Development of behavioral control: Analysis of performance and motor-related brain potentials
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CHAPTER 1

General introduction
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The ability to interrupt or adjust ongoing actions is essential for adjusting optimally to instant changes in the environment. This cognitive ability affords flexible and adaptive behavior to meet external or internal demands. For example, say you were walking down a busy street with your mind on the day's chores. You hear someone calling out from across the street and you have the feeling that it was directed at you. The man looks familiar, however you cannot quite place him, perhaps you have just forgotten his name or it's simply been so long since you have last seen him. The person in question smiles and waves excitedly in your direction. Now you are certain that you really must know him, why else would he be so enthusiastic? However you are still frustrated that you can't recall him in any way, shape or form. In all the excitement and confusion you go to raise your hand in the air to wave back. However, and luckily, out the corner of your eye you notice someone else standing right next to you waving back to him, and then reality hits you square in the face: you really don't know this person, you have never seen him before, and that's why you cannot recall his name or face. Thankfully, you lowered your arm just in time, before anyone noticed your potentially embarrassing mistake. And off you go, feeling quite happy with the fact that you have escaped this awkward situation. If this situation were to happen again, especially within a short time period of this last experience, you would probably, more likely than not, wait a long enough to be sure the person in question is waving at you. This situation demonstrates that the inhibition of the inappropriate behavior (waving) prevents an awkward social situation and illustrates the necessity of cognitive control over responses in daily life situations.

This dissertation is concerned with the investigation of cognitive and motor-related processes involved in the inhibition of initiated actions in order to adjust behavior to meet environmental demands. Action inhibition can be generated internally, for example, one might decide to stop walking, turn around and ignore the person on the street waving, after remembering to collect the shopping list that was accidently left on the kitchen table back home. Alternatively, the inhibition of the initiated action can also be triggered by an external event that requires withholding the action. In case of the situation described above, the unrecognized person walking on the street represents the ‘action’ signal (the go signal) and the person appearing in the corner of your eye represents the ‘inhibition’ signal (the stop signal). Evidently, the inhibition signal was processed just in time to prevent the action from occurring (successful inhibition).
However, this every-day life situation might have turned out differently if children or elderly adults were concerned. Children might respond too quickly to the unrecognized person by waving back excitingly and might not realize in time that the person next to them is also waving to the same person. Senior citizens might take their time to wait and check whether this unrecognized person is actually waving at him, and if they did raise their hand to wave, they might also show difficulties in quickly stopping their movement. Accordingly, the developmental literature has shown that the ability to execute appropriate and inhibit inappropriate behavior improves over the course of development until adulthood and declines when people grow older (e.g., Williams, Ponesse, Schachar, Logan, & Tannock, 1999).

A novel approach of the present dissertation is the focus on lifespan patterns of response activation and inhibition of actions in relation to neural substrates of response execution related to the human motor cortex. It is relatively easy to capture the latency associated with overt behavior; it can be derived by calculating the time difference between the presentation of the go signal and the overt response. In a laboratory setting, the time between signal onset and the button press is referred to as reaction time (RT), reflecting the summation of the duration of the cognitive processes involved. However, capturing the latency of the covert inhibition process is more difficult; clearly, successful inhibition is defined as the absence of overt behavior and does not involve a button press. Although, the inhibition latency cannot be directly observed, it can be derived indirectly with the stop-signal paradigm (Logan, 1994). This experimental task provides a useful tool to investigate the cognitive processes that comprise the overt reactions to the go signal, but also the processes involved in the covert inhibitory reaction to the stop signal (Logan & Cowan, 1984). The remaining part of this chapter introduces the stop-signal task that has been widely used to investigate the go and inhibition process and provides a selective overview of the stop-task literature. A behavioral chronometric approach to investigate response execution and inhibition is described followed by an explanation of relevant electrophysiological indices to investigate the temporal dynamics of the RT process. In addition, two ERP (event-related potential) techniques to investigate the motor cortex will be described which is of particular relevance to Chapter 4. ERPs are derived from the EEG (electroencephalogram) to investigate brain activity in relation to cognitive processes. Then follows a brief description of brain areas involved in response execution and inhibition. Finally, the remaining chapters of this dissertation will be outlined.
The stop-signal paradigm

In the stop-signal task, participants perform a computerized primary task, usually a choice reaction time (RT) task that requires the discrimination of two visual stimuli and a fast button press with either the left or right hand. For example, participants are required to execute a fast button press with the right hand when seeing the letter ‘O’ and a left-hand press after seeing the letter ‘X’. It is emphasized that the participant responds quickly to the letters, while avoiding a button press with the incorrect hand, i.e., right-hand press to the letter ‘X’ or a left-hand press to the letter ‘O’. The choice RT task is also referred to as the go task and the stimulus letters are referred to as go signals. Occasionally and unpredictably, a second stimulus (usually a tone) is presented that follows shortly after the onset of the go signal on a proportion of the trials (typically 25%). These stimuli are referred to as stop signals and instruct the participant to cancel the pending response to the go signal. Obviously, when the stop signal is presented very shortly after the go signal, the participant is more likely to inhibit the response successfully, whereas the participant will probably fail to inhibit the response when the stop signal is presented late relative to the go signal. To avoid undesirable waiting strategies in attempt to increase successful inhibition, the interval between the go signal and the stop signal (i.e., the stop-signal delay) is under experimental control. During the task, stop-signal delay is dynamically adjusted from stop trial to stop trial according to stopping performance; that is, the stop-signal delay is increased on a subsequent stop trial if the response was successfully inhibited, whereas the stop-signal delay is decreased upon a failure to stop. This staircase-tracking algorithm (Levitt, 1971) ensures that the proportion of successful inhibition is around 50% and has proven to yield accurate estimation of inhibition latency (see next section, Band, van der Molen, & Logan, 2003). A clear advantage of the tracking procedure is that the stop-signal delay is adjusted according to the participant’s own response speed to the go signal. This is crucial when comparing different groups of individuals that likely differ in RT.

Estimating the latency of inhibition (SSRT)

An important dependent measure that can be derived from the stop-signal task is the latency of the covert inhibition response to the stop signal; the stop-signal RT or SSRT (Logan, 1994; Logan & Cowan, 1984). Figure 1 presents a graphical representation of a hypothetical distribution of RTs on go trials. It is assumed that the RT distribution of responses to go signals in a choice RT task is similar to the distribution of RTs on go trials with stop signals inserted into the trials series (i.e., according to the assumption of context independence, see below). This
means that the overt RTs on stop-signal trials should be similar to the fast RTs depicted as the left side of the go RT distribution. Observed RTs on stop-signal trials are usually referred to as the failed-inhibit RT and can be predicted from the proportion fast RTs on go-signal trials.

**Figure 1** Graphical representation of the computation of stop-signal RT (SSRT). The curve depicts the distribution of RT on go trials. The finish time of the stop process bisects the go-RT distribution (vertical dashed line).

RTs on go trials are rank-ordered and the percentage of failed inhibits (n, here 55%) is taken to bisect the go-RT distribution in a fast and slow part. The nth percentile of the go-RT distribution approximately equals to the finishing time of the inhibition process (here 300 ms). Thus, RTs on the right side of the go-RT distribution represent slow responses that were successfully inhibited. Subtracting the mean stop-signal delay (here 100 ms) from the nth go RT provides an estimation of the duration to inhibit the response, the SSRT (here 200 ms; Logan & Cowan, 1984).

**Assumptions of the horse-race model**

In the stop-signal task, the process activated by the go signal and the process activated by the stop signal race against each other. The race is referred to as the horse-race model and describes the behavioral outcome on a stop trial (Logan & Cowan, 1984). Figure 2 presents a graphical description of the race model.
As shown in Figure 2, the go signals are left and right-pointing arrows presented in the color green, whereas the stop signal is the change of color from green to red. Processing of the go signal involves the detection and discrimination of the signal (is it a left- or right-pointing arrow?) and the selection of the overt response (should I respond with the left or right hand?) followed by the execution of the response. Processing of the stop signal entails stop-signal detection (change of color) and the abortion of the go process. As can be seen in Figure 2, successful response inhibition depends on which process finishes first. When the go process finishes before the stop process, the go response is executed, whereas the response is successfully inhibited when the stop process finishes before the go process.

The horse-race model relies upon a set of formal assumptions that should be met in order to obtain reliable SSRT estimates. The major assumption holds that the go and inhibition process run independently (Logan, 1994; Logan & Cowan, 1984). The independence assumption covers context (or functional) independence and stochastic independence. Context independence means that the processing of the go signal is not affected by the presence of a stop signal. As such, the latency of the go process should not be affected by stop-signal processing. Consequently, the latencies of the go and inhibition process are not correlated. This is referred to as stochastic independence between the two processes. However, when a tracking algorithm is used, the race model appears robust against violations of stochastic independence (see a series of computer simulation studies by Band, van der Molen, & Logan, 2003). However, there have
been several reports of violations of the context independence assumption (e.g., de Jong, Coles, Logan, & Gratton, 1990; Jennings, van der Molen, Brock, & Somsen, 1992). A typical observation is that go RT increases when the probability of stop signals increases (e.g., Ramautar, Kok, & Ridderinkhof, 2004; van den Wildenberg & van der Molen, 2004a; Verbruggen & Logan, 2009). This means that the processing of the stop signal affected the latency of go-signal processing, thus violating the context independence assumption. Boucher, Palmeri, Logan, and Schall (2007) argued that the independence assumption can never be met when performing the stop-signal task, because the inhibition process always interacts at some point with the go process in order to successfully abort the pending button-press response. This interaction occurs through interacting neurons that are active when the stop process interrupts the go process. This dependency lasts only for a very brief period and Boucher and colleagues (2007) argued that the two processes do run independently from stop-signal onset to the point of interaction. In addition, extensive computer simulations by Band, van der Molen and Logan (2003) showed that SSRTs could be reliably estimated despite violations of the assumptions of context independence between the go and inhibition process.

**SSRT as a widely used index of inhibitory control**

Over the last decades, the stop-signal task has often been used to estimate the efficiency of the stop process captured by the latency of inhibition. The standard (or global) stop-signal task involves the use of a single stop-signal that requires the global inhibition of all go responses. A range of stop-signal studies found that it takes young adults about 200 ms, ranging from 170 to 250 ms, to inhibit a variety of movements (e.g., Logan, Cowan, & Davis, 1984; van den Wildenberg, van Boxtel, & van der Molen, 2003; Verbruggen & Logan, 2008). This latency appears quite robust across various studies and global stop task designs in healthy adults.

The stop-signal task has been implemented in clinical settings to investigate inhibitory processing in groups of individuals allegedly suffering from deficits in inhibitory control. A longer SSRT in clinical groups compared to that of a healthy control group is then indicative of poor response inhibition. SSRT appeared substantially longer in individuals with attention deficit / hyperactivity disorder (AD/HD; e.g., Bekker, Overtoom, Kooij, Buitelaar, Verbaten, & Kenemans, 2005; Oosterlaan, Logan, Sergeant, 1998; Schachar & Logan, 1990), individuals diagnosed with Parkinson’s disease (e.g., Gauggel, Rieger, & Feghoff, 2004; van den Wildenberg, van Boxtel, van der Molen, Bosch, Speelman, & Brunia, 2005), substance abuse (e.g., Fillmore & Rush, 2002), schizophrenia (e.g., Bellgrove, Chambers, Vance, Hall, Karamitsios, & Bradshaw, 2005) and patients with damage to the prefrontal cortex (e.g., Aron,
Fletcher, Bullmore, Sahakian, & Robbins, 2003). The stop-signal task has also been used to track the development of response inhibition over the lifespan. Those studies showed that inhibition becomes faster throughout childhood (Bedard, Nichols, Barbosa, Schachar, Logan, & Tannock, 2002; Ridderinkhof, Band, & Logan, 1999; van den Wildenberg & van der Molen, 2004b) and declines steadily during senescence (Kramer, Humphrey, Larish, Logan, & Strayer, 1994; Rush, Barch, & Braver, 2006; Williams, Ponesse, Schachar, Logan, & Tannock, 1999).

The global stop-signal task investigates the inhibition of whatever go response is activated. In daily-life situations, environmental demands often require more complex actions than global stopping. For example, it may be required to inhibit behavior to a subset of stimuli while continuing the ongoing response to other stimuli. In the every-day life example described at the beginning of this introduction, the waving action should not be stopped if you happen to recognize, the person waving at you, to be a close colleague of yours. To investigate stopping ability in more complex situations, the stop-signal task has been extended by an additional category of stop-signals. Participants should then inhibit their response only to one stop-signal category while executing the go response to the other category (see Logan 1994 for earlier investigations of selective stopping). Alternatively, participants may be instructed to stop if the stop and go signal correspond spatially but to execute the response when the stop and go signal do not (de Jong, Coles, & Logan, 1995; van den Wildenberg & van der Molen, 2004b). The latency of selective stopping appears to be substantially longer than the latency of global inhibition. Like global SSRT, selective SSRT follows a developmental pattern; that is, SSRT decreases throughout childhood and increases again when people grow older (Bedard et al., 2002). Van den Wildenberg and van der Molen (2004b) found that the speed of global, not selective, inhibition improved from 7-year-olds to 10-year-olds indicating that global and selective inhibition follow separate developmental trends. The studies described above show that global and selective SSRT provide useful measurements to investigate the development of response inhibition. However, a lifespan analysis of global and selective stopping is still lacking in the literature and this might provide valuable insights into the maturational and age-related changes in inhibitory control, and is one of the main aims of Chapter 3 of the present dissertation.

Chronometric analysis of RTs

There is more to say about inhibition than just its latency, the SSRT. Mental chronometry is an approach to study information processing that attempts to decompose the RT into a sequence of distinct processes. This approach assumes that processing of information, conveyed by the
imperative signal, unfolds in a consecutive manner, through stages. Each stage of processing requires time in order to yield an outcome (Smith, 1968; Sternberg, 1969). It has been proposed that both go RT and SSRT include the duration of a signal-detection stage and the actual implementation of response execution or inhibition respectively (Schall, 2004). Furthermore, Go RT also includes intermediate stages, such as stimulus discrimination and response selection (Sternberg, 1969). Manipulating the duration of distinct processing stages may affect the total length of go RT and SSRT. Donders (1868/1969) was the first to investigate stage duration. He compared three classical tasks that ought to differ with respect to one processing stage. The Donders’ A task was a simple RT task that involved one vocal response to one sound (for example, when hearing the letter ‘i’ the participant is required to respond with saying out loud ‘i’). In the Donders’ B task, participants were instructed to respond to two sounds (the letters ‘a’ or ‘i’) designated to two responses (saying out loud ‘a’ or ‘i’ respectively), also coined a choice RT task. It was assumed that processing in the Donders’ B task compared to the A task involved two additional processes, namely the stimulus discrimination and the response choice processing stages. The Donders’ C task is also known as a go/no-go task and involved responding vocally (saying out loud ‘i’) to one sound (the letter ‘i’), but not to the other sound (the letter ‘a’). The duration of the stimulus discrimination stage was obtained by subtracting the go RT attained in the C task from the go RT in the A task. The RT difference between the Donders’ C and B task reflected the duration of the response selection stage.

Donders’ subtraction method received some criticism (Hackley, Schäffer, & Miller, 1990; Miller & Low, 2001; Sternberg, 1969). The subtraction method assumes that processing stages can be inserted without affecting the duration of other processing stages. The logic of pure insertion might not be applicable to other experimental tasks, because the processing stages might not remain constant in different situations. Nevertheless, the subtraction method is still a common experimental technique and still receives much attention nowadays (e.g., Lida, Miyazaki, & Uchida, 2010; Vidal, Burle, Grapperon, & Hasbroucq, 2011). An alternative method that allows identifying the properties of stages of the RT process is that of the additive-factor method (Sternberg, 1969). This method involves investigating the relation among stages without adding or deleting stages. It is thought that if two task manipulations affect different processing stages then the manipulations have additive effects on RT, while an interaction effect indicates that the two task manipulations share at least one processing stage. Van den Wildenberg and van der Molen (2004a) applied the additive-factor logic to identify processing stages of the SSRT using different versions of the stop-signal task. The two task manipulations involved stimulus similarity and stimulus-response compatibility and the two independent
stages were stimulus identification and response selection of the choice RT process. Participants were required to respond with the right or left hand when the eyebrows of a schematic face changed from a neutral position into a happy or sad face that was designated to one of the response hands. Stop signals were left- or right-positioned pupils that occurred in the schematic face. Response inhibition was required when the location of the response hand corresponded with the location of the stop signal, but not when the stop signal indicated the opposite direction than the response indicated by the go signal. The discriminability of stop signals was manipulated by varying the distance of the pupils with respect to the center of the eyes, i.e., easy-to-discriminate stop-signals were pupils appearing 8 mm to the left or right side of the center of the eye, whereas difficult-to-discriminate stop-signals had a distance of 4 mm from the center of the eye. The results revealed that the additional stop stimulus-discrimination stage in selective stopping was less sensitive to task manipulations than that of the reaction process. Moreover, it showed that the effects of stop-stimulus discriminability and stop-stimulus response compatibility did not interact, suggesting that the manipulations affected different stages of stop-signal processing and that the stages were additive. This study reveals that the additive-factor method to manipulate processing stages of the RT process is a valuable tool to investigate stop-signal processing. For example, it shows that SSRT comprises of different processing stages just as go RT. It also indicates that changes in specific perceptual and response-related processing stages induce changes in the latency of the inhibition process.

It appears that the application of the additive-factor logic on RTs is a useful tool to identify subcomponents of the inhibition process, whereas the Donders’ subtraction method is an informative technique to uncover the duration of processing stages of the RT process. To date, the Donders’ subtraction method has not yet been applied on SSRTs to estimate the duration of processing stages. The study presented in Chapter 2 is the first attempt to apply this method on three stop-task variants.

Chronometry in psychophysiology

The behavioral chronometric approach of RTs allows inferring particular processing stages by comparing the latencies of processes derived from overt behavior. Another chronometric approach to investigate the temporal aspects of the RT process includes electrophysiological indices (dubbed ‘chronopsychophysiology’ by van der Molen, Bashore, Halliday, & Callaway, 1991). Event-related potentials (ERPs) are very suitable to investigate components of information processing, as they index the timing of brain processes in relation to information processing. ERPs are derived from electroencephalographic (EEG) recordings, a non-invasive
method of measuring neural brain activity that is captured by electrodes placed on the scalp. EEG is displayed as continuous electrical activity that changes in voltage over time. To capture cognitive processes associated with a specific event, a series of stimuli are presented at a particular point in time. Subsequently, the ERP is obtained by averaging the voltage signals associated with a repetitive stimulus or response. Since ERPs provide high temporal resolution, it is able to track mental processes in relation to neural substrates in a milliseconds time range. The obtained averaged ERP waveform consists of positive and negative fluctuations that are dubbed ‘components’ and are expressed sequentially according to polarity and time of occurrence, for example, a relatively early component after stimulus onset peaks around 100 ms and can be either positive (P100) or negative (N100).

Two ERP components have been used to decompose the RT process: the P300, a positive component peaking approximately 300 ms following the stimulus, and the Lateralized Readiness Potential (LRP), a compound potential peaking approximately at the time of a button-press response. Duncan-Johnson and Donchin (1982) argued that the timing and duration of stimulus evaluation processes could be examined using the peak latency of the P300. This conjecture is based on the assumption that the P300 latency marks the information processing time conveyed by the stimulus and is relatively less affected by processes that mediate response selection and execution (Kutas, McCarthy, & Donchin, 1977, but see Magliero, Bashore, Coles, & Donchin, 1984).

Alternatively, response-related processes can be examined using the LRP. Neurons in the primary motor cortex (M1) reach a particular level of activation during movement initiation. This is expressed by a negative potential at the contralateral side of M1 associated with the responding hand that is larger compared to the ipsilateral side. This activation difference between the contralateral and ipsilateral M1 is captured by the LRP (Coles, 1989; Gratton, Coles, Sirevaag, Eriksen, & Donchin, 1988). Thus, the LRP reflects the difference in electrophysiological activation between the hemisphere that is involved in the response and the hemisphere that is involved in the incorrect response alternative. The LRP is computed as follows:

\[(M1_{\text{right}} - M1_{\text{left}})_{\text{left-hand responses}} + (M1_{\text{left}} - M1_{\text{right}})_{\text{right-hand responses}}\]

where M1 denotes the primary motor cortex. For left-hand responses, the ERP trace measured with the electrode covering the left M1 (M1 left) is subtracted from the ERP trace of the electrode covering the right M1 (M1 right). For right-hand responses, the ERP trace measured
with the electrode covering the right M1 is subtracted from the ERP trace associated with the electrode covering the left M1. The hemispheric voltage difference associated with left-hand responses is added to the voltage difference associated with right-hand responses (see also, Coles, 1989). The onset of the negative deflection of the LRP trace precedes the overt response and provides a marker that bisects the RT in two processing parts: 1) the interval from stimulus onset to LRP onset reflects the pre-selection interval and captures predominantly processes related to stimulus processing, and 2) the interval from LRP onset until the overt response (RT) reflects the post-selection interval capturing motor-related processes of the RT process. Osman, Moore, and Ulrich (1995) used the P300 latency and the LRP onset to investigate the duration of stimulus- and response-related processes of the RT in a pre-cued choice RT task. In this task, participants responded to go signals that were preceded by informative pre-cues (i.e., cues that conveyed information about the upcoming response) or by non-informative pre-cues (i.e., cues that did not contain information regarding the correct response). It appeared that non-informative pre-cues lengthened the RT, the P300 latency, and the pre-selection interval compared to informative cues. This suggests that pre-cues can change the duration of stimulus evaluation processes. Moreover, non-informative pre-cues also lengthened the post-selection interval compared to informative cues indicating that response-related processes also contributed to the longer RT on trials without foreknowledge. This study illustrates that the P300 and LRP onset provide useful markers to bisect the RT in stimulus- and response-related parts that might help to elucidate the processes underlying RT differences between task conditions.

The P300 and the LRP have also been used to investigate age-related changes in response execution. Typically, go RT sharply decreases from childhood to early adulthood followed by a less pronounced increase from early adulthood to senescence (Cerella & Hale, 1994; Kail, 1991; Salthouse, 1996). The latency of the P300 and the LRP onset can be used to examine the differential involvement of stimulus- and response-related processes with respect to the typical U-shaped RT pattern. Although only a few developmental and aging studies investigated the development of the speed of motor response activation, the results that emerged from these studies revealed that the P300 latency and the LRP were differentially sensitive to age-related changes in response activation. For example, participants (8-year-olds, 12-year-olds and 22-year-olds) in the study by Ridderinkhof and van der Molen (1995) were required to respond, as fast and accurately as possible, to go signals (a left- or right-pointing arrow) flanked by two arrows on the left and two arrows on the right side of the go signal. The flankers were to be ignored, but could point to the same direction as the go signal (congruent flankers) or could
point to the opposite direction (incongruent flankers). It is assumed that the array of stimuli in the incongruent condition activates two responses simultaneously, i.e., the correct response activated by the go signal and the competing incorrect response associated with the flanker stimuli (distractors). The common finding in studies using the Eriksen flanker task (Eriksen & Eriksen, 1974) is that the latency of responses to the go signal is longer when the flankers are incongruent. Ridderinkhof and colleague (1995) found that RT, the P300 latency, and the pre-selection interval associated with congruent and incongruent trials decreased from childhood with advancing age until early adulthood. However, the developmental pattern of P300 latency did not differentiate between the congruent and incongruent condition, whereas the LRP onset did. They concluded that children and adults suffer to a similar degree from perceptual conflict and that the age-related magnitude of response competition can be related to response-related processes. This outcome is in line with reports in the literature indicating that response-related stages of the RT process contributed most significantly to the development in the ability to resist interference (see also, Bryce, Szucs, Soltész, & Whitebread, 2010; Szucs, Soltész, Bryce, & Whitebread, 2009; Szucs, Soltész, Jármi, & Csépe, 2007).

To date, three aging studies used the P300 and LRP onset to investigate aging changes in stimulus- and response-related stages of the RT process (Falkenstein, Yordanova, & Kolev, 2006; Kolev, Falkenstein, & Yordanova, 2006; Yordanova, Kolev, Hohnsbein, & Falkenstein, 2004). The task involved responding to four letters designated to four fingers (two of each hand). The studies revealed that RTs, the P300 latency, and the post-selection interval (not the pre-selection interval) were longer in elderly adults compared to young adults. However, Yordanova et al. (2004) also administered a simple RT task (respond with the right-index finger to all four letters) and observed that the pre- and post-selection intervals were substantially longer in the choice RT compared to the simple RT task. The P300 was present only in the choice RT task, but peaked later than the RT and was therefore not considered to contribute to the behavioral slowing on choice RT. The age-related effects on the post-selection interval and the absence of age effects on the pre-selection interval let the authors to conclude that the response-related stages of the RT process drive the observed slowing in choice RT (see also Bashore, Osman, & Heffley, 1989; Bashore, Ridderinkhof, & van der Molen, 1997). Electrophysiological studies using the mental chronometric approach to investigate the temporal aspects of the RT process show that ERPs can provide very useful and complementary information regarding the reaction process. It shows that specific ERP components are differentially sensitive to manipulations of stimulus- or response-related processes. This is specifically useful in investigating lifespan changes in information processing. Notably, the
developmental and aging literature revealed that the age-related behavioral slowing might be related to response-related stages of the RT process. No study to date performed a lifespan analysis of M1-related activity and its contribution to the age-related change in response speed by decomposing the RT in a pre-selection and post-selection time using motor-related electrophysiological indices. This is the focus of the study described in Chapter 4. Such an analysis might address the question whether stimulus- or response-related stages of the RT process are differentially sensitive to age-related changes in response activation along the lifespan. However, the LRP as a compound measure does not dissociate the motor-related activity from the two hemispheres. Thus, observed changes in LRP might be attributed to activity of one or both hemispheres. A technique that allows investigating the contribution of each motor cortex to the activation associated with the response is the Laplacian transformation of ERP signals. This method will be discussed in the next section.

Laplacian transformation of motor-related ERPs

The Laplacian transformation is the spatial second derivative of the interpolated signals (see Perrin, Pernier, Bertrand, & Echallier, 1989). This procedure reduces the blurring effects of the currents evoked by the low conductance of the skull (Babiloni, Carducci, Babiloni, & Urbano, 1998; Nunez, 1981). It improves the spatial resolution (up to 2-3 cm depending on the quantity of spatial sampling) and the temporal resolution of the EEG potentials (Law, Rohrbaugh, Adams, & Eckardt, 1993). Studies using choice RT tasks applied the Laplacian transformation method on ERP signals recorded from electrodes covering M1 to investigate the duration and activation of motor-related processes in choice behavior (e.g., Tandonnet, Burle, Hasbroucq, & Vidal, 2005; Taniguchi, Burle, Vidal, & Bonnet, 2001; Vidal, Grapperon, Bonnet, & Hasbroucq, 2003). Figure 3 presents an example of Laplacian activity observed over the contralateral and ipsilateral M1 associated with the correct response to go signals in a choice RT task.
Typically, in healthy adults, approximately 100 ms prior to the mechanical choice response, a negative wave develops over the contralateral M1 and a positive wave develops over the ipsilateral M1 with its onset preceding the onset of the negative wave (e.g., Praamstra & Seiss, 2005; Vidal et al., 2003).

Several studies investigated the differential involvement of the contralateral negative and the ipsilateral positive wave in response execution processes (e.g., Tandonnet, Burle, Vidal, & Hasbroucq, 2003; Vidal, Burle, Grapperon, & Hasbroucq, 2011). For example, Tandonnet, Burle, Vidal, and Hasbroucq (2006) manipulated the time between a warning stimulus and the go signal, i.e. the foreperiod. The task consisted of a blue warning signal that was followed by a go signal that appeared on either the left or right side of the warning signal. The foreperiod was either 800 ms or 2800 ms that alternated between blocks of trials. RT was dissected in a pre-motor part, i.e., the interval between the onset of the contralateral negative Laplacian wave and EMG onset, and a motor part, i.e., the interval from EMG onset to overt response. The results showed that when the foreperiod was short, RTs were shorter, the pre-motor and motor times were shorter and the amplitude of the negative wave was reduced compared to when the foreperiod was long. The authors concluded that the contralateral negative Laplacian wave reflects the central motor command to the correct response (see also Tandonnet et al., 2003; Vidal et al., 2003). Moreover, when the participant could prepare the response just prior to go-
signal onset it improved the efficiency of the motor command and decreased RTs. A positive Laplacian wave was also present at the ipsilateral M1 associated with the incorrect response alternative, however its onset and magnitude did not differ between the two foreperiods. These findings show that the timing of the upcoming go signal (time preparation) affects the contralateral negativity, however it does not affect the ipsilateral positivity indicating that the negative wave can be modulated without affecting the activity at the ipsilateral M1. This finding let the authors to conclude that advance information regarding the timing of the go signal affected the implementation of the central motor command associated with the correct response but not the response alternative.

It has been argued that the ipsilateral positive wave is a result of reciprocal (or lateral) inhibition between the motor cortices, i.e., activation and inhibition through an interaction of the left and right motor cortex (Praamstra & Seiss, 2005) (definition proposed by Sherrington in 1906 to indicate the spinal circuitry of simultaneous excitation and inhibition of flexors and extensors of the same joint). Accordingly, various task manipulations should automatically induce, in parallel, an increase of negative and positive amplitudes over, respectively, the contralateral and ipsilateral M1. Meynier, Burle, Possamai, Vidal, and Hasbroucq (2009) investigated this issue. Participants in their study performed a within-hand choice RT task (i.e., two fingers of the same hand were required to respond to two go signals), and a between-hand choice RT task (responses were made with either the left or right hand to two go signals). In both tasks, a negative wave developed prior to the overt response that revealed somewhat lower amplitudes in the within-hand condition compared to the between-hand condition. Remarkably, the positive wave was clearly present in the between-hand condition, but was absent in the within-hand condition. The authors suggested that the positive wave reflects the active inhibition of the ipsilateral M1 to prevent responses with the incorrect hand (see also Burle, Vidal, Tandonnet, & Hasbroucq, 2004). Meckler, Allain, Carbonnell, Hasbroucq, Burle, and Vidal (2010) extended this pattern of findings by showing that the risk of committing an error affected the ipsilateral positive wave. Participants in their study performed a choice RT task that consisted of an unequal probability of left- and right-hand responses, e.g. 80% right-hand responses and 20% left-hand responses. It was hypothesized that the risk of committing an incorrect response is lower for the high compared to the low response probability condition, as the most probable response is more prepared allowing the incorrect response a lower chance to execute. The results revealed that the ipsilateral positivity preceded the contralateral negativity in both conditions. Most, importantly, the less probable response showed longer RTs, higher error rates and a larger positive wave compared to the most probable response. Interestingly, the
steepness of the initial deflection of the positive wave also correlated negatively with error rates across individuals. These findings show that the more the response was expected, the more prepared the response and the less need for implementation of inhibition of the ipsilateral M1 to prevent incorrect responses.

Taken together, the pattern of contralateral negative and ipsilateral positive Laplacian activation seems to contribute to efficient motor control when performing a choice RT task. The comparison of fractions of the RT process, using the onsets of the contralateral negative wave and EMG, provided valuable information regarding the efficiency of response execution during task performance. It seems that the duration (the interval between the onset of the negative wave and EMG onset) and magnitude (reflected in peak amplitudes) of contralateral negative activation provides information concerning, respectively, the speed and strength of the central motor command associated with the overt response. The timing and magnitude of the ipsilateral positive activation might reflect the amount of inhibition-related activity to prevent incorrect responses from occurring. A novel aspect of the present dissertation is the focus on the developmental pattern of the contralateral negative and ipsilateral positive Laplacian waves during choice responses in a choice RT task and in a selective stop-signal task. The temporal dynamics of response activation and inhibition associated with selective stop-signal processing have not yet been investigated and might help to elucidate developmental changes in action control. This is the main goal of the study presented in Chapter 5. Before discussing the structure of the outline of this dissertation, it is imperative to introduce the neural mechanisms involved in reaction and inhibition processes.
Neural correlates of response activation and inhibition

Figure 4 is a diagram that illustrates the main structures and pathways of the human motor system that are involved in a voluntary movement.

**Figure 4** An illustration of the human motor system partly adopted from Scott (2004: Optimal feedback control and the neural basis of volitional motor control in *Nature Reviews Neuroscience*, 5, 534-546). V1 (primary visual cortex), area 7 (posterior part of the parietal cortex), area 5 (anterior parietal cortex), SI (primary somatosensory cortex), M1 (primary motor cortex), dPM (dorsal premotor cortex), SMA (supplementary motor area), PF (prefrontal cortex), BG (basal ganglia), TH (thalamus), C (cerebellum), regions of the brain stem are RF (reticular formation) and VN (vestibular nuclei). Stimulus information that travels through the visual system is marked in green arrows, central pathways are marked in black arrows, descending (in red) and ascending (in blue) motor pathways to and from the spinal cord.

When performing a choice RT task, the stimulus information associated with the go signal travels through the visual cortex towards pre-motor areas of the brain. The basal ganglia and cerebellum form connections with the cerebral cortex in two distinct loops (Akkal, Dum, & Strick, 2007). The anterior loop (also called the direct fronto-striatal pathway, Aron & Poldrack, 2006) contains projections from the basal ganglia and motor nuclei of the thalamus to the
supplementary motor area (SMA, Nachev, Kennard, & Husain, 2008; Simmonds, Pekar, & Mostofsky, 2008) that projects to the last central area of the brain, the primary motor cortex (M1) (see also Chouinard & Paus, 2006). Additionally, the SMA and basal ganglia receive projections from areas of the prefrontal cortex, which is also involved in the planning and selection of the response (Middleton & Strick, 2000). The posterior loop has projections through the cerebellum and motor nuclei of the thalamus to M1 (Halsband & Lange, 2006). This loop serves to adjust the motor activity in M1 and is involved in refining and integrating actions (Goldberg, 1985; Taniwaki, Okayama, Yoshiura, Togao, Nakamura, et al., 2006). Finally, information travels from the primary motor cortex (M1) through the spinal cord (where it receives projections from the brain stem for body orientation, Gdowski & McCrea, 1999) to trigger the muscles associated with the responding hand for an overt button press.

Obviously, when a stop signal appears, it needs to be processed quickly to trigger the inhibition system that interrupts the response process before it reaches the response button (Boucher, Palmeri, Logan, & Schall, 2007). Band and van Boxtel (1999) suggested that the prefrontal cortex or basal ganglia, or an interaction between the two, might be the source that instigate the inhibition process, whereas the actual implementation (the site) of inhibition might be the motor cortex. The contribution of the fronto-subthalaric circuitry in the implementation of response inhibition was later confirmed by fMRI (e.g., Aron & Poldrack, 2006, but see Aron, 2007 for a review). A consistent finding is that the right inferior frontal cortex (IFC) is activated during the processing of the stop signal (e.g., Aron, Behrens, Smith, Frank, & Poldrack, 2007; Aron, Robbins, & Poldrack, 2004; Chambers, Bellgrove, Stokes, Henderson, Garavan et al., 2006; Rubia, Smith, Brammer, & Taylor, 2003). The specific involvement of the right IFC in response inhibition is supported by clinical studies investigating stop-signal performance in patients with damage to the right IFC (e.g., Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Rieger, Gaugel, & Burmeister, 2003). For example, Aron et al. (2003) found that the volume of damage to the right IFC correlated positively with SSRT, whereas SSRT was not related to lesions of adjacent regions to the IFC. It remains unclear as to precisely how the right IFC is involved in the fronto-subthalaric network when performing the stop-signal task. Aron and Verbuc (2008) proposed that the processing of the stop signal triggers the right IFC that activates areas of the basal ganglia (i.e., subthalaric nucleus and globus pallidus), resulting in a suppresses of thalamic output and M1. Moreover, it was suggested that the deployment of such ‘hyperdirect’ neural pathway of the basal ganglia allows for fast inhibition of all initiated response. Additionally, they argued that when one response should be inhibited but not the other (selective inhibition), an ‘indirect’ neural pathway of the basal ganglia is implemented that is
able to selectively inhibit the inappropriate response but not the appropriate response. The striatum might therefore play a key role in the neural mechanism of selective inhibition (e.g., Zandbelt & Vink, 2010). Despite the differential involvement of the hyperdirect vs. the indirect pathway in inhibitory control, both mechanisms are believed to have inhibitory effects onto the motor system.

Van den Wildenberg, Burle, Vidal, van der Molen, Ridderrinkhof, and Hasbroucq (2010) investigated the involvement of intra-cortical inhibitory circuits in M1 with transcranial magnetic simulation (TMS) of the motor cortex. This technique allows investigating the temporal dynamics of cortical motor excitability during cognitive tasks. Magnetic stimulation of the motor cortex excites populations of neurons that will fire rapidly for a few milliseconds. This excitation is followed by a period of GABAergic inhibition to suppress the induced motor activity. Participants in the study by van den Wildenberg et al. (2010) received TMS to M1 at various intervals after presentation of the stop signal to track the corticospinal excitability related to response inhibition. The results revealed an increase of corticospinal excitability associated with failed stopping. An initial increase was also found on successfully stopped trials but less pronounced and directly followed by a marked reduction of corticospinal activity that was not present on failed inhibition trials. They interpreted the initial increase being related to motor-related activity associated with processing of the go signal, whereas the decrease was associated with inhibition-related activity induced by stop-signal processing. The results were taken to suggest that the actual implementation of response inhibition occurs at M1 (see also Coxon, Stinear, & Byblow, 2006; Swann, Tandon, Canolty, Ellmore, McEvoy, et al., 2009).

Dissertation outline

The aim of this dissertation is to improve the understanding of the development of activation and inhibition of responses. Although there are a number of studies addressing age-related differences in inhibitory processing using the stop-signal task, research that specifically examines the temporal dynamics of response activation and inhibition using response-related potentials across the lifespan are rare. The empirical chapters presented in this dissertation directly address several issues of go- and stop-signal processing that underlie performance on the stop-signal task. As previously discussed, the mental chronometry approach assumes that responding to the go signal involves the processing of information conveyed by distinct stages that together comprises the RT process. Go signals require detection and discrimination of the signal, response selection and the actual implementation of response execution. Like the go process, the inhibition process also involves a series of component processes that leads to the
implementation of response inhibition (van den Wildenberg & van der Molen, 2004a). Logan, Kantowitz and Riegler (1986, but see Logan, 1994) found that SSRT latency increased in a condition when inhibition was required based on correspondence of stop and go signals (selective stopping) compared to a stop-all response condition (global stopping). This implies that the prolonged selective SSRT might include a processing stage that is absent in global SSRT. In Chapter 2, we explore in more detail the processing stages involved in the inhibition process under the assumption that stop-signal processing is analogous to the go process. A behavioral chronometric technique, the Donders’ subtraction method, is applied to SSRTs obtained by three stop-signal task variants to capture the latency of distinct inhibitory processing stages. The stop tasks are designed in such a way that go signals are always administered as a choice RT task and the inserted stop signals differ between tasks regarding additional processing requirements. Following the serial architecture of the RT process, it is expected that the insertion of an additional processing stage leads to prolonged inhibitory processing.

Lifespan literature on stop-signal inhibition showed that global SSRT improves from childhood to adulthood and declines during senescence (Williams, Ponesse, Schachar, Logan, & Tannock, 1999). This lifespan pattern is also observed for selective inhibition latencies (Bedard, Nichols, Barbosa, Schachar, Logan, & Tannock, 2002). Additionally, van den Wildenberg and van der Molen (2004b) showed that the developmental gain during childhood was considerably reduced for selective stopping compared to global stopping. The study described in Chapter 3 extends these findings by examining whether global and selective inhibition latencies are differentially sensitive to age-related changes along the lifespan. Such an analysis might reveal valuable insights into the maturational and aging process of inhibitory control. A second aim of this chapter is the focus on response adjustments when performing the stop-signal tasks. A consistent finding in the stop-signal literature is that participants delay responding to go signals when stop signals are expected (see also Bisset & Logan, 2011; Ramautar, Kok, & Riddervold, 2004). These processes are also referred to as proactive response adjustments and are thought to reflect a deliberate control strategy by the participant to increase the chance of successful inhibition. The delay in response speed is also observed on go trials following stop-signal trials (e.g., Rieger & Gauggel, 1999; Verbruggen, Logan, Liefooghe, & Vandierendonck, 2008) and was referred to as reactive control processes. Chapter 3 examines lifespan changes in proactive and reactive control processes associated with global and selective stopping. The analysis of performance adjustments might provide valuable information regarding the implementation of control strategies by each of the four age groups. Based on the developmental literature, it was expected that the response delay associated with proactive and reactive control
strategies are more pronounced in children compared to young and elderly adults (Fleischman, 2007; Smulders, Notebaert, Meijer, Crone, van der Molen, & Soetens, 2005; van den Wildenberg & van der Molen, 2004b).

Several studies used electrophysiological indices to investigate whether stimulus- or response-related processes are differentially sensitive to age-related change in response speed. Moreover, those studies revealed that the response-related stages of the RT process were most sensitive to the effects of advancing age (e.g., Ridderinkhof & van der Molen, 1995; Yordanova, Kolev, Holmsbein, & Falkenstein, 2004). The study described in Chapter 4 provides a lifespan analysis of response activation and inhibition during choice reactions using response-related potentials. Such an analysis is still lacking and might reveal potentially interesting differences between age groups in action control. The RT is dissected in three processing parts using the onsets of the central motor command (the LRP and contralateral negative Laplacian wave) and the response-related EMG: 1) the pre-selection interval; from stimulus onset to the onset of the central motor command, 2) pre-motor time; from onset of the central motor command to EMG onset, and 3) motor time; from EMG onset to overt response. It was expected that pre-motor and motor times, rather than pre-selection time, contribute to the lifespan pattern of RT. An additional focus is on the positive wave that develops over the ipsilateral M1 controlling the alternative response. Previous literature revealed that children commit substantially more incorrect responses than adults (e.g., Cerella & Hale, 1994; Ridderinkhof, Band, & Logan, 1999), whereas the amount of incorrect responses did not differ between young and elderly adults (e.g., Smith & Brewer, 1995). The study presented in Chapter 4 is the first to provide data associated with the ipsilateral positive wave that is interpreted in relation to the age-related patterns of percentage incorrect responses.

The results presented in Chapter 4 were used to guide the research questions for the study in Chapter 5. Chapter 5 deals with the dynamic interplay between response activation and inhibition of choice responses in a selective stop-signal task using the Laplacian transformation of response-related potentials in two child groups and one adult group. Literature using the Laplacian transformation of ERP signals revealed that the contralateral negative Laplacian wave can provide valuable information concerning the efficiency of the central motor command associated with the correct response hand, whereas the ipsilateral positive Laplacian wave provides information regarding the inhibition of M1 associated with the alternative response (e.g., Meynier, Burle, Possamai, Vidal, & Hasbroucq, 2009; Tandonnet, Burle, Vidal, & Hasbroucq, 2006; Vidal, Grapperon, Bonnet, & Hasbroucq, 2003). The analysis of the contralateral negative and ipsilateral positive waves associated with choice responses in a
selective stop task might help to gain more insights in the development of action control when performing a stop-signal task. Furthermore, this study extends the findings on the development of proactive control in Chapter 3 by directly comparing central and peripheral motor processes associated with go trials in a choice RT task vis-a-vis go trials in a selective stop-signal task. According to the horse-race model underlying information processing in the stop-signal task (Logan & Cowan, 1984), responses on failed inhibition trials escaped inhibition and won the race against the stop process. It is examined whether selective processing of stop signals impacts on response-related processes. Band, van der Molen, Overtoom, and Verbaten (2000) argued that children might apply a global stopping strategy when performing a selective stop-signal task. The study presented in Chapter 5 also examines invalid stop-signal trials, i.e., stop signals that should have been ignored. Longer RTs on invalid stop-signal trials compared to RTs on go trials might indicate that the invalid stop-signal is not ignored and that the participant might have initially inhibited all responses followed by reactivation of the appropriate response after complete invalid stop-signal processing (e.g., Aron & Verbruggen, 2008). The current investigation is the first in providing data of central and peripheral motor processes associated with invalid stop-signal processing to uncover differential stopping strategies employed by children and adults when performing a selective stop-signal task.

All studies reported in the empirical chapters have been submitted for or have been published in international journals. The list of studies is presented below to acknowledge the valuable contribution of the co-authors:

