the brain (Jahanshahi, et al. 2015; Bari & Robbins, 2013).

The reactive system shown in Figure 1a originates within the right inferior frontal cortex (rIFC) in the ventral PFC and projects to the presupplementary motor area (preSMA). The cortical PFC signal is a cancellation command that counteracts action facilitation while the PreSMA modulates the cancellation signal (Aron, 2011; Bari & Robbins, 2013). The PreSMA then projects to the subthalamic nucleus (STN) of the basal ganglia, which in turn projects to the output nucleus of the basal ganglia (Globus pallidus internal or GPi). The GPi maintains inhibitory control over the thalamus, preventing the cortex from releasing an action or thought.

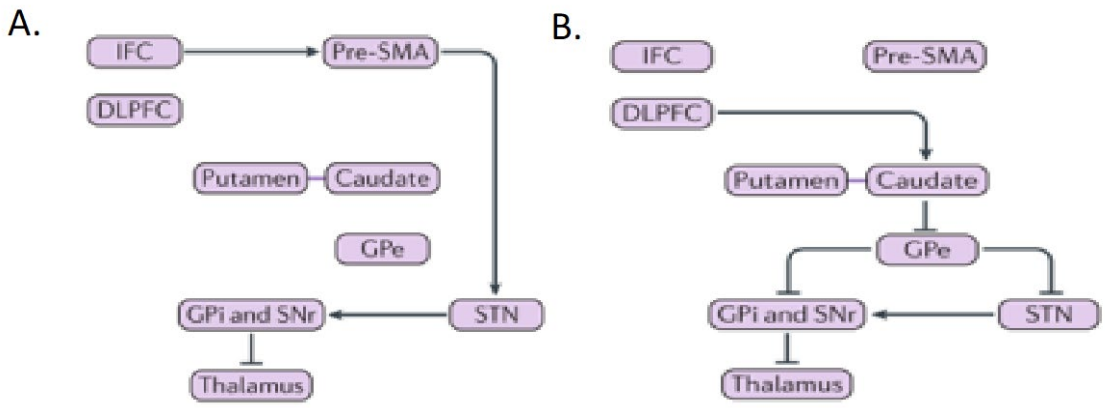


**Figure 1.1** The fronto-basal ganglia pathways mediating reactive (A) and proactive inhibition (B) (Jahanshahi et al., 2015).

This cortico-subthalamo-pallidal pathway is also called the hyperdirect pathway (Nambu et al., 2002) and is considered the fastest way to stop action facilitation (Jahanshahi et al., 2015; Soghomonian, 2016). Unlike the direct pathway which selectively releases an action, the inhibitory braking signal of the hyperdirect pathway functions globally to cancel all motor programs. The activation of the subthalamic nucleus (STN) through the hyperdirect pathway may occur "in less than 10 ms" (Aron, 2011, p.58).

Proactive inhibition requires the engagement of higher order cognitive control and is thought to originate in the dorsolateral prefrontal cortex (DLPFC) (Albert, López-Martín, Hinojosa, & Carretié, 2013; Aron, 2011). As per Figure 1b, the DLPFC projects to the striatum of the basal ganglia, then through the nuclei of the globus pallidus and onto the thalamus to prevent cortical facilitation. It is considered a slower form of inhibition and apparently comprises the indirect basal ganglia pathway making it the competing pathway for the direct basal ganglia pathway (Cui et al., 2013).

On the neurochemical level, motor and non-motor behaviours are released or inhibited through the dynamic and complex system of dopaminergic pathways (e.g., Nieoullon, 2002). The well-balanced regulation of dopaminergic neurons connecting cortical regions and the basal ganglia allows flexibility and stability on the one hand and suppression of unwanted behaviours /thoughts on the other. Effective inhibition relies on the exchange of dopamine, which is regulated by D1 and D2 presynaptic and postsynaptic receptor families (Cools, 2008). Inhibition is increased by the stimulation of dopamine receptor agonists, presynaptic D2 receptors. Otherwise, the D1 receptor family in the direct pathway is associated with behavioural release (Nieoullon, 2002).

Briefly, dysregulation of dopamine exchange is related to different clinical populations. For example, Parkinson's disease (PD) is characterized by selective dopaminergic neuronal degeneration. Previous studies show that hypodopaminergic state in the pars compacta of the substantia nigra (SNpc) results in the slowness of motor initiation and increased inhibition (Hisahara & Shimohama, 2011). In addition, growing evidence suggests dopaminergic pathology in children with attention deficit and hyperactivity (ADHD) (Heijtz, Kolb, & Forssberg, 2007; Hisahara & Shimohama, 2011). Motor overactivity, impulsivity and lack of attention are considered to be caused by hyperdopaminergic state (Solanto, 2002). More complex and dynamically changed dopamine alternations were observed in patients with Huntington's Disease (Cepeda, Murphy, Parent, & Levine, 2014). In early stages, hyperdopaminergic state causes hyperkinesia and decreased inhibition; whereas the late stages are characterized by hypokinetic movements and atypically strong inhibition (Cepeda et al., 2014). Dopamine regulation in people who stutter is considered in the section of "Inhibitory control in stuttering."

### 1.2.3 Models of inhibitory control

**1.2.3.1 Independent horse-race model.** Alongside the recent neurological advances in understanding inhibition, there have been attempts to model and quantify response inhibition (e.g., Verbruggen & Logan, 2009; Schall, Palmeri, & Logan, 2017; Dunovan et al., 2015). One of the most influential models of response inhibition is the horse-race model (e.g., Vince, 1948; Lapin & Eriksen, 1966; Ollman, 1973; Logan & Cowan, 1984; Verbruggen & Logan, 2009) that introduced the idea of a race between the two independent processes of action facilitation (a GO process) and action inhibition (a STOP process). These processes are modeled as independent random variables in constant competition. Successful inhibition or execution depends on the outcome of the race between the GO and STOP processes (Logan, 1994; Schall, Palmeri, & Logan, 2017). If the GO response "wins" the race or reaches a threshold faster than the STOP response, then a response will be executed. If the STOP response finishes before the GO response, the action will be canceled.

The independent race model introduces two central concepts (See Figure 1.2): the stop-signal delay (SSD) and a quantitative measure of response inhibition or stop-signal reaction time (SSRT). The horse-race model assumes that SSD directly affects the finishing time of inhibition. If the SSD occurs at long intervals following a GO signal (300 ms, 350 ms, 400 ms, etc.), stopping will likely be initiated too late or will fail to occur; in other words, a lower probability of successful inhibition. In contrast, a short SSD (0 ms, 50 ms, 100 ms, etc) allows for a higher probability of stopping. The SSD can be a fixed or dynamic measure of stop-signal timing. In the fixed method, the SSD has constant intervals typically ranging from 50 to 400 ms. If SSD is dynamic (also called *tracking procedure*), it follows an adaptive staircase procedure. After a successful inhibition, SSD is increased by 50 ms on the next STOP trial; whereas if inhibition

fails, SSD is decreased on the next STOP trial. The probability of successful stopping or failures to stop are determined for each SSD.

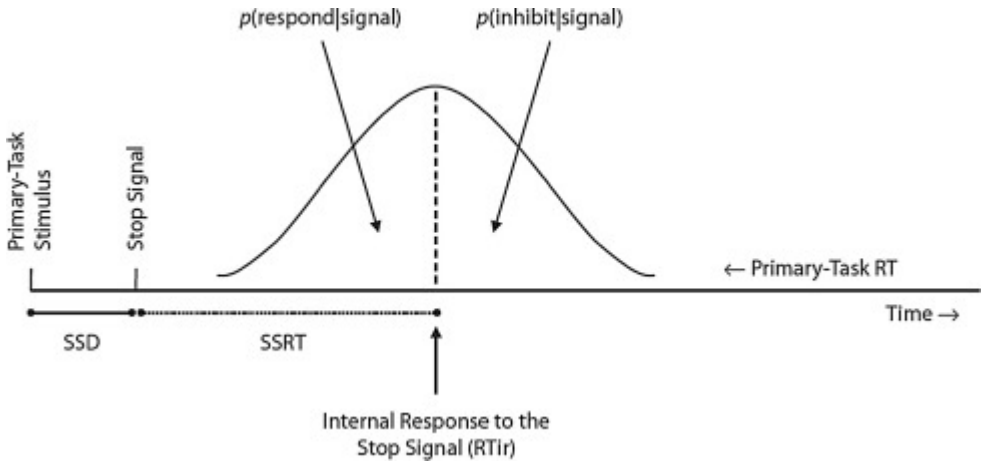


**Figure 1.2** The independent race model. Graphic representation of the assumptions of the independent race model, indicating how the probability of responding [p(respond/signal)] and the probability of inhibiting [p(inhibit/signal)] depend on SSD, the distribution of GO RTs and SSRT (Verbruggen & Logan, 2008).

The SSRT is an indirect quantitative index of the latency of the STOP process or how long it takes to inhibit a response (Verbruggen & Logan, 2008). SSRT is indirect because stopping/withholding cannot be measured overtly and is thus estimated indirectly as a function of GO trials. There are several different methods of estimating SSRT, but the most common approach is called the *Integration Method*, which assumes SSRT is a random variable. Basically, SSRT is estimated as the interval between when the stop-signal starts (i.e., SSD) and the point when inhibition is finished. In other words, it comes from the reaction time distribution of GO trials and the observed probability of responses for a certain SSD (Verbruggen & Logan, 2009). Other methods are used but the integration method more closely approximates how the SSRT is conceptualized (Verbruggen & Logan, 2009).

The independent race model has been widely adopted (Schall, Palmeri, & Logan, 2017); However, it has been criticized because it does not account for underlying neural processes

(Schall, Palmeri, & Logan, 2017) and why SSRT varies with the context of the SSD. For example, SSRT decreases if the experiment has a larger number of STOP versus GO trials and if the preceding trial was a STOP trial. To account for these limitations, an interactive race model has been suggested (Boucher, Palmeri, Logan & Schall, 2007).

**1.2.3.2 Interactive Race Model.** A better fit in comparison to the independent race model for the control dynamics in the oculomotor systems was demonstrated by the interactive horse-race model. Boucher et al. (2007) proposed that the complete independence of GO and STOP processes is not possible. Instead, the model presents GO and STOP processes as independent only at the initiation stage of the GO-STOP race. The GO process is initiated by the GO signal, typically in the beginning of the experimental trial, and activated after an afferent delay. The STOP mechanisms are activated only after the stop-signal and after an afferent delay (Verbruggen & Logan, 2008b). The interaction between two processes happens when both GO and STOP paths are active, especially near the end of a trial when response preparation is inhibited (Boucher et al., 2007; Schall et al, 2002; Verbruggen & Logan, 2009). Thus, the model presents GO and STOP paths as initially separate and then briefly interacting at the end of the decision-making process.

**1.2.3.3 Dependent Process Model (DPM).** A more adequate framework for manual responses and most relevant for the proposed study is the Dependent Process Model (DPM) offered by Dunovan et al. (2015). It is designed to account for the architecture of the corticobasal ganglia pathways. Similar to the interactive race model (Boucher et al., 2007), the model assumes that the action execution is a single variable that combines a decision to facilitate (direct pathway) or inhibit an action (indirect pathway). If more facilitative resources are engaged in the decision process than suppressive resources, the action execution reaches a decision boundary

and will be executed. To stop an already initiated motor action, the model offers a braking mechanism (hyper-direct pathway) that "is modeled as a latent competing signal" (Dunovan et al., 2015, p. 3). The effectiveness of braking depends on the state (timing) of the competition process between action facilitation and action suppression.

In contrast to other inhibition models, DPM recognizes a clear difference between the reactive and proactive inhibition processes. It argues that reactive and proactive inhibition types are distinctive but interacting processes where reactive inhibition relies on the state of the execution signal (e.g., various length of SSDs) and proactive inhibition depends on modulation of executive process (i.e., when the No-GO decision does not reach the decision threshold). In other words, reactive inhibition involves active cancellation of a response whereas proactive inhibition is a decision not to initiate a response (see Dunovan et al., 2015). In summary, Dunovan et al. (2015) emphasizes that effective response inhibition is a complex process which relies on both convergent but distinctive reactive and proactive inhibitory mechanisms. Similar to the other models, SSD is a fundamental variable used to characterize STOP and GO processes. However, DPM does not measure SSRT, instead it relies on a psychometric measure to evaluate stopping effectiveness (Point of Subjective Equality, PSE) that is calculated by fitting a sigmoid curve on the data with observed probability of stopping across the SSDs. PSE is the point at which the psychometric curve crosses the 50% probability of successful stopping and is reported in ms. The DPM assumptions are followed in this proposal to estimate reactive and proactive inhibition in AWS.

### 1.2.2 Inhibition of Verbal and Manual Responses

The proposed studies of verbal and manual inhibitory control in stuttering are motivated partly by the differential difficulty that people who stutter show for speech. While speech

production and skilled manual actions share important similarities in terms of how the cortex plans and organizes coordinated gestures, they differ in other ways as speech involves different brain regions, has particular laterality, uses different effectors and is organized around different goals. However, these differences are related to movement execution while the relationship between inhibition of manual versus speech systems could be more similar. In fact, recent inhibition studies posit that all motor activities, including hand movements, arm movements, leg movements, and verbal gestures, are potentially subject to a general or global inhibitory system, i.e., inhibition might not be effector or system specific (Xue et al., 2008; Wessel et al., 2016; Etchell, Sowman, & Johnson, 2012; Ghahremani et al., 2018). Yet, most of our current knowledge of inhibition still comes from manual tasks, as this effector is presumably easier to study (Xue et al., 2008). Manual inhibition will be reviewed first followed by verbal inhibition to provide a context for studying both effector systems.

Inhibitory control has been investigated across various fine and gross motor gestures of the arm and hand (Henry & Harrison, 1961; Logan, 1982; De Jong, Coles, & Logan, 1995; Morein-Zamir et al., 2010), but most studies have used fine manual movements such as typing and key presses with the index finger (e.g., Chambers et al., 2006; Verbruggen, Liefooghe, & Vandierendonck, 2004; White et al., 2014; Verbruggen & Logan, 2008). The pertinent patterns of inhibition shown in these studies generally come from the GO/No-GO (GNG) and stop-signal task paradigms.

In a classic GNG paradigm, participants typically asked to complete two trial types. They either need to respond on a frequently occurring GO stimulus or withhold a respond on an infrequently occurring No-GO stimulus. The GNG paradigm has shown that the proportion of failures to inhibit manual movements (i.e., false alarms) increase as the number of No-GO trials

decreases in proportion to GO trials. The dependent variable of the GNG paradigm is the false alarm rate that is generally thought to require braking through the hyper-direct pathway; the stop-signal task paradigm also shows patterns of false alarms, but in addition, permits prediction of inhibition time (SSRT). In the stop-signal task, the delay of stop signal (or SSD) presentation varies from short to long latencies. For short SSD's, the proportion of false alarms is low and increases as SSD's become more delayed. To calculate inhibition time, the reaction time (RT) of GO trials must first be measured. Across these studies, manual RT is faster when exclusively GO trials are presented versus when GO and STOP trials are intermixed. For example, Rieger and Gauggel (1999) reported the manual RT of exclusive GO trials was 485 ms (SD = 48) compared to 507 ms of intermixed GO trials (SD = 57). Second, the distribution of manual RT estimates of GO trials is sampled to predict SSRT (the stopping time of movements, see above). Across studies, SSRT ranges from 200-300 ms (Band et al., 2003), which is faster than the RT of GO responses. SSRT is also faster for the dominant hand than the nondominant hand (Chambers et al., 2006).

Manual inhibition remains the most common approach for studying inhibitory control in neurological and psychiatric disorders. Children with attention-deficit/hyperactivity disorder (ADHD) display a marked deficiency in inhibition shown by prolonged and variable SSRTs and excessive false alarms (Jennings et al., 1997; Lipszyc & Schachar, 2010; for a review see Nigg, 2001). The consistency of these inhibition deficits has led to use of inhibition as a diagnostic feature of ADHD (Lipszyc & Schachar, 2010). Manual response tasks have been employed to test inhibition in other neurological and psychiatric disorders such as Tourette's syndrome, Huntington's disease, Parkinson's disease, and cravings (Sánchez-Carmona et al., 2016). Bannon et al. (2002) showed that patients with obsessive-compulsive disorder (OCD) made more errors

on a manual GNG study. Patients with substance abuse disorders (e.g., abstinent cocaine-dependent) had slower SSRT and more false alarms than control participants (Li et al., 2006).

Verbal inhibition in either healthy individuals or in disorders is under-studied relative to manual inhibition as only 5 studies were identified in the literature (Xue et al., 2008; Wessel et al., 2016; Etchell, Sowman, & Johnson, 2012; Ghahremani et al., 2018; Ning et al., 2017). However, the need to refrain from speaking or interrupt speaking intuitively seems as critical as manual inhibition. For example, typical speakers are able to halt a speech event when a conversation partner is about to speak (Etchell, Sowman, & Johnson, 2012) or when a speaker wants to revise a message. Even though efforts to investigate speech inhibition as a finely-tuned system are still needed, the small number of inhibitory studies of both manual and speech systems have taken a different direction.

These investigations point to a general inhibitory mechanism that crosses effector systems, as opposed to effector specific inhibitory mechanisms (Xue et al., 2008; Badry et al., 2009; Majid et al., 2011; Cai et al., 2012; Wessel et al., 2013; Wessel et al., 2016). Firstly, Xue et al. (2008) found that inhibition of a manual task, letter naming task and pseudoword production consistently activated the same rIFC opercular/insula region. The SSRT results corroborated the proposal of a general inhibitory mechanism because strong correlations between speech and manual responses were found ($r = .57$, $p < .03$ for Manual and Letter Naming; $r = .55$, $p < .035$ for Manual and Pseudoword naming (Xue, Aron, & Poldrack, 2008). Secondly, in two recent STN LFP recording studies of PD patients (Wessel et al., 2016; Ghahremani et al., 2018), spectral analysis of spoken and manual responses showed a consistent increase in beta [13-30 Hz] power on successful stopping in comparison to false alarms (Wessel et al., 2016; Ghahremani et al., 2018). Second, alpha power peaked after the GO signal and frequency was

elevated in response to the braking of spoken and manual responses. Thirdly, a TMS/EMG study by Cai et al. (2012) showed that vocal inhibition affects corticospinal excitability in the task-irrelevant hand. Similarly, Majid et al., 2011 observed a decrease in corticomotor excitability of the task-irrelevant leg using TMS while subjects had to rapidly stop a hand motion. In conclusion, more research on verbal inhibition is needed, but, converging studies point to a common suppression system that is not effector specific. This proposal needs to be explored in the context of disorders that are localized to specific effector systems such as focal dystonias and stuttering, in which imbalances in inhibition are proposed. It remains possible that different effector systems have varying susceptibility to imbalances in inhibition that could be expressed as focal disorders but do not involve systemic inhibitory disease.

### 1.3 Inhibitory control in stuttering

Inhibitory control dysfunction in people who stutter has been proposed by several researchers, but systematic work on this topic is relatively new (e.g., Fox et al., 1996; Eggers et al., 2010; Markett et al., 2016; Metzger et al., 2017). Although the internal mechanisms of a compromised inhibitory system are still not clear, findings obtained from speech and non-speech related tasks point to a possible dysregulation in the inhibitory control system resulting from aberrations in behavioural, neurological and neurochemical levels. The hypothesis of dysregulation in inhibitory control is supported by behavioural, neuroimaging and electrophysiological studies.

**1.3.1 Behavioural studies.** Most importantly, behavioural studies indicate ineffective inhibitory control in people who stutter. Markett et al. (2016) showed that adults who stutter (AWS) have slower SSRT on a manual stop-signal Task (SST). The SSRT of AWS was significantly longer (SSRT ~ 350 ms, SEM ~ 40 - estimated from Figure 1) compared to adults

who do not stutter (AWNS) (SSRT ~ 255 ms, SEM ~ 15 - estimated from Figure 1), which suggests that AWS have slower braking of reactive manual responses (Markett et al., 2016). In contrast, no differences in accuracy of STOP trials between AWS and AWNS were found (M = .6157, SEM = .03 in AWNS; M = .6094, SEM = .04 in AWS), and there were no group differences in GO RT (M = 695.28 in AWNS, SEM = 28.1; M = 758.33, SEM = 25.1 in AWS). These findings demonstrate that stuttering might be associated with motor action cancellation ineffectiveness and not motor action initiation.

A growing number of behavioural studies of children who stutter (CWS) have shown evidence of compromised inhibitory control and atypical self-regulation. In these manual GNG tasks, CWS revealed increased impulsivity and a less controlled response style, i.e. less able to adapt their response style. CWS failed to withhold a response more often and showed more premature responses than CWNS (Eggers et al., 2013; Eggers & Jansson-Verkasalo, 2017). Similar to adults, CWS and CWNS showed no differences between groups in RT of GO trials (Eggers et al., 2013; Eggers & Jansson-Verkasalo, 2017).

An additional study by Anderson and Wagovich (2017) expanded the investigation of inhibitory control beyond the traditionally studied exogenously triggered response to test CWS on explicit and implicit verbal response inhibition. In keeping with previous findings, they also revealed less effective inhibition in CWS in suppressing a dominant response while executing a conflicting response in the explicit verbal inhibition tested with the grass–snow task (Carlson & Moses, 2001), as well as the implicit verbal response inhibition tested with the baa–meow task. In particular, the findings indicated that CWS showed a slower RT and lower accuracy of inhibition and they required more practice than CWNS. The study sustains the suggestion that CWS might have an ineffective mechanism of selection of competing lexical representations and

inhibition of the ones that are no longer wanted during speech planning and/or speech monitoring.

The findings from the developmental studies, however, do not uniformly support the hypothesis of increased impulsivity and less effective inhibitory control as an index of stuttering. Harrewijn et al. (2017) suggest that CWS can be less impulsive and more inhibited in comparison to CWNS. In the experiment on voluntary inhibitory control in an SST, CWS showed a faster SSRT (M = 265, SD = 13.54 in CWS; M = 289, SD = 12.43 in CWNS) and decreased motor and cognitive impulsivity on the BIS-11 questionnaire. Finally, Eggers, De Nil, & Van den Bergh (2018) challenged the previous reports and showed no differences in SSRT (M = 594, SD = 114 in CWS; M = 604, SD = 123 in CWNS) and similar accuracy of stopping between CWS and CWNS based on their performance in a manual task with an online adaptable SSD. CWS showed faster RT in GO and STOP trials, which led to shorter SSD due to the online adaptable staircase-tracking procedure. This finding contrasts previous studies by suggesting that CWS were as efficient in exogenously triggered response inhibition as CWNS.

**1.3.2 Neurological studies.** Recent neuroimaging studies report ineffective inhibitory control in people who stutter. An fMRI study by Metzger et al. (2017) employed a manual GNG task that indicated two important differences involving the activation of the Substantia Nigra (SN) and the globus pallidus (GP) in AWS. First, they found a positive correlation between stuttering severity and activity in SN during the anticipation phase of manual responses. They report possible aberrations in the indirect inhibitory pathway of AWS involving increased connectivity between the cortex and the GP. In sum, the authors predicted an increase in inhibitory activity in the fronto-basal network responsible for speech production in AWS. One

limitation of this study is that behavioural differences in inhibitory control were not found between the groups.

In addition, the authors offered a simplified connectivity model of the basal ganglia for AWS to illustrate their prediction of how inhibition is altered in stuttering. Briefly, altered connectivity between the cortex and external segment of the globus pallidus (GPe) is predicted to cause stuttering disfluencies. These predictions cannot be evaluated directly in the current proposal, but predictions of GPe function are important, as this structure is the gatekeeper of inhibitory control.

In a follow-up study, Neef et al. (2017) combined diffusion tensor imaging (DTI) and fMRI to investigate white matter connectivity in brain regions activated by a task that required active inhibition of speech. Their findings showed that stuttering severity in 31 AWS correlated with both hyperactivity in right frontal brain regions during the active inhibition task and the strength of their white matter connections in cortical-subcortical pathways. Neef et al. (2017) suggested that AWS have stronger connections within the cortical-subcortical pathways that mediate cortically driven inhibition. They proposed AWS have an overly active global response suppression mechanism in comparison to AWNS. Overactive global suppression might interfere with speech motor program selection in AWS to potentially cause stuttering disfluencies.

The hypothesis that stuttering is associated with a dysregulation in motor inhibition has been supported by Harrewijn et al (2017) in their fMRI study on CWS. CWS were instructed to play a rolling marble task. Their finding showed less motor inhibition and decreased SSRT in CWS than in CWNS. At the neural level, CWS showed a decreased activation in the rostral cingulate zone (RCZ) activated during voluntary action selection in CWS. This effect was even stronger for CWS with higher stuttering severity and had a significant correlation with SSRT and

impulsivity ratings. Their findings reflect a domain general difficulty with action selection and self-control extending across verbal and non-verbal domains.

Non-invasive brain stimulation methods have been also employed in adults to assess the facilitation-inhibition balance in stuttering (Neef, et al., 2011). The main outcome of a transcranial magnetic stimulation study was reduced short-term intracortical inhibition in the right hemisphere along with reduced intracortical facilitation shown bilaterally. This process may lead to compromised inhibitory control over movement prevention and suggests a possible imbalance in inhibitory-facilitatory circuit underpinning tongue motor control in AWS.

The timing of inhibitory related electrophysiological responses in persons who stutter has been compared to fluent controls in two event-related potential (ERP) studies that measured N2 and P3 waves in the context of inhibition tasks. The N2 wave, more common in the No-GO stimulus, represents the identification of a mismatch between competing GO and STOP responses (Luck, 2014). The P3 wave is typically viewed as a neural marker of the response inhibition process (Sur & Sinha, 2009; Wessel & Aron, 2015). The amplitude of P3 is considered to be modulated by attentional resource allocation (i.e., the larger amplitude is associated with the greater allocation of resources and better performance (Polich, 2007), while its latency (onset) is typically associated with speed of stimulus categorization and processing speed (Sur & Sinha, 2009). Wessel and Aron (2015) state the peak timing of the P3 is a reliable "predictor for the speed and success of the response inhibition process" (Wessel & Aron, 2015, p. 473), and P3 anomalies have been identified in Parkinson's disease (e.g., Stanzione et al., 1998). The first ERP study of stuttering employed a cued color-naming GNG task (Ning et al., 2017); it showed significantly decreased P3 amplitude in AWS. As this was a speech task, this P3 anomaly might point to aberrations in inhibition of planned speech responses in AWS. Behaviourally, no

differences between AWS and AWNS were revealed (Reaction Time (RT): M = 576 ms (SD = 77) in AWS; RT = 567 ms (SD = 100) in AWNS; False Alarms: M = 5.33 (SD = 2.13) in AWS; M = 4.60 (SD = 2.61) in AWNS).

A second ERP study by Piispala et al. (2016) tested N2 and P3 in CWS during a visual GNG task. The major difference between the groups was a longer P3 latency for GO trials in AWS, which might point on some aberration in stimulus evaluation and response selection. No difference in the amplitude of these two ERP's were found and also no behavioural differences in No-GO responses or GO RT. Additional analysis on the same data by Piispala et al. (2017) and Piispala et al. (2018) revealed smaller (less positive) mean amplitude for both GO and No-GO trials, which might arise as a post-effect after a prolonged and asymmetrical N2 component. Additionally, they reported that CWS exhibited less alpha activity than CWNS which might indicate problems with stimulus evaluation and response selection as well as more general atypical function of attentional gating.

There has also been a report on inhibitory function aberrations in AWS combining TMS and EEG methods (Busan et al., 2019) in which the supplementary motor area (SMA), commonly thought to be related to planning/execution of movements, was stimulated during rest. The findings favored the association of stuttering with the inhibition pathways. They showed lower activity of neural sources in early time windows in SMA, in the inferior frontal cortex and inferior parietal lobule in the left hemisphere, and the opposite dynamics in later time windows (i.e. from 260-460 ms) in temporal/premotor regions of the right hemisphere. Busan et al. (2019) postulated that deviant function of the inhibitory control might play a key role in ineffective neural dynamics in terms of timing of motor processes in which timing errors can provoke disfluencies.

Finally, there is some indication of altered dopamine uptake in AWS that implicates the inhibitory system because dopamine is the critical neurotransmitter within the basal ganglia. The FDOPA PET study by Wu et al. (1997) suggested that AWS might have overactive mesocortical dopamine tracts implying that dopamine uptake or higher dopamine levels in the basal ganglia could be related to stuttering. Interestingly, an increase in stuttering symptoms was evident in one AWS when taking levodopa, which is converted to dopamine (Anderson et al., 1999). In contrast, D2 receptor blockers such as haloperidol, olanzapine, and risperidone increased speech fluency in AWS (Lavid et al., 1999; Maguire et al., 2004). Such an augmented effect on speech might be reached due to the decreasing strength of inhibition of planned motor responses (Metzger et la., 2017). An early treatment study with apomorphine (a mixed D1-D2 receptor agonist) also demonstrated a positive effect on speech fluency in AWS (Burns et al., 1978). This finding might infer that stimulation of D1 receptors helps to improve stuttering symptoms, similar to blocking D2 receptors. Clearly, the directionality and effectiveness of the dopamine antagonists is complicated and controversial despite these interesting preliminary findings. Controlled and large-scale pharmacological studies are still needed to unravel the role of dopamine and its associated receptors in stuttering.

In summary, there is preliminary behavioural and neurological evidence for atypical inhibitory function in stuttering, but not all studies have found inhibitory differences and the studies have several limitations. First, the GNG task does not provide a quantitative measure of inhibition (Aron, 2011). The absence of a response in a No-GO trial could either be the braking of an initiated response or a decision to omit a response, or even failure to response can happen due to inattention which coincidentally happens on a No-GO trial. Second, previous studies have not measured speech responses in inhibition paradigms, which are more relevant because

stuttering symptoms are primarily verbal. Third, reactive and proactive inhibition need to be contrasted in the same individuals who stutter in order to assess the full inhibitory system. We propose a comprehensive behavioural study to address these gaps by using recently developed paradigms to test reactive and proactive inhibition in the verbal and manual domains. An EEG experiment is proposed to test if the N2-P3 complex associated with inhibitory responses is aberrant in AWS.

## Hypotheses

The novel proposal to be tested in this project is that persons who stutter manifest dysregulation of inhibitory control in both reactive and proactive contexts. Deficient inhibitory control of speech production in stuttering could involve an imbalance between inhibitory and excitatory pathways that perturbs speech motor planning (Neef et al, 2011; 2015) and disrupts the forward flow of speech. Although inhibitory control will only be measured for manual and vocalization tasks in the proposed studies, it will lead to future studies of inhibition during speech production. The following hypotheses are proposed:

(1) AWS will demonstrate less effective inhibition (measured in PSE) on reactive manual and verbal tasks - Study 1 & Study 2;

(2) AWS will demonstrate lower observed probability of stopping on reactive and proactive inhibition tasks – Study 1 & Study 2;

(3) The amplitude of the N2 and P3 event related potentials will be decreased in AWS for reactive manual inhibitory responses - Study 3.

(5) The peak of the P3 event related potential will be delayed in AWS for reactive manual inhibitory responses - Study 3.

# CHAPTER 2

## Reactive and proactive stopping in persistent developmental stuttering

### 2.1 Introduction

Stuttering is a hereditary neurodevelopmental disorder (Yairi & Ambrose, 1996; Suresh et al., 2006) affecting approximately one percent of the adult population worldwide. The incidence of stuttering is approximately five percent in children below the age of six years, and around 70% recover from stuttering within one to two years (Yairi & Ambrose, 1999, 2013). The motor signs of stuttering are sound prolongations, sound and syllable repetitions, and speech blocks which are commonly accompanied by concomitant movements, such as facial grimacing and head and limb movements (Bloodstein & Ratner, 2008). Furthermore, negative experiences with oral communication may lead to anxiety and social isolation in children and adults who stutter (AWS) (Alm, 2004; Craig & Craig, 2003). Consequently, depending on severity, stuttering can significantly alter a person's lifestyle and decrease their overall quality of life (Koedoot et al., 2011).

It is still unknown what causes stuttering, but the consensus view involves an abnormal timing of neuronal signals in language regions of the brain (Busan et al., 2019; for a review see Etchell et al., 2014). For example, mistiming of neuronal communication in the left superior longitudinal fasciculus that connects frontal, parietal, and temporal cortical areas could disrupt speech processing (Neef, Anwander, & Friederici, 2015). Other recent investigations have emphasized irregularities in brain networks connected via the left and right frontal aslant tracts (Kronfeld-Duenias et al., 2014; Duffau et al., 2014). The frontal aslant tract connects the inferior frontal gyrus with the supplementary motor area, and supports the voluntary control of motor processes, including the initiation and termination of actions. The operations supported by the

aslant tracts interact with the basal ganglia as part of 'cortico-basal ganglia-thalamo-cortical loops' that apparently mediate coordinated inhibition of movements, including speech (Ghahremani et al., 2018). It appears that people who stutter (PWS) display increased activity in the right hemisphere inhibitory network during speech tasks (for a review see Belyk, 2014; Budde, 2014; Brown, 2005), and anatomical connection strength scales positively with stuttering severity (Neef et al., 2018). These findings suggest inhibitory processes, which govern initiation and termination of speech movements, are amplified in stuttering. It's still unclear if and how overactive inhibition is causally related to stuttering, but potential aberrations of inhibitory function are theoretically interesting (Neef et al., 2018).

A series of behavioural investigations of inhibition in stuttering have been reported in parallel with the neurological studies and proposals. The behavioural studies of response inhibition in stuttering have employed GO/No-GO tasks (GNG) and Stop-Signal Tasks (SST) (Verbruggen & Logan, 2008). The GNG paradigm is typically used to measure failures to inhibit a response (i.e., false alarms) in which a low (or high) false alarm rate is interpreted as less efficient inhibitory control and increased impulsivity. The false alarm rate is generally thought to require a rapid response suppression. Evidence for atypical inhibitory control in stuttering has been supported in two GNG studies in which children who stutter (CWS) showed elevated false alarm rates compared to children who do not stutter (CWNS) (Eggers et al., 2013; Eggers & Jansson-Verkasalo, 2017). High false alarm rates are considered to display increased impulsivity or a less controlled response style. However, the GNG task used by Piispala et al. (2016; 2017) did not elicit behavioural differences in stopping style among CWS, even, unusual aspects of inhibition were by the event-related potential (ERP) results. The only comparable GNG task of

adults who stutter (AWS) that used a cued color-naming task (Ning et al., 2017) did not identify atypical false alarm rates.

Another well-established experimental paradigm to test response inhibition is the reactive SST. Patterns of GO/STOP trials are also important, but in addition, the STOP signal reaction time (SSRT) is estimated. The SSRT is a quantitative prediction of how long it takes to inhibit a movement. To estimate SST, the STOP-Signal delay time (or SSD) presentation is varied from short to long latencies. For short SSDs, the proportion of successful STOPs is lower but increases as SSD's become longer. Essentially, the proportion of successful stops is multiplied by the unsuccessful stop reaction times at different SSDs to give the SSRT. So far, only two studies have used the SST to examine stuttering. In the most influential, Markett et al. (2016) demonstrated that AWS have slower SSRT on a manual task, suggesting slower braking of reactive manual responses. Differences in the accuracy of stopping or reaction times on GO trials were not found compared to adults who do not stutter (AWNS). More recently, Eggers et al. (2018) reported that CWS do not have longer SSRTs or a higher frequency of missed stops than CWNS.

We consider the strongest evidence for unusual inhibitory function in stuttering comes from the Markett et al (2017) study because the SST allows for quantitative measures of response braking time. The evidence for inhibitory function aberrations in children is also compelling but has been inconsistent. Furthermore, inhibitory control is a complex process that may not be adequately revealed by relatively simple GNG tasks measures. We also selected to begin our study of inhibition with adults as certain children may be in the stuttering recovery trajectory.

Although the SSRT is widely used, we selected a recent variation of the SST that provides more direct estimates of the probability of stopping per SSD. Essentially, a psychometric function is generated to estimate the point of subjective equality or PSE, which is the 50% probability of successful stopping and is reported in milliseconds (see Methods for details). We also combined manual and verbal tasks in this study to overcome limitations of previous studies that did not measure inhibitory control with speech tasks. This is relevant because stuttering only occurs during speech. Finally, holding back a response could either be reactive 'braking' of an intended response or an anticipatory decision to omit a response. Each inhibition study of stuttering has focused solely on quickly suppressing behaviours in reaction to an external cue, i.e., reactive inhibition (Chambers, Garavan, & Bellgrove, 2009). However, intrinsically-generated anticipatory decisions to withhold responses or proactive inhibition is another aspect of inhibition (e.g., Bartholdy et al., 2016; Aron, 2011; Jaffard et al., 2008). Proactive inhibition requires the engagement of higher order cognitive control and is thought to originate in the dorsolateral prefrontal cortex (DLPFC) (Albert, López-Martín, Hinojosa, & Carretié, 2013; Aron, 2011). Elaborated cognitive function that depends on frontal lobe regions is considered responsible for shifting response biases towards an inhibitory strategy or an execution strategy.

In order to be more comprehensive, we combined reactive and proactive inhibition conditions to test a broader range of inhibitory control in AWS using a paradigm adapted from Dunovan et al. (2015).

For the reactive task, we predicted: (1) AWS will have a shorter PSE in comparison to AWNS, and, (2) AWS will have a lower probability of stopping (pSTOP) - indicating less effective braking of movement. The inclusion of speech and manual response conditions will

probe for effector differences. The proactive inhibition tasks differ in that stopping requires a probabilistic strategy based on context and rules to suppress speech or manual responses. On these proactive manual and speech tasks, we predicted that AWS would have: (1) a lower PSE, and, (2) a lower probability of stopping across probability of GO trials - again indicating less effective braking due to a less inhibited response style. Finally, the inclusion of speech and manual response conditions will probe for effector differences in the proactive task.

## 2.2 Methods

### 2.2.1 Participants

31 AWS (22 males, 9 females; mean age = 28.1; SD = 6.4) and 31 AWNS (21 males, 10 females; mean age = 26.4; SD = 5.7) were recruited from the Institute for Stuttering Treatment and Research (ISTAR) and advertisements in the local community. Apart from stuttering, there were no medical, neurological or health differences between the groups. The participant groups were matched for sex, age, handedness (Oldfield, 1971) and education (1 = school; 2 = high school; 3 = less than 2 years university; 4 = 2 years university; 5 = 4 years university; 6 = postgraduate). None of the AWNS reported a family history of stuttering or other speech-language disorders. Table 2.1 provides a summary of the demographic information of the participants. Appendix A (Table 1) provides a detailed overview of the individual characteristics of participants included in the task measurement. All participants provided written informed consent as approved by the University of Alberta.

**Table 2.1** Brief summary of study participants. Parametric and non-parametric statistical comparisons of group characteristics; standard deviations are in brackets; all tests were two-tailed.

| | AWS | AWNS | *p* value |
|---|---|---|---|

| | | | |
|---|---|---|---|
| N | 31 | 31 | n/a |
| Age in years (mean)[a] | 28.1 (SD = 6.44) | 26.4 (SD = 5.7) | .85 |
| Sex (male) (%)[b] | 22 (71) | 21 (68) | .78 |
| Handedness (right-handed) (%)[b] | 27 (87) | 27 (87) | 1 |
| Education(mean)[c] | 5 (SD = 1.11) | 5.23 (.84) | .61 |
| SSI-4 total score (mean) | 9 (SD = .8) | n/a | n/a |
| OASES total score (mean) | 2.24 (.6) | n/a | n/a |

[a] *t*-test
[b] $\chi$2-test
[c] MWU

To evaluate stuttering severity, both groups of participants read a text aloud, tell a story about their life, and described their experience during the experiment. The speech samples were video-recorded and two trained research assistants analyzed the samples offline. The inter-rater reliability was .94 $p < .001$. A quality check of the severity estimates was completed with a qualified speech-language pathologist. The stuttering severity index (SSI-4) was employed to determine severity based on the frequency of stuttering dysfluencies, their duration, and physical concomitants of stuttering (Riley, 2009). Based on the SSI-4, 24 participants showed very mild stuttering, 4 showed mild, and 3 showed moderate. To supplement the SSI-4 estimates, the participants' general experience of stuttering was assessed by employing the Overall Assessment of the Speakers' Experience of Stuttering (OASES, Yaruss & Quesal, 2006). The questionnaire consists of four sections that cover (1) general perspectives about stuttering, (2) affective, behavioural and cognitive reactions to stuttering, (3) communication difficulties in everyday life, (4) impact of stuttering on the quality of life. The OASES also generates an impact score that

represents the overall impact of stuttering, which indicated 2 participants had a mild impact, 14 were mild-moderate, 12 were moderate, and 3 were moderate-severe.

### 2.2.2 Apparatus and procedure

Participants sat in a quiet room to complete the tasks. The stimuli were presented on a BenQ XL2411Z monitor with a screen refresh rate set at 144 Hz. Stimulus presentation and response recording were controlled by NBS Presentation software (https://www.neurobs.com/). Participants responses were recorded using a Black Box Toolkit response pad and Black Box Toolkit voice (microphone) key (www.blackboxtoolkit.com).

## 2.3 Study 1 - Reactive Inhibition

**2.3.1. Reactive Inhibition Task Description.** To evaluate reactive inhibition, we employed a modified version of the stop signal task from Dunovan et al. (2015). Figure 1 gives a schematic representation of the reactive inhibition task. During each trial, the participant saw a blue bar that moved vertically toward a target line. On GO trials, the participant had to stop the blue bar as it touched the target line at exactly 500 ms. The time accuracy of the response was measured as a Response Time (later referred as RT). In the manual condition, the participant stopped the bar by pressing a button with the right index finger. In the speech condition, the bar was stopped by saying the word 'TIP'. In both conditions, a GO trial would terminate after a participant's response or the total trial time was reached (650 ms). On STOP trials, the blue bar changed to red at five different SSDs (200-250-300-350-400 ms). The red signal indicated the participant had to suppress the manual or speech response.

As per Dunovan et al. (2015), we employed a reward system for successful performance in GO and STOP trials that involved feedback. Participants could earn or lose reward points

depending on how well they performed. The total points were converted to a dollar amount on a gift card in addition to the standard reimbursement of $10 for participating in the study. The highest possible award was 100 points for a correct response on either GO trials or STOP trials. During a GO trial, the amount of points decreased according to how far the participant stopped from the target line. If a response was not completed within the trial period, a participant lost 100% of points for the trial. If a STOP signal was presented, participants needed to stop immediately. The participant earned 100 points for stopping successfully but if a participant failed to stop, all the points for that trial would be lost.

The manual and speech reactive tasks started with a training (or baseline) block with only GO trials (n = 40). The baseline block was intended to familiarize participants with the task and to measure the RT of GO trials. Both tasks continued with 9 blocks of 40 trials per block and effector (total trials = 720; 360 manual trials, 360 speech trials). STOP signals occurred on 25% of the trials and were randomly distributed over the experimental blocks. The entire experiment lasted 60 minutes.

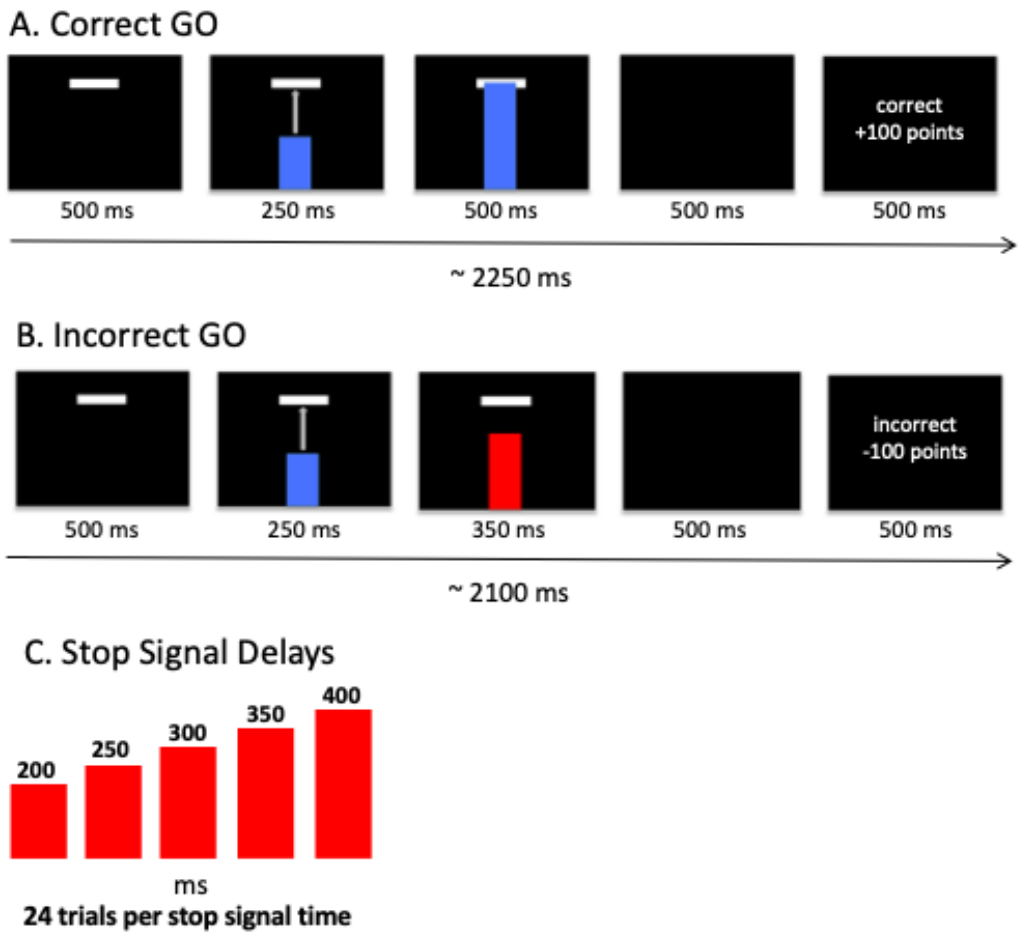


**Figure 2.1** Schematic of the reactive inhibition task. Timeline and feedback of a GO (A), STOP trial (B), and stop-signal delays (C).

## 2.4 Study 2 -Proactive Inhibition

**2.4.1 Proactive Inhibition Task Description.** The general procedure of the proactive SST resembled the reactive task. Participants had to stop the bar when it touched the target line at 500 ms. Similar to the reactive SST, we applied a reward system in which correct responses were rewarded and incorrect responses were penalized. The proactive task differed in the following ways: 1) The total duration of each trial was shorter, allowing 500 ms until the bar reached the target line and 55 ms for possible overshoot. After the trial was completed, the program continued to monitor speech or manual responses for 100 ms to detect late responses. 2)

Only one SSD (450 ms) was presented (Dunovan et al., 2015), which was too late to be a reactive cue, so participants were not able to withhold responses. 3) Participants needed to be proactive by predicting whether the bar would stop or continue extending depending on the color of the stimuli (Figure 2). A bright blue bar indicated 100% GO probability and bright red bar indicated 0% GO probability. Intermediate shades of these colors indicated the relative probability that the stop signal would be presented. By varying color codes, participants needed to anticipate whether a GO or STOP trial would occur. The experiment consisted of 20 blocks per condition (manual and speech conditions). Manual and speech conditions were counterbalanced across participants. Each block had 24 trials (n = 4 per color) for a total of 240 manual and 240 speech trials across the 480 total trials. The entire experiment was administered after Study 1 and lasted 60 minutes.

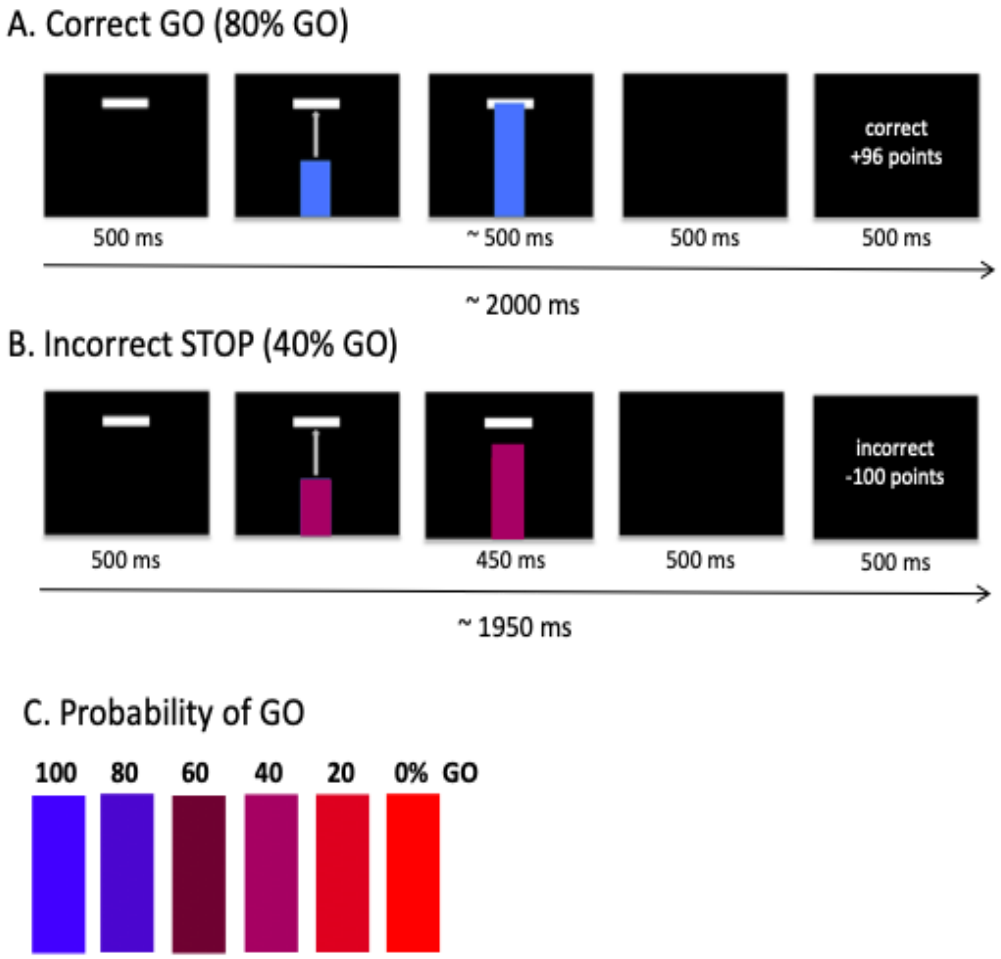


**Figure 2.2** Schematic of the proactive inhibition task. Timeline and feedback of a correct high probability GO trial with a high probability of GO (80%) (A) and a failed STOP trial with low probability of GO (40%) (B) and GO probabilities per color cue (C).

### 2.5 Statistical Analysis

Reactive and proactive tasks were analyzed separately. Additionally, it was decided to conduct a separate statistical analysis for manual and speech task because of a potential small delay of the microphone which might have led a slower RT in the speech condition.

**2.5.1 Statistical Analysis of the Reactive Task.** The primary dependent variables for the reactive task in manual and speech conditions were:

(1) The observed probability of successful stopping (pSTOP) per SSD: The measure was calculated as the mean number of failed STOP trials divided by the number of STOP trials per SSD.

(2) The point of subjective equality (PSE): The psychometric measure to evaluate stopping effectiveness was calculated by fitting a sigmoid curve on the data with observed probability of stopping across the SSDs. PSE is the point at which the psychometric curve crosses the 50% probability of successful stopping and is reported in ms.

The secondary dependent variables for the reactive task in manual and speech conditions were as follows:

(1) GO Response time (GO RT of Baseline): GO RT of Baseline was an RT measure from the onset of stimulus to the response during the initial training block when no STOP signals were presented. An error or RT earlier than 200 ms was considered premature and deleted from the analysis.

(2) GO Response time (Go RT): GO RT was a measure from the onset of stimulus to the response. An error or RT earlier than 200 ms was considered premature and deleted from the analysis.

(3) Adjusted GO RT (adjRT): To account for whether STOP trials influenced general performance, the mean of GO RTs following a failed STOP trial (fSTOP) was calculated.

(4) STOP Response time (fSTOP RT): fSTOP RT was calculated as RT of responses on failed STOP trials (fSTOP).

The statistical analysis was similar for manual and speech conditions. Independent sample t-tests were used to compare PSE between the two groups. The pSTOP variable was examined with a 2 x 5 (Group [AWS, AWNS] x SSD [200, 250, 300, 350, 400] analysis of

variance (ANOVA). GO RT, adjGO, and RT of Baseline were examined with a 2 x 3 (Group [AWS, AWNS] x RT type [GO, adj, Baseline] analysis of variance (ANOVA). The fSTOP RT variable was examined with a 2 x 5 (Group [AWS, AWNS] x SSD [200, 250, 300, 350, 400] analysis of variance (ANOVA).

**2.5.2 Statistical Analysis of the Proactive Task.** The primary dependent variables for the proactive task were similar to the reactive inhibition task. The only difference was that pSTOP was calculated per color cue which indicated six probabilities of GO trials (pGO). The variables were (1) PSE, measured in percentages; and (2) The observed probability of successful stopping (pSTOP) per pGO: The measure was calculated as the mean number of failed STOP trials divided by the number of trials per pGO. The secondary dependant variables are (1) GO RT, (2) adjGO RT, and (3) fSTOP RT.

The statistical analysis was similar for manual and speech conditions. Independent sample t-tests were used to compare PSE and adjGO RT between the two groups. The pSTOP variable was examined with a 2 x 6 (Group [AWS, AWNS] x pGO [0, 20, 40, 60, 80, 100%] analysis of variance (ANOVA). Go RT and fSTOP RT were examined separately with a 2 x 5 (Group [AWS, AWNS] x pGO [0, 20, 40, 60, 80%] analysis of variance (ANOVA). The post-hoc testing among the was examined with Bonferroni correction.

## 2.6 Results

### 2.6.1 Reactive Inhibition

The means for the inhibition and RT dependent variables for AWS and AWNS are shown in Table 2.2.

#### 2.6.1.1 Manual Condition

**PSE:** The point at which 50% accuracy of stopping was reached did not differ between AWS and AWNS ($t(60) = .9$, $p = .37$).

**pSTOP:** Across all SSDs, pSTOP did not differ statistically between AWS and AWNS ($F(1, 300) = 3.31$, $p = .069$). Although, the effect of SSD was significant ($F(4, 300) = 515.7$, $p < .0001$, $\eta_p^2 = .87$) the Group by SSD interaction was not significant ($F(4, 300) = .47$, $p = .75$). Post-hoc testing showed that pSTOP decreased significantly for longer SSDs (see Table 2.2).

**RT:** The RT of GO trials (GO RT of Baseline, GO RT, and adjGO RT) did not differ between the groups ($F(1, 180) = .33$, $p = .57$). However, differences between the RT type were highly significant ($F(2, 180) = 49.43$, $p < .0001$, $\eta_p^2 = .36$). Post-hoc testing indicated the three RT conditions differed statistically: adjGO RT was the longest, GO RT was intermediate and GO RT of Baseline was the fastest (see Table 2.2). The interaction between group and RT type was not significant ($F(2, 180) = 1.38$, $p = .25$).

**fSTOP RT:** fSTOP RT did not differ significantly between AWS and AWNS ($F(1, 213) = 1.89$, $p < .17$); however, the interaction between group and SSD was significant ($F(4, 213) = 3.74$, $p = .0058$, $\eta_p^2 = .066$). Longer SSDs elicited longer RTs in AWS compared to AWNS at 200 and 250 ms (see Table 2.2). The main effect of SSD was highly significant ($F(1, 213) = 34.68$, $p < .0001$, $\eta_p^2 = .39$). Post-hoc testing indicated fSTOP RT increased with longer SSDs (see Table 2.2).

#### 2.6.1.2 Speech Condition

**PSE:** The point at which 50% accuracy of stopping was reached did not differ between groups ($t(60) = .49$, $p = .62$).

**pSTOP:** pSTOP did not differ statistically between AWS and AWNS ($F(1, 300) = 1.32$, $p = .25$) and the Group by SSD interaction was not significant ($F(4, 300) = .37$, $p = .83$). The main effect of SSD was significant ($F(4, 300) = 394.3$, $p < .0001$, $\eta_p^2 = .84$) indicating the probability of stopping decreased for later SSDs.

**RT:** The RT of GO trials (GO RT of Baseline, GO RT, and adjGO RT) did not differ between the groups ($F(1, 180) = .4$, $p = .53$). However, differences between the RT type were highly significant ($F(2, 180) = 21.86$, $p < .0001$, $\eta_p^2 = .2$). Post-hoc testing indicated the three RT conditions differed statistically with adjGO RT taking the longest time, GO RT was intermediate and Baseline RT was fastest. The interaction between Group and RT type was again significant ($F(2, 180) = 3.46$, $p = .034$), indicating a stronger effect of the RT of GO trials on AWNS than AWS (see Table 2.2).

**fSTOP RT:** fSTOP RT did not differ significantly between AWS and AWNS ($F(1, 252) = 2.85$, $p < .092$). The main effect of SSD was significant again ($F(1, 213) = 34.68$, $p < .0001$, $\eta_p^2 = .39$), but the interaction between SSDs and Group was not significant ($F(4, 252) = 1.77$, $p = .135$). (see Table 2.2). Post-hoc testing indicated fSTOP RT increased with later SSDs across both groups (see Table 2.2).

**Table 2.2** Descriptive statistics (means, standard errors, *p*-value of the pairwise comparison based on t-test) for response times, number of unsuccessful trials and Point of Subjective Equality in reactive inhibition task

| | Experimental Condition | | | |
|---|---|---|---|---|
| | Manual | | Speech | |
| Measure | AWS | AWNS | AWS | AWNS |
| PSE | 315.7 (SD = 24.59) | 321.6 (SD = 27.5) | 315.1 (SD = 33.57) | 319 (SD = 29.15) |
| GO RT of Baseline | 492.1 (SD = 18.85) | 487.5 (SD = 21.29) | 541.1 (SD = 27.41) | 526 (SD = 25.32) |
| GO RT | 509.3 (SD = 16.84) | 512.6 (SD = 11.87) | 534.7 (SD = 18.62) | 534.2 (SD = 16.45) |
| adjGO RT | 519.5 (SD = 22.08) | 525.6 (SD = 18.84) | 555.7 (SD = 29.16) | 564.2 (SD = 31.18) |
| *mean fSTOP RT* | 490.4 (SD = 38.36) | 480 (SD = 62.96) | 505.1 (SD = 42.85) | 506.6 (SD = 49.29) |
| fSTOP RT (SSD = 200 ms) | 433.7 (SD = 14.22) | 361.1 (SD = 174) | 452.5 (SD = 54.74) | 424 (SD = 82.1) |
| fSTOP RT (SSD = 250 ms) | 461.2 (SD = 26.8) | 410 (SD = 82.5) | 480.2 (SD = 27.34) | 472.1 (SD = 41.13) |
| fSTOP RT (SSD = 300 ms) | 476.3 (SD = 51.44) | 475.8 (SD = 19.75) | 496.7 (SD = 31.7) | 504.6 (SD = 25.31) |
| fSTOP RT (SSD = 350 ms) | 504.6 (SD = 20.29) | 505 (SD = 16) | 527.9 (SD = 23.61) | 528.3 (SD = 22.41) |
| fSTOP RT (SSD = 400 ms) | 510.9 (SD = 18.18) | 513.3 (SD = 15.85) | 540.4 (SD = 21.72) | 540.7 (SD = 20.61) |
| *mean pSTOP* | .55 (SD = .42) | .59 (SD = .41) | .55 (SD = .37) | .57 (SD = .37) |
| pSTOP (SSD=200 ms) | .99 (SD = .25) | .99 (SD = .022) | .097 (SD = .047) | .95 (SD = .088) |
| pSTOP (SSD=250 ms) | .93 (SD =.097) | .95 (SD = .084) | .85 (SD = .16) | .88 (SD = .15) |
| pSTOP (SSD=300 ms) | .66 (SD = .27) | .7 (SD = .27) | .61 (SD = .22) | .65 (SD = .23) |
| pSTOP (SSD=350 ms) | .18 (SD = .14) | .25 (SD = .18) | .25 (SD = .18) | .29 (SD = .17) |
| pSTOP (SSD=400 ms) | .01 (SD = .018) | .036 (SD = .04) | .07 (SD = .064) | .075 (SD = .062) |

Note
PSE = point of subjective equality; GO RT = Response Time of GO trials; adjGO RT = adjusted GO Response Time; fSTOP RT = RT of failed STOP trials; pSTOP = probability of STOP trials; SSD = stop-signal delay.

#### 2.6.2.3 Correlations between Stopping Time and Stuttering Severity

To assess whether inhibitory control was influenced by stuttering severity, we calculated correlations between stuttering impact scores (OASES & SSI-4) and stopping variables. Spearman correlation analyses showed that lower PSE was related to a higher stuttering impact (OASES score) in both manual (R = -.41; $p$ = .024) and speech domains (R = -.39, $p$ = .031) (Fig. 2.3).The SSI score, however, was not significantly related to the inhibition variables in either the manual or speech condition.

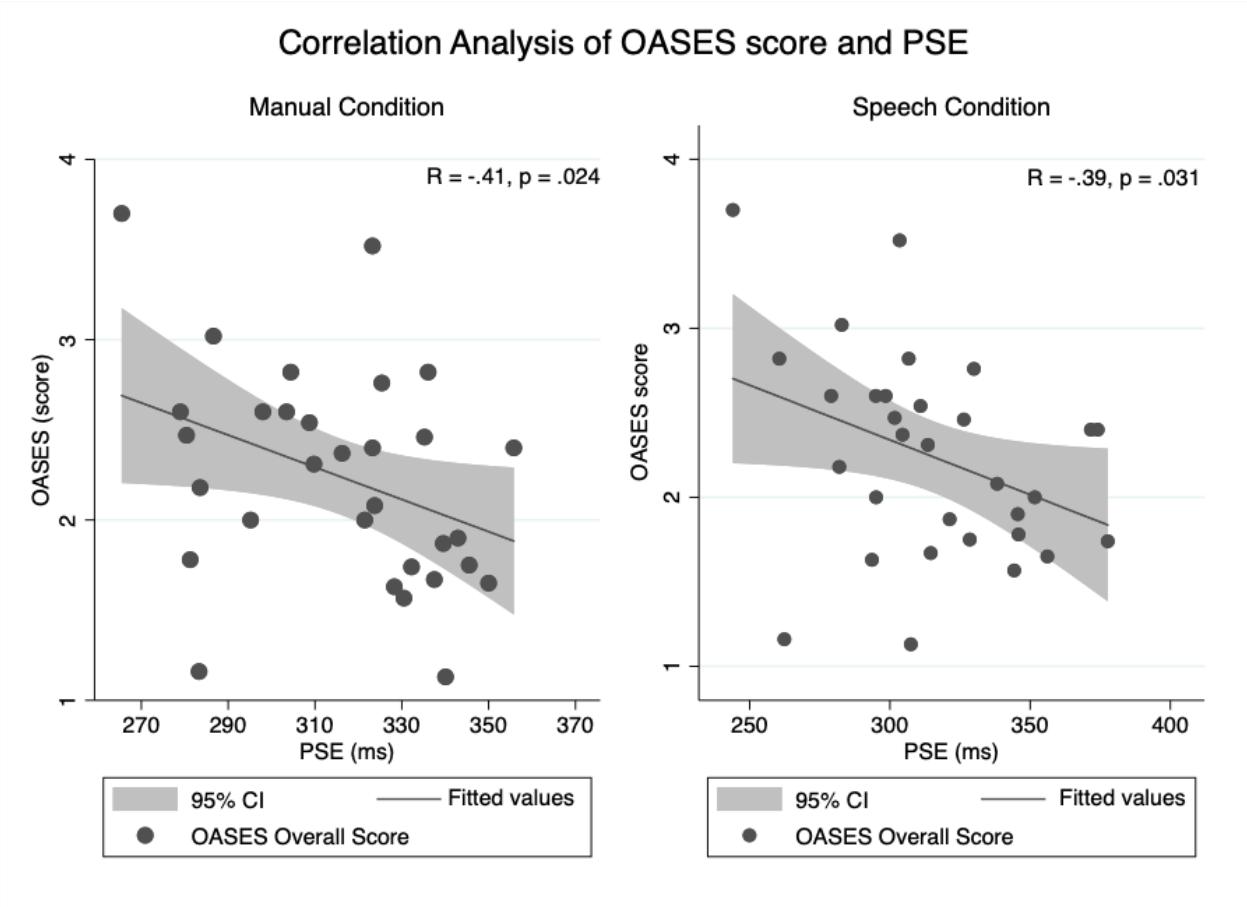


**Figure 2.3** Spearman correlation analyses of PSE and OASES score in manual (A) and speech conditions (B).

### 2.6.3 Proactive stopping

The mean PSE, pSTOP, GO RT, adjGO RT, and fSTOP RT for AWS and AWNS are listed in Table 2.3.

#### 2.6.3.1 Manual Condition

**PSE:** The point at which 50% accuracy of stopping was reached did not differ between AWS and AWNS ($t(60) = 1.7$, $p = .09$).

**pSTOP:** AWS had a lower probability of stopping than AWNS (Group: $F(1, 360) = 6.97$, $p < .01$, $\eta_p^2 = .019$), but the interaction between group and pGO levels was not significant ($F(5, 360) = 1.55$, $p > .17$). The main effect of pSTOP was significant ($F(5, 360) = 697$, $p < .0001$ , $\eta_p^2 = .91$) with post hoc testing indicating a decrease in pSTOP as pGO increased (pGO 0% > pGO 20% > pGO 40% > pGO 60% > pGO 80% > pGO 100%) (see Table 2.3).

**GO RT:** A significant main effect of Group ($F(1, 274) = 7.73$, $p = .006$, $\eta_p^2 = .027$) was detected indicating AWS had a faster GO RT than AWNS (Table 2.3). The main effect of pGO was also significant ($F(4, 274) = 3.68$, $p = .006$, $\eta_p^2 = .051$), but the interaction between Group and pGO was not significant ($F(4, 274) = .21$, $p = .93$).

**adjGO:** The adjGO RT of AWS was faster on GO trials followed by a fSTOP compared to AWNS ($t(60) = 2.08$, $p = .04$, $d = .53$).

**fSTOP RT:** The RT on fSTOP trial was significantly faster for AWS than AWNS ($F(1, 284) = 11.65$, $p < .001$, $\eta_p^2 = .039$; Table 2.3). The main effect for pGO was not significant ($F(4, 284) = 1.94$, $p > .1$) and the interaction with group did not reach significance ($F(4, 284) = .05$, $p > .99$).

#### 2.6.3.2 Speech Condition

**PSE:** The point at which 50% accuracy of stopping was reached did not differ between groups ($t(60) = .55$, $p = .58$).

**pSTOP:** The AWS had a lower pSTOP than AWNS (Group: $F(1, 360) = 9.97$, $p < .002$, $\eta_p^2 = .027$). The main effect of pGO was also significant ($F(5, 360) = 524.5$, $p < .0001$, $\eta_p^2 = .88$). Post hoc testing indicated a decrease in pSTOP as pGO increased (pGO 0% > pGO 20% > pGO 40% > pGO 60% > pGO 80% > pGO 100%), as shown in Table 2.3). However, the interaction between Group and pGO was not statistically significant ($F(5, 360) = 2.06$, $p = .07$).

**GO RT:** The AWS were faster in terms of Go RT than AWNS ($F(1, 274) = 7.73$, $p = .006$, $\eta_p^2 = .027$). The main effect of pGO and the interaction between Group and pGO were not significant (pGO: $F(4, 263) = 2.13$, $p = .078$; Group by pGO: $F(4, 263) = .42$, $p = .8$).

**adjGO:** The AWS had faster response times than AWNS following failed stops ($t(60) = 1.73$, $p = .08$).

**fSTOP RT:** The AWS responded faster on fSTOP trials than AWNS (Group: $F(1, 255) = 7.94$, $p = .005$, $\eta_p^2 = .03$; see Table 2.3). The main effect of pGO ($F(4, 255) = 6.94$, $p < .0001$, $\eta_p^2 = .88$) was significant at the 20, 40, 60, and 80 probabilities (Table 2.3). The interaction between Group and pGO was not significant ($F(4, 255) = 1.47$, $p = .21$).

**Table 2.3** Descriptive statistics (means, standard errors, *p*-value of the pairwise comparison based on t-test) for response times, number of unsuccessful trials and Point of Subjective Equality in proactive inhibition task

| | Experimental Condition | | | |
|---|---|---|---|---|
| | Manual | | Speech | |
| Measure | AWS | AWNS | AWS | AWNS |
| PSE | .51 (SD = .019) | .52 (SD = .025) | .54 (SD = .07) | .55 (SD = .07) |
| adjGO RT | 495.9 (SD = 27.41) | 508.9 (SD = 21.64) | 514.1 (SD = 18.9) | 524 (SD = 25.2) |
| mean GO RT | 488.5 (SD = 26.92) | 495.9 (SD = 16.37) | 491.5 (SD = 19.35) | 497.9 (SD = 21.68) |
| GO RT (pGO = 20%) | 493.7 (SD = 39.98) | 500.6 (SD = 18.93) | 491.9 (SD = 28.57) | 492.9 (SD = 61.75) |
| GO RT (pGO = 40%) | 494.1 (SD = 26.29) | 505 (SD = 16.02) | 494.1 (SD = 26.29) | 505 (SD = 16.02) |
| GO RT (pGO = 60%) | 485 (SD = 23.94) | 489.3 (SD = 16.53) | 494.8 (SD = 12.53) | 498.1 (SD = 13.73) |
| GO RT (pGO = 80%) | 482.8 (SD = 21.83) | 491.9 (SD = 13.46) | 485.3 (SD = 12.9) | 493.4 (SD = 10.87) |
| GO RT (pGO = 100%) | 488.7 (SD = 24.6) | 495 (SD = 13.78) | 491.5 (SD = 16.29) | 497 (SD = 13.26) |
| mean fSTOP RT | 486.5 (SD = 25.17) | 495.1 (SD = 17.6) | 490.3 (SD = 20.97) | 498.4 (SD = 20.1) |
| fSTOP RT (pGO = 0%) | 484.7 (SD = 28.06) | 494.5 (SD = 20.57) | 484.6 (SD = 29.31) | 480.8 (SD = 24.9) |
| fSTOP RT (pGO = 20%) | 489.2 (SD = 28.8) | 499.3 (SD = 20.41) | 489.1 (SD = 28.17) | 501.6 (SD = 19.84) |
| fSTOP RT (pGO = 40%) | 491.3 (SD = 22.8) | 500 (SD = 13.71) | 501.1 (SD = 15.11) | 505.8 (SD = 24.35) |
| fSTOP RT (pGO = 60%) | 484 (SD = 24.1) | 491.3 (SD = 15.35) | 488.2 (SD = 14) | 502.5 (SD = 10.15) |
| fSTOP RT (pGO = 80%) | 483.4 (SD = 22.98) | 491 (SD = 16.7) | 487.3 (SD = 14.3) | 494.2 (SD = 14.7) |
| mean pSTOP | .46 (SD = .4) | .43 (SD = .39) | .48 (SD = .39) | .53 (SD = .42) |
| pSTOP (pGO = 0%) | .91 (SD = .08) | .96 (SD = .08) | .92 (SD = .09) | .98 (SD = .05) |
| pSTOP (pGO = 20%) | .85 (SD = .11) | .87 (SD = .11) | .89 (SD = .11) | .94 (SD = .068) |
| pSTOP (pGO = 40%) | .54 (SD = .2) | .63 (SD = .18) | .64 (SD = .2) | .78 (SD = .16) |
| pSTOP (pGO = 60%) | .23 (SD = .18) | .28 (SD = .19) | .34 (SD = .23) | .37 (SD = .29) |
| pSTOP (pGO = 80%) | .023 (SD = .022) | .011 (SD = .017) | .04 (SD = .04) | .045 (SD = .059) |
| pSTOP (pGO = 100%) | .015 (SD = .018) | .011 (SD = .018) | .05 (SD = .05) | .04 (SD = .05) |

Note
PSE = point of subjective equality; GO RT = Response Time of GO trials; adjGO RT = adjusted GO Response Time; fSTOP RT = RT of failed STOP trials; pSTOP = probability of STOP trials; pGO = probability of GO trial

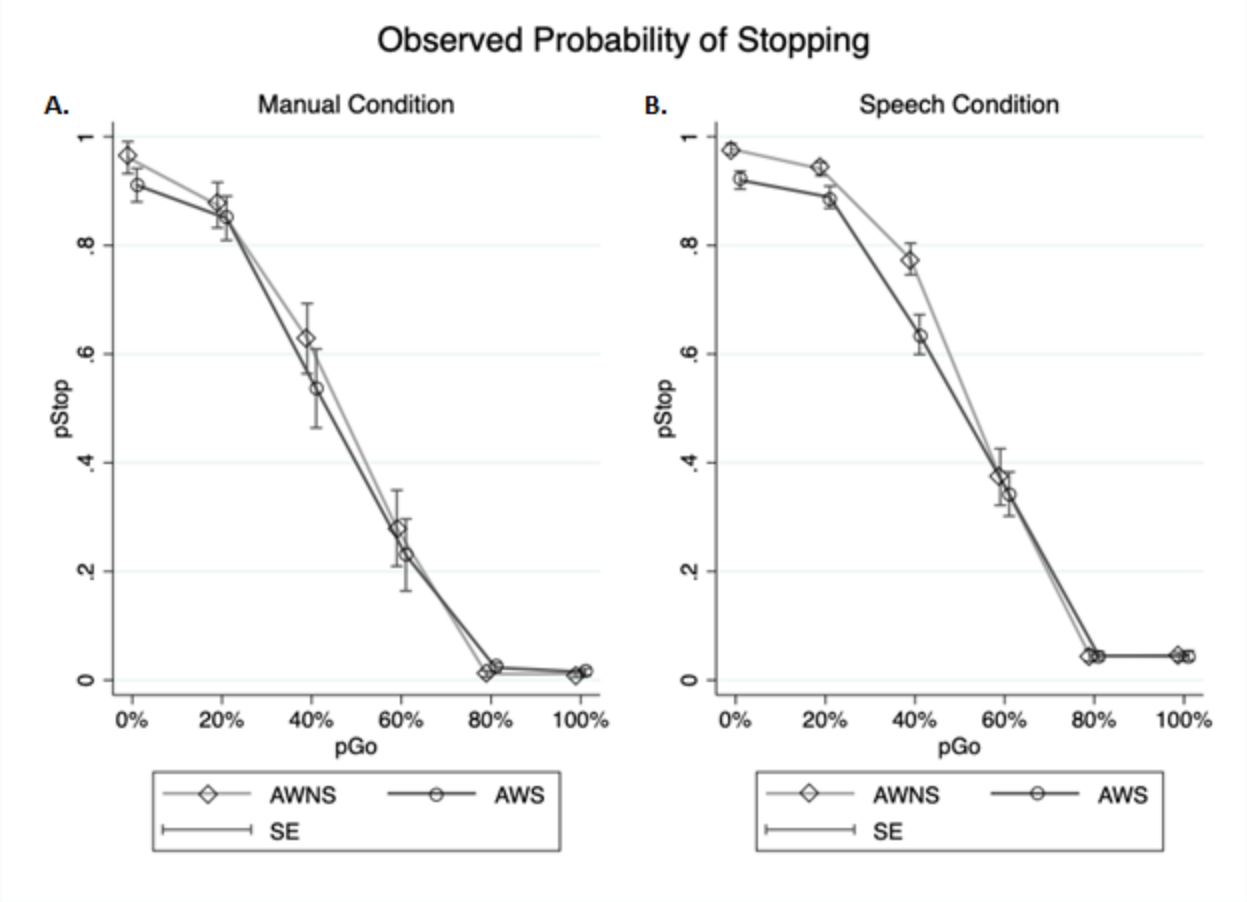


**Figure 2.4** Comparison of the observed probability of stopping (pSTOP) per probability of GO trials (pGO) in AWS and AWNS in manual (A) and speech conditions (B) in proactive inhibition task. Means and standard errors shown. Points are offset horizontally so that error bars are visible.

#### 2.6.3.3 Correlations between Inhibition and Stuttering Severity

Stuttering severity and its impact were not related to any measure of performance on the proactive task**.**

## 2.7 Discussion

In the current study, computer-based reactive and proactive inhibition tasks (adapted from Dunovan et al., 2015) with manual and speech responses were used to investigate inhibitory control in AWS.

### 2.7.1 Reactive stopping in stuttering

The main measure of inhibition in our study is the point of subjective equality or PSE, which has classically been employed in psychometrics to measure precision and accuracy. In our study, PSE was employed to evaluate stopping effectiveness by representing the point at which 50% probability of successful stopping is reached. According to our original hypothesis, we predicted that reactive inhibition tasks would be a sensitive marker of dysregulated inhibition in AWS. Instead, our results showed that AWS had a similar PSE compared to AWNS in both manual and speech responses. This implies that behaviourally, AWS were able to suppress both types of responses equally well as AWNS. Comparable reactive stopping was also corroborated by the finding that pSTOP did not differ across groups. Together these findings support the conclusion that AWS are as efficient in evaluating visual stop signals and generate braking responses as AWNS, regardless of whether manual or speech responses are involved. These findings are in accord with the secondary finding in Markett et al. (2016), which indicated no group differences in stopping accuracy. They also align with a recent study of response inhibition in CWS (Eggers, De Nil, and Van den Bergh, 2018), which showed no differences in stopping accuracy and SSRT between CWS and CWNS.

The evidence supporting dysregulated inhibition in AWS is largely based on the main finding by Markett et al. (2016) that showed AWS had significantly delayed SSRT compared to AWNS. The SSRT is an indirect quantitative index of the latency of the stop process or how long it takes to inhibit a response (Verbruggen & Logan, 2008). SSRT is indirect because stopping/withholding is not measured overtly, but instead is derived from the distribution of reaction time trials and the observed probability of responses for a certain SSD (Verbruggen & Logan, 2008). Our experimental paradigm does not support SSRT estimation because response

time is measured instead of reaction time. Consequently, our findings cannot be directly compared with Markett et al. (2016). The PSE and pSTOP variables are better potential approaches for estimating inhibition because their calculation relies on observed (direct) behaviour associated with stopping effectiveness. Moreover, longer SSRT in stuttering is not a consistent finding. Two developmental studies showed that CWS can demonstrate faster SSRT (Harrewijn et al., 2017) and no difference in SSRT between CWS and CWNS (Eggers et al., 2018). The discrepancy in SSRT results together with the current results do not support assertions of deviant reactive inhibition in stuttering. Formal comparisons between SSRT and PSE have not been conducted in the same participants. This work is ultimately necessary to determine which of these measures is more sensitive to an inhibitory control disorder or limitation. Persons who stutter show longer reaction times and also longer response times across a variety of paradigms (e.g., Jones et al., 2002; Hulstijn et al., 1992; Archibald and De Nil, 1999; Smits-Bandstra et al., 2006), but reaction time delays are perhaps more pervasive; therefore, it remains possible that an inhibitory probe based on reaction time, such as SSRT, could be more sensitive.

Inhibition studies also generate timing results in the form of the RT responses for the GO and failed STOP trial varieties. For the most part, no differences between AWS and AWNS emerged between RT performance in either manual or speech conditions. AWS were equally fast as AWNS for each manual and speech RT measure across the entire experiment including Go RT, adjGO RT and fSTOP RT. The sole group difference was a slower baseline GO RT for AWS in the speech condition, which might indicate a longer time was needed for initiation of speech responses in the training stage. Slower speech RTs have been reported for AWS in numerous studies that did not involve inhibition (e.g., Hulstijn et al., 1992; Archibald and De

Nil, 1999; Smits-Bandstra et al., 2006). The recent findings on inhibitory control by Metzger et al. (2017) and Markett et al. (2016) showed no differences in GO and fSTOP RTs between AWS and AWNS. In the developmental study by Eggers et al. (2018), CWS showed faster RT on GO and STOP trials than CWNS but there were no other group differences in timing. The highly comparable RT results between the groups in this study means that both performance and reactive inhibition outcomes do not differentiate stuttering.

A modest but significant correlation between stopping effectiveness and a stuttering impact (OASES score) was found in both manual and speech conditions. As the impact of reported stuttering increased, stopping time was shorter and less effective. Associations between stuttering severity and inhibition has previously been suggested by two neuroimaging studies. Metzger et al. (2017) showed a positive correlation between stuttering severity and activity within the substantia nigra during the anticipation phase of manual responses in a GNG task. Neef et al. (2018) found more severe stuttering was associated with anatomical and functional differences in right frontal regions that moderate inhibition. These associations suggest more severe stuttering might be linked to less effective reactive inhibition. However, this possibility needs further investigation with individuals who display more severe stuttering.

### 2.7.2 Proactive inhibition in stuttering

Ineffective self-regulation and impulsivity have been previously suggested to be factors in stuttering among both adults and children (Alm, 2004; Doneva, Davis, & Cavenagh, 2017). To investigate this possibility, we took the novel step of using a proactive stopping paradigm with manual and speech responses. Proactive inhibition involves a decision-making process in which a top-down selection of making or not making a response is required based on the rules of the task.

In comparison to suppressing an ongoing response as per the reactive task, our results revealed a profile of subtle but persistent lapses in performances in AWS. Although PSE was not sensitive to group differences, the probability of stopping (pSTOP) was lower in AWS, showing AWS had more difficulty evaluating when to stop. This might indicate subtle limitations in deactivating motor commands in response to frequently changing signals. Differences between AWS and AWNS were also evident in RT in manual and speech conditions as AWS responded faster on failed STOP trials and GO trials. Faster movements were also found for adjGO RT in AWS meaning their RT after fSTOP trials was more impulsive but only for the manual response condition. These faster RT suggest AWS were prioritizing speed in their responses and were less able to adapt their response style to improve their accuracy in stopping (Smits-Bandstra & De Nil, 2007).

Overall, AWS had slightly more difficulty with suppressing a motor plan in both manual and speech domains and tended to complete responses faster, which might also factor into less effective stopping. To our knowledge, this is the first study that directly tested proactive inhibition in AWS, but our hypotheses stem from previous work on response selection and impulsivity in stuttering (see Alm, 2014 for a review). Evidence for less effective self-regulation in stuttering comes from developmental studies (e.g., Eggers et al., 2013, Eggers et al., 2012, Subramanian and Yairi, 2006), in which CWS showed a less controlled and more impulsive response style. The CWS had a higher number of false alarms, more failures to inhibit responses to No-GO signals, faster RT in GNG tasks (e.g., Eggers et al., 2013) and shorter RTs in attention shifting paradigms (Eggers et al., 2012, Subramanian and Yairi, 2006).

### 2.7.3 Theoretical implications

The relationship between inhibitory control and speech fluency is not fully understood. However, it is thought that fluent speech is a product of effective sequencing of motor actions consisting of overlapping action initiation, execution, and termination, while inhibiting previous and competing actions. In our study, AWS were equally efficient in reactive inhibition as AWNS. On the other hand, proactive inhibition was sensitive to group differences in that AWS were more impulsive shown through a lower probability of stopping. This potentially implicates higher level inhibitory control limitations in stuttering that might allow for failures to inhibit irrelevant/competing speech motor commands or interrupt processes of motor command activation and deactivation.

This perspective conforms with the theoretical account that speech monitoring is deviant in stuttering (Postma & Kolk, 2013; Vasic & Wijnen, 2005; Civier, 2013). One of the most influential speech production models - DIVA, Directions Into Velocities of Articulators (Bohland et al., 2010) - accounts for feedforward and feedback control systems in speech. Given the generation of a feedforward command, appropriate sound maps are selected, sensory representations (i.e., efferent copies) of their motor plans are created for internal comparison, the resultant feedforward commands are transformed to articulator velocity maps in order to be executed. An advance model of "dysfluent speech" based on the DIVA model (GODIVA - Gradient Order Directions Intro Velocities of Articulators, Civier, 2013) relies on the hypothesis of abnormal inhibitory control which accounts for two disfluency mechanisms including an inability to suppress the activation of an already executed syllable and an inability to initiate the next syllable, both of which are caused by abnormally "slow activation (see Howell, 2007) of the next motor program (Civier, 2013). If inhibitory regulation is reduced, it can have an impact on

both the inability to detect incorrect motor plans and suppress already executed and thus non-relevant motor plans (Engelhardt et al., 2009; Eggers et al., 2013).

Another important parameter in which inhibition might impact speech fluency is within high level cognitive systems, i.e., executive control. Response inhibition is a core phenomenon in executive control that involves a system of top-down mental processes which include self-control (or behavioural inhibition), cognitive flexibility (also called mental set shifting), working memory, and interference control (selective attention and cognitive inhibition) (Diamond, 2013). Speech preparation and production can be demanding processes for executive function (Doneva, Davis, & Cavenagh, 2018) and possibly even more effortful for people who stutter. Higher executive control demands in stuttering might arise from to a potential imbalance of executive function resources governing speech-supporting motor, linguistic, cognitive, and socio-emotional subsystems (e.g., Bosshardt, 2006; Heitman et al., 2004; Eichorn, Marton, Pirunsky, 2018; Doneva, Davis, & Cavenagh, 2018). The empirical evidence in AWS suggests that fluency depends on the complexity of the utterance as well as interference load as suggested by findings from dual-task studies (e.g., Bosshardt, 2006; Smits-Bandstra & De Nil, 2009, Saltuklaroglu, Teulings, & Robbins, 2009). Thus, deficits in fluency may arise from the inability to prioritize relevant information and/or suppress the distractors, which ties in well with our results on proactive inhibition in which AWS had a lower stopping probability and faster RTs. Proactive inhibition requires the engagement of higher order cognitive control, attention, and memory (Albert, López-Martín, Hinojosa, & Carretié, 2013; Aron, 2011) which are presumably involved in the preparatory step for the possibility of completing a response or withholding it before the actual response can be made (Aron, 2011). Inefficiency in the proactive preparation of correct motor sequences, in which the needed command is activated and the irrelevant/already executed

and/or competing ones are inhibited, can lead to a potential error (manifested by attempts to repeat or blocking of an ongoing behaviour). In other words, if people who stutter have difficulties in focusing their attentional resources on selecting a correct response and a weaker ability to tune inhibition to specific speech motor plans, it can lead to a choice of an erroneous speech motor command and subsequent disfluency.

Evidence for atypical inhibitory control in stuttering is also suggested by neuroimaging research (for an exhaustive review, see Etchell, 2018; Alm, 2004). Several MRI studies have identified structural and functional anomalies in the right hemisphere and basal ganglia, which could implicate atypical development cortico-basal ganglia-thalamo-cortical loops necessary for response inhibition (Neef et al., 2018; Alm, 2004; Brown, 2005; Belyk, 2014; Budde, 2014). First, abnormal activity was found in the basal ganglia of AWS, which regulates motor command selection and inhibition (e.g., Metzger et al., 2017; Neef et al., 2018). Second, weaker connections throughout cortico-basal ganglia-thalamo-cortical loops and greater activation in the right inferior frontal gyrus and insula were reported by Lu et al., (2010). Third, increased activation in the frontostriatal regions during incongruent trials that required stopping suggests inadequate readiness to execute a motor command as reported by Liu et al. (2014). Fourth, connectivity differences present in CWS point to abnormal development of the basal ganglia network (Chang & Zhu, 2013). Lastly, stuttering severity was also shown to be linked to the basal ganglia function, in which severity correlated positively with the activity in the caudate nucleus and negatively with the left substantia nigra (Giraud et al., 2008).

While the foregoing studies suggest neurological differences in brain regions that regulate inhibition, there are several recent studies of basal-ganglia-thalamo-cortical circuitry more relevant to a proactive inhibition deficit in stuttering (see review by Etchell et al., 2018).

For example, abnormal activation in the regions such as SMA complex and basal ganglia, associated with the timing of self-initiated planning and execution of motor actions and their sequencing and monitoring, was reported by Qiao et al. (2017). Busan et al. (2019) recently confirmed abnormal functioning of SMA and suggested it could delay internal timing mechanisms in stuttering. Metzger et al. (2017) showed potential aberrations in the indirect inhibitory pathway of AWS that involves increased connectivity between the cortex and the globus pallidus (GPe). Finally, the recent fMRI study on CWS by Harrewijn et al. (2017) showed decreased activation in the rostral cingulate zone (RCZ) activated during voluntary action selection in CWS and suggested a potential general difficulty with action selection and self-control across the speech and non-speech domains. Although our study is limited to behavioural observations, inability to anticipate stop signals and faster response times are consistent with atypical activation and deactivation of movements that are regulated by these brain regions.

The chief limitation of these neuroimaging studies is the inability to test the temporal aspects of inhibition. The temporal domain of when inhibition begins, and its related signal strength can be studied with EEG and related methods. We propose the next step towards understanding inhibitory control will involve the timing of the N2-P3 complex during proactive inhibition. The N2 potential is an index of attention while P3 is an index of inhibition. Together, these potentials reflect how and when inhibition occurs during performance of specific tasks. Some work on these potentials in stuttering has been reported (e.g., Etchell et al., 2012; Elchlepp et al., 2016) but not in the context of speech and manual movements or with proactive inhibition.

**2.7.3.1 Stuttering as a domain-general motor inhibition disorder.** A vast body of literature associates stuttering with a speech motor problem as evidenced by the symptomatic motor breakdowns - blocks, prolongations, and repetitions (for a review, see Ludlow & Loucks,

2003; Smith & Weber, 2017). The presence of secondary behaviours such as involuntary facial expressions or hand or leg movements might motivate a hypothesis that stuttering symptoms stem from a more general disorder, which compromises not only speech motor control but the entire motor system (Jones et al., 2002; Busan et al., 2003; Busan et al., 2019; for a review, see Etchell et al., 2014). We tried to tackle the question by investigating whether motor response inhibition of manual and speech effectors demonstrate similar behavioural patterns in stuttering. We found that the difficulty of the reactive inhibitory task did not change in the condition when speech and manual responses were required. AWS were able to maintain the same stopping probability in both conditions and were comparable to AWNS. However, and most importantly, the results of the proactive task revealed differences between AWS and AWNS. AWS had a lower probability of stopping than AWNS in both manual and speech conditions.

Such an overactive impulse for response execution present in the proactive task might account for a broader subtle motor inhibition disorder that may be more evident in speech of AWS but also have a subtle effect on general motor inhibition skills. This claim finds support in previous research pointing to a general inhibitory mechanism that crosses effector systems, as opposed to effector-specific inhibitory mechanisms (Xue et al., 2008; Wessel et al., 2016; Etchell, Sowman, & Johnson, 2012; Ghahremani et al., 2018). This body of evidence proposes that speech production and skilled manual actions are potentially subject to a general or global inhibitory system (Xue et al., 2008; Wessel et al., 2016; Etchell, Sowman, & Johnson, 2012; Ghahremani et al., 2018). Firstly, Xue et al. (2008) found that inhibition of a manual inhibition task, letter-naming task and pseudoword production consistently activated the same rIFC opercular/insula region. The SSRT results corroborated the proposal of a general inhibitory mechanism because strong correlations between speech and manual responses were found (Xue,

Aron, & Poldrack, 2008). Secondly, in two recent STN LFP recording studies of PD patients (Wessel et al., 2016; Ghahremani et al., 2018), spectral analysis of spoken and manual responses showed a consistent increase in beta [13-30 Hz] power on successful stopping in comparison to false alarms (Wessel et al., 2016; Ghahremani et al., 2018). Additionally, alpha power peaked after the GO signal and was elevated in frequency in response to braking of spoken and manual responses. Thirdly, a TMS/EMG study by Cai et al. (2012) showed that vocal inhibition affects corticospinal excitability in the task-irrelevant hand. Similarly, Majid et al. (2011) observed a decrease in corticomotor excitability of the task-irrelevant leg using TMS while subjects had to rapidly stop a hand motion. Although these findings do not clarify whether the inhibition mechanisms in stuttering are equally affected across effectors, these findings are important to point to a common motor inhibition system in a typical population and in other clinical populations, a result which supports the findings in our study.

As expected, AWS were overall more biased toward GO responses in both manual and speech conditions. Thus, it can be hypothesized that stuttering as a disorder can be not only a failure to sustain speech fluency but is also associated with a more general disbalance of motor control. This claim found support in a number of behavioural studies that reveal atypical general motor features related to AWS (for a discussion, see Max, Guenther, Gracco, Ghosh, & Wallace, 2004; Neilson & Neilson, 1987). AWS were shown to have delayed motor onset times in both speech and manual responses (e.g., Hulstijn et al., 1992; Archibald & De Nil, 1999; Smits-Bandstra et al., 2006). In addition, poorer manual sequencing motor skills such as poorer finger tapping and increased variability and lower accuracy in bimanual finger tapping have been reported by Smits-Bandstra & De Nil (2013) and by Zelaznik et al. (1997), respectively.

Finally, CWS and adolescents who stutter also displayed a non-speech motor synchronization deficit for accuracy and over-anticipation of an external rhythmic event (metronome or musical stimuli) as well as lower consistency of motor responses (Falk, Müller, & Dalla Bella, 2015). Therefore, despite the methodological differences, the results of these studies and our studies all point to how poorly coordinated the speech and manual effectors are when a proactive choice of a motor command is needed. Altogether, these results demonstrating deficits across speech motor and non-speech motor effectors are compatible with the idea that stuttering could reflect wider difficulties in motor control that may jointly affect the entire inhibition motor system but is more evident in speech.

### 2.8 Conclusion, Limitations, and Future Research Directions

In sum, response inhibition differences have been linked to developmental stuttering in children and adults (e.g., Markett et al., 2016; Ning et al., 2017; Neef et al., 2018; Eggers et al., 2013). Our findings in the proactive condition link atypical inhibition to the unreliable anticipation of stopping commands rather than more basic stimulus-response stopping. Therefore, not all inhibitory control paradigms will be equally sensitive to a deficit in stuttering. Other strengths of this work include the large sample of AWS and carefully matched profiles of the control participants.

Several methodological issues that may warrant consideration. First, it should be noted that AWS in our study fell disproportionately in the mild range of stuttering severity. Second, our methodology cannot be used to calculate the SSRT, which is thought to be slower in AWS. (Markett et al., 2016). We suggest that future behavioural studies should compare both approaches to inhibitory control in the same participants. Third, we observed a potential small delay of the microphone which might have led a slower RT in the speech condition. This delay

might have been produced lower sensitivity of the microphone or/and the voiceless initial sounds [t] in the word [tip] and needs further investigation.

Although recent research work on stuttering has offered a number of important findings, we are still left with the question as to what role inhibition plays in speech motor sequencing in stuttering and whether behavioural investigations are a sensitive measure to group differences or more time-precise instruments are needed. Future investigations into response inhibition need to continue targeting this question. As for the potential involvement of cortico-basal ganglia-thalamo-cortical loops associated with response inhibition in stuttering, neuroimaging and electrophysiological work is warranted to provide a more direct and precise evidence. Such investigations may also target questions of differences in severity and variability of speech disfluencies and secondary behaviours. These findings will shed more light on our understanding of the etiological nature of stuttering and contribute to the development of new effective interventions. If stuttering is a domain-general motor control disorder, distinct treatments might focus on sequential activation and deactivation of motor commands. Combining motor practice with highly specific brain stimulation may facilitate more effective performance in this domain.

# CHAPTER 3

## ERP components associated with successful and failed stopping in a reactive inhibition task by adults who stutter

### 3.1 Introduction

Stuttering is recognized as a genetically transmitted neurodevelopmental disorder (Yairi & Ambrose, 1996; Suresh et al., 2006). The core symptoms of stuttering are the interruption of the progression of speaking that include speech disfluencies, such as prolongations, blocks, part-word repetitions, and arguably word repetitions (Ward, 2018; Bloodstein & Ratner, 2008; Yairi & Ambrose, 1996). The incidence of stuttering is approximately 5 % in children below the age of 6 years: of these 5 % 70 % will recover naturally; however, 30 % will persist in stuttering for life (Cavenagh, Costelloe, Davis, & Howell, 2015; Yairi & Ambrose, 1999). Stuttering is often associated with increased anxiety of speaking and isolation that can limit individuals' social experiences and potentially negatively effect on a person's quality of life in both childhood and adulthood (Alm, 2004; Blood, Blood, Bennett, Simpson, & Susman, 1994; Craig & Craig, 2003).

Although a comprehensive understanding of mechanisms causing stuttering has not been offered; the most recent causal research focuses on neurophysiological factors and atypical brain activity in pre-motor, motor and sensory motor areas (e.g., Chang et al., 2018; Daliri & Max., 2015; Chang et al., 2009; Watkins et al., 2008; see for a review Belyk, Kraft, & Brown, 2015; Etchell et al., 2018). A recent area of interest involves a potential link between stuttering and abnormalities in inhibitory control (see Etchell et al., 2018, for a review). An influential study by Markett et al. (2016) showed that AWS have slower stop signal reaction time (SSRT) on a manual Stop-Signal Task (SST); they suggested that AWS have slower braking of reactive

manual responses (Markett et al., 2016). Evidence for less controlled inhibition and increased impulsivity in stuttering has also been supported by two GO-No-GO (GNG) studies in which children who stutter (CWS) showed higher number of false alarms compared to children who do not stutter (CWNS). Neuroimaging research in stuttering has further supported inhibitory aberrations because of unusual function and structure of the right hemisphere 'cortico-basal ganglia-thalamo-cortical loops' that are thought to mediate inhibition (see Etchell 2018, for a review). Stuttering was shown to be associated with overactivity in the right frontal hemisphere structures during speech tasks (Brown, 2005; Belyk, 2014; Budde, 2014; Neef et al., 2015), and differences in anatomical connectivity between these regions correlates positively with stuttering severity (Neef et al., 2018).

However, not all previous findings are consistent with inefficient inhibitory function in stuttering. The findings from our previous study (Study 1) did not support the conclusions by Markett et al. (2016) because stopping effectiveness and accuracy in AWS did not differ from AWNS. Although findings from the developmental studies need to be taken with caution when comparing with adults, it is important to mention Eggers et al. (2018) also did not identify differences in SSRT or accuracy of stopping between CWS and CWNS. So far, the evidence for deficient inhibitory control in stuttering is inconclusive.

Such inconsistency between these studies might stem from the small number of studies to date, but also the sensitivity of the methods. Behavioural manifestation of a complex cognitive operation can be obscured by variation in methods and small sample sizes. Neurophysiological study of inhibition may also be sensitive to atypical inhibition (Bari & Robins, 2013) even when behavioural measures are not used. Our approach will combine event-related neurophysiological measures of inhibition with innovative behavioural methods to provide a more comprehensive

investigation in AWS. Electroencephalography (EEG) is a noninvasive neurophysiological method with millisecond precision that has shown sensitivity to anomalies of inhibition (Luck, 2014). Of particular interest are the event-related potentials (ERP), N2 and P3 (often referred to as a N2-P3 complex), which are associated with inhibitory processes (Ramautar & Ridderinkhof, 2006; Luck, 2014).

P3 is considered a direct biomarker of inhibition because its amplitude is decreased in successful STOP trials in healthy individuals (Wessel & Aron, 2015; Albert et al., 2013; Kok, Ramautar, Ruiter et al., 2004; Bekker, Kenemans, Hoeksma, Talsma, & Verbaten, 2005; Donkers & van Boxtel, 2004; Smith, Johnstone, & Barry, 2006; Smith, Jamadar, Provost, & Michie, 2013). The inhibitory P3 peak occurs around 300 ms and is thought to have a central-parietal origin. N2 is considered an index of attentional resources and also related to conflict monitoring between competing response options (Luck, 2014; for review, see Van Veen & Carter, 2002). Although the N2 occurs before P3, its latency and amplitude were shown to be associated with inhibition of the pre-potent stopping response in stop-signal and GNG paradigms (e.g., Lavric et al., 2004). The N2 peak has a fronto-central origin and precedes P3 by around 150 ms.

The research on the timing of inhibitory related electrophysiological responses in persons who stutter is minimal. A sole ERP study of AWS employed a cued color-naming GNG task (Ning et al., 2017), which showed decreased P3 amplitude in AWS. As this was a speech task, this P3 anomaly was interpreted as aberrations in inhibition of planned speech responses in AWS. Behaviourally, however, no differences in percentage of false alarms or reaction times between AWS and AWNS were indicated. The sole ERP study of CWS by Piispala et al. (2016) tested N2 and P3 in CWS during a visual GNG task. The major group difference was a longer

latency for P3 in GO trials for AWS that was interpreted as an aberration in stimulus evaluation and response selection. No differences in the amplitude of N2 and P3 were found and also no behavioural differences in No-GO responses or GO RT. Additional analysis of the same data by Piispala et al. (2017) and Piispala et al. (2018) revealed smaller (less positive) mean amplitude of P3 for both GO and No-GO trials, which might arise from prolonged and asymmetrical N2 component and exhibit less alpha activity than CWNS, which might indicate problems with stimulus evaluation and response selection between GO or STOP command which can compromise or delay inhibition.

Although the findings to date on neurological anomalies in inhibition are not fully consistent, the behavioural evidence from our previous Stop-signal tasks (Chapter 2) suggest anomalies in the timing and amplitude of inhibition measures will be found with more sensitive inhibition tasks. In this study, we tested inhibition in AWS by monitoring the amplitude and latency of the N2-P3 complex while participants performed a stop signal task, identical to the task in Chapter 2 (Dunovan et al., 2015). If AWS may have a less finely-coordinated or more fragile inhibitory control, we predict the N2-P3 potentials will have smaller amplitude peaks and delays compared to AWNS.

## 3.2 Methods

### 3.2.1 Participants

All participants were recruited from the Max Planck Institute for Human Cognitive and Brain in Leipzig, Germany. The participants included 12 AWS (4 female, 2 left-handed, mean age 30.75, SD = 5.17, age range = 22 - 40 years) and 14 AWNS (4 female, 2 left-handed, mean age 30.36, SD = 5, age range = 22 - 40 years), matched for age, handedness, and education (1 = school; 2 =

high school; 3 = less than 2 years university; 4 = at least 2 years university; 5 = 4 years university; 6 = postgraduate). Apart from stuttering, no medical history, neurological impairment, or drug use, potentially influencing their neurological function, were reported by the participants. The AWNS reported a negative family history of stuttering or any other speech-language disorders. All participants provided written informed consent and received 9 Euros per hour, with an additional bonus up to 6 Euros for performance on the behavioural tasks. Table 1 provides a summary of the demographic information.

To evaluate stuttering, both groups of participants were asked to read a text aloud, tell a story about their lives, and describe their experience during the experiment while being video recorded. The samples were transcribed offline to estimate the stuttering severity index (SSI-4), which includes the frequency and duration of stuttering dysfluencies along with physical concomitants of stuttering (Riley, 2009). Based on the SSI-4, 2 AWS showed very mild stuttering, 5 AWS showed mild stuttering, 2 AWS showed moderate stuttering, 1 AWS showed severe stuttering, and 1 AWS showed very severe stuttering. One participant refused video recording. His stuttering severity was not evaluated and was excluded from the correlational analysis. Evidence of stuttering was not observed among the AWNS.

Each AWS also completed the Overall Assessment of the Speaker's Experience of Stuttering (German version of the Overall Assessment of the Speakers Experience of Stuttering; Yaruss & Quesal, 2006) that is designed to evaluate (1) general perspectives on stuttering, (2) affective, behavioural and cognitive reactions to stuttering, (3) communication difficulties in everyday life, and (4) impact of stuttering on the quality of life. The OASES also provides an index of stuttering impact which indicates 1 AWS had a mild stuttering impact score, 2 were mild-moderate, 6 were moderate, 1 was moderate-severe, and 1 was severe. One participant did

not fill out the OASES and his/her stuttering impact was not evaluated and excluded from the correlational analysis.

**Table 3.1** Brief summary of study participants. Parametric and non-parametric statistical comparisons of group characteristics; standard deviations are in brackets; all tests were two-tailed.

| | AWS | AWNS | *p* value |
|---|---|---|---|
| N | 12 | 14 | n/a |
| Age in years (mean)[a] | 30.75 (SD = 5.17) | 30.36 (SD = 5.02) | .85 |
| Sex (male) (%)[b] | 8 (66) | 10 (71.43) | .79 |
| Handedness (right-handed) (%)[b] | 10 (85) | 12 (86) | .87 |
| Education (mean)[c] | 4.66 (SD = 1.37) | 5.36 (SD = .93) | .21 |
| SSI-4 total score (mean) | 23.1 (SD = 8.94) | n/a | n/a |
| OASES total score (mean) | 2.61 (.77) | n/a | n/a |

[a] t test
[b] $\chi$2-test.
[c] MWU

### 3.2.2 Apparatus, stimuli, and procedure

A computerized stop signal game, adapted from Dunovan et al. (2015), was employed as a reactive inhibition task (Fig. 1), which was identical to the Reactive Manual task in chapter 2. The game was programmed in NBS Presentation (https://www.neurobs.com/). During each trial, a participant watched a blue bar that rose vertically toward a white horizontal target line.

Similar to the prototypical design of the stop signal paradigm (e.g., Verbruggen & Logan, 2008), the task consisted of predominantly GO trials to increase participants' bias to respond, thereby, maximizing inhibition requirements for STOP trials. In 75% of trials, the bar would cross the target line (later referred as GO trials). Participants were asked to press a button on the

button box to stop the bar as close to the target as possible. GO trials terminated after a participant's response or the total trial time was reached (650 ms) and the bar would freeze and stay on the screen for another 1000 ms. In 25% of trials (STOP trials), the bar would change to red, indicating the button press response must be held back (inhibited). This color change is s a visual stop signal that was presented at five stop signal delays (200-250-300-350-400 ms). After the trial was completed, after-trial accuracy feedback was displayed on the screen for 1000 ms. Each trial was followed by an interstimulus interval jittered between 800 and 1200 ms. Figure 1 gives a schematic representation of the reactive inhibition task.

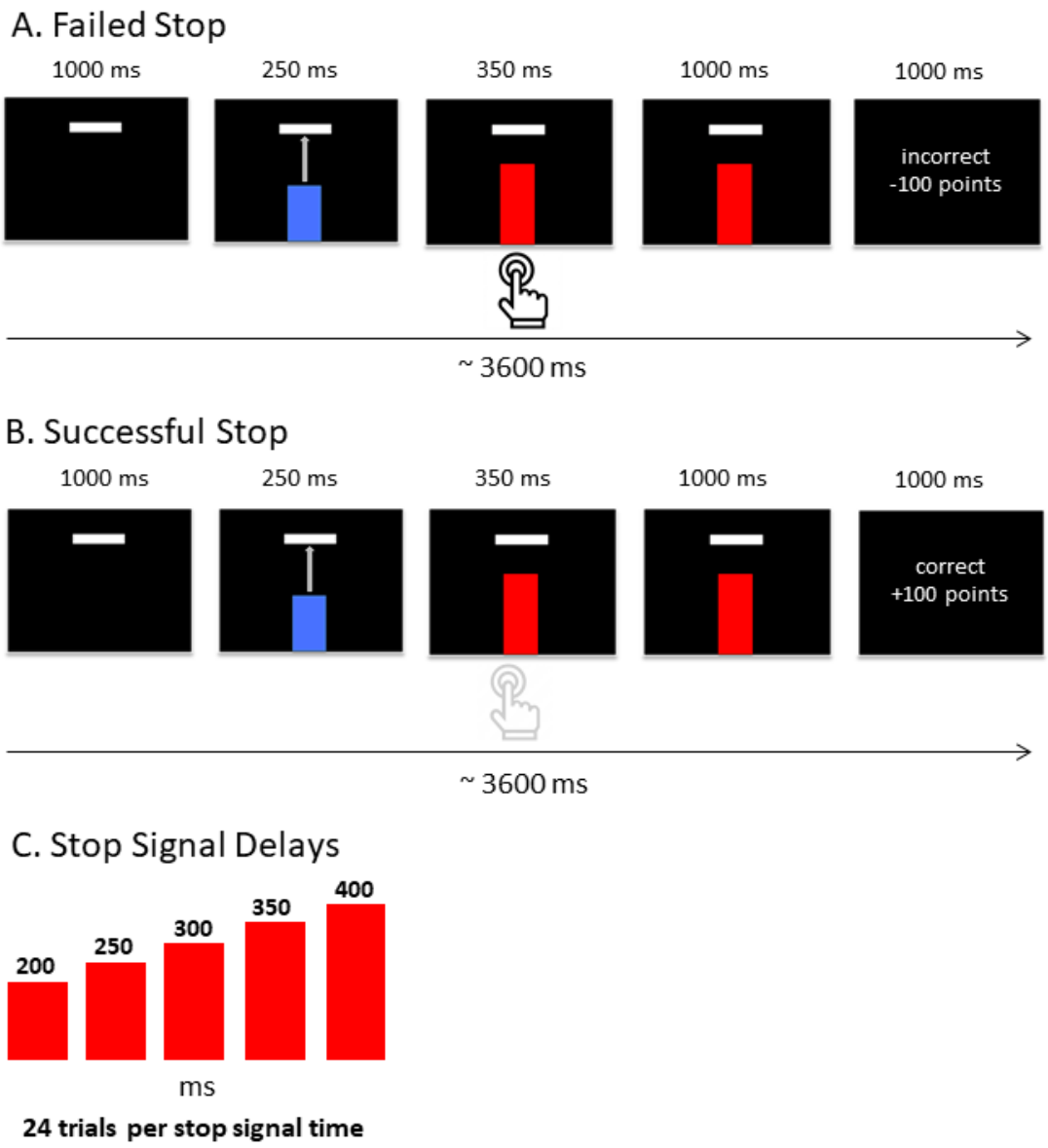


**Figure 3.1** Timeline and feedback of failed STOP trials (a), successful STOP trials (b), and stop signal delays (c) in the reactive task.

At the beginning of the task, participants were shown a slide with instructions, which followed a practice block of 22 trials. The practice included solely GO trials in order to familiarize participants with the experimental procedures. After the practice was completed, a new slide with further instructions was presented, explaining that a stop signal would appear unexpectedly. There were a total of 19 experimental blocks with 40 trials each and took

approximately 30 minutes. After each block of trials, participants were given an option to take a short break.

All stimuli were presented on a 17-inch monitor with a screen refresh rate set at 75 Hz and administered on a computer running Windows XP. Subjects were tested in a dimly lit, sound-attenuating room and were comfortably seated in a chair. The screen was 108 - 109 cm away from participants' nasion. Participants were instructed to look at the target line for the duration of the task.

Subjects responded to GO and STOP trials by using a custom-made button box that was placed on a pillow on a participant's lap. Response timing was accurate to 1 ms. Assignment of response effectors (left or right index finger) was assigned depending on a participant's handedness test. Participants were instructed to respond as accurately as possible to the GO trials by pressing the central button on the button box in GO trials and not pressing the button in STOP trials. Participants were instructed not to sacrifice speed to anticipate the stop signal. Additionally, it was explained that they would not always be able to cancel their response after the color changes. However, participants were asked to be as accurate as possible. To keep participants motivated, we employed a reward system similar to Study 1. After each trial, the feedback with a number of earned reward points (up to 100 points) depending on the response precision to the target line. If a participant successfully suppressed a response on a STOP trial, they received 100 points. Conversely, if a participant pressed the response button, they lost 100 points. After each block, a participant saw a summary with the total number of points earned. At the end of the experiment, the total reward points were converted into the monetary bonus (up to 6 Euro).

### 3.2.3 Dependent Variables for the Behavioural Analysis

As per Chapter 2, the following dependent variables were acquired.

(1) The point of subjective equality (PSE): The psychometric measure of stopping effectiveness was calculated by fitting a sigmoid curve on the data with observed probability of stopping. PSE is the point at which the psychometric curve crosses the 50% probability of successful stopping.

(2) The observed probability of successful stopping (pSTOP) per SSD: the mean number of failed STOP trials divided by the number of STOP trials per SSD.

(3) Reaction time of failed STOP trials (fSTOP RT): RT of responses on failed STOP trials.

(4) Go Response time (Go RT): GO RT was a measure from the onset of stimulus to the response. An error or RT earlier than 200 ms was considered premature and deleted from the analysis.

### 3.2.4 Statistical Analysis of the Behavioural Data

All statistical analyses were conducted by using STATA version 15.0 (StataCorp, 2017) and R (R Core Team, 2013). The PSE, GO RT and fSTOP of the AWS and AWNS were compared with independent sample t-tests. pSTOP was analyzed with a 2 [Group (AWS, AWNS)] x 5 [SSD (200, 250, 300, 350, 400 ms)] Analysis of Variance (ANOVA).

## 3.3 EEG Analysis

### 3.3.1 EEG data acquisition

EEG activity was recorded continuously with Ag/AgCl electrodes from 64 locations of the 10-20 system using a REFA amplifier. First, a participant's head circumference was measured to mark the vertex. The ground electrode was placed on the sternum. The horizontal

and vertical electrooculogram (EOG) were recorded by using two electrodes placed on the outer canthus of each eye and two electrodes above and below the right eye. In addition, two electrodes were placed over the left and right mastoids. The online reference was the electrode on the left mastoid, and the right mastoid electrode was used later for the offline referencing. The impedances were measured and maintained below 10 kΩ. If needed, additional gel was added to electrodes with high impedances during experimental breaks. During task performance, EEG data were recorded continuously at a sampling rate at 500 Hz.

### 3.3.2 EEG preprocessing

Data analyses were conducted using the EEGLAB toolbox (Delorme & Makeig, 2004) and custom-written scripts, implemented in MATLAB 2018b (Mathworks, Inc., Sherborn, MA, USA). For each subject, the EEG signals were re-referenced to an off-line reconstructed average of the mastoid reference. The signals were then filtered offline using a band-pass filter [0.5 80] Hz. Due to a bridging issue in the cap Cz and Oz were interpolated together with individually identified bad channels. The data were visually evaluated, and all large non-brain related artifacts were removed. Independent Components Analysis (ICA) (runica) was run on each subject to identify and remove eye blinks, heart activity, muscle activity, or line noise. All other components that could not be readily identified as a one-of-a-kind biological artifacts or pure line noise were left in the data; as we could not justify their removal in case they were mixtures containing real cortical data. The remaining ICA activations were then multiplied with the continuous EEG data and filtered with a band-pass filter [0.5 80] Hz resulting in scalp data that was free of identifiable artifacts.

### 3.3.3 EEG Data Analysis

The preprocessed signal was segmented into 1200 ms epochs (-200 to 0 ms pre-stimulus for baseline correction and 1000 ms, following stop signal stimulus onset). The epochs were baseline-corrected using the pre-cue activity. For each subject, the trial-by-trial data were manually inspected again in order to remove any trials with visible artifacts. The remaining trials were from each participant were then averaged separately according to successful and failed STOP trials. Practice trials were not included in the analysis. To match GO trials to STOP trials, we tried three following methods: (1) to select GO trials at the beginning of the raising bar; (2) select GO trials at 300 ms; and (3) to select 24 GO trials at 200, 250, 300, 350, 400 ms after the start of the bar raising. None of the attempts to match GO trials to STOP trial was appropriate because the bar in GO trials was continuously moving after the time-locking event. For this reason, GO trials were included only in the behavioural analysis and excluded from the ERP analysis.

The next analysis step involved automatic detection of the peak amplitude and peak latency of N2 and P3 in each participant in each condition (successful stops, failed stops) using a customized Matlab script. Peak amplitude was defined as the highest point of the waveform within the time window estimated for each ERP. Visual inspection of waveforms showed that the N2 component was more pronounced in fronto-central regions. The P3 component was more pronounced in centro-posterior regions. Peak latency was defined as the time of peak amplitude of the ERP waveform within the same time window. These time windows were based on grand ERP averages of the groups and conditions combined. The time window for N2 based on F1, Fz , F2 , FC1 , FCz , FC2 , C1 , and C2 electrodes was 190 - 250 ms. The time window for P3 based on F1, Fz, F2, FC, FCz, FC2, C1, C2, CP1, CPz, CP2, P1, Pz, and P2 electrodes was 250 - 400

ms. Peak latency and mean amplitude measures were averaged across electrodes within clusters selected to be compatible with the 10 - 20 electrode placement system.

### 3.3.4 EEG Dependent Variables

The following dependent variables were analyzed:

(1) N2 amplitude: The most negative (or upgoing) point of the waveform within the time window (190 - 250 ms)

(2) N2 latency: the timing of the peak amplitude for N2 within the time window (190 - 250 ms)

(3) P3 amplitude: The most positive (or downgoing) point of the waveform within the time window (250 - 400 ms)

(4) P3 latency: the timing of the peak amplitude for P3 within the time window (250 - 400 ms)

In the ERP analysis, N2 mean amplitude and latency at Fz were analyzed with a 2 x 2 ANOVA with Group (AWS, AWNS) as a between-subject factor and Conditions (failed stops, successful stops) as a within-subject factor. As a secondary test of ERP analysis, N2 mean amplitude and latency were analyzed with a three-way repeated-measures ANOVA with Group (AWS, AWNS) as a between-subject factor and Conditions (failed stops, successful stops) and region [Frontal (Fz, F1, F2) x Fronto-Central (FC, FCz, FC2) x Central (C1, C2)] as a between-subject factor.

P3 mean amplitude and latency at Pz were analyzed with a 2 x 2 ANOVA with Group (AWS, AWNS) as a between-subject factor and Conditions (failed stops, successful stops) as a within-subject factor. As a secondary test, P3 mean amplitude and latency were analyzed with a three-way repeated-measures ANOVA with Group (AWS, AWNS) as a between-subject factor and Conditions (failed stops, successful stops), region [Frontal (Fz, F1, F2) x Fronto-Central (FC, FCz, FC2) x Central (C1, C2) x Centro-Posterior (CP1, CPz, CP2) x Posterior (P1, PZ, P2)]

as a between-subject factor. If the effect of Electrode region was significant, the post-hoc test of Tukey-Kramer pairwise comparisons was applied ($p < .05$). If the interaction between the factor condition and the between-subjects factor was significant, we computed post hoc pairwise comparisons at the group level (AWS, AWNS) to analyze the significance of N2 and P3. To account for potential violations of the sphericity assumption, degrees of freedom were adjusted using the Greenhouse-Geisser correction. Finally, the Pearson correlation between N2 and P3 peak latency on successful STOP trials and PSE was measured (Aron & Wessel, 2015).

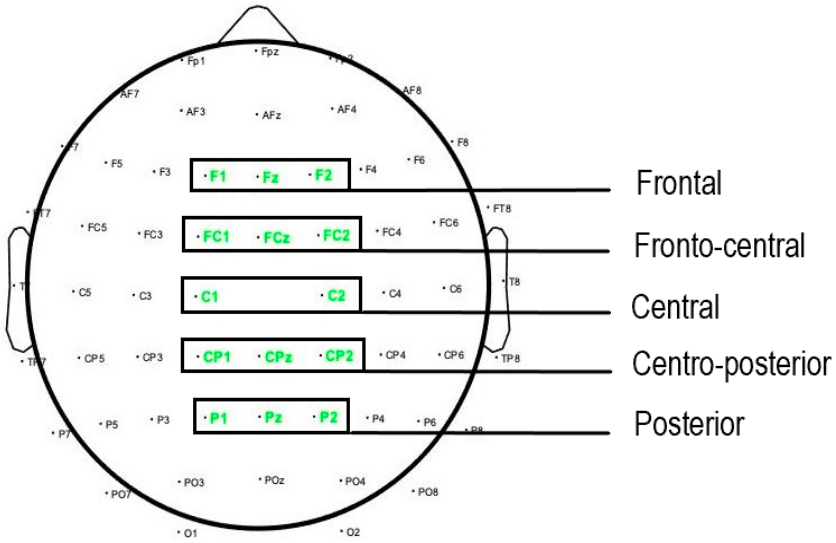


**Figure 3.2** Layout illustrating the electrodes that were included in the ERP analyses at frontal, fronto-central, central, centro-parietal, and parietal regions.

### 3.4 Results

Descriptive statistics for ERP peak and latency measures are presented in Table 3.2 according to groups and condition. Grand averaged ERP waveforms are shown in Figure 3.3 for each electrode cluster. Descriptive statistics for PSE, pSTOP, and fSTOP RT are presented in Table 3.3 by groups and condition.

### 3.4.1 ERP amplitude and latency

#### 3.4.1.1 P3 amplitude

**Initial Analysis:** There was no significant effect of Group at Pz ($F(1, 24) = 2.92$, $p = .1$) (AWS: M = 20.48 μV, SD = 6.5; AWNS: M = 24.99 μV, SD = 7.07). The effect of Accuracy was also not significant ($F(1, 24) = .02$, $p = .89$). No two-way interactions between Group and Accuracy was significant ($p > .3$).

**Post-hoc Analysis:** The grand average P3 amplitude was significantly lower in AWS compared to AWNS ($F(1, 253) = 18.88$, $p < .0001$, $\eta_p^2 = .07$) (AWS: M = 21.47 μV, SD = 6.78; AWNS: M = 25.47 μV, SD = 9.87). The effect of Accuracy was not significant ($F(1, 253) = .04$, $p = .85$), but the effect of Electrode region was significant ($F(4, 253) = 9.12$, $p < .001$, $\eta_p^2 = .13$). Post-hoc testing using using Tukey's HSD procedure indicated significant differences between region Frontal and Fronto-Central electrodes (M = 18.31 μV , SD = 7.13; M = 25.63 μV , SD = 9.94, respectively) , Frontal and Central (M = 18.31 μV , SD = 7.13; M = 26.73 μV , SD = 9.19, respectively), Frontal and Centro-Posterior (M = 18.31 μV , SD = 7.13; M = 25.48 μV , SD = 8.14, respectively), and Central, and Posterior electrode regions (M = 26.73 μV , SD = 9.19; M = 22.12 μV , SD = 6.8; respectively). No two-way or three-way interactions between Group, Accuracy, and Electrode region were significant ($p > .8$) (see Figure 3.6).

#### 3.4.1.2 P3 latency

**Initial Analysis:** There was no significant effect of Group at Pz ($F(1, 24) = .28$, $p > .5$) (AWS: M = 337 ms, SD = 37.6; AWNS: M = 343.9 μV, SD = 37.1). The effect of Accuracy was also not significant ($F(1, 24) = 3.02$, $p > .1$). No two-way interactions between Group and Accuracy was significant ($p > .4$).

**Post-hoc Analysis:** The grand average latency of P3 latency was significantly earlier ($F(1, 253) = 4.07$, $p = .045$, $\eta_p^2 = .016$ - AWS: M = 322.4 ms, SD = 36.12; AWNS: M = 331 ms , SD = 36.16). There was a significant effect of Accuracy ($F(1, 253) = 15.79$, $p < .001$, $\eta_p^2 = .059$), showing that P3 latency peaked earlier in successful STOP trials (M = 318.6 ms, SD = 35.87) than in failed STOP trials (M = 335.37 ms, SD = 34.95). Additionally, there was a significant effect of Electrode region ($F(4, 253) = 5.64$, $p < .008$, $\eta_p^2 = .082$). Post-hoc testing indicated significant differences between region Frontal and Centro-Posterior (M = 315.5 ms , SD = 35.136; M = 336.28 ms , SD = 34.56, respectively), Frontal and Posterior (M = 315.5 ms , SD = 35.6; M = 341 ms , SD = 34.71, respectively), and Fronto-Central and Posterior electrode regions (M = 318.2 ms , SD = 34.77; M = 341 ms , SD = 34.71, respectively). No two-way or three-way interaction between Group, Accuracy, Electrode regions were significant ($p > .8$) (see Figure 3.6).

#### 3.4.1.3 N2 amplitude

**Initial Analysis:** There was no significant effect of Group at Fz ($F(1, 24) = .4$, $p = .53$) (AWS: M = -2.94 μV, SD = 4.2; AWNS: M = -1.85 μV, SD = 5.66). The effect of Accuracy was also not significant ($F(1, 24) = .4$, $p = .53$). No two-way interactions between Group and Accuracy was significant ($p > .8$).

**Post-hoc Analysis:** For the grand average N2 amplitude, there was no significant effect of Group ($F(1, 151) = 2.45$, $p = .12$) and no significant effect of Accuracy (failed STOP vs. successful STOP) ($F(1, 151) = .02$, $p = .9$). The effect of Electrode region was also not significant ($F(2, 151) = .5$, $p < .61$). No two-way or three-way interaction between the effect of Group, Electrodes region, and Accuracy were significant ($p > .6$) (see Figure 3.6)..

#### 3.4.1.4 N2 latency

**Initial Analysis:** There was no significant effect of Group at Fz ($F(1, 24) = .02$, $p > .89$) (AWS: M = 192.8 ms, SD = 18.95; AWNS: M = 193.9 μV, SD = 27.06). The effect of Accuracy was also not significant ($F(1, 24) = .34$, $p > .57$). No two-way interactions between Group and Accuracy was significant ($p > .57$).

**Post-hoc Analysis:** For the grand average N2 latency, there was no significant effect of Group ($F(1, 151) = .02$, $p = .9$) and no significant effect of Accuracy ($F(1, 151) = 1.49$, $p = .22$). The effect of Electrode region also was not significant ($F(2, 151) = 1.67$, $p < .19$). No two-way or three-way interaction between the effect of Group, Region electrodes and Accuracy were significant ($p > .15$) (see Figure 3.7).

**Table 3.2** Means and standard deviations (in parentheses) for ERP waveform characteristics (amplitude and latency), by group and trial accuracy (successful STOP and failed STOP trials).

| Component | AWS | | AWNS | |
|---|---|---|---|---|
| Region | successful STOP | failed STOP | successful STOP | failed STOP |
| **P3 Amplitude (μV)** | | | | |
| Frontal | 17.65 (SD = 3.94) | 16.33 (SD = 5.63) | 19.37 (SD= 8.55) | 19.53 (SD = 8.91) |
| Fronto-Central | 23.92 (SD = 6.05) | 22.72 (SD = 8.33) | 27.68 (SD = 11.81) | 27.52 (SD = 11.82) |
| Central | 23.87 (SD = 6.28) | 23.71 (SD = 7.89) | 29.08 (SD = 10.13) | 29.44 (SD = 10.63) |
| Centro-Posterior | 22.37 (SD = 6.53) | 22.76 (SD = 7.59) | 27.99 (SD = 8.41) | 27.96 (SD = 8.67) |
| Posterior | 19.56 (SD = 6.13) | 20.07 (SD = 6.67) | 24.38 (SD = 6.73) | 23.82 (SD = 6.92) |
| **P3 Latency (ms)** | | | | |
| Frontal | 300.4 (SD = 31.36) | 319.1 (SD = 40.02) | 311.3 (SD = 32.37) | 329.4 (SD = 35.9) |
| Fronto-Central | 302.1 (SD = 34.23) | 323.9 (SD = 37.87) | 312.4 (SD = 30.31) | 332.8 (SD = 32.9) |
| Central | 309.1 (SD = 30.74) | 327.6 (SD = 36.54) | 320 (SD = 37.25) | 337.9 (SD = 37.37) |
| Centro-Posterior | 323.6 (SD = 38.73) | 324.72 (SD = 27.98) | 331.14 (SD = 37.26) | 346.8 (SD = 32.17) |

| | | | | |
|---|---|---|---|---|
| Posterior | 332.4 (SD = 36.08) | 343.1 (SD = 28.77) | 340 (SD = 37.82) | 347.6 (SD = 37.1) |
| **N2 Amplitude (μV)** | | | | |
| Frontal | -2.45 (SD = 3.67) | -4.2 (SD = 4.23) | -1.02 (SD = 5.67) | -2.62 (SD = 5.74) |
| Fronto-Central | -3.8 (SD = 4.93) | -4.39 (SD = 4.2) | -2.5 (SD = 6.78) | -3.03 (SD = 8.18) |
| Central | -4.22 (SD = 5.07) | -2.05 (SD = 4.74) | -2.35 (SD = 6.15) | -.82 (SD = 8.27) |
| Centro-Posterior | -4.28 (SD = 4.99) | -1.11 (SD = 4.53) | -2.08 (SD = 5.33) | .11 (SD = 7.41) |
| Posterior | -4.21(SD = 5.12) | -1.32 (SD = 4.32) | -2.47 (SD = 4.99) | -.9 (SD = 5.68) |
| **N2 Latency (ms)** | | | | |
| Frontal | 194.6 (SD = 16.81) | 193.7 (SD = 19.62) | 197.5 (SD = 24.38) | 190 (SD = 27.38) |
| Fronto-Central | 188.8 (SD = 22.15) | 191.7 (SD = 19.19) | 189.5 (SD = 21.8) | 194.7 (SD = 23.64) |
| Central | 179.9 (SD = 19.86) | 192.5 (SD = 21.84) | 179.2 (SD = 20.15) | 193 (SD = 25.21) |
| Centro-Posterior | 177.3 (SD = 19.86) | 190.6 (SD = 24.26) | 181.8 (SD = 21.6) | 192.1 (SD = 25.58) |
| Posterior | 176.5 (SD = 19.1) | 188.7 (SD = 27.37) | 181.4 (SD = 24.93) | 191.8 (SD = 28) |

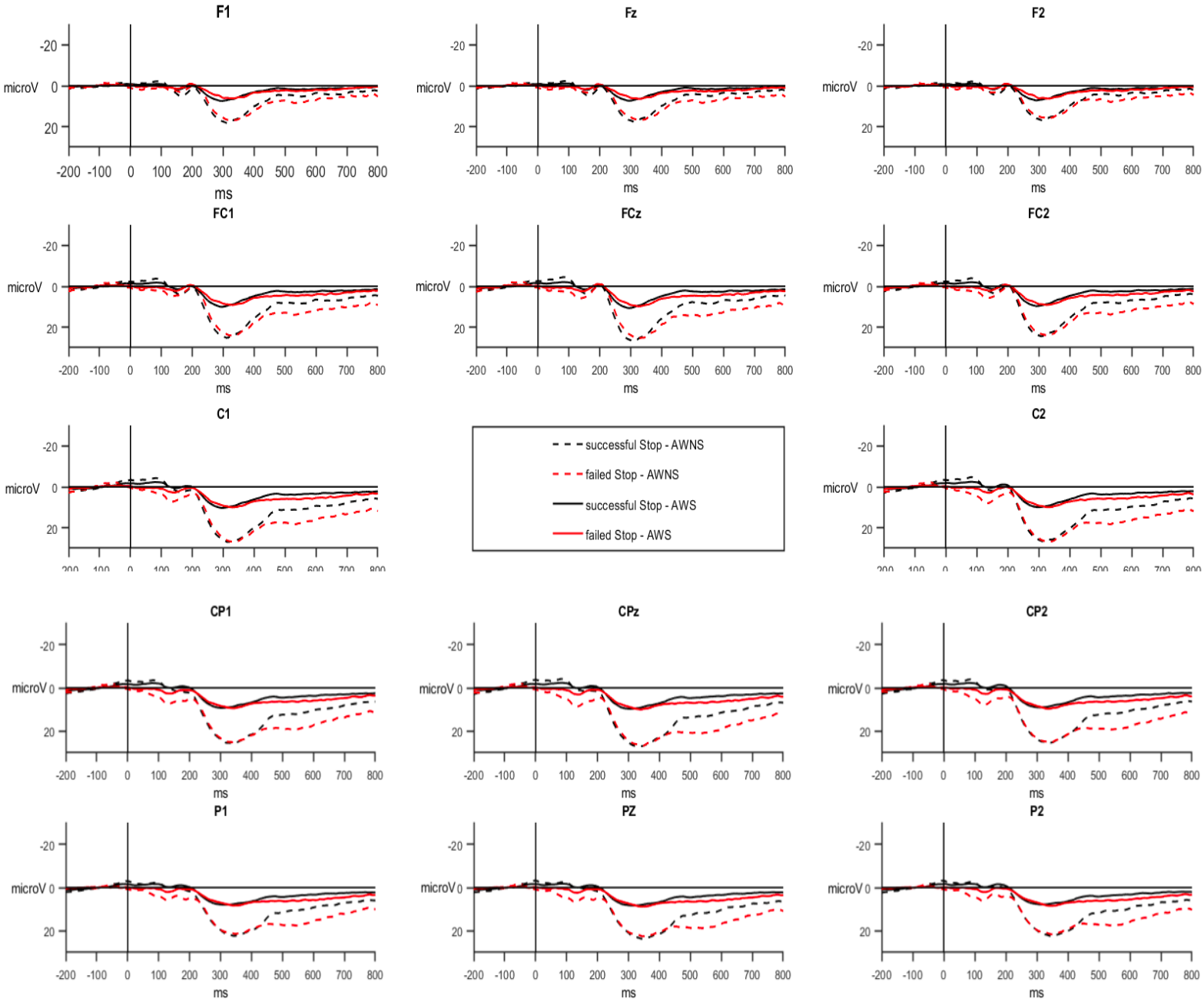


**Figure 3.3.** Grand average ERPs. Grand average waveforms are shown for 14 electrodes (F1, Fz, F2, FC, FCz, FC2, C1, C2, CP1, CPz, CP2, P1, PZ, and P2) for all trial types and groups. AWS are depicted with solid lines and AWNS with dashed lines. Successful STOP trials are depicted with solid lines and failed STOP trials with dashed lines.

**Successful STOP trials**

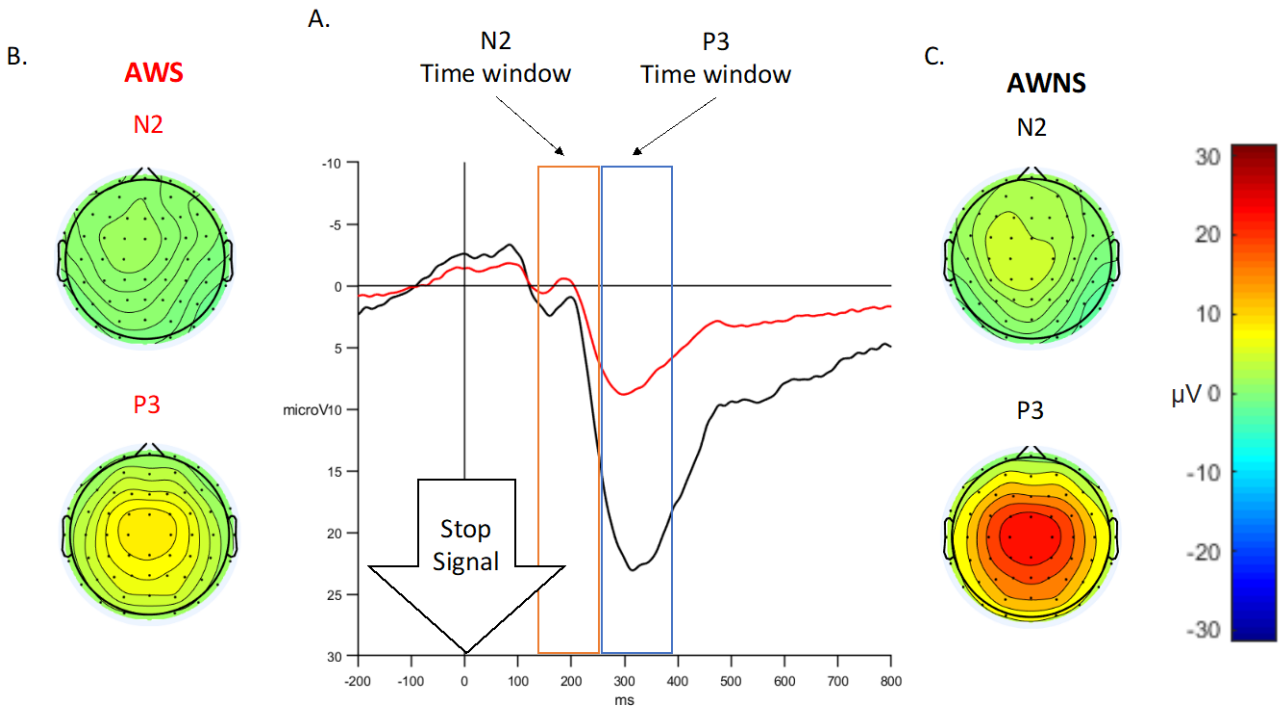


**Figure 3.4** ERP grand averages of successful STOP trials for AWS and AWNS. A: Grand-averaged ERPs computed at the average of 14 electrodes (F1, Fz, F2, FC, FCz, FC2, C1, C2, CP1, CPz, CP2, P1, PZ, and P2) for all artifact-free trials, corrected for eye movements, for both AWS and AWNS. Positive is plotted down, and shaded areas illustrate the N2 and P3 time windows (indicated in light grey), 190 - 250 ms (in orange) and 251 - 400 ms (in blue) after the stop signal, respectively. EEG was re-referenced to the average of the left and right ear lobe electrodes. B: Scalp topographies of the grand-averaged ERP in the N2 and P3 time windows for AWS. C: Scalp topographies of the grand-averaged ERP in the N2 and P3 time windows for AWNS.

**Failed STOP trials**

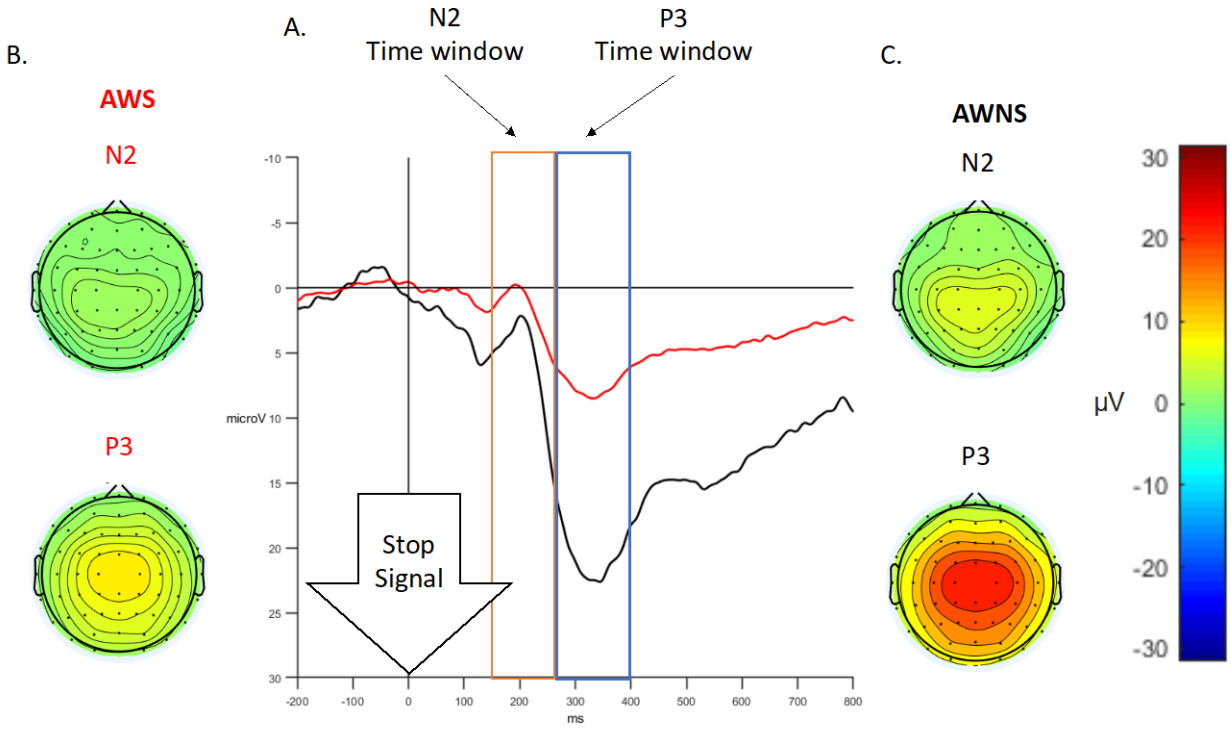


**Figure 3.5** ERP grand averages of failed STOP trials for AWS and AWNS. A: Grand-averaged ERPs computed at the average of 14 electrodes (F1, Fz, F2, FC, FCz, FC2, C1, C2, CP1, CPz, CP2, P1, PZ, and P2) for all artifact-free trials, corrected for eye movements, for both AWS and AWNS. Positive is plotted down, and shaded areas illustrate the N2 and P3 time windows (indicated in light grey), 190 – 250 (in orange) ms and 251 – 400 (in blue) ms after the stop signal, respectively. EEG was re-referenced to the average of the left and right ear lobe electrodes. B: Scalp topographies of the grand-averaged ERP in the N2 and P3 time windows for AWS. C: Scalp topographies of the grand-averaged ERP in the N2 and P3 time windows for AWNS.

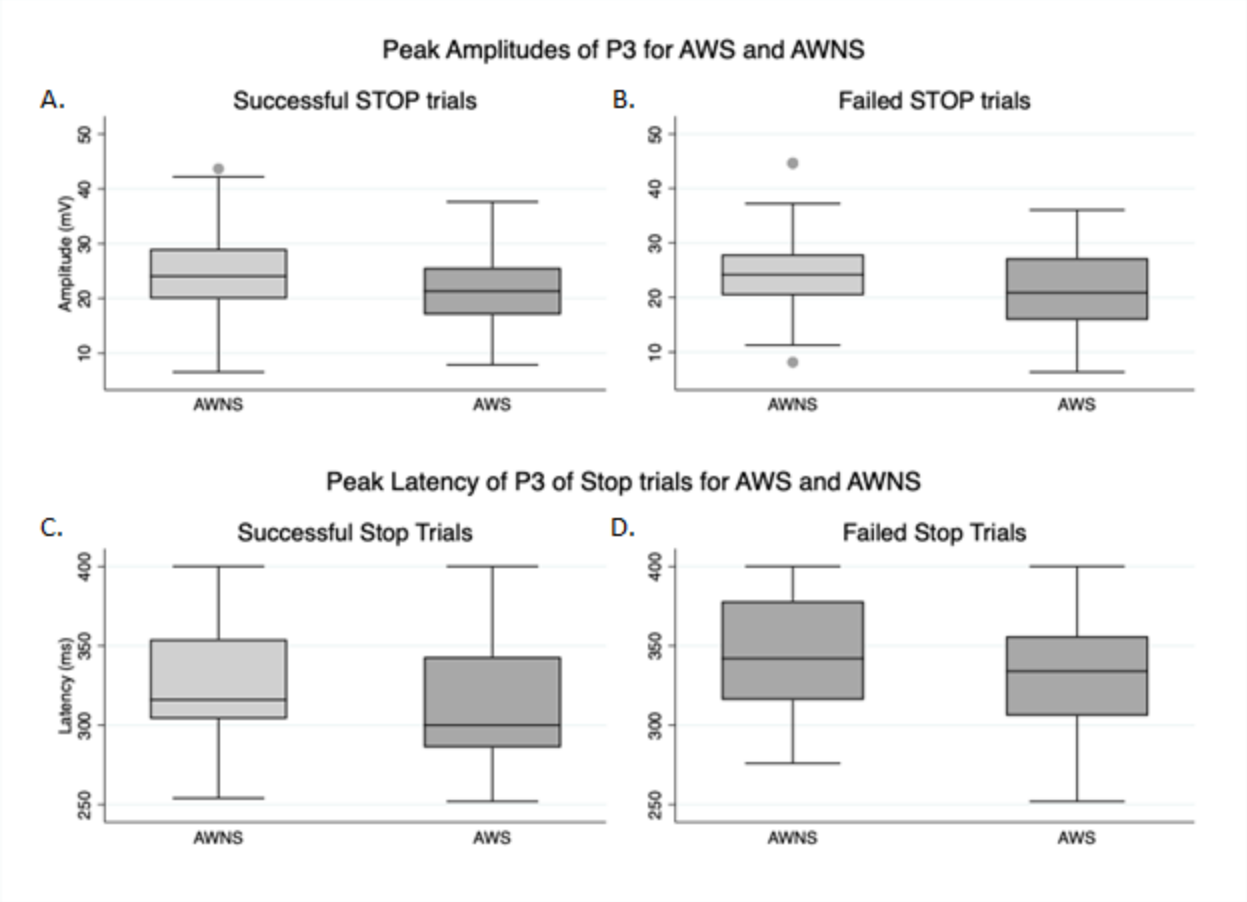


**Figure 3.6** Peak Amplitude and latency of P3. The mean amplitudes of P3 for AWS and AWNS in successful trials (A) and failed trials (B) across 14 electrodes (F1, Fz, F2 , FC , FCz, FC2, C1, C2, CP1, CPz, CP2, P1, PZ, and P2).The mean latency of P3 for AWS and AWNS in successful trials (C) and failed trials (D) across 14 electrodes. The dark line within the boxes indicates the median. The bottom and top lines of the rectangle represent the first and third quartiles respectively, while the whiskers represent the minimum and maximum. Circles below or above the boxes indicate extreme observations.

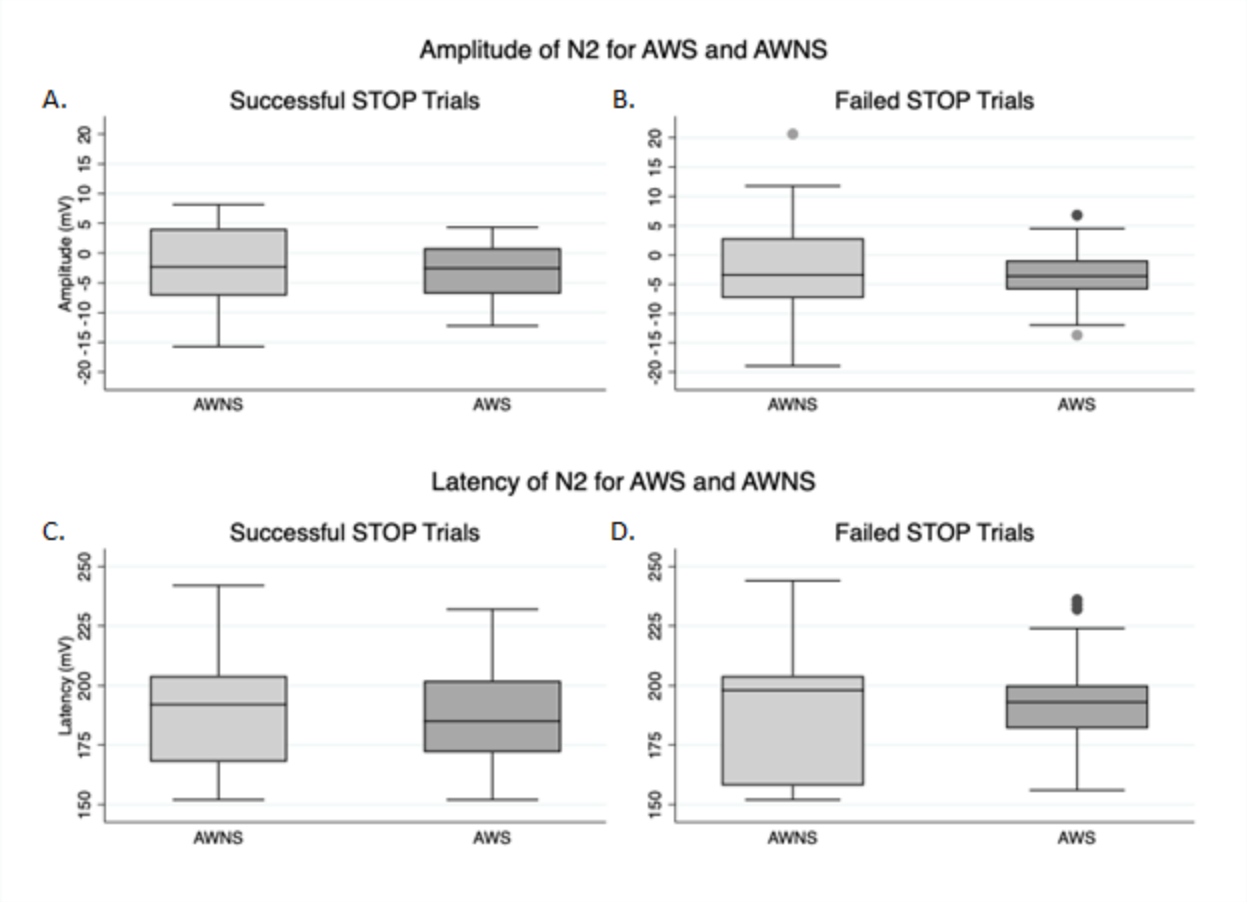


**Figure 3.7** Peak Amplitude and latency of N2. The mean amplitudes of N2 for AWS and AWNS in successful trials (A) and failed trials (B) across 8 electrodes (F1, Fz, F2 , FC , FCz, FC2, C1, and C2).The mean latency of N2 for AWS and AWNS in successful trials (C) and failed trials (D) across 8 electrodes (F1, Fz, F2 , FC , FCz, FC2, C1, and C2). The dark line within the boxes indicates the median. The bottom and top lines of the rectangle represent the first and third quartiles respectively, while the whiskers represent the minimum and maximum. Circles below or above the boxes indicate extreme observations.

### 3.4.2 Behavioural Performance

**PSE:** The point at which 50% accuracy of stopping was reached did not differ between groups ($t(24) = .7$, $p = .49$).

**pSTOP:** pSTOP did not differ statistically between AWS and AWNS ($F(1,124) = 1.06$, $p = .304$, $\eta 2 = .009$). The effect of SSD was significant ($F(1, 124) = 178.2$, $p < .0001$, $\eta 2 = .857$)

with post-hoc testing showed that pSTOP decreased significantly for longer SSDs (see Table 3.3). The Group by SSD interaction was not significant ($F(1, 124) = .96$, $p = .434$).

**fSTOP RT:** The fSTOP RT was not significantly different between AWNS and AWS ($t(24) = -.568$, $p = .575$; Table 3.3).

**GO RT:** The GO RT was not significantly different between AWNS and AWS ($t(24) = -.06$, $p = .95$; Table 3.3).

**Table 3.3** Descriptive statistics (means, standard deviation, *p*-value of the pairwise comparison based on t-test) for response times, of stopping, and Point of Subjective Equality in the reactive inhibition task.

| | AWS | AWNS | *p* value [a] |
|---|---|---|---|
| mean fSTOP RT | 508.3 (SD = 3.42) | 505.6 (SD = 3.35) | .58 |
| fSTOP RT (SSD = 200 ms) | 492.1 (SD = n/a) | 500.1 (SD = n/a) | n/a |
| fSTOP RT (SSD = 250 ms) | 460.2 (SD = 8.83) | 426.7 (SD = 13.47) | .058 |
| fSTOP RT (SSD = 300 ms) | 477.5 (SD = 4.67) | 473 (SD = 5.07) | .53 |
| fSTOP RT (SSD = 350 ms) | 499.3 (SD = 4.15) | 496.4 (SD = 2.42) | .55 |
| fSTOP RT (SSD = 400 ms) | 518.7 (SD = 3.93) | 514.8 (SD = 2.88) | .42 |
| pSTOP (SSD = 200 ms) | .024 (SD = .084) | .003 (SD = .011) | .36 |
| pSTOP (SSD = 250 ms) | .08 (SD = .047) | .021 (SD = .01) | .2 |
| pSTOP (SSD = 300 ms) | .219 (SD = .056) | .134 (SD = .028) | .17 |
| pSTOP (SSD = 350 ms) | .549 (SD = .069) | .524 (SD = .053) | .77 |

| | | | |
|---|---|---|---|
| pSTOP (SSD = 400 ms) | .87 (SD = .042) | .93 (SD = .027) | .22 |
| PSE (ms) | 341.1 (SD = 8.94) | 348.1 (SD = 5.35) | .49 |
| mean GO RT | 515.4 (SD = 11.18) | 515.1 (SD = 15.63) | .95 |

Note
[a] t-test
*p < .05, **p < .01, ***p < .001
PSE = point of subjective equality; GO RT = Response Time of GO trials; fSTOP RT = RT of failed STOP trials; pSTOP = probability of STOP trials; SSD = stop-signal delay.

### 3.4.3 Correlations

To further interpret the role of stopping in stuttering severity, we correlated behavioural performance of stopping effectiveness measured in PSE with SSI-4 and OASES scores. None of the correlations were statistically significant. We similarly tested whether the ERP variables were associated with stuttering severity and its impact score (SSI-4, OASES). The Spearman correlation analyses showed that OASES scores were negatively correlated with N2 amplitude ($R = -.35$; $p = .01$) and positively correlated with N2 latency ($R = .68$; $p < .0001$). No other correlations were significant.

## 3.5 Discussion

We set out to examine the neural correlates of response inhibition in AWS by employing a stop-signal task. As per our hypothesis, P3 amplitude in AWS was significantly lower than AWNS, but contrary to our prediction, the P3 peak latency was significantly earlier in AWS rather than later. No other differences in the neural or behavioural variables were found.

### 3.5.1 P3 and inhibitory control in AWS

Following our first hypothesis, P3 amplitude was significantly reduced in AWS for both failed and successful STOP trials compared to AWNS. Generally, P3 is considered to reflect resource allocation during decision-making (Johnson, 1984; Johnson & Donchin, 1982; Kramer et al., 1985) but evidence has accumulated that it also signals inhibition processes (Aron et al., 2014; Wessel & Aron, 2015). Reduced P3 amplitude in STOP trials might reflect deficient generators of inhibitory function, which are thought to be located in pre-SMA, inferior frontal cortex (Enriquez-Geppert et al., 2010; Huster et al., 2011), and cingulate regions (Fallgatter, Bartsch, & Herrmann, 2002; Strik, Fallgatter, Brandeis, & Pascual-Marqui, 1998). These regions have been previously implicated for atypical activity or anatomy in stuttering (Brown et al., 2005; Budde et al. 2014; Neef et al., 2015; Neef et al., 2018; Neef et al., 2016) making it possible that P3 reduction in STOP trials reflects atypical motor suppression processes.

*The interpretation of the attenuated P3 amplitude is threefold.* First, persons who stutter may have an abnormal balance of attentional resources to support inhibition. P3 amplitude is sensitive to stimulus uncertainty (Johnson, 1984, 1986) and attentional demands (e.g. Kramer et al., 1985; Polich, 2004). In a study of AWNS by Verleger et al. (2005), P3 amplitude exhibited a smaller peak when the response decision was more difficult than when the task was not demanding. In relation to the current experiment, stopping for AWS might be more difficult than for AWNS in more complex inhibition tasks. The reactive manual braking task of the current experiment might not be demanding enough to elicit behavioural differences between the groups. If a more challenging proactive stopping task similar to our report in chapter two was used, then a correspondence between reduced P3 amplitude and less efficient stopping might have been detected. It's also possible that AWS use different strategies to compensate for ineffective

stopping that were not evident in reactive tasks. Second, ineffective stopping by AWS could involve more recruitment of cognitive resources to inhibit movements, such as inability to share attentional resources to prioritize a STOP command over a more frequent GO command. Greater demands on attentional resources for cognitive tasks in people who stutter has been suggested previously. The ERP study by Maxfield et al. (2017) of attention in lexical-semantic and phonological processes with dual-tasks observed a significant attenuation in amplitude in P3 compared to AWNS. They suggested AWS were not able to allocate sufficient resources to support lexical-semantic processing. Hamilton & Weber-Fox (2008) also reported reduced P3 amplitude on a non-linguistic auditory processing task that was attributed to lower efficiency of attention and working memory. Our finding of attenuated P3 amplitude is consistent with greater demand for attentional resources to generate inhibitory signals in AWS.

A third interpretation of attenuated amplitude of P3 is that AWS have increased impulsivity, which has been shown previously to be negatively related to P3 amplitude (Russo et al., 2008; Mathias & Stanford,1999). High impulsive individuals typically show reduced P3 amplitude presumably reflecting inability to inhibit task-irrelevant information. This could compromise performance on stop-signal tasks, which require sustained attention (Russo et al., 2008). According to this view, AWS have less efficient self-regulatory mechanisms, which has been discussed previously (see Alm, 2014 for a review). In developmental studies (e.g., Pisspala et al., 2017, Eggers et al., 2013, Eggers et al., 2012, Subramanian and Yairi, 2006), CWS produced a more false alarms, more failures to inhibit responses to No-GO signals, and faster RTs in unsuccessful No-Go trials (e.g., Eggers et al., 2013). Findings in AWS also partially corroborates an impulsivity interpretation based on unbalanced speed-accuracy trade-offs (e.g., Smits-Bandstra & De Nil, 2007) and the significantly faster response times on proactive stopping

tasks as reported in Chapter 2. Taken together, abnormality in P3 amplitude might be linked to less effective attentional control, but the evidence is still preliminary and limited by the small sample size of our experiment and absence of behavioural differences on the reactive task.

The AWS did not demonstrate a delayed P3 after the stop signal as predicted, but instead showed a significantly earlier peak. Previous literature suggests P3 latency is attributed to the speed of inhibitory response (Aron & Wessel, 2015; Aron et al., 2014) or evaluation of the response process (Huster et al., 2011) evoked by a conflict between competing GO and STOP responses. As we expected the stopping task to be difficult for AWS, extra time would be required for processing a stop signal that would be consistent with a delayed stop signal reaction time as reported by Markett et al. (2017). However, the more rapid P3 peak in stuttering might reflect premature inhibitory signals that are less effective for inhibiting motor actions or impulsive tendencies, but further work on this possible connection is needed.

Unlike the P3 results, the amplitude and timing of the N2 peak did not differ between the groups. N2 has traditionally been interpreted as the inhibition of the pre-potent stopping response in stop-signal and GNG paradigms (Lavric et al., 2004) but also conflict monitoring in command selection (Donkers & van Boxtel, 2004; Gajewski, Kleinsorge, & Falkenstein, 2010). According to this view, N2 is modulated in inhibitory tasks because of the conflict of command selection between frequent GO trials and infrequent STOP trials. Both groups had a clear N2 response without strong enhancement in the accuracy of responses. This may indicate that the combined demand of selecting between GO and STOP commands does not create a challenge for AWS.

### 3.5.2 Stuttering severity and ERP components

Our exploratory analysis of a potential association between the stuttering impact scores showed that N2 peak was smaller and more delayed in participants with more severe stuttering

(based on OASES). These correlations are perplexing because N2 did not differ between the groups. However, analysis of the other conditions may reveal that N2 is sensitive to group differences on the proactive task and will show that deficient inhibition is a factor in stuttering impact.

### 3.6 Limitations

While the findings reported here are intriguing, it should be noted that there are several methodological questions that may warrant consideration. First, we employed an inhibition task by Dunovan et al. (2015) which differs from a classical stop signal paradigm (Verbruggen & Logan, 2009). The paradigm used an animation in which a bar grows up and changes its color when a stop signal is presented. In GO trials the bar grows up continuously and reaches a target. This continuous movement in GO trials did not allow us to use a GO trial as a matched trial type for Successful and Failed STOP trials. GO trials are not of primary interest in our study and, thus, were not included in the final analysis.

Second, an estimation of reactive stopping is SSRT, an indirect quantitative index of the latency of the stop process or how long it takes to inhibit a response (Verbruggen & Logan, 2008). SSRT is indirect because stopping/withholding cannot be measured overtly and is estimated indirectly as a function of reaction time of GO trials and the observed probability of responses for a certain SSD (Verbruggen & Logan, 2009). Our experimental paradigm was not able to provide a reliable estimation of SSRT; this was due to an important difference in our design. There was an absence of a pure estimation of RT of GO which is critical for estimation of SSRT. RT in our study was rather GO accuracy RT to the target line (see Figure 1). These methodological characteristics did not allow us to directly compare the results of the study with

previous findings on SSRT in stuttering (Markett et la., 2016) as well as in other clinical populations (e.g., Jennings et al., 1997; Lipszyc & Schachar, 2010; for a review see Nigg, 2001).

Finally, it is important to acknowledge that the study had a small sample size. It is common in EEG research and in clinical EEG research (Light et al., 2010), in particular, to have a smaller number of participants because of the difficulty in recruitment and the length of the preparations and experiments themselves. Despite the modest sample size in this study, the data contains some strong trends important for research in stuttering. Further research is required in order to validate the findings in this study and to answer some of the questions that were raised.

### 3.7 Future Research Directions

Our data point towards inhibitory control as a promising target for further investigations. Although recent research work on stuttering has offered a number of important findings, we are still left with the question as to what role inhibition plays in speech motor sequencing in stuttering and whether investigations are needed in speech motor inhibition, rather than manual motor control. Future studies are needed to investigate if our findings can be replicated in inhibition tasks with speech responses as an effector. Such studies can become one step closer in order to make a conclusion if inhibition is an index of speech motor system in AWS. Additionally, functional neuroimaging could be used to investigate whether the basal ganglia circuit activates differently in people who stutter during SST performance. This would provide more direct evidence for our hypothesis that disruptions in the basal ganglia circuit underlie impaired motor control in people who stutter. These findings will expand our understanding of the etiological nature of stuttering and contribute to the development of new effective interventions.

### 3.8 Conclusion

In this study, we ventured to understand the neural correlates underlying successful and failed motor response inhibition in AWS. In sum, the results of the present study suggest that the ERP analysis of response inhibition can be considered a sensitive method to reveal group differences in AWS and AWNS. P3 amplitude in AWS was attenuated in comparison to AWNS in successful and failed STOP trials. Furthermore, P3 latency was earlier in AWS than AWNS, while N2 component did not show any atypicality in AWS performance. Taken together, these results demonstrate that ERP testing of inhibitory control can provide evidence for brain activity differences in motor inhibition in stuttering.

# CHAPTER 4

## General Discussion and Conclusions

### 4.1 Introduction

Stuttering is a neurodevelopmental hereditary speech motor disorder (Yairi & Ambrose, 1996; Suresh et al., 2006; Ludlow & Loucks, 2003). The definition of stuttering is based on symptoms, as the cause of stuttering is still unknown (e.g., Smith & Weber, 2017). Its core symptoms are most evident in speech and include prolongations, repetitions, and blocks (e.g., Yairi & Ambrose, 1996). The present doctoral thesis focused on investigating whether response inhibition is a biomarker of stuttering.

Two major types of inhibition responses were tested. The first type is *reactive inhibition* that requires withholding an undesired and intrusive behaviour in reaction to an externally presented stop signal. The role of reactive inhibition in stuttering was examined in Study 1. Reactive inhibition has been previously tested in adults who stutter (AWS) (e.g., Markett et al., 2016), in which AWS were found to have a delayed stop-signal reaction time (SSRT), an indirect measure of inhibition speed. We expected to replicate their results. The second type of inhibition response examined was *proactive inhibition*, which is the ability to anticipate the necessity of withholding a response through an intrinsically-generated decision. Proactive inhibition in AWS was examined in Study 2. This type of inhibition, which has never been tested in stuttering, requires more cognitive control and could expose limitations in the inhibition system of people who stutter.

The experiments in the present thesis examined two different effectors, *speech* and *manual* responses. Manual tasks have been used in the majority of inhibition studies, so including a manual task allows more direct comparisons with the broader literature. Importantly,

testing both effectors allowed assessment of whether inhibition of speech and skilled manual actions are related in AWS, because inhibition is potentially generated through a domain-general system. (Parrell et al., 2014; Xue et al., 2008; Wessel et al., 2016; Etchell, Sowman, & Johnson, 2012; Ghahremani et al., 2018). Alternately, speech tasks may introduce unique demands on inhibitory control that are not typical for other effectors.

In order to connect the inhibitory behaviours with neurophysiology, we used event-related potentials (ERP) to examine the reactive inhibition task in Study 3. ERPs provide a time-precise measure of brain activity events which happen right after a stop signal is presented and, thus, can evaluate at which stage a difference in stopping process occurs, such as selection of a STOP response, its initiation, and completion. The first and primary ERP component was P3, a neural marker with a posterior distribution which is specific to inhibition initiation and execution (e.g., Wessel & Aron, 2015; Albert et al., 2013; Kok, Ramautar, Ruiter et al., 2004). The second component is the frontally distributed N2, associated with action selection in the competition between GO and STOP processes (Luck, 2014; for review, see Van Veen & Carter, 2002). Below are the summaries of the behavioural studies and the EEG study, followed by a discussion of the main research questions, followed by future directions.

### 4.2 Summary of Experimental Data and Major Findings

In *Study 1,* we investigated a potential dysregulation of reactive response inhibition in AWS using a computer-based inhibition task with manual and speech response conditions (adapted from Dunovan et al., 2015). The reactive inhibitory task tested the ability of AWS to make a rapid 'braking' response by cancelling an ongoing motor response. We hypothesized that AWS would have more difficulty with reactive stopping processes, which would influence the overall accuracy of stopping and decrease its probability. Contrary to our expectations, the

results of the task indicated that AWS showed a similar point of subjective equality (PSE - a psychometric measure of stopping effectiveness) when compared to AWNS. The probability of stopping (pSTOP) for AWS was also similar to AWNS in both speech and manual response conditions. Additionally, response times (RTs) were comparable across the groups. Our results demonstrated that behavioural reactive inhibition appears similarly effective in AWS as in AWNS.

In *Study 2*, we examined a potential dysregulation of proactive response inhibition in AWS. The design of the task was similar to Study 1 and employed a computer-based inhibition task with manual and speech response conditions (adapted from Dunovan et al., 2015). The proactive inhibitory task tested the ability of AWS to anticipate the probability of a trial type (GO or STOP) and adjust their response accordingly. We hypothesized that AWS would demonstrate dysregulation in the overall accuracy of stopping. AWS showed a decreased pSTOP compared to AWNS in both speech and manual response conditions. However, PSE was similar in AWS and AWNS. Additionally, AWS responded faster when on failed STOP trials (fSTOP) and GO trials in manual and speech conditions. These findings indicated a subtle yet present inhibitory control deviance in AWS.

In *Study 3,* we conducted an electrophysiological study to test stopping abilities of AWS and AWNS in a reactive inhibition paradigm. We hypothesized AWS would have smaller amplitude and delayed N2 and P3 responses. Importantly, the widely recognized index of inhibition, the P3 peak, was significantly attenuated and earlier in AWS compared to AWNS. The N2 component, however, did not differ between groups. The behavioural measures including PSE, probability of stopping, and RT of failed STOP trials were additionally similar

across groups. Overall, the EEG results demonstrate that differential attenuation P3 with an inhibition context could be a temporally precise neural marker in people who stutter.

## 4.3 Discussion of research questions

### 4.3.1 Is reactive inhibition a valid index of stuttering?

**4.3.1.1 Behavioural measures.** Several previous studies indicate stuttering is potentially associated with an imbalance in the neural system that regulates reactive inhibition (e.g., Neef et al., 2016; Markett et al., 2016; Ning et al., 2017; Neef et al., 2018). The findings of our large-scale behavioural investigation (Study 1) differed from previous studies (e.g., Markett et al., 2016; Eggers et al., 2013) and suggest that reactive inhibition behaviour is not dysregulated in stuttering. Specifically, AWS and AWNS did not exhibit any differences in PSE and pSTOP across different stop-signal delays (SSD). Moreover, response time (RT) in both groups were similar. This finding was surprising because we expected to see that AWS would have a delayed inhibition following Markett et al. (2016), which would result in less efficiency and decreased accuracy in stopping.

The outcome of Study 1 might be attributable to a selection bias because the AWS fell disproportionately in the mild range of stuttering severity. However, there was an opportunity to further examine reactive inhibition in the EEG Study 3. The stuttering severity range of the participants in that study (Study 3) ranged from mild-moderate. However, the behavioural data resembled study 1 as AWS did not differ from AWNS when cancellation of a manual motor response was required. Across the two studies, our findings diverge from Markett et al. (2016) and instead, resemble the developmental stop-signal study in children who stutter (CWS)

(Eggers, De Nil, and Van den Bergh, 2018) that showed no differences in stopping accuracy between CWS and CWNS.

**4.3.1.2 ERP measures.** ERP could provide a more meaningful measure of inhibitory control in stuttering. In contrast to the reactive behavioural measures that did not show group differences, the P3 component, associated with inhibition (e.g., Aron & Wessel, 2015), was both significantly attenuated and earlier in both successful and failed STOP trials in AWS compared to the controls. These findings implicate a deficient P3 generator for inhibitory function in stuttering. An attenuated P3 peak might reflect an abnormal balance of attentional resources to support inhibition in AWS that makes stopping more challenging for AWS and perhaps inefficient self-regulation. These findings conform to previous discussions that stuttering is associated with increased impulsivity (see Alm, 2004 for a review), particularly in CWS (e.g., Piispala et al., 2017, Eggers et al., 2013, Eggers et al., 2012, Subramanian and Yairi, 2006).

In addition, we predicted the difficulties in stopping in AWS would be reflected by delays in the evoked potentials. On the contrary, P3 latency was significantly earlier in AWS. If the latency of P3 is attributable to the speed of inhibitory response (Aron & Wessel, 2015; Aron et al., 2014), our finding might reflect that the onset of an inhibitory response happens prematurely before there are insufficient resources to cancel an ongoing motor response. The ERP differences appear to reveal that reactive manual braking in AWS could diverge from typically fluent speakers even when there are no behavioural differences. Inhibitory differences may be present in this early stage of inhibition (prior to behavioural change); however, compensation could later in the generation of a response.

Finally, the analysis of the N2 amplitude and latency revealed no group differences. N2 has commonly been considered an index of conflict monitoring in command selection (Donkers

& van Boxtel, 2004; Gajewski, Kleinsorge, & Falkenstein, 2010), which is modulated in inhibitory tasks because of the conflict between frequent GO trials and infrequent STOP trials. Both groups had a clear N2 response without strong enhancement in the accuracy of responses. This may indicate that the combined demand of selecting between GO and STOP commands does not create a challenge for AWS. Future studies are needed to clarify a potential compensatory mechanism in stuttering and its effect on speech motor control.

### 4.3.2 Is proactive inhibitory control aberrant in neurodevelopmental stuttering?

Our study on proactive inhibition is the first test of anticipatory stopping in stuttering. In contrast to reactive inhibitory control, which is a simple rapid braking of an ongoing response, proactive inhibition requires the engagement of top-down cognitive control. Our results showed that pSTOP was lower in AWS than AWNS. AWS also completed their responses faster. The lower probability of stopping and more impulsive motions both suggest that AWS have less effective stopping. However, these differences are subtle given the PSE score was similar in both groups. AWS might be less effective in selecting the correct motor response when cognitive demands are increased, similar to the conclusions of Bosshardt (2006).

The proactive task includes a preparatory step with the possibility of either completing a response or withholding it, which makes it more challenging than reactive inhibition. A possible GO bias in AWS points to difficulties in focus and a lack of attentional resources when selecting a correct response in proactive stopping. This difficulty does not allow AWS to prioritize relevant information and/or suppress the distractors, which results in an erroneous choice of a motor command. Our findings of slightly less controlled command selection and motor impulsivity are supported by a number of previous studies (see Alm, 2004; Etchell et al., 2018, for a review). AWS may have less balanced speed-accuracy trade-offs (e.g., Smits-Bandstra &

De Nil, 2007; Jones et al., 2002), while CWS demonstrate less controlled and more impulsive response style - a higher number of false alarms, a failure to inhibit a response to No-GO signal, and faster RTs for those trials in GNG tasks (Eggers et al., 2013, Eggers et al., 2012, Subramanian and Yairi, 2006). Overall, the present experiments suggest less effective proactive inhibition in AWS. Evidence for behavioural inhibitory abnormalities in stuttering may therefore depend on task difficulty, even though neurological differences are present for simpler reactive tasks.

### 4.4 Is inhibition dysregulation specific to speech?

Previous studies argue for the existence of a general cross-domain coupling of speech and non-speech inhibitory processing (Xue et al., 2008; Wessel et al., 2016; Etchell, Sowman, & Johnson, 2012; Ghahremani et al., 2018). Dysregulation of inhibition in stuttering was, therefore, hypothesized to affect both manual and speech motor effectors. Study 1 and Study 2 employed two response effectors: a manual effector, a participant was asked to press a response button with the index finger of the dominant hand, or a speech effector, a participant had to respond by saying the word "TIP." The reactive inhibition task revealed that AWS were able to maintain the same stopping probability as AWNS for both manual and speech conditions. In the proactive inhibition task (Study 2), both types of responses were sensitive to group differences between AWS and AWNS. AWS had a lower probability of stopping for button press and verbal responses. This absence of a differential deficit for verbal responses is consistent with a series of studies showing differences in stuttering are not limited to speech production (for a discussion, see Max, Guenther, Gracco, Ghosh, & Wallace, 2004; Neilson & Neilson, 1987). People who stutter have delayed motor reaction times for both speech and manual responses (e.g., Hulstijn et al., 1992; Archibald and De Nil, 1999; Smits-Bandstra et al., 2006), dis-synchronization and

over-anticipation of external rhythmic events (metronome or musical stimuli) and lower consistency of motor responses (Falk, Müller, Dalla Bella, 2015). Therefore, despite methodological differences, non-speech tasks are sensitive to differences in stuttering meaning there could be wider difficulties in inhibitory control that affect the entire motor system.

However, even if effector differences are not an aspect of inhibitory function (i.e. tongue motions are inhibited in the same manner as index finger motions), different tasks could differentially impinge on inhibitory control. Speech movement sequencing could place unique demands on inhibition that are not typical for other effectors. If more sensitive behavioural measures are developed, then speech in AWS might show a differential limitation as demands on inhibitory function are increased.

## 4.5 Theoretical implications

**4.5.1 Hypoinhibition in stuttering.** The link between inhibitory control and speech fluency is still a novel proposal that is not fully understood. However, it is thought that fluent speech is a product of effective sequencing of motor actions that rely on motor execution and inhibition (e.g., Parrell et al., 2014). Our findings contribute to the growing body of evidence that inhibitory dysfunction is associated with stuttering (e.g., Eggers et al., 2010; Markett et al., 2016; Metzger et al., 2017) and specifically, decreased effectiveness of inhibitory control, later referred to as hypoinhibition. Evidence for this comes first in that AWS had more difficulties in stopping when anticipating a STOP command revealing motor impulsivity. Second, AWS had a smaller and earlier P3 component that is considered a weak inhibitory response or there are diminished resources to facilitate motor cancellation.

This hypoinhibition interpretation corresponds to elements of the neurocomputational model ‘Gradient Order Directions Into Velocities of Articulators’ (GODIVA) as developed by

Civier and colleagues (2013). They predicted fluent speech relies on the metabolic balance of dopamine and white matter integrity in the cortico-basal-ganglia pathways. In stuttering, there is elevated dopamine (the excitatory neurotransmitter of the direct pathway of the cortico-basal-ganglia inhibition circuit), which biases cortical competition between execution and inhibition choices by overactivating the execution of an initial syllable, which subsequently is not efficiently inhibited. This hypoinhibition causes a delay in speech initiation or sequencing of speech motor commands, which in turn results in blocks, prolongations, or repetitions. Second, the model suggests that stuttering results from inadequate development of white matter in the cortico-basal-ganglia circuit. This structural abnormality may also cause delays in motor command generation of consecutive syllables, similar to the dopaminergic imbalance. This delay disrupts normal function of the basal ganglia by preventing it from adequately inhibiting motor commands for a currently executed syllable and interfering with initiation of the next syllable.

If our findings are accurate and in accordance with the GODIVA model showing that inhibitory regulation is reduced, then it can impact both the ability to select the desired motor plans and suppress already executed, non-relevant motor plans. In our findings, hyporegulation of motor command selection was evident behaviourally in the proactive inhibition task, in which AWS had a lower pSTOP when there is a competition between GO and STOP command was present. AWS tended to prioritize the GO command and displayed a weaker ability to inhibit a motor response. Our data also suggested that hyporegulation can occur much earlier than behavioural outcomes and was shown as an attenuated P3. Our data are in line with the GODIVA model on inhibitory control in stuttering.

Other theoretical considerations could account for the influence of hypoinhibition beyond elicitation of symptoms. A subtle profile of hypoinhibition could hold relevance for the onset and

maintenance of stuttering. Stuttering emerges around 30-48 months (Smith & Weber, 2017), during the stage when inhibition and multiple systems supporting systems, such as motor control and executive control go through rapid development (Carver, Livesy & Charles, 2001; Garon, Bryson, & Smith, 2008; Wiebe, Sheffield, & Espy, 2012). As both CWS and AWS display atypical inhibition it could be an enduring feature of the disorder. The understanding of the importance of inhibition in shaping the speech motor control at early stages of developmental stuttering is of interest because it can potentially lead to understanding whether inhibition is one of the factors that promote or compromise recovery from stuttering. Therefore, extending testing of inhibition to children who recover versus children who persist will be an important step in testing whether inhibitory control influences recovery.

Testing inhibitory developmental delays with quantitative measures, such as the PSE and pSTOP, around the onset of stuttering is more challenging given the younger ages, so experimental paradigm development is still likely required. But these methodological issues should not override the importance of a theoretical perspective on a broader role for inhibition dysregulation in stuttering. Moreover, the maturation of inhibitory control in typical development is still a nascent research area (Asato et al., 2010; Tamm et al., 2002). Little is known about how the P3 signal changes with development (Abdul Rahman et al., 2017), or how the cortico-basal ganglia connections develop (Asato et al., 2010)., and if these connections influence the P3 during development; so caution and extensive research will be needed.

In close relation is the need to uncover the theoretical relationship between P3 generation and unsuccessful stopping. So far, the P3 anomalies and behavioural deficits have not been linked directly in stuttering. The current research holds some promise for advancing this research as ERP data were also collected during speech production and during the proactive tasks. Time

constraints did not allow for analysis of these other completed experiments but associations between the ERPs and behavioural findings in the more challenging proactive conditions are an exciting possibility.

**4.5.2 Can the findings be interpreted as a dysregulation of cognitive functioning in stuttering?** An alternative theoretical consideration could account for the influence of cognitive function in stuttering. Inhibitory control is one of the core executive processes which functions intricately and dynamically with such processes as working memory and attention; together they facilitate effective self-regulation, cognitive flexibility (also called mental set shifting), and interference (e.g., Diamond, 2013). In case of speech production, fluency needs to be facilitated by a number of demanding processes for executive function (Doneva, Davis, & Cavenagh, 2018). Previous theories propose these higher executive control demands might create extra effort for AWS and, thus, disfluencies might result from to a potential breakdown in the balance of executive function resources governing speech-supporting motor, linguistic, cognitive, and socio-emotional subsystems (e.g., Bosshardt, 2006; Heitman et al., 2004; Eichorn, Marton, Pirunsky, 2018; Doneva, Davis, & Cavenagh, 2018).

Bosshardt (2006) proposed cognitive load as a determinant of stuttering. In his series of studies, AWS showed greater interference between speaking and concurrent attention-demanding processing. Stuttering rate was shown to depend on the complexity of the utterance as well as the interference load, as suggested by findings from dual-task studies (e.g., Bosshardt, 2006; Smits-Bandstra & De Nil, 2009, Saltuklaroglu, Teulings, & Robbins, 2009). Additionally, people who stutter performed worse on secondary tasks while doing a speech task (Saltuklaroglu, Teulings, & Robbins, 2009), showing that speech is less automatized and requires more attentional

resources. Therefore, retaining stuttering-free speech might require greater attentional resources in AWS than in AWNS.

The findings in our studies do not contradict the cognitive load framework by Bosshardt (2006). The employed proactive task required the engagement of higher order cognitive control, attention, and working memory (Albert, López-Martín, Hinojosa, & Carretié, 2013; Aron, 2011), which are presumably involved in a preparatory decision-making step for the possibility of completing a response or withholding it before the actual response can be made (Aron, 2011). The simpler task, which tested reactive inhibition (Study 1) and did not involve an additional preparatory stage, did not show any behavioural group differences. However, the results of behavioural data from Study 2, a more complex task that required remembering a rule, showed that AWS were able to respond less accurately and more impulsively. Inefficiency in the preparation of correct motor sequences in the more complex proactive task can be caused by a dysregulated balance of more general executive resources and not the inhibition process only. In other words, if AWS might have difficulties in focusing their attentional resources on selecting a correct response. These difficulties might cause a deficit in preparation and decision making and, thus, potentially weaken the ability to tune preparation of specific speech motor plans and lead to a speech dysfluency.

Overall, previous theoretical views show that a potential working memory and attention deficit can also explain our findings and motivate future interest in the role of executive functioning in stuttering. Future studies should test attention of AWS in variety of psychometric tasks including spatial and verbal working memory, short-term memory, and resilience to interferences to understand the nature of an executive function component in developmental stuttering.

### 4.6 Clinical Implications

The primary clinical implication is the potential relationship between inhibitory function and stuttering severity. Our correlation analyses did not support this relationship, but the analysis could have been limited by floor effects given the milder severity of the clients. Subsequent testing with a wider severity range is warranted, particularly since both neurological and behavioural evidence of hypoinhibition was found.

Another consideration is whether hypoinhibition interacts with therapeutic efficacy. Hypoinhibition conceivably interferes with therapy outcomes or long-term maintenance. Particularly given potential for neuro-behavioural links in this inhibition research, future clinically driven work could relate pre/post therapy outcomes to hypoinhibition. These clinical studies should encompass a broad age range as well to further understand whether hypoinhibition is a pervasive issue with all clients who stutter.

### 4.7 Future Research and Conclusions

The current doctoral thesis provided evidence that AWS show a decrease of inhibitory control, herein labeled hypoinhibition. We were able to show that AWS performed more impulsively in a proactive inhibition task when either manual or speech responses were required. However, behavioural measures on reactive inhibition were not sensitive to stuttering. Electrophysiological findings point to hypoinhibition that might occur early at the neural level but can be compensated for in reactive behavioural tasks, but not in more challenging proactive tasks. Further exploration employing different experimental tools and paradigms are needed, as we are only beginning to uncover the role of inhibitory control in stuttering. Several lines of future research could follow from the current dissertation. Regarding inhibitory control, we are

still left with the question where exactly the generators of atypical motor suppression processes are located in AWS compared to AWNS. As for the potential involvement of cortico-basal ganglia-thalamo-cortical loops associated with response inhibition in stuttering, neuroimaging work is warranted to provide a more direct and precise evidence. By employing a stop-signal paradigm, future fMRI and MRI studies can provide a detailed description of inhibitory pathways in stuttering and disentangle the involvement of indirect and hyperdirect pathways. Such investigations may also target questions of differences in severity and variability of speech disfluencies and secondary behaviours. Therefore, the future imaging investigation can focus on localization of neuroanatomical and neurophysiological differences in stuttering and become a logical progression of our time-precise ERP findings.

Additionally, all our studies examined motor inhibition in response to a visual stop-signal. It would be interesting to examine the extent to which our findings would generalize to auditory stop-signal processing in stuttering. Previous studies indicated that AWS show the atypical auditory modulation during movement planning (e.g., Daliri & Max, 2015; Daliri et al., 2016). To further elucidate inhibitory differences in stuttering, it would be interesting to examine the ability of AWS to suppress a response in reaction to auditory signals.

Next, further behavioural studies are warranted to expand understanding of inhibitory control in continuous speech. So far, the investigation on inhibitory control are limited primarily to manual motor effectors and speech effectors which test single-word usage. Speech, however, is a more complex system and relies on quick and precise sequencing of motor commands. Such investigations may also target questions of stopping in the multisyllabic speech production or even sentence production. To gain more insight into the process of inhibition in speech production, new more complex speech-like inhibitory paradigms need to be developed.

Additionally, the question about a general theoretical framework of inhibitory control in stuttering is still open. The goal of such framework is to integrate and generalize findings gained experimentally and computationally into a coherent theoretical structure. This theoretical framework on inhibitory control in stuttering can provide a unifying account of inhibitory system development and its vulnerability in CWS and AWS.

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# APPENDICES

## Appendix A

**Table 1.** Clinical features of study participants for Study 1 and Study 2. For each participant Sex, Age (years), Native Language, Education (ED, Scale: 1 = school; 2 = high school; 3 = less than 2 years university; 4 = 2 years university; 5 = 4 years university; 6 = postgraduate), Handedness (HD), Rating of Stuttering Severity Instrument 4 (SSI-4 Rating), SSI-4 Score, Overall Assessment of the Speaker's Experience of Stuttering Impact Rating (OASES IR), and OASES Score.

| Participant | AWS/AWNS | Sex | Age, y | Native Language | ED | HD | SSI-4 Rating | SSI-4 Score | OASES IR | OASES Score |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | AWS | f | 25 | English | 5 | r | very mild | 6 | moderate/severe | 3.52 |
| 2 | AWS | m | 36 | English | 6 | r | very mild | 14.5 | mild/moderate | 2.08 |
| 3 | AWS | f | 24 | English | 5 | l | very mild | 8.5 | moderate | 2.37 |
| 4 | AWS | f | 47 | English | 5 | r | very mild | 6 | mild/moderate | 1.9 |
| 5 | AWS | f | 20 | English | 5 | r | moderate | 26 | moderate | 2.4 |
| 6 | AWS | f | 31 | English | 6 | r | very mild | 6 | mild/moderate | 1.75 |
| 7 | AWS | m | 23 | English | 6 | r | very mild | 14 | moderate | 2.31 |
| 8 | AWS | f | 30 | English | 5 | r | very mild | 14.5 | mild/moderate | 1.65 |
| 9 | AWS | f | 18 | English | 2 | r | very mild | 15 | moderate | 2.76 |
| 10 | AWS | m | 27 | English | 6 | r | very mild | 8 | moderate | 2.6 |
| 11 | AWS | m | 39 | English | 5 | r | moderate | 27 | moderate | 2.6 |
| 12 | AWS | m | 27 | English | 5 | r | very mild | 6.5 | mild | 1.16 |
| 13 | AWS | m | 26 | English | 3 | l | mild | 18 | moderate/severe | 3.02 |
| 14 | AWS | m | 35 | English | 6 | r | very mild | 7.5 | moderate | 2.6 |
| 15 | AWS | f | 21 | English | 3 | r | very mild | 8 | moderate | 2.4 |
| 16 | AWS | m | 28 | English | 5 | r | very mild | 6.5 | moderate | 2.54 |
| 17 | AWS | m | 31 | English | 5 | r | very mild | 7.5 | mild/moderate | 1.87 |
| 18 | AWS | m | 27 | English | 5 | r | very mild | 9.5 | mild/moderate | 1.67 |
| 19 | AWS | m | 29 | Russian | 6 | r | very mild | 15 | mild/moderate | 1.567 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 20 | AWS | m | 23 | English | 6 | r | very mild | 13 | moderate | 2.46 |
| 21 | AWS | f | 35 | Spanish | 6 | r | very mild | 7.5 | mild/moderate | 1.74 |
| 22 | AWS | m | 26 | English | 5 | r | very mild | 7.5 | mild | 2 |
| 23 | AWS | m | 24 | English | 5 | r | moderate | 25.5 | moderate | 2.82 |
| 24 | AWS | f | 31 | English | 6 | l | very mild | 7.5 | mild/moderate | 1.63 |
| 25 | AWS | m | 36 | English | 5 | r | very mild | 9.5 | moderate | 2.82 |
| 26 | AWS | m | 26 | English | 5 | r | mild | 18 | moderate/severe | 3.7 |
| 27 | AWS | m | 21 | English | 5 | r | mild | 16 | moderate | 2.47 |
| 28 | AWS | m | 28 | English | 5 | r | very mild | 10 | mild/moderate | 2.18 |
| 29 | AWS | m | 27 | Italian/English | 6 | l | very mild | 10 | mild/moderate | 1.78 |
| 30 | AWS | m | 17 | English | 2 | r | very mild | 7.5 | mild | 1.13 |
| 31 | AWS | m | 32 | English | 6 | r | very mild | 8.5 | mild/moderate | 2 |
| 32 | AWNS | m | 25 | English | 5 | r | n/a | n/a | n/a | n/a |
| 33 | AWNS | m | 29 | English | 6 | r | n/a | n/a | n/a | n/a |
| 34 | AWNS | f | 27 | English | 5 | r | n/a | n/a | n/a | n/a |
| 35 | AWNS | m | 31 | Russian/English | 6 | r | n/a | n/a | n/a | n/a |
| 36 | AWNS | m | 23 | English | 5 | r | n/a | n/a | n/a | n/a |
| 37 | AWNS | m | 22 | English | 6 | r | n/a | n/a | n/a | n/a |
| 38 | AWNS | m | 31 | English | 6 | r | n/a | n/a | n/a | n/a |
| 39 | AWNS | f | 25 | English | 6 | l | n/a | n/a | n/a | n/a |
| 40 | AWNS | m | 48 | English | 5 | r | n/a | n/a | n/a | n/a |
| 41 | AWNS | f | 22 | English | 5 | r | n/a | n/a | n/a | n/a |
| 42 | AWNS | f | 32 | English | 6 | r | n/a | n/a | n/a | n/a |
| 43 | AWNS | f | 30 | English/Spanish | 6 | r | n/a | n/a | n/a | n/a |
| 44 | AWNS | m | 23 | English | 5 | r | n/a | n/a | n/a | n/a |
| 45 | AWNS | m | 24 | English | 5 | r | n/a | n/a | n/a | n/a |
| 46 | AWNS | f | 29 | English | 6 | l | n/a | n/a | n/a | n/a |
| 47 | AWNS | f | 26 | English | 5 | r | n/a | n/a | n/a | n/a |
| 48 | AWNS | f | 23 | English | 4 | r | n/a | n/a | n/a | n/a |
| 49 | AWNS | m | 37 | English | 5 | r | n/a | n/a | n/a | n/a |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 50 | AWNS | f | 20 | English | 3 | r | n/a | n/a | n/a | n/a |
| 51 | AWNS | m | 21 | English | 6 | r | n/a | n/a | n/a | n/a |
| 52 | AWNS | m | 22 | English | 5 | r | n/a | n/a | n/a | n/a |
| 53 | AWNS | m | 19 | English/Bengalhi | 3 | r | n/a | n/a | n/a | n/a |
| 54 | AWNS | m | 25 | English | 5 | r | n/a | n/a | n/a | n/a |
| 55 | AWNS | m | 25 | English | 6 | l | n/a | n/a | n/a | n/a |
| 56 | AWNS | m | 21 | English | 4 | r | n/a | n/a | n/a | n/a |
| 57 | AWNS | m | 25 | English | 6 | r | n/a | n/a | n/a | n/a |
| 58 | AWNS | m | 28 | English/Russian | 6 | r | n/a | n/a | n/a | n/a |
| 59 | AWNS | m | 25 | English | 6 | r | n/a | n/a | n/a | n/a |
| 60 | AWNS | m | 31 | English | 5 | r | n/a | n/a | n/a | n/a |
| 61 | AWNS | m | 25 | English | 5 | r | n/a | n/a | n/a | n/a |
| 62 | AWNS | m | 25 | English | 5 | l | n/a | n/a | n/a | n/a |

## Appendix B

**Table 1.** Clinical features of study participants. For each participant Sex, Age (years), Native Language, Education (ED, Scale: 1 = school; 2 = high school; 3 = less than 2 years university; 4 = 2 years university; 5 = 4 years university; 6 = postgraduate), Handedness (HD), Rating of Stuttering Severity Instrument 4 (SSI-4 Rating), SSI-4 Score, Overall Assessment of the Speaker's Experience of Stuttering Impact Rating (OASES IR), and OASES Score.

| Participant | AWS/AWNS | Sex | Age, y | Native Language | ED | HD | SSI-4 Rating | SSI-4 Score | OASES IR | OASES Score |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | AWS | m | 30 | German | 6 | r | severe | 34 | moderate | 2.88 |
| 2 | AWS | m | 40 | German | 3 | r | very mild | 12 | mild/moderate | 1.76 |
| 3 | AWS | m | 22 | German | 4 | l | very mild | 12 | mild/moderate | 1.99 |
| 4 | AWS | f | 34 | German | 3 | r | mild | 22 | mild | 1.27 |
| 5 | AWS | f | 32 | German | 3 | r | mild | 23 | moderate | 2.8 |
| 6 | AWS | m | 35 | German | 6 | r | very severe | 41 | moderate | 2.52 |
| 7 | AWS | m | 34 | German | 6 | r | mild | 15 | moderate | 2.59 |
| 8 | AWS | f | 27 | Romanian/Russian | 6 | r | mild | 21 | moderate | 2.78 |
| 9 | AWS | m | 34 | German | 6 | l | mild | 20 | n/a | n/a |
| 10 | AWS | m | 29 | German | 5 | r | n/a | n/a | moderate/severe | 3.56 |
| 11 | AWS | m | 29 | German | 5 | r | moderate | 26 | moderate | 2.6 |
| 12 | AWS | f | 23 | German | 3 | r | moderate | 28 | severe | 4.01 |
| 13 | AWNS | m | 26 | German | 5 | r | n/a | n/a | n/a | n/a |
| 14 | AWNS | f | 31 | German | 6 | r | n/a | n/a | n/a | n/a |
| 15 | AWNS | m | 33 | German | 6 | r | n/a | n/a | n/a | n/a |
| 16 | AWNS | m | 28 | German | 6 | r | n/a | n/a | n/a | n/a |
| 17 | AWNS | f | 23 | German | 4 | r | n/a | n/a | n/a | n/a |
| 18 | AWNS | m | 35 | German | 6 | r | n/a | n/a | n/a | n/a |
| 19 | AWNS | m | 22 | German | 5 | l | n/a | n/a | n/a | n/a |
| 20 | AWNS | m | 29 | German | 6 | r | n/a | n/a | n/a | n/a |
| 21 | AWNS | f | 34 | German | 3 | r | n/a | n/a | n/a | n/a |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 22 | AWNS | m | 29 | German | 5 | r | n/a | n/a | n/a | n/a |
| 23 | AWNS | f | 27 | German | 6 | r | n/a | n/a | n/a | n/a |
| 24 | AWNS | m | 35 | German | 6 | l | n/a | n/a | n/a | n/a |
| 25 | AWNS | m | 40 | German | 5 | r | n/a | n/a | n/a | n/a |
| 26 | AWNS | m | 33 | German | 6 | r | n/a | n/a | n/a | n/a |