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NEUROPLASTICITY OF INHIBITORY CONTROL

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Neuroplasticity of inhibitory control

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ABSTRACT (ENGLISH)

Executive control refers to a set of abilities enabling us to plan, control and implement our behavior to rapidly and flexibly adapt to environmental requirements. These adaptations notably involve the suppression of intended or ongoing cognitive or motor processes, a skill referred to as “inhibitory control”. To implement efficient executive control of behavior, one must monitor our performance following errors to adjust our behavior accordingly. Deficits in inhibitory control have been associated with the emergence of a wide range of psychiatric disorders, ranging from drug addiction to attention deficit/hyperactivity disorders. Inhibitory control deficits could, however, be remediated. The brain has indeed the amazing possibility to reorganize following training to allow for behavioral improvements. This mechanism is referred to as neural and behavioral plasticity. Here, our aim is to investigate training-induced plasticity in inhibitory control and propose a model of inhibitory control explaining the spatio-temporal brain mechanisms supporting inhibitory control processes and their plasticity.

In the two studies entitled “Brain dynamics underlying training-induced improvement in suppressing inappropriate action” (Manuel et al., 2010) and “Training-induced neuroplastic reinforcement of top-down inhibitory control” (Manuel et al., 2012c), we investigated the neurophysiological and behavioral changes induced by inhibitory control training with two different tasks and populations of healthy participants. We report that different inhibitory control training developed either automatic/bottom-up inhibition in parietal areas or reinforced controlled/top-down inhibitory control in frontal brain regions. We discuss the results of both studies in the light of a model of fronto-basal inhibition processes.

In “Spatio-temporal brain dynamics mediating post-error behavioral adjustments” (Manuel et al., 2012a), we investigated how error detection modulates the processing of following stimuli and in turn impact behavior. We showed that during early integration of stimuli, the activity of prefrontal and parietal areas is modulated according to previous performance and impacts the post-error behavioral adjustments. We discuss these results in terms of a shift from an automatic to a controlled form of inhibition induced by the detection of errors, which in turn influenced response speed.

In “Inter- and intra-hemispheric dissociations in ideomotor apraxia: a large-scale lesion-symptom mapping study in subacute brain-damaged patients” (Manuel et al., 2012b), we investigated ideomotor apraxia, a deficit in performing pantomime gestures of object use, and identified the anatomical correlates of distinct ideomotor apraxia error types in 150 subacute brain-damaged patients. Our results reveal a left intra-hemispheric dissociation for different pantomime error types, but with an unspecific role for inferior frontal areas.

ABSTRACT (FRENCH)

Les fonctions exécutives désignent un ensemble de processus nous permettant de planifier et contrôler notre comportement afin de nous adapter de manière rapide et flexible à l'environnement. L'une des manières de s'adapter consiste à arrêter un processus cognitif ou moteur en cours ; le contrôle de l'inhibition. Afin que le contrôle exécutif soit optimal il est nécessaire d'ajuster notre comportement après avoir fait des erreurs. Les déficits du contrôle de l'inhibition sont à l'origine de divers troubles psychiatriques tels que l'addiction à la drogue ou les déficits d'attention et d'hyperactivité. De tels déficits pourraient être réhabilités. En effet, le cerveau a l'incroyable capacité de se réorganiser après un entraînement et ainsi engendrer des améliorations comportementales. Ce mécanisme s'appelle la plasticité neuronale et comportementale. Ici, notre but est d'étudier la plasticité du contrôle de l'inhibition après un bref entrainement et de proposer un modèle du contrôle de l'inhibition qui permette d'expliquer les mécanismes cérébraux spatiaux-temporels sous-tendant l'amélioration du contrôle de l'inhibition et de leur plasticité.

Dans les deux études intitulées "Brain dynamics underlying training-induced improvement in suppressing inappropriate action" (Manuel et al., 2010) et "Training-induced neuroplastic reinforcement of top-down inhibitory control" (Manuel et al., 2012c), nous nous sommes intéressés aux changements neurophysiologiques et comportementaux liés à un entraînement du contrôle de l'inhibition. Pour ce faire, nous avons étudié l'inhibition à l'aide de deux différentes tâches et deux populations de sujets sains. Nous avons démontré que différents entraînements pouvaient soit développer une inhibition automatique/bottom-up dans les aires pariétales soit renforcer une inhibition contrôlée/top-down dans les aires frontales. Nous discutons ces résultats dans le contexte du modèle fronto-basal du contrôle de l'inhibition.

Dans "Spatio-temporal brain dynamics mediating post-error behavioral adjustments" (Manuel et al., 2012a), nous avons investigué comment la détection d'erreurs influençait le traitement du prochain stimulus et comment elle agissait sur le comportement post-erreur. Nous avons montré que pendant l'intégration précoce des stimuli, l'activité des aires préfrontales et pariétales était modulée en fonction de la performance précédente et avait un impact sur les ajustements post-erreur. Nous proposons que la détection d'erreur ait induit un « shift » d'un mode d'inhibition automatique à un mode contrôlé qui a à son tour influencé le temps de réponse.

Dans "Inter- and intra-hemispheric dissociations in ideomotor apraxia: a large-scale lesion-symptom mapping study in subacute brain-damaged patients" (Manuel et al., 2012b), nous avons examiné l'apraxie idémotrice, une incapacité à exécuter des gestes d'utilisation d'objets, chez 150 patients cérébro-lésés. Nous avons mis en avant une dissociation intra-hémisphérique pour différents types d'erreurs avec un rôle non spécifique pour les aires frontales inférieures.

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LIST OF ABBREVIATIONS

ACC:	Anterior Cingulate Cortex
ADHD:	Attention-Deficit/Hyperactivity Disorder
BG:	Basal Ganglia
BPO:	Body Part as Object error
CS:	Configural/Spatial error
DLPFC:	Dorsolateral Prefrontal Cortex
EEG:	Electroencephalography
ERN:	Error-Related Negativity
ERP:	Event-Related Potential
FA:	False Alarm
fMRI:	Functional Magnetic Resonance Imaging
GNG:	Go/NoGo task
GPi:	Internal Globus Pallidus
IFG:	Inferior Frontal Gyrus
M1:	Primary Motor Cortex
PES:	Post-Error Slowing
Pre-SMA:	Pre-Supplementary Motor Area
RT:	Response Time
SLF:	Superior Longitudinal Fasciculus
SSRT:	Stop Signal Reaction Time
SST:	Stop Signal task
STN:	Subthalamic Nucleus
tDCS:	Transcranial Direct Current Stimulation
TMS:	Transcranial Magnetic stimulation
VLPFC:	Ventrolateral Prefrontal Cortex

CHAPTER 1 INTRODUCTION

Imagine yourself driving a car. As you are about to reach the light, it turns orange. In this situation, you might continue pressing on the gas pedal and cross the junction (surely at the red light) or quickly stop accelerating and brake. If you crossed at the red light at this junction, you might drive more carefully at the next light in order to be ready to stop in case the light turns orange. Importantly, with experience your driving behavior might also change (you become better at predicting a possible red light) and impact subsequent decisions (accelerate or brake).

Learning-induced changes in behavior are referred to as “plasticity”. Inhibiting motor responses (inhibition of pressing the gas pedal) and adapting following erroneous behavior (slowing before the next intersection to avoid being surprised by the orange light) are essential executive processes required to adapt to our ever-changing environment. The ability to withhold or stop a prepotent or ongoing motor response i.e. inhibitory control, has been widely studied in controlled laboratory settings with the Go/NoGo or Stop Signal tasks, which respectively require a speeded response to a category of stimuli and an inhibition of the motor response to another class of stimuli. Converging evidence indicate that even in adulthood, the anatomo-functional organization of the brain changes with experience and training. However, the brain mechanisms supporting training-induced improvements in inhibitory control are underestimated and will be the main focus of the current thesis. Additionally, we investigated motor control in brain-damaged patients.

In Manuel et al. (2010, 2012c), our aim was to understand whether and how the ability to suppress a motor response can be trained and to assess the supporting brain mechanisms. In Manuel et al. (2012a), we investigated how processing of stimuli following inhibition errors shaped subsequent behavior. Additionally, Manuel et al. (2012b) addressed motor control in a broader approach, namely motor control in the case of apraxia which consists in a deficit in performing manual gesture either on imitation or on verbal command.

1.1 Executive functions

"Executive function" is a multidimensional psychological construct referring to a set of abilities enabling us to plan, control and update behavior to adapt to a changing environment (Banich, 2009; Chambers et al., 2009). Executive functions allow us to act and select actions based on internal plans and goals (Koechlin and Summerfield, 2007), without depending solely on stimulation from the environment. The three main components of executive functions are working memory (the ability to maintain incoming information relevant for the task, by replacing it by newer, more relevant information to perform the task), response inhibition (the ability to suppress cognitive or motor processes) and set shifting (the ability to switch between mental sets or tasks) (Gazzaley and D'Esposito, 2007; Friedman et al., 2008). Psychiatric or neurologic patients with executive deficits are typically not able to flexibly maintain information for generating abstract hypotheses or links between categories or objects, to inhibit a response or shift responses facing competing task demands (Cummings, 1993). Our work will focus on one executive function, namely inhibitory control.

1.2 Inhibitory control

We constantly need to inhibit motor actions, thoughts or emotions. Many situations in daily life require a timely choice between executing and withholding an action (e.g. cross at the intersection or stop). Throughout this work, we will focus on motor inhibition, the ability to suppress planned or ongoing motor processes (Aron et al., 2004; Aron, 2007). Motor inhibition constitutes an ideal model for studying inhibitory control because the behavioral effects of motor inhibition are easily measurable (response time, false alarms) and the neural systems supporting motor inhibition largely overlap with those involved in the inhibition of cognitive or affective processes (Anderson et al., 2004; Dillon and Pizzagalli, 2007).

To make the terms used in the following chapters clear to the reader, the terms *inhibition* or *suppression* will be used when describing the general inhibitory control process, i.e. inhibition goal, while other terms will be used in task-related contexts: Go/No task (*withholding*, *refraining*) or Stop Signal task (*stopping*, *canceling*). Similarly, action generation, initiation or activation will be used as synonyms to describe the Go process, i. e. activation goal.

1.2.1 Measures of inhibition

Many well operationalized and validated behavioral paradigms have been developed to explore inhibitory control: Go/NoGo, Stop Signal, Stroop, Wisconsin card sorting or Eriksen flanker tasks to cite only a few. In this thesis we will focus on two widely used tasks, the Go/NoGo and Stop Signal tasks. In the Go/NoGo task (GNG), participants are required to respond as quickly as possible to a category of stimuli (Go stimuli) and withhold responses to another set of stimuli (NoGo stimuli). Pressure is typically set on response speed to ensure a strong response tendency/prepotency to respond to stimuli. The ability to inhibit responses is indexed by the response time (RT) to Go stimuli and the amount of false alarms (FA, response on NoGo trials). In the Stop Signal task (SST), participants are instructed to respond as quickly as possible to every stimuli except if immediately followed by another stimulus (i.e. the stop signal). The main index of performance of the SST task is the latency of the stop process referred to as the Stop Signal Reaction Time (SSRT). The SSRT is the time needed to inhibit a response once the stop signal occurs (Verbruggen and Logan, 2009). In addition to the response time and accuracy, the GNG and SST tasks reported above may also allow exploring the trade-off between accurate inhibition and fast responding.

Even though the two tasks reported above are validated tools for measuring inhibitory control, they differ in the timing of the inhibitory process (Schachar et al., 2007; Eagle et al., 2008a). These authors recently described two types of motor inhibitory control: action restraint and action cancellation. While actions must be *restrained* before the engagement of the motor response in the GNG task, motor actions have to be *cancelled* in the SST task indicating that participants must inhibit an already initiated motor response. Altogether, these paradigms enable us to study in details the behavioral and neural basis underlying inhibitory process which could benefit for the rehabilitation of patients suffering from inhibitory control deficits.

1.2.2 Deficits in inhibitory control

Inhibitory control plays a critical role in optimal functioning. This is notably supported by evidence showing that deficits in inhibitory control participate in the emergence of symptoms like impulsivity (Knoch et al., 2006; Whelan et al., 2012), inattention (Aron and Poldrack, 2005), obsessional thinking (Greenberg et al., 1997), perseveration (Clark et al., 2007), compulsivity or mania (Aron, 2007). Deficits in inhibitory control and loss of self-control have

been repeatedly advanced as constituting a causal factor, or at least as being associated with more severe psychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD; Overtoom et al., 2002; Aron and Poldrack, 2005; Whelan et al., 2012), substance addiction (Fillmore and Rush, 2002), pathological gambling (Potenza, 2008), obsessive-compulsive disorders (Chamberlain et al., 2006) or schizophrenia (Enticott et al., 2008). For exemple, studies using the SST paradigm reported slower SSRT in ADHD patients compared to controls (Lijffijt et al., 2005), but comparable Go RT, indicating a specific deficit of inhibition. Similarly, methamphetamine individuals with better inhibitory control (shorter SSRTs) exhibited lower drug craving (Tabibnia et al., 2011). Along with inhibition deficits, post-error behavioral adjustments seem to be affected in ADHD children as well: they slow down less after errors than control subjects, suggesting a deficit in adjusting their behavior following unsuccessful inhibition (Schachar et al., 2004).

Inhibitory control in healthy individuals has repeatedly been found to activate fronto-basal brain regions. Likewise, lesion or transcranial magnetic stimulation (TMS) of the same fronto-basal network has been shown to lead to deficits in inhibitory control, indicating a specific role of the mentioned network for suppressing prepotent or ongoing responses.

1.2.3 Overview of the neural systems supporting inhibitory control

To inhibit an ongoing motor response, sensory information of the stop-stimulus (the stimulus feature allowing to distinguish between the NoGo and the Go stimuli) processed by sensory areas have to be quickly relayed to prefrontal areas where the inhibitory command is initiated. Convergent evidence point towards the involvement of a right lateralized fronto-basal circuit as being the key network involved in response inhibition in humans (for recent reviews see: Aron et al., 2007a,b; Aron, 2007; Eagle et al., 2008a; Verbruggen and Logan, 2008a; Chambers et al., 2009; Chikazoe et al., 2010; Aron et al., 2011) and in animals (Eagle et al., 2008b). This network includes three critical regions that are consistently involved in inhibitory control in Go/NoGo and Stop Signal tasks: the right inferior frontal gyrus (IFG), the pre-supplementary motor area (pre-SMA) and underlying basal ganglia structures (particularly the subthalamic nuclei (STN) and striatum).

Figure 1 describes the fronto-basal network underlying inhibitory control adapted from Aron (2011). The model advances that two frontal brain areas, namely the IFG and pre-SMA, work in concert to produce motor suppression via direct projections to the underlying subcortical structures (Aron and Poldrack, 2006; Aron et al., 2007b; Swann et al., 2009). Once the inhibitory command is generated in the IFG, the information flows to basal ganglia

structures via the hyperdirect pathway to signal the suppression of the motor response (Maurice et al., 1998; Nambu et al., 2002; Magill et al., 2004). STN then has a massive output to the globus pallidus (GPi), which in turn inhibits the thalamocortical output, reducing activation in the primary motor cortex (M1) to finally inhibit the motor response (Gillies and Willshaw, 1998). In other words, the frontal cortex has downstream effects on the neurons in M1 via the basal ganglia to "brake" the output from M1, i.e. the motor command (Aron et al., 2007b; Swann et al., 2011; Chambers et al., 2009; Aron, 2011) and inhibit the ongoing motor response.

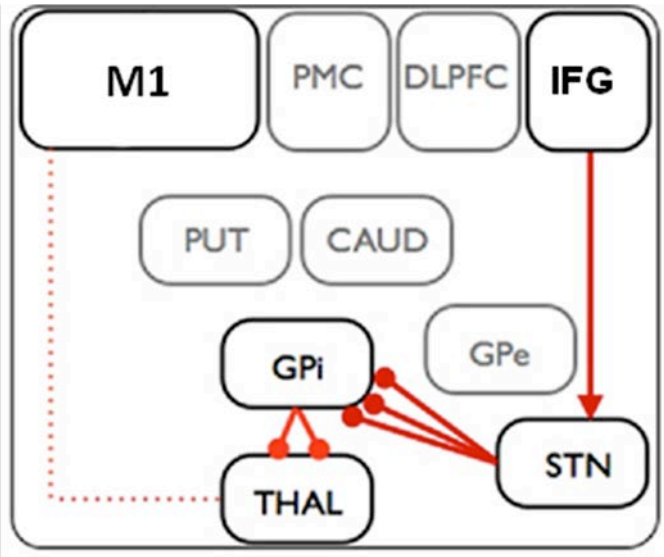

Figure 1: Fronto-basal model of inhibitory control (adapted from Aron, 2011). The model represents the inhibitory process during a stop trial. The brain regions in grey are part of other inhibitory control pathways (e.g. indirect pathway) and will not be discussed here. Arrows depict excitatory and round inhibitory connections. IFG: Inferior frontal gyrus; STN: Subthalamic nucleus; GPi: Internal Globus Pallidus; THAL: Thalamus; M1: primary motor cortex. The pre-SMA is not shown here for simplicity.

In the next chapters, the specific contributions and connections between each brain region of the motor inhibition control network as well as the precise brain dynamics underlying inhibitory control will be outlined.

1.2.3.a Frontal areas

The right inferior frontal gyrus and the pre-supplementary motor area have been consistently advanced to play a critical role in inhibitory control. Neuroimaging studies reported robust activity in the IFG (Garavan et al. 1999; Rubia et al., 2003; Aron and Poldrack, 2006; Aron et al., 2007a,b) and pre-SMA (Li et al., 2006; Xue et al., 2008;

Simmonds et al., 2008) during motor inhibition. Likewise, lesion studies revealed that patients with damage to the right IFG or right pre-SMA showed impaired inhibitory control as evidenced by an increase in stop signal reaction times in the SST task or in false alarms in the Go/NoGo task (Décary and Richer, 1995; Aron et al., 2003; Rieger et al., 2003; Floden and Stuss, 2006; Picton et al., 2007). Similarly, using TMS to disrupt the normal functioning of a specific brain area, few studies reported impaired inhibitory control when TMS was applied over the IFG and pre-SMA (but not over other brain regions) (Chambers et al., 2006, 2007; Nachev et al., 2007; Chen et al., 2009; Verbruggen et al., 2010). The above mentioned studies confirm the involvement of the IFG and pre-SMA in the inhibitory control over motor responses.

Evidence indicate that the pre-SMA is responsible for the updating of motor plans and the selection of appropriate motor response based on sets of action-selection rules (Rushworth et al., 2004; Mostofsky and Simmonds, 2008). The right IFG would play an important role in inhibitory control but may also be critical for other executive processes as well as attentional detection in inhibitory control tasks (Swann et al., 2009; Hampshire et al., 2010). Collectively, Aron (2011) advanced that the pre-SMA would signal the need for control based on action-selection rules while the IFG would implement inhibitory control.

To inhibit responses, the right IFG sends inputs to the pre-SMA and basal ganglia to engage a “kill switch” process on action initiation (Aron et al., 2007a,b; Chambers et al., 2009; Swann et al., 2012). If the “kill switch” is triggered on time through the hyperdirect pathway, then response execution is suppressed. Macrostimulation studies suggest that the pre-SMA would act as a “negative motor area”, because stimulation produces arrest of all manual movements and even speech (Luders et al., 1988; Fried et al., 1991). Evidence indicate that the IFG and pre-SMA, are directly connected between each other (whether pre-SMA precedes or succeeds IFG is still debated; Duann et al., 2009; Neubert et al., 2010) and have direct, monosynaptic, connections to the subthalamic nucleus in the basal ganglia (Inase et al., 1999; Aron et al., 2007b; Aron, 2011). Studies using diffusion tractography in humans (Aron et al., 2007b) or tract tracing in monkeys (Inase et al., 1999) indeed demonstrated that the pre-SMA was directly connected via white matter tracts to the right IFG and to the basal ganglia (STN and striatum), but also with parietal brain regions (Bates and Goldman-Rakic, 1993; Picard and Strick, 1996). To note, increased white matter connections between pre-SMA and subthalamic nuclei have been shown to result in better inhibitory performance (Forstmann et al., 2012). Swann et al., (2009) proposed that the functional communication between the right IFG and the STN would be mediated by oscillatory activity within specific frequency bands as e.g. the beta 20 herz frequency.

1.2.3.b Basal ganglia structures

Growing neuroimaging, lesion and neurophysiological data suggest a central role of basal ganglia in inhibitory control (Eagle and Baunez, 2010). Functional neuroimaging studies (fMRI) reported activation in the subthalamic nucleus and striatum during motor inhibition (Vink et al., 2005; Aron and Poldrack, 2006; Chevrier et al., 2007). Likewise, lesion to the STN has been shown to decrease inhibitory efficiency in rodents and humans (Rieger et al., 2003; Eagle et al., 2007; Eagle et al., 2008b; Ballanger et al., 2009), whereas deep-brain stimulation of the same structures in Parkinson patients suffering from movement disorders enhanced inhibitory control (van den Wildenberg et al., 2006).

The putative roles of basal ganglia structures likely comprise the selection and sequence of movements as well as the inhibition of competing motor programs. Basal ganglia structures therefore interact with motor areas for motor preparation (Mink, 1996; Chakravarthy et al., 2010). Researchers proposed that basal ganglia would suppress motor output in a global way by suppressing task-relevant but also task-irrelevant muscles (Coxon et al., 2006, 2007; Aron and Verbruggen, 2008; van den Wildenberg et al., 2010; Majid et al., 2011; see Badry et al., 2009 for tibia muscle suppression). This global suppression follows from a hyperdirect connection from IFG to the STN (Nambu et al., 2002). Subthalamic nucleus then sends outputs to the internal globus pallidus which in return has widespread effects on the motor system by inhibiting the thalamocortical loop (Mink et al., 1996; Gillies and Willshaw, 1998).

1.2.3.c Involvement of parietal areas

In addition to this well studied fronto-basal network involved in response inhibition, other studies have emphasized the role of parietal areas in the control over prepotent responses. Rubia et al. (2001) found overlapping brain areas for both GNG and SST tasks in lateral and medial prefrontal cortex, but also in inferior parietal cortices (see also Garavan et al., 1999; Watanabe et al., 2002; Dosenbach et al., 2006; Chikazoe, 2010 and Swick et al., 2011).

The function of parietal areas in inhibitory control has been attributed to the control of motor planning (Rushworth et al., 1997; Watanabe et al., 2002) and to the preparation for movements (Decety et al., 1992; Deiber et al., 1996), rather than to motor inhibition per se. Importantly, parietal areas may integrate sensori-motor information essential to realize the inhibitory control task. Supporting the role of parietal areas in the transformation of sensory information into motor action, human and animal data reported connections between parietal areas and motor cortex or pre-SMA, (Bates and Goldman-Rakic, 1993; Picard and Strick, 1996; Matelli and Luppino, 2001).

Altogether, the studies reviewed above support the involvement of a fronto-parieto-basal network responsible for inhibitory control comprising: right ventral prefrontal regions (IFG), medial prefrontal regions (pre-SMA), basal ganglia structures (STN, striatum) and parietal regions. Parietal areas process the sensory information, then the IFG and pre-SMA select the appropriate motor plans and finally send suppression signals to the STN to stop the motor output in M1 and to timely inhibit the inappropriate response.

1.2.1 Latency of inhibitory control

Electroencephalography (EEG) studies on inhibitory control consistently report differences in NoGo compared to Go trials, namely for two stimulus-locked event-related potential (ERP) components, the N2 and P3 components (Falkenstein et al., 1995; Bokura et al., 2001). The N2 component is generated by a NoGo condition (Nogo-N2) and is described by a negative shift peaking approximately 200ms post-stimulus onset (Jodo and Kayama, 1992; Eimer, 1993). Mounting evidence associate the N2 component with response inhibition in the Go/NoGo (Eimer, 1993; Falkenstein et al, 1999) or SST paradigms (Pliszka et al., 2000; Kok et al., 2004; Dimoska and Johnstone, 2008) and demonstrate that this component is generated in frontal areas (Pliszka et al., 2000; Bokura et al., 2001). Supporting the involvement of the Nogo-N2 in inhibitory control, Pliszka et al. (2000) showed on one hand that the N2 correlated with the efficiency of inhibition and on the other hand that it was considerably reduced in ADHD children.

The second ERP component involved in response inhibition, the P3, is a positive wave peaking between 300-600ms with larger amplitude for NoGo than Go (Eimer, 1993; Kopp et al., 1996). However, authors argued that the P3 component rather reflects movement-related activities differentiating the Go and NoGo (Falkenstein et al., 1999).

Despite the extensive research concerning the latency and network supporting inhibitory control, several questions still remain: 1. Is it possible to improve inhibitory performance by training on the Go/NoGo task (Manuel et al., 2010) and Stop Signal task (Manuel et al., 2012c)? 1b. If yes, what are the neurophysiological and behavioral changes underlying inhibitory control training? 2. How is a specific stimulus processed as a function of previous performance (success or error) and how does it affect post-error behavioral adjustments? (Manuel et al., 2012a). These questions will be addressed in the following chapters.

1.3 Training-induced plasticity of inhibitory control

Training-induced plasticity has been at the heart of numerous studies in animals and humans aiming to demonstrate how the brain and behavior adapt and reorganize with training (Karni et al., 1998; Kolb et Wishaw, 1998; see Kelly and Garavan, 2005 for a review). Examining experience-driven changes of the neural system (i.e. plasticity) provides a compelling framework for investigating the underlying behavioral and neurophysiological processes supporting inhibitory control (Buonomano and Merzenich, 1998). For instance, training-induced changes manifesting at the *neurophysiological* level, such as the locus or the strength of synaptic connections, provides insights into the neural correlates underlying task processing, i.e. whether training reorganized the neural network or rather sharpened the existing neural network (Kelly and Garavan, 2005). Conversely, changes occurring at the *behavioral* level may give us information on the level of learning, i.e. whether training modified bottom-up or top-down processing. For instance, if training-induced changes occurred at an early latency in sensory brain areas, then we can argue that training modified in a bottom-up, automatic fashion. In this case, training-induced improevements on a specific task are driven by the characteristics of the salient stimulus (stimulus-driven); the effects of training will likely be specific to the trained stimuli. Conversely, if changes modified at a late latency in high-level fronto-executive areas, then training modified controlled, top-down inputs. In this situation, improvements in a specific task are based on stored intentional knowledge and task-demands (knowledge-driven); the effects of training would likely generalize to other tasks and conditions. Understanding how the healthy individuals' brain reshapes with training may help to better focus on the mechanisms of brain recovery in brain-damaged patients.

Only few behavioral studies tested for practice effects in inhibitory control but their conclusions were controversial. Training-induced improvements have been reported in various behavioral studies, but the effects rarely generalized to other tasks, indicating that training modified bottom-up processing of sensory stimuli. For example, a recent study reported that training on a Go/NoGo task lead to shorter RT in children, but effects were specific to the trained task as improvements did not generalize to other tasks measuring executive functions (e.g. working memory task) (Thorell et al., 2009). Similarly, on the Stop Signal task, Cohen and Poldrack (2008) did not report any decrease in the SSRT with training. The authors trained participants on a serial reaction time task during three hours (the SRT is a four-choice reaction time task, with no emphasis on inhibitory control). This task was preceded and followed by a stop signal task. Inhibitory performance (SSRT) at the beginning versus end of training did not statistically differ, meaning that motor sequence

learning did not affect the ability to inhibit responses. Because training was on the serial reaction time task and not on the SST task, we cannot draw conclusions on the training-induced effects of training on the Stop signal task. Logan and Burkhell (1986) trained participants for 6 days on the SSRT task, but did not report any changes in inhibitory efficiency over practice (see also Logan and Cowan, 1984 for similar results).

However, convergent evidence suggest that motor inhibition on the Go/NoGo and Stop signal tasks is supported by controlled/top-down executive processes. Neuroimaging and lesion data consistently report that inhibition activates brain regions traditionally associated with higher-order executive functions (the fronto-basal network). Further corroborating that inhibitory control is supported by top-down mechanisms, ERP studies of GNG and SST tasks reported that inhibition manifests after early sensory processing, and peak around 200–400ms post-stimulus onset (N2-P3 complex; see chapter 1.2.1) over fronto-central electrodes (Eimer, 1993; Falkenstein et al., 1999). Based on evidence that motor inhibition on Go/NoGo and Stop signal tasks are supported by top-down mechanisms we could expect that training would reinforce the fronto-parieto-basal network described in chapter 1.2.4. In line with this assumption, Schapkin et al. (2007) reported that decreased RT and FA in a Go/NoGo task were associated with a larger N2 component. However, the authors did not assess the underlying brain sources of learning-induced plasticity of inhibitory control. Although not specific to inhibition, few studies gave insight on the underlying network supporting training-induced improvement on various executive function tasks. For example, Beauchamp et al. (2003) reported that RT decrease on a Tower of London task (a task assessing planning abilities) was associated with changes within a fronto-striatal network. More recently, Ditye et al. (2012) reported decreased SSRTs when transcranial direct current stimulation (tDCS; a positively charged electrode) was applied over the right IFG but not in the control group where no stimulation was applied. Based on these compelling results, training should reinforce a top-down, fronto-basal, late latency (200-400ms) executive network.

Another model proposes that an automatic/bottom-up form of inhibitory control could develop with training. Based on memory retrieval tasks, theories of automaticity propose that automatic processes may develop with training, depending on recurrent and repeated stimulus-response associations. These theories advance that due to consistent and repeated stimulus-response mappings, i.e. associations between NoGo stimuli and withholding a response (inhibition goals) and between Go stimuli and going (activation goals), an automatic form of inhibitory control could take place over the course of learning on the GNG task (Shiffrin and Schneider, 1977; Logan, 1988; Verbruggen and Logan, 2008b). Verbruggen and Logan (2008b) further hypothesized that since inconsistency between the stimulus and

the response exist in the Stop Signal task (each Go stimulus is associated with activation or inhibition goals) automatic inhibition is unlikely to develop. Because stimulus-response mappings become stored with Go/NoGo training, a certain stimulus will automatically initiate the associated response and hence automatic inhibition will develop (Shiffrin and Schneider, 1977; Logan, 1988). These results suggest that training effects rather manifest during early sensory processing stages, at the level of integration of the stimuli (stimulus-response associations) and reduce the need for top-down executive control processes. With training, participants would switch from a controlled to an automatic form of inhibition. More generally, automatic retrieval of stimuli and response would allow bottom-up control of goal-directed behavior (Bargh and Ferguson, 2000; Verbruggen and Logan, 2008b).

To better disentangle under which circumstances automatic versus controlled inhibition develop, we performed two EEG studies on motor inhibition. In Manuel et al. (2010), we addressed this issue by comparing how training affected the processing of Go and NoGo stimuli in an auditory spatial Go/NoGo task. In another population of healthy participants, In we contrasted the processing of Go stimuli as a function of training in a Stop Signal task (Manuel et al., 2012c). These studies allowed us to better understand how training modified inhibitory control proficiency and which inhibitory mode developed with training (controlled or automatic inhibition).

The ability to suppress an inappropriate prepotent or ongoing response is complemented by performance monitoring processes. To implement efficient executive control of behavior, one must monitor our performance following errors or high conflict between competing responses, to adjust our behavior accordingly (Botvinick et al., 2001).

1.4 Post-error behavioral adjustments

When our brain detects an error, it will call for adaptations to potentially improve following performance. Participants modify their response strategies (for example by responding slower on the following trial) after the commission of an error in order to increase the probability of stopping on the following trial (Danielmeier and Ullsperger, 2011). A well-known and consistently reported post-error adjustment is the post-error slowing (PES), described as a slowing down of response time following error commission (Rabbit, 1966; see Danielmeier and Ullsperger, 2011 for a review). Few studies also reported improvements in accuracy following error comission (PIA; Marco-Pallares et al., 2008; Danielmeier et al., 2011).

Examining post-error behavioral adjustments is another approach to better disentangle between the two inhibition modes described in the previous chapter: automatic/bottom-up inhibition or controlled/ top-down inhibition. As advanced by Verbruggen and Logan (2008b), participants likely engage automatic inhibition once stimulus-response mappings are learned. According to this model, we hypothesize that error commission would induce a shift from an automatic to a controlled form of inhibitory control. Because participants have to adjust their responses after errors, greater top-down control is required. While the neural correlates of error processing and post-error behavioral adjustments have been extensively studied, little is known on how errors influence the processing of following stimulus and how behavioral adjustments are affected.

Error detection mechanisms have been consistently associated with activity in the anterior cingulate cortex (ACC, Dehaene et al., 1994; Yeung et al., 2004; van Veen and Carter, 2006). The neural signature of error commission is the fronto-centrally distributed ERP component called error-related negativity (ERN) which peaks around 50-100ms post-error commission (time-locked to the execution of the incorrect response) (Falkenstein et al., 1991; Gehring et al., 1993). Interestingly, the ERN and amount of ACC activity correlated with the magnitude of post-error slowing, arguing in favor of a role of error detection mechanisms in subsequent behavioral adjustments (Gehring et al., 1993; Holroyd and Coles, 2002; Kerns et al., 2004; Debener et al., 2005; Holroyd et al., 2005).

Two main accounts have been proposed to explain post-error slowing: the cognitive control account and the orienting account. The cognitive control account posits that PES is a compensatory mechanism reflecting a switch to a more conservative and controlled response mode in order to improve on subsequent trial (Botvinick et al., 2001; Holroyd et al., 2005). These improvements occur by actively maintaining attentional demands of the task and activating relevant, top-down, representations of task demands (MacDonald et al., 2000; Kerns et al., 2004). This model posits that in case of an error, monitoring processes driven by the ACC trigger the engagement of the DLPFC (Kerns et al., 2004; Ridderinkhof et al., 2004; Rushworth et al., 2007; Marco-Pallarés et al., 2008). This latter area would in turn mediate behavioral adjustments, (i.e. the extent of post-error slowing) by decreasing activity in related motor areas (Botvinick et al., 2001; Kerns et al., 2004; Ridderinkhof et al., 2004; King et al., 2010). Neuroimaging studies reported that the decrease in motor activity in post-error trials correlated with larger post-error slowing effects (King et al., 2010; Danielmeier et al., 2011). Therefore, if an error is detected, cognitive control (mediated by ACC-DLPFC interactions) increases and motor response activation decreases, ensuring that in the following trial response time will be slower but accuracy greater.

However, if post-error slowing has a functionally meaningful purpose related to behavioral

improvements, one would expect improvements in the following accuracy. Although the two processes (post-error slowing and post-error improvement of accuracy) co-occur in a few studies (Marco-Pallares et al., 2008; Danielmeier et al., 2011), it is not always the case (Fiehler et al., 2005). To explain the lack of post-error accuracy combined with post-error slowing, recent evidence suggest that post-error slowing is rather the result of an orienting response to an unexpected event, i.e. the orienting account (Notebaert et al., 2009; Nunez Castellar et al., 2010). The unexpected event, which is often the error, leads to a slowing down following errors. Response speed would increase because participants need to refocus attention to the task following the distraction induced by the error. Interestingly, when correct trials were more frequent than errors, Notebaert and collaborators (2009) reported a post-correct slowing. According to this account, PES reflects the behavioral cost arising from distraction, rather than a form of cognitive or attentional control.

The studies reviewed above demonstrate that in case of an error, the ACC, the key region involved in error detection, signals the need for increased attentional control to the DLPFC which in turn allow the adjustment of behavioral responses at the next trial. However, most of the previous studies either focused on the neural correlates of error detection, those involved in adjusting one's ongoing behavior or on the correlation between error detection mechanisms and subsequent post-error behavioral measures (e.g. Garavan et al., 2002; Kerns et al., 2004; Ridderinkhof et al., 2004; Fiehler et al., 2004). For instance, Garavan and colleagues (2002) focused on the brain network involved in post-error behavioral adjustments, without disentangling how the subsequent post-error stimulus was processed as a function of previous performance. Similarly, Kerns et al. (2004) reported a correlation between activity in the ACC on the previous erroneous trial and activity in the DLPFC in the current, post-error trial. However, the specific neural correlates of the *processing* of subsequent stimulus itself, and not the specific behavioral response (i.e. post-error slowing), were not assessed.

Only few studies specifically addressed how error detection impacts the processing of following stimulus to consequently adjust behavior. Using a stop signal task, Li and colleagues (2008) studied the brain mechanisms involved in the processing of Go stimuli as a function of previous performance. They contrasted brain activations of Go trials when Go was preceded by a successful performance (hit) vs when it was preceded by an error (FA). Their results point towards a greater involvement of the right ventrolateral prefrontal cortex (VLPFC) in post-error than post-correct slowing. Moreover, the authors pointed out that the greater the PES, the greater the activation in the VLPFC. Nevertheless, the precise brain dynamics underlying post-error behavioral adjustments were not assessed because of the low temporal resolution of the fMRI technique.

However, how and when the stimulus is processed as a function of previous success or error and the precise brain dynamics supporting post-error behavioral adjustments remain unclear. In Manuel et al. (2012a), we addressed this issue in a Go/NoGo task by contrasting brain responses during the processing of Go or NoGo stimuli, as a function of whether it was preceded by successful or unsuccessful inhibitory control. This procedure allowed us to determine the neural correlates and the precise brain dynamics supporting post-error behavioral adjustments.

A part from the studies on inhibitory control (Manuel et al., 2010; 2012a; 2012c), we were further interested in assessing the brain network involved in impaired motor control, here in the case of apraxia in brain-damaged patients.

1.5 Motor control in the case of ideomotor apraxia

Ideomotor apraxia is classically defined as a deficit in performing a manual gesture either on imitation or on verbal command. Interestingly, according to Liepmann (1908), at least two aspects differentiate ideomotor apraxia from a pure motor impairment or a general cognitive deficit (Goldenberg 2003a, 2009). First, apraxia concerns both sides of the body, although unilateral lesions cause it. This seems striking as the right side of the body is controlled by the left hemisphere and vice versa (Woolsey et al., 1979; Porter and Lemon 1993; see Martin, 2005 for a review). If it were a pure motor deficit, apraxia would only be reported on the contralesional site. Second, in apraxia, the ability to perform the movement depends on the context of elicitation. A few studies (e.g. Leiguarda et al., 2000) reported that apraxic patients perform gestures correctly in their daily lives, but not when voluntarily asked to perform the exact same gesture (although the movement is similar). If apraxia were a general motor or cognitive deficit, patients would not be able to perform the indented gesture in either of the conditions.

Deficits in pantomiming object use (which consist in pretending to use an object) is the main characteristic of brain-damaged patients with ideomotor apraxia (Wheaton and Hallett, 2007). Patients perform errors because they are not able to adopt the correct limb configuration and produce the correct sequence of movements. In this chapter we will examine ideomotor apraxia with the production of communicative learned gestures, i.e. pantomimes. Pantomimes share important commonalities with language, since they

symbolize communicative manual actions in relation to the proper use of a tool or object (Roby-Brami et al., 2012).

The production of understandable pantomimes requires a) selection of the relevant movements representing the action, b) an accurate representation and semantic representation of the spatial/configural relationships between the body parts involved in the movement and of how they interact with the object as well as c) a fine-grained gestural motor control (Goldenberg, 2009).

Lesion studies advanced that the selection of task-relevant features among the available gestures was supported by frontal regions. For instance, in a lesion study, Goldenberg et al. (2007) advanced that the IFG was critical for performing accurate pantomime of object use. Likewise, lesions to the pre-SMA have been shown to disrupt the transformation of gesture representation into motor command (Watson et al., 1986; Hermsdörfer et al., 2001). Several authors pointed out that the pre-SMA was not only involved in motor execution, but also in movement preparation (Lee et al., 1999), selection (Deiber et al., 1996) and observation (Decety et al., 1997; Grézes, 1998). Therefore, frontal areas seem important for selecting task-related actions from the individual action repertoire (Tanji and Shima, 1994; Passingham, 1996).

By contrast, neuroimaging studies of healthy humans suggest that storage of motor representations of tool use and spatial coding of body parts are supported by parietal areas (Moll et al., 2000; Choi et al., 2001; Goldenberg 2003b; Peigneux et al., 2004; Daprati and Sirigu, 2006; Vingerhoets et al., 2011). Parietal areas seem thereby crucial for integrating visual/external information with internal/sensory proprioceptive information in order to prepare for motor execution (Deiber et al., 1996; Haaland et al., 1999).

Furthermore, the sequencing, fine tuning and selection of movements have been proposed to be supported by basal ganglia (Leiguarda, 2001). However, apraxia is rarely reported following isolated basal ganglia lesion, but rather occurs together with white matter damage. Accordingly, lesions to the basal ganglia may cause apraxia by disconnecting cortico-cortical white matter tracts, i.e. the superior longitudinal fasciculus, which connects parietal to frontal motor regions (Pramstaller and Marsden, 1996; Leiguarda, 2001; Zadikoff and Lang, 2005). These connections would play a critical role in the production of pantomimes by transmitting information on motor programs from the parietal areas to frontal motor regions (Heilman et al., 1982). A few studies reported apraxia in patients with corticobasal degeneration (Leiguarda et al., 1994) or Parkinson's disease (Leiguarda et al., 1997) supporting the involvement of basal ganglia in apraxia.

Surprisingly, results of neuroimaging and lesion studies in pantomime diverge. While parietal areas are mostly reported in neuroimaging studies, lesion studies report that the integrity of frontal areas is crucial to perform pantomimes on demand. Disparities between the two approaches have been hypothesized to depend on the condition under which pantomimes were performed. In neuropsychological assessment of pantomimes, brain-damaged patients perform the gestures within a natural body-centered reference frame accompanied by visual feedback whereas in fMRI studies participants' movements are spatially constrained to the scanner and thus require spatial transformation to unfamiliar reference frames (Goldenberg et al., 2007; Goldenberg, 2009). These further spatial requirements might explain the additional parietal activations reported in neuroimaging, but rarely in lesion studies (Andersen et al., 1997).

Nevertheless, several other hypotheses could account for the inconsistency between these two approaches. Previous lesion studies included patients based on apriori hypotheses regarding the region of interest or deficit, (e.g. only left-lateralized brain lesions, only frontal areas or only patients with aphasia) or divided neuropsychological scores in two categories: with or without apraxia (Hanna-Pladdy et al., 2001; Goldenberg et al., 2003b; Goldenberg et al., 2007; Dovern et al., 2011). It has been shown that dichotomizing data leads to loss of power and reduced effect size (Cohen, 1983). Furthermore, the chronic state in which patients were tested (i.e. more than one month post-lesion onset) in previous studies might have obscured potential parietal contribution in pantomimes (Goldenberg et al., 2003b; Dovern et al., 2011). Specificity of parietal areas might only be revealed during the post-acute phase: between the resorption of the ischemic penumbra (Witte et al. 2000) and the plastic anatomo-functional reorganizations (Adriani et al. 2003; Saur et al. 2006; Rey et al. 2007; Altamura et al., 2009).

Another aspect we addressed in Manuel et al. (2012b) is the association between the lesion site and the type of pantomime error. The hypothesis put forward in this paper is that the specific contribution of parietal and frontal areas might depend on the neuropsychological scoring of pantomimes. A wide range of errors (spatial, temporal, semantic) have been reported in apraxia. Nevertheless, the errors were often collapsed in previous studies to reveal the common underlying neural structure of apraxia (although it has been shown that lesions to distinct brain areas may induce different types of error; Hanna-Pladdy et al., 2001). For instance, one particular type of error, the Body Part as Object (BPO) error, which consists in representing objects or tools with a part of the body rather than pretending to use the imaginary object (Goodglass and Kaplan, 1963) has been suggested to be frequent after frontal but not parietal lesions (Peigneux and Van der Linden 1999; Arzy et al. 2006). For that

reason, we differentiated BPO errors from configural/spatial (CS) errors which concern the sequence, timing or amplitude of the gestures.

Collectively, these potential caveats (apriori selection of patients, dichotomization of behavioral data, spatial constrain of the scanner) and the use of compound scores might have obscured previous parietal involvement, and more specifically putative inter and intra-hemispheric dissociations regarding different types of errors.

In Manuel et al. (2012b), we tested whether different lesion site may induce distinct types of errors and whether this fronto-parietal dissociation is rather the result of the state in which patients are tested (chronic versus acute). In this respect, we conducted large-scale retrospective voxel-based lesion symptom mapping analyses on a group of 150 subacute, unselected, brain-damaged patients (stroke and tumor etiologies) and their pantomime scores differentiating CS errors from BPO errors.

CHAPTER 2 METHODS

To test the questions raised in this thesis, namely 1) if it is possible to train inhibitory control (on a GNG or SST task) and what are the underlying brain dynamics; 2) how does error detection impact the processing of the following stimulus and affect behavioral adjustments; 3) which brain regions play a causal role in motor control deficits in brain-damaged patients with ideomotor apraxia? we used two different techniques of investigation of brain-behavior relationships.

Training-induced inhibitory control in Manuel et al. (2010) and post-error behavioral adjustments were investigated with a speeded auditory Go/NoGo task in the same population of healthy participants. In Manuel et al. (2012c), training-induced inhibitory control was assessed with an auditory Stop Signal task in another sample of healthy participants. We investigated these executive processes with electroencephalography (EEG).

To address the question of apraxia in brain-damaged patients and to point out which brain regions support pantomimes, we performed a large-scale, voxel-based lesion-symptom mapping analysis (VLSM) on a group of 150 brain-damaged patients.

In this chapter, the advantages of the two methods we used will be exposed. First, the use of electrical neuroimaging methods will be compared to traditional waveform analyses of event-related potentials (ERPs). Second, the benefits of using voxel-based lesion-symptom analyses (VLSM) over traditional analyses of lesion-symptom mapping will be considered.

2.1 Electrical neuroimaging

The electroencephalography (EEG) measures the electric field at the scalp generated by the sum of post-synaptic potentials in the brain. In the three EEG studies presented in this thesis, we analyzed event-related potentials (ERP), which refer to the electrical response of the brain to a specific stimulus. Importantly, here we used topographic ERP analyses instead of applying traditional waveform analyses (Murray et al., 2008). The main benefits of topographic ERP analyses over traditional waveform analysis is that they are data-driven and

allow interpreting results in terms of neurophysiologic mechanisms. Topographic ERP analyses indeed don't require to a priori select a period of interest, a set of electrodes (scalp location) nor a reference electrode.

EEG measures differences in scalp potentials (in microvolt), between a given electrode and a reference against which the electrical potential of the given electrode is compared. If a new reference is chosen, the voltage differences between the same given electrode and the new reference will change as well. As a result, the waveform's amplitude of peaks and troughs, its variance as well as the latency of the statistically significant effects will be affected. To avoid misleading results due to reference-dependant nature of single ERP waveforms analyses, we based our analyses on the shape of the electric field, namely the electric field topography. Because the topography (or map) reflects the relative potential differences of the whole electrode montage, it is not affected by the choice of reference electrode; the shape of the topography remains the same but just shifts vertically along the 0 line (Michel et al., 2009; Michel and Murray, 2012).

A further advantage of our topographic analyses over classical waveform analyses is that they allow to statistically and independently distinguish between the effects due to modifications of the strength of signal from the effects due to differences in topography. Global Field Power (GFP) measures the strength of the electric field at a given instant in time independently of spatial distribution of scalp fields across the electrode montage (Lehman and Skrandies, 1980; Murray et al., 2008). A change in GFP across conditions without concomitant topographic modulation may be interpreted as a change in the strength (amount of simultaneously activated generators or synchronization of brain activity) of statistically undistinguishable brain generators. Conversely, if two topographies differ at a given time independently of their strength, it indicates that the location of underlying brain sources changed (Michel and Murray, 2012).

In addition, topographic ERP analyses also allow getting insights into the neurophysiological mechanisms underlying modulations of scalp-recorded ERPs. Different scalp fields or topography are indeed necessarily generated by distinct underlying brain generators (while the reverse is not forcibly true) (Lehmann, 1987). The location of the brain generator responsible for the observed topography can then be reliably estimated using inverse solutions (Michel et al., 2004b).

Compared to fMRI studies, the estimation of the electrical source underlying scalp-recorded ERPs are less accurate because it is a rather indirect reconstruction of brain sources (although fMRI too, but to a lesser extent). To maximally overcome this limitation, we increased the number of electrodes and used most optimal inverse solutions models which

largely circumvent this major drawback of the EEG technique (Michel et al., 2004). Nonetheless, EEG techniques have nonetheless the advantage that the EEG signal is directly coupled to the underlying neuronal electrical activity. This method therefore provides a very good temporal resolution (sub-millisecond level) and could assess the dynamics of the plasticity of inhibitory control with high precision (Debener et al., 2006). For a detailed description of ERP analyses, the reader is referred to the Methods sections of Manuel et al. (2010), Manuel et al. (2012a) and Manuel et al. (2012c).

2.2 Voxel-based lesion-symptom mapping

Voxel-based lesion-symptom mapping (VLSM; Bates et al., 2003) allows investigating the relationship between brain and behavior by establishing a parallel between lesion locations and the specific symptoms they induce on a voxel-by-voxel basis (a voxel is a volume element in 3D space). In practice, the brain lesions are manually reported on axial slices of a brain template according to stereotaxic coordinates and then submitted to VLSM analyses which calculates a t-test for each voxel and compares performance in patients with a lesion vs without a lesion by only testing voxels damaged in N patients (for example 4 patients) (Rorden and Brett, 2000; Brett, 2001; Rorden et al., 2007). For further details, see the Methods section of Manuel et al., 2012b.

The VLSM method (Bates et al., 2003) has the non negligible advantage of being data-driven compared to previous lesion-symptom mapping studies. In that sense, the method used in our work does not require the selection of an apriori or arbitrarily defined region of interest or cut-off score for behavioral performance. Previous lesion-symptom mapping methods indeed grouped patients either according to their *lesion* site or according to their *behavioral* score. In the former method, the behavioral performance of a group of patients with an a priori selected common lesion (e.g. a lesion of the inferior frontal gyrus) is compared to a control group or to a group with another injured area. Although it gives information on the involvement of a brain area in a behavioral deficit (e.g. the involvement of inferior frontal gyrus in apraxia), it does not allow making a distinction between the different subregions of this specific brain region nor of other brain regions that might also be involved in this specific task (e.g. Chao and Knight, 1998). In the latter, patients are grouped according to whether or not they have a specific behavioral deficit (e.g. apraxia) and the overlap of their brain lesions is compared to patients not showing this deficit or those showing a different deficit (e.g. Ptak et al., 2011). While it can highlight the contribution of a

brain lesion to a specific cognitive deficit, this method doesn't deal with continuous data. In this case, a (generally arbitrarily defined) cut-off has to be defined to dichotomize the scores into normal or impaired, which leads to a loss of information regarding the degree of impairment. Bates and collaborators (2003) proposed a statistical lesion-symptom mapping tool (VLSM) which has on one hand the advantage of analyzing the relation between damaged tissue and behavior on a voxel-by-voxel basis and on the other hand to process continuous data, at the lesion and behavior levels (since it does not require grouping patients according to lesion site or the presence of a cognitive deficit). The inclusion of both left and right hemispheric lesions, without any selection, leads to a gain in statistical power across the whole brain (i.e. power is distributed almost equivalently across the whole brain and not restricted to a part of the brain). Importantly, new techniques for analyzing lesion data, such as VLSM, statistically assess with high spatial precision (voxel-by-voxel basis) whether lesion locations are reliable predictors of a symptom (Rorden and Karnath, 2004).

A potential limitation of the method is the problem of multiple comparisons. Because so many tests are conducted in VLSM analysis (one at each voxel, with 7109137 voxels in the brain) there is a considerable risk for false positive (identifying a critical brain region involved in the task, although it is not). Because the Bonferroni test is too strict (very few real effects will be detected) and it dramatically reduces the statistical power, false discovery rate correction was used to keep a fair statistical power while avoiding the problem of false positives (Benjamini and Hochberg, 1995; Yekuteli and Benjamini, 1999). In addition, to implement a fiability criterion; we only computed t-tests for voxels injured in at least 4 patients. Another way of dealing with the multiple comparisons problem is to create regions of interest (ROIs) which will greatly reduce the number of tests to be performed (Rorden and Karnath, 2004). Another caveat to take into consideration is the fact that some brain areas show greater vulnerability to lesions than others due to the vascular architecture (ca 60% of strokes occur in the middle cerebral artery territory) biasing the distribution of the statistical power of the tests towards a certain region of the brain (Bogousslavsky et al., 1988; Arboix et al., 2008).

In contrast to other neuroimaging methods (fMRI or EEG), lesion-symptom mapping allow a strong level of inference: while VLSM is causal (it assesses whether a region is critical for a certain task), classical neuroimaging techniques are only correlational (they determine if the specific brain region observed is involved in the task; Rorden et al., 2009). However, in lesion studies reorganization of brain damaged regions (plasticity) might obscure the findings (Pascual-Leone et al., 2000).

The strength and weaknesses of the EEG and VLSM methods are complimentary. While EEG methods provide information on which brain region has an activity *associated* in a

particular task, VLSM can provide complimentary information on which brain region is *necessary* to perform the task correctly. Moreover, VLSM can analyze gray and white matter, while ERP inverse solutions are restricted to the gray matter.

CHAPTER 3 RESULTS

Brain dynamics underlying training-induced improvement in suppressing inappropriate action

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Contribution: designed research; acquired data; analyzed data; wrote the paper.

Abstract:

Inhibitory control, a core component of executive functions, refers to our ability to suppress intended or ongoing cognitive or motor processes. Mostly based on Go/NoGo paradigms, a considerable amount of literature reports that inhibitory control of responses to “NoGo” stimuli is mediated by top-down mechanisms manifesting ~200ms post-stimulus onset within fronto-parietal networks. However, whether inhibitory functions in humans can be trained and the supporting neurophysiological mechanisms remain unresolved. We addressed these issues by contrasting auditory evoked potentials (AEPs) to left-lateralized "Go" and right "NoGo" stimuli recorded at the beginning vs. the end of 30 minutes of active auditory spatial Go/NoGo training, as well as during passive listening of the same stimuli before vs. after the training session, generating two separate 2*2 within-subject designs. Training improved Go/NoGo proficiency. Response times to Go stimuli decreased. During active training, AEPs to NoGo, but not Go, stimuli modulated topographically with training 61-104ms post-stimulus onset, indicative of changes in the underlying brain network. Source estimations revealed that this modulation followed from decreased activity within left parietal cortices, which in turn predicted the extent of behavioral improvement. During passive listening, by contrast, effects were limited to topographic modulations of AEPs in response to Go stimuli over the 31-81ms interval, mediated by decreased right anterior temporo-parietal activity. We discuss our results in terms of the development of an automatic and bottom-up form of inhibitory control with training and a differential effect of Go/NoGo training during active executive control vs. passive listening conditions.

Spatio-temporal brain dynamics mediating post-error behavioral adjustments

Aurélie L. Manuel, Fosco Bernasconi, Micah M. Murray, and Lucas Spierer

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Contribution: designed research; acquired data; analyzed data; wrote the paper.

Abstract:

Optimal behavior relies on flexible adaptation to environmental requirements, notably based on the detection of errors. The impact of error-detection on subsequent behavior typically manifests as a slowing-down of response times following errors. Precisely how errors impact the processing of subsequent stimuli and in turn shape behavior remains unresolved. To address these questions we used an auditory spatial Go/NoGo task where continual feedback informed participants of whether they were too slow. We contrasted auditory evoked potentials (AEPs) to left-lateralized "Go" and right "NoGo" stimuli as a function of performance on the preceding Go stimuli, generating a 2x2 design with “Preceding Performance” (Fast Hit; Slow Hit) and Stimulus type (Go; NoGo) as within-subjects factors. Slow hit trials yielded slow hit trials on the following trials more often than did fast hits, supporting our assumption that slow hits engaged effects similar to errors. Electrophysiologically, AEPs modulated topographically as a function of preceding performance 80-110ms post-stimulus onset and then as a function of stimulus type at 110-140ms, indicative of changes in the underlying brain networks. Source estimations revealed a stronger activity of prefrontal regions to stimuli after successful than error trials, followed by a stronger response of parietal areas to the NoGo than Go stimuli. We interpret these results in terms of a shift from a fast-automatic to a slow-controlled form of inhibitory control induced by the detection of errors, manifesting during low-level integration of task-relevant features of subsequent stimuli, which in turn influences response speed.

Inter- and intra-hemispheric dissociations in ideomotor apraxia: a large-scale lesion-symptom mapping study in subacute brain-damaged patients.

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Cerebral Cortex, **2012b**; in press

Contribution: designed research; acquired data; analyzed data; wrote the paper.

Abstract:

Accurate pantomimes of object use require precise representations and execution of movements as well as a selection of the most task-relevant gestures. Prominent models of apraxia and functional neuroimaging evidence consistently predict a critical role for left parietal cortices in pantomime and advance that these areas store representations of tool use. In contrast, lesion data points to the critical involvement of left inferior frontal areas, in turn suggesting that defective selection of features is the cause of pantomime errors. Here, we investigate the anatomical correlates of ideomotor apraxia in the subacute stage and whether distinct error types occur depending on lesion site. We conducted large-scale retrospective voxel-based lesion-symptom mapping statistical analyses on a group of 150 unselected right and left brain-damaged patients. We analyzed separately continuous scores of configural/spatial and body part as object pantomime error types collected during the subacute stage. Our results reveal that left parietal damage impairs pantomime. Spatial/configural pantomime errors were associated with left parietal and inferior frontal lesions, while body part as object errors were associated with left inferior frontal lesions. Collectively, our results reveal a left intra-hemispheric dissociation for various aspects of pantomime, but with an unspecific role for inferior frontal regions.

Spatio-temporal brain mechanisms of training-induced neuroplastic reinforcement of inhibitory control

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2012c, in revision

Contribution: designed research; acquired data; analyzed data; wrote the paper.

Abstract:

Inhibitory control refers to our ability to suppress ongoing motor, affective or cognitive processes and depends on a fronto-basal brain network. Inhibitory control deficits have been shown to participate in the emergence of several prominent psychiatric disorders, including attention deficit/hyperactivity disorder or addiction. The rehabilitation of these conditions might therefore benefit from training-based behavioral interventions aiming at improving inhibitory control proficiency and reinforcing the underlying neurophysiological mechanisms. The development of efficient inhibitory control training regimen first requires determining whether and how inhibitory control can be trained. We addressed these questions by contrasting behavioral and electrical neuroimaging analyses of auditory evoked potentials recorded in human at the beginning vs. the end of one hour of training on a stop signal task involving to withhold responses when a stop signal was presented during a speeded auditory discrimination task. Our results indicate that a short training improved inhibitory control proficiency. Electrophysiologically, AEPs modulated topographically at ca. 200ms post-stimulus onset, indicative of the engagement of distinct brain network with training. Source estimations localized this effect within the inferior frontal gyrus, pre-SMA and basal ganglia. Critically, the modulation of the activity within IFG during the training predicted the behavioral improvements. Our collective results indicate that inhibitory control is subject to fast plastic changes and provide the first evidence that high-order fronto-basal executive networks can be reinforced. Moreover, our results indicate that modulations in the activity of the inferior frontal gyrus could be used to index the efficiency of rehabilitation protocol of inhibition-related disorders.

CHAPTER 4 DISCUSSION

In this chapter we will mainly discuss our results on training-induced plasticity of inhibitory control in the light of the fronto-basal inhibitory control model notably advanced by Aron (2011) and propose new inputs to complete the existing model. Second, we will discuss the mechanisms underlying the processing of stimuli following errors and how they shape subsequent behavior. Namely, we propose an additional path in the fronto-basal model which seems critical for switching between different inhibition modes. Modeling inhibitory control will be the main focus of the discussion.

To better understand how training modulates inhibitory control, we'll further discuss the neurophysiological plasticity mechanisms putatively underlying improvements in inhibitory performance, and under which conditions the effects of training may generalize to other tasks or conditions and be of potential interest for the rehabilitation of inhibition-related pathologies.

Additionally, we will discuss our results on disturbed motor control in the case of apraxia. Interestingly, we report evidence that a lesion in the fronto-parieto-basal network we advanced as underlying efficient inhibitory control might also affect motor control in the case of apraxia

At last, we will propose perspectives to further explore our results while focusing on potential rehabilitation programs.

4.1 Modeling training-induced improvement of inhibitory control

Our work on training-induced inhibitory control and post-error behavioral adjustments enabled us to refine the model of inhibitory control proposed by Aron and collaborators (see model page 5; Aron, 2011). Current models propose that inhibitory control is supported by a large fronto-basal network (Aron et al., 2007a,b; Eagle et al., 2008a,b; Verbruggen and Logan, 2008a; Chambers et al., 2009; Chikazoe et al., 2010; Aron, 2011). According to this

model, the inferior frontal gyrus (IFG) and pre-supplementary motor area (pre-SMA) act in concert to produce motor suppression via direct projections to subcortical structures to inhibit the motor command (Aron and Poldrack, 2006; Aron et al., 2007a,b; Swann et al., 2009). Once the inhibitory command is generated in the IFG, the information flows to the subthalamic nucleus (STN) via the hyperdirect pathway (Maurice et al., 1998; Nambu et al., 2002; Magill et al., 2004). STN then excites the internal globus pallidus (GPi), which in turn inhibits the thalamocortical (THAL) output to suppress activation in M1 and stop motor response (Gillies and Willshaw, 1998).

We further refine the fronto-basal inhibitory control model and propose a model wherein two types of inhibition co-occur: the top-down/controlled inhibition mode described by the model, but also a bottom-up/automatic inhibition mode. Moreover, we add non negligible information to the understanding of the dynamics of inhibitory control, by reporting the timing of respective inhibition modes. We will not discuss the areas highlighted in grey in Aron's (2011) original model for simplicity.

In Manuel et al. (2010) we demonstrated that following consistent and repeated association between a stimulus and inhibition goal during Go/NoGo training, bottom-up, automatic inhibitory control developped (Figure 2 A). At the beginning of GNG training, stimulus-response mapping have not been yet integrated and repeated, and thus stronger top-down inhibitory control is required (Figure 2 A, grey path). With training, sensory features of the stimuli (Go or NoGo) are directly conveyed to sensory areas (e.g. parietal areas for spatial processing; Spierer et al., 2008) by shortcutting inputs from top-down controlled modules (IFG) (Figure 2 A, green path). With training, parietal areas convert sensory information to the basal ganglia and then to the motor cortex (M1) to inhibit the motor response. We demonstrate here that short-cutting frontal areas results in faster inhibition (a gain of 40ms between controlled and automatic inhibition in the Go/NoGo task). In contrast, because stimulus-response mappings in the Stop Signal task are not consistent (each Go stimulus is associated with activation or inhibition goals), Manuel et al. (2012c) demonstrated that top-down/controlled executive mechanisms (Figure 2 B) were reinforced with training, in turn leading to slower inhibition.

GNG training (Manuel et al., 2010) modified low-level processing of stimuli around 60-100ms, while SST training (Manuel et al., 2012c) reinforced the fronto-basal network around 200ms. To give additional information on the dynamics of inhibitory control, we assessed the timing in other brain areas as well based on previous literature. There is approximately 100ms between the minimal latency of initiation in M1 and the motor response (Thorpe and Fabre-Thorpe, 2001). We therefore calculated the timing of activity in M1 as the mean RT-100ms. This measure gives a rough estimation of the dynamics in the primary motor areas.

Additionally, neurophysiological studies demonstrated that the IFG had direct, monosynaptic, connections to the STN in the basal ganglia. IFG can therefore quickly (~10ms) activate the STN via the hyperdirect pathway.

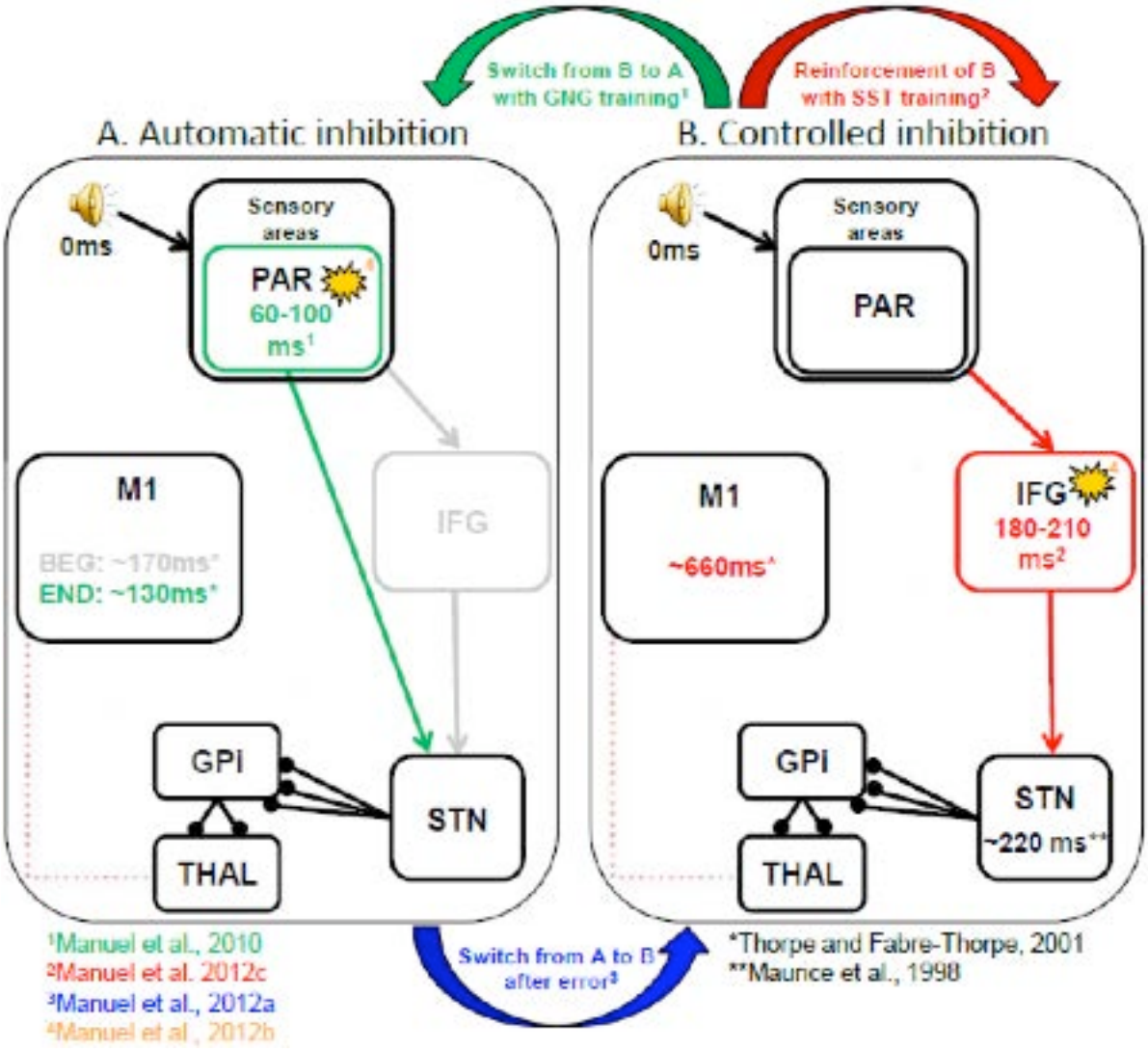

Figure 2: Modeling training-induced plasticity of inhibitory control (adapted from Aron, 2011). The auditory inhibition stimulus appears at 0ms and is then converted to sensory areas processing auditory spatial stimuli (for the GNG task) or pitch stimuli (as in the SST task) at ~ 60-100ms (Spierer et al., 2008; Hyde et al., 2008). **A.** With Go/NoGo training, participants switch from a controlled inhibition mode to an automatic inhibition mode (green arrow). Automatic inhibition develops in PAR around 60-100ms and shortcuts top-down inputs IFG, in turn leading to faster inhibition. **B.** During SST training, top-down/controlled inhibition is reinforced around 188-210ms in the IFG. The IFG then activates STN via the hyperdirect pathway in approx. 10ms (Maurice et al., 1998; Magill et al., 2004). STN then sends output to the GPi to inhibit the thalamocortical output which globally suppresses motor execution. Timing in M1 was calculated as following: Mean RT-100ms, which corresponds to the minimal latency of initiation in M1 before response execution (Thorpe and Fabre-Thorpe, 2001). If an error occurs, participants engaged in an automatic inhibition mode, switch to a controlled inhibition mode (Figure 2, blue arrow). Finally, lesions underlying motor control deficits in the case of ideomotor apraxia are reported in orange. PAR: parietal;

M1: primary motor cortex; IFG: Inferior frontal gyrus; STN: Subthalamic nucleus; GPi: Internal Globus Pallidus; THAL: Thalamus. Arrows indicate excitatory connections and rounds inhibitory connections.

When comparing panel A and B of Figure 2, there is ~80ms between activity in parietal areas and M1 in automatic inhibition, while ~400ms distance activity in STN from M1 in controlled inhibition. Although further studies are required to better explain the processing of information between/from basal ganglia structures to the initiation of motor activity in M1, a few accounts could still be put forward to possibly disentangle their dynamics. First, the Go/NoGo task might be simply easier than the Stop Signal task. The Go/NoGo task is a "simple reaction time task", whereas the SST task is a "choice reaction time task". In the GNG task, there is only one Go stimulus, while in the SST task there is a choice between two Go stimuli (before the Stop signal can potentially appear) therefore requiring additional control. Response time in choice RT tasks has indeed been shown to be slower than in simple RT tasks (Logan, 1984). Second, the flow of information from the IFG to STN might not have followed the hyperdirect pathway, but rather the indirect pathway (Aron, 2011). Indirect pathway would not globally suppress thalamocortical output (as the hyperdirect pathway does), but rather inhibit specific substrates of basal ganglia. Instead of having a direct connection between the IFG and STN, the indirect pathway is composed of several steps: IFG, caudate, GPe (External globus pallidus), GPi (Internal globus pallidus), thalamus and finally primary motor area (Aron, 2011; see Figure 1 page 5 for an illustration of the indirect pathway). These additional steps could have possibly led to slower RT. Nevertheless, future studies are needed to better disentangle the dynamics of basal ganglia in inhibitory control.

Manuel et al. (2012a) further demonstrated that the model proposed on page 29 was not static, but rather that participants could switch from one inhibition mode to another. Accordingly, if the stimulus-response mapping rule is straightforward (as in the GNG task), participants are likely engaged in an automatic inhibition mode. Automatic mode could develop quickly as participants get familiarized with the task and stimuli and engage sensory gating mechanisms to prevent overflow of information in high-level representations (and therefore save available cognitive resources). Manuel et al. (2012a) demonstrated that if an error occurs when automatic inhibition is engaged, participants switch to a slow, controlled form of inhibitory control by engaging frontal executive modules, in turn slowing down subsequent responses (i.e. post-error slowing) (Figure 2, blue arrow).

At last, the results reported in Manuel et al. (2012b) investigating motor control in the case of ideomotor apraxia, interestingly converge with the fronto-parieto-basal model in Figure 2 (orange lesions). Manuel et al. (2012b) showed that brain-damaged patients with lesions to

parietal or inferior frontal areas were impaired in performing object-related manual gestures (pantomimes). Because these latter structures are directly connected between each other and with basal ganglia, a lesion of either parietal or frontal areas can possibly affect motor control. We will discuss the results of Manuel et al. (2012b) in the framework of the fronto-parieto-basal network in chapter 4.6.

4.1.1 *Automatic* inhibition

Manuel et al. (2010) provides new insights into the neural correlates of training-induced plasticity of inhibitory control and shows for the first time that inhibitory processes can also be engaged automatically by recruiting early, low-level sensory brain areas and shortcutting executive modules.

Beginning with the seminal work of James in 1890 (James, 1890), the idea that with repeated experience, a human skill can become automatic and lead to motor skill learning has been widely accepted and investigated in the last decades. The ability to perform a skilled (motor) task with relatively little demand on executive control is referred to as automaticity (Poldrack, 2005). As one executes a skilled behavior again and again, this specific skill will gradually require less attention and cognitive control and become automatic, as evidenced by improved response time or accuracy. Since executive functions are by definition controlled processes supported by a frontal, executive network, one could have predicted that automaticity would not develop during executive control training. Yet, Manuel et al. (2010) demonstrated that automatic inhibitory control could also develop with training. In that sense, Manuel et al. (2010) challenges traditional views linking executive functions solely with intentional, controlled processes by putting forward the notion that inhibitory *control* is not forcibly engaged by intentional and conscious control over prepotent responses along with modulations of a top-down executive network. We demonstrate here for the first time that automaticity does not only concern activation goals, but also concerns inhibition goals once stimulus-response mapping rules are learned.

The early latency and brain regions supporting training-induced improvements in the GNG task speak in favor of the development of an automatic, low-level form of inhibitory control which may act in concert with top-down, intentional, executive processes (Shiffrin & Dumais, 1981). The latency of our effect in active training (i.e. 61-104ms) suggests that training occurred after the processing of auditory stimuli in primary auditory cortices (15-20ms; Liégois-Chauvel et al., 1994) but substantially earlier than previous studies on inhibitory control (approx. 200ms post-stimulus onset, see chapter 1.2.1). Once inhibition goals were

associated with NoGo stimuli, inhibitory control was no longer only supported by top-down processes but was automatically engaged in response to the NoGo stimuli by engaging fast, bottom-up processes which in turn improved inhibitory control proficiency.

Corroborating our results stating that inhibitory control can be engaged automatically, a recent study found evidence that inhibitory control could even be triggered subliminally without explicit control of the individual (Van Gaal et al., 2010). Similarly, Verbruggen and Logan (2008b) advanced that the decrease in response time over the course of Go/NoGo training followed from fast, bottom-up suppression signals mediated by congruent mappings between stimulus and response. Put differently, because stimulus-response mappings become stored with training, a stimulus will automatically initiate the associated response and hence decrease response time (Shiffrin and Schneider, 1977; Logan, 1988). Supporting our hypothesis that training modified low-level, automatic processing of NoGo stimuli based on consistent associations between NoGo stimuli and inhibition goals, we found evidence for training-induced modulations in parietal areas. Parietal areas, which have been involved in various GNG studies (Garavan et al., 1999; Rubia et al., 2001; Watanabe et al., 2002; Chikazoe, 2010), are suitable candidates for supporting learned stimulus-response associations. The role of parietal areas in optimal inhibitory performance, namely their role in sensorimotor transformation (Andersen et al., 1997), in movement preparation (Deiber et al., 1996) and auditory spatial processing (Spierer et al., 2007, 2008) speak in favor of the engagement of a low-level form of inhibitory control with training. Inhibitory improvements in the GNG task are thus achieved by developing an automatic form of inhibition in which response suppression is directly elicited by specific stimuli and involve feed-forward processing of learned stimulus-response mapping in parietal areas over the initial stages of sensory integration by bypassing top-down/controlled executive modules (Figure 2, green path).

Another line of support for the engagement of automatic inhibition mode is illustrated by the results of the passive listening task in Manuel et al. (2010). Before and after the Go/NoGo training, participants heard the same sounds as those used for the Go/NoGo task but were not instructed to perform any task. The effects of training modified topographically to left-lateralized Go stimuli at 31-81ms post-stimulus onset in right temporo-parietal cortices. We hypothesize that changes occurred in response to Go stimuli in passive listening (a task-irrelevant context) because during training participants were instructed to only respond to behaviorally relevant stimuli (i.e. Go stimuli). Consistent with this hypothesis, AEPs modulated around 50ms which corresponds to the auditory P50 component. This component has been associated with sensory gating mechanisms which have been proposed to prevent

irrelevant auditory information to assess high-level representations (Hsieh et al., 2004; Kisley et al., 2004; Lijffijt et al., 2009; Yadon et al., 2009).

During training, the activation decrease in left parietal areas with Go/NoGo training could possibly follow from different mechanisms. Training might have reduced the conflict between Go and NoGo stimuli (Nieuwenhuis et al., 2003) or refined brain activity to increase the selectivity and efficiency of neural responses (Schoups et al., 1998; Song et al., 2002; Kelly and Garavan, 2005). Alternatively, learned stimulus-response mappings could have decreased the attentional or cognitive demands to inhibition goals (Hill and Schneider, 2006). Because task irrelevant stimuli (i.e. the NoGo stimuli) are less deeply and reliably processed by the brain, we propose that the decrease in activity for NoGo stimuli across training could signify the diminution of behavioral relevance to NoGo stimuli, which in turn would have lead to behavioral improvements (Kanwisher and Wojciulik, 2000; Lamme and Roelfsema, 2000). Consequently, brain responses were confined to Go stimuli in the passive listening task because of the high-relevance of Go stimuli during the task.

Manuel et al. (2010) demonstrated that automatic inhibitory control developed with training, challenging current theoretical frameworks linking inhibitory control with executive (and by definition non-automatic) processes. However, because automatic (but not controlled) inhibition developed with training, the effects of training will likely be specific to the trained stimulus, consequently challenging potential neurorehabilitation of patients showing deficits in inhibitory control. If training inhibitory control can rather reinforce participants' top-down executive processes, patients would benefit from this inhibitory control training in their neurorehabilitation stay. Manuel et al. (2012c) further investigated training-induced plasticity of inhibitory control and assessed whether training on a Stop Signal task would rather modify top-down, controlled, late latency executive modules.

4.1.2 *Controlled* inhibition

In the previous chapter, we curiously reported that GNG training modified low-level, automatic processing of inhibition goals rather than reinforcing controlled executive modules. Although Manuel et al. (2010) challenged the fact that executive functions were only supported by controlled processes, it has a limited value for the rehabilitation of inhibition-related disorders, since the effects of training are likely very specific to the trained stimuli. Our aim was therefore to propose a task wherein training would reinforce top-down/controlled executive module and where the effects of training would likely generalize to other untrained condition relying on the same network. In the introduction chapter (p. 9), we

advanced that due to inconsistent stimulus-response mappings, controlled (but not automatic) inhibition would likely manifest in the Stop Signal task (see also Verbruggen and Logan, 2008b). We therefore hypothesized that SST training would reinforce the fronto-basal network supporting inhibitory control.

Supporting our assumption, Manuel et al. (2012c) demonstrated that performance improvements in the Stop Signal task were supported by modulations of a right lateralized, late latency, top-down fronto-basal executive network (Aron, 2011; Figure 2, red path). The latency and locus of our training-induced effects speak in favor of a reinforcement of top-down/controlled inhibition.

The latency of our effects (i.e. 185- 213ms post-stimulus onset) suggests that training did not modify the early processing of stimuli but rather reinforced controlled executive processes. Corroborating our results, event-related potential studies report evidence for a frontally distributed NoGo-N2 ERP component peaking around 200ms in conditions where inhibition is required (e.g. Falkenstein et al., 1999; Dimoska and Johnstone, 2008).

Further supporting the assumption that SST training modulated controlled, frontal executive modules, we reported that the modulations over the latter period (185-213ms) followed from decreased activity in right IFG areas, pre-SMA and basal ganglia. Accordingly, previous studies consistently reported the involvement of right-lateralized fronto-basal brain areas in the SST task (Rubia et al., 2003; Aron and Poldrack, 2006; Aron et al., 2007a,b; Chevrier et al, 2007; Aron, 2011) at this latency (Pliszka et al., 2000). For instance, TMS over the right IFG (but not the left IFG or right middle frontal gyrus) impaired stopping performance (Chambers et al., 2006; 2007). Likewise lesions in the right IFG or right pre-SMA lead to impairments in the stopping performance (Aron et al., 2003; Floden et al., 2006). In addition, our finding for training-induced activity in the basal ganglia is in line with growing evidence suggesting a central role of basal ganglia in inhibitory control (Aron and Poldrack, 2006; Chevrier et al., 2007).

With training, activity in the fronto-basal network put forward in Manuel et al. (2012c) decreased. This finding contrasts with previous evidence for enhanced activity in the right prefrontal areas and greater inhibitory control (short SSRTs; Aron and Poldrack, 2006; Rubia et al., 2007). Nevertheless, a recent study demonstrated that by dividing participants into fast SSRT and slow SSRT groups, activity was greater in the pre-SMA, but not in the IFG, for the short SSRT group but not for the long SSRT group, supporting our results demonstrating an association between activity decrease in the IFG and improvements in SSRT (Chao et al., 2009). Yet, the decrease of fronto-basal activity with improvements in inhibitory efficiency could follow from neural refinement and greater efficiency of neural responses (Schoups et

al., 1998; Song et al., 2002; Kelly and Garavan, 2005). The mechanisms of training-induced decrease in activation reported in Manuel et al. (2010, 2012c) will be discussed in chapter 4.2.

That the decrease in activity in prefrontal areas correlated with the improvement on the stop signal task (SSRT), indicates not only a functional role of the right inferior frontal cortex in the plasticity of inhibitory control but also that the change in the IFG with training might serve to monitor functional recovery in inhibition-related pathologies.

Manuel et al. (2010) and Manuel et al. (2012c) demonstrate that inhibition can be triggered automatically or in a controlled way. We propose that these inhibition modes are not static, but rather that one can shift from one inhibition mode to another.

4.1.3 A shift from automatic to controlled mode following errors

To illustrate the proposition that automatic and controlled inhibition modes can be engaged differently according to condition, we analyzed these two inhibition modes in the case of error detection. In “Spatio-temporal Brain Dynamics Mediating Post-error Behavioral Adjustments” (Manuel et al., 2012a), a reanalysis of the data from Manuel et al. (2010), we reported a post-error slowing effect and differential effects to Go and NoGo stimuli as a function of preceding performance (correct/error). AEPs modulated topographically over the 70-110ms post-onset as a function of preceding performance followed by stronger prefrontal activity for Go and NoGo stimuli following correct than error trials. Then over the 110-150ms period, we reported a modulation of parietal areas as a function of stimulus type with stronger parietal activity for NoGo than Go stimuli independently of preceding performance.

This pattern of result suggests that the detection of error modulates early, low-level processing of subsequent stimuli, influencing inhibitory control in turn. Because our Go/NoGo task emphasized speed over accuracy (response speed determined efficient/*correct* vs inefficient/*error* inhibitory control) and that speed but not accuracy modulated with training in Manuel et al. (2010), participants were likely engaged in an automatic response mode during correct trials. Consequently being engaged in an automatic response mode would allow speeded inhibitory decisions by short-cutting inputs from late-latency, controlled top-down executive modules (Manuel et al., 2010). Here, we demonstrate that if an error occurs when automatic inhibition is engaged, participants switch to a slow, controlled form of inhibitory control by engaging frontal executive modules, in turn slowing down responses (see Figure 2, blue arrow, for the switch between automatic and controlled inhibition modes). Supporting our results, a very recent study (Chiu et al., in press) demonstrated that automatic and

controlled inhibition modes could indeed jointly contribute to performance in a same task. These authors advance that automatic inhibition is rather on a continuum between no inhibition and top-down/controlled inhibition.

It is interesting to note that prefrontal and parietal clusters were correlated following correct performance but not following inaccurate performance (errors). We interpret these results in terms of a facilitation of stimulus-response mappings following correct trials, directly depending on the prefrontal activity over the very initial stages of sensory integration. In turn automatic, fast response inhibition to NoGo stimuli (*correct* inhibition) is engaged. Following errors, the functional interaction between prefrontal and parietal areas would break down to deal with increase in attention and engagement of new, complex stimulus-response mapping rules (Verbruggen and Logan, 2008b). Consistently, Prado et al. (2010) reported decreased functional connectivity in fronto-parietal circuits along with decrease in performance during a selective attention task, indicating that fronto-parietal connectivity would facilitate response selection when mediated by attention (Rushworth et al., 2007). We hypothesize that fronto-parietal interactions are necessary for improving on the GNG task.

Collectively, Manuel et al. (2012a) supports the model proposed in chapter 4.1, where two inhibition modes (low-level/automatic vs high-level/controlled) can be engaged to resolve inhibitory control tasks. Manuel et al. (2012a) allowed us to further refine our model by adding a critical path in the model, namely the *switch* between automatic and controlled response modes (Figure 2). Post-error slowing would therefore reflect a switch from an automatic to a controlled form of inhibitory control following errors. The next question we'll address is: why did automatic inhibition developed with Go/NoGo training while controlled inhibition was reinforced with Stop Signal training?

4.2 Training-induced differences in the Go/NoGo and Stop Signal tasks

Manuel et al. (2010) advanced that with Go/NoGo training, automatic inhibition developed and lead to improvement in inhibitory control. Based on these intriguing results (that with training automatic but not controlled inhibition developed), we proposed another inhibition task, the Stop Signal task, which we hypothesize would (and it did!) reinforce a top-down, controlled executive network. In this chapter we'll discuss the differences between both motor inhibition tasks. Why are the effects of training on a Go/NoGo task and a Stop Signal

task not similar? Why does training on the GNG task modulates early latency, low-level integration of stimuli while training on the SST task reinforces late latency, high-level executive modules?

Verbruggen and Logan (2008b) argued that different inhibition modes could be engaged according to stimulus-response associations. We corroborate their results and report that in the GNG task, repeated and consistent mappings between Go stimuli and activation goals as and between NoGo stimuli and inhibition goals enabled automatic, low-level, stimulus-driven inhibition to develop. In contrast, since Go stimuli are inconsistently associated with activation and inhibition goals in the SST task, controlled inhibition developed with training.

Other distinctions between the GNG and SST tasks have been proposed and could possibly explain the different processes involved in training-induced inhibitory control. In the Go/NoGo task, participants need to refrain from responding, i.e. actions need to be inhibited before the motor response is initiated, whereas in the SST task actions must be cancelled, i.e. inhibition of an already engaged motor action (Schachar et al., 2007; Eagle et al., 2008a). In other words, the distinction between inhibition of *prepotent* stimuli in the GNG task versus inhibition of *ongoing* stimuli in the SST task might explain our findings. We hypothesize that the SST task sets higher load on response inhibition than the GNG task because the motor response has already been built up and is in the process of completion before the stop signal appears thus requiring the cancellation of an already initiated motor response. Moreover, the Go/NoGo task contains a decision making component (to go or to inhibit), based on the learned categorical discrimination between the Go and NoGo stimuli that is absent in the Stop Signal task (Rubia et al., 2001; Eagle et al., 2008a). Because the GNG task contains a categorical discrimination component, this could putatively explain why parietal, but not frontal, areas supported training-induced improvements in inhibitory proficiency. By contrast, in the SST task, each trial starts with a Go stimulus, so there is no pre-response activation or inhibition goal to select; if the stop signal occurs, participants have to change and switch their actual response requiring further involvement of frontal, executive areas. Further supporting our hypothesis, Swick et al. (2011) advanced that NoGo trials are similar to Stop Signal trials where no delay is set between the Go and the Stop signal, in a way that no strong motor response has been engaged in the Go/NoGo task by the time the NoGo signal occurs. Figure 3 describes the differences between the Go/NoGo and Stop Signal tasks reported in this chapter which could possibly explain the training-induced differences we reported in our results (automatic inhibition with GNG training vs controlled inhibition with SST training).

Altogether the (in) consistency of stimulus-response mappings and the timing of the inhibitory process (withhold vs cancel) could putatively underlie the differences we reported in the networks supporting training-induced improvements in inhibitory control.

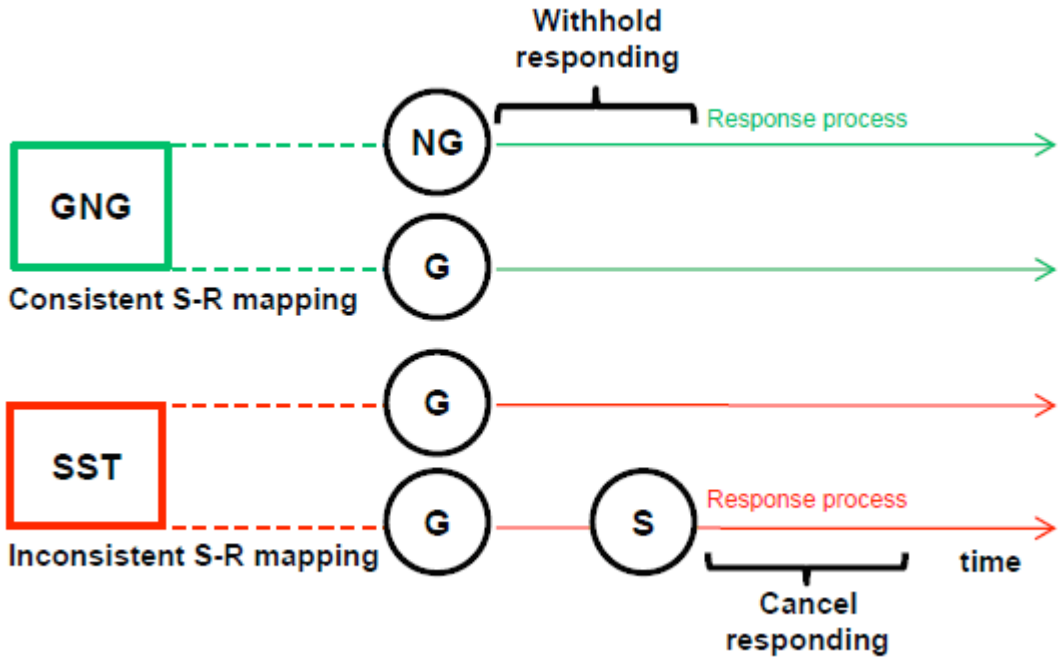

Figure 3: Differences between inhibition in the GNG and SST tasks. In the Go/NoGo task, stimulus-response mappings are congruent. In the Stop Signal task, stimulus-response mappings are incongruent (the Go stimulus can be associated with going or inhibiting). In the Go/NoGo task, the NoGo signal is presented before the motor response has been engaged; the motor response has to be withheld. In the Stop Signal task, the Stop signal is presented during the completion of the motor response; the motor response has to be cancelled. G = Go stimulus, NG = NoGo stimulus, S = Stop signal.

Manuel et al. (2010, 2012c) both demonstrated that brain activity in regions supporting training-induced improvements decreased with training. The next section will address the putative neurophysiological mechanisms underlying training-induced decrease in activity underlying inhibitory control improvements.

4.3 Neurophysiological mechanisms of training-induced plasticity

In our study, we demonstrated that training modified the functional organization of the brain, and maybe also its structure. Structural changes refer to anatomical changes of the

brain, whereas functional changes refer to differences in activation patterns following training (Galvan, 2010).

4.3.1 Structural changes?

Experience-dependant structural changes in grey matter may be the result of various non-mutually exclusive neuronal changes, including growth of new neurons, synapses or glial cells and changes in neuronal morphology (Zatorre et al., 2012). Training-induced structural changes in white matter modify the transmission of information (modification of the number or diameter of axons and their trajectories; Zatorre et al., 2012). Although we acknowledge that structural changes could have occurred, we do not have the neuroimaging techniques to investigate it (e.g. structural MRI). Moreover, the amount of training (35 minutes in the Go/NoGo task and one hour in the SST task) might be insufficient to induce experience dependant structural changes. Structural changes have been reported in long training regimen, ranging from two hours to months (Draganski et al., 2004; Sagi et al., 2012).

4.3.2 Functional changes underlying training-induced improvement in inhibitory control

Here, in contrast, differences in activation patterns, i.e. functional plasticity, likely supported training-induced improvement in inhibitory control. While some studies reported activation increases following training (e.g. Karni et al., 1995; Westerberg and Klingberg, 2007), in Manuel et al. (2010, 2012c), training induced plasticity manifested as a decrease in activity along with training. Activation decrease with training has been related to changes in synaptic efficacy and increased neural efficiency (Haier et al., 1992). With training, brain activity becomes refined: only a minority of neurons fire strongly in response to the particular trained task (Schoups et al., 1998; Poldrack, 2000; Song et al., 2002; Kelly and Garavan, 2005). Refinement follows from a tightening of synaptic connections between neurons essential in task processing and a weakening of connections between those that are not (Galvan, 2010). With training, neuronal circuits supporting improvements in inhibitory control become more efficient (Petersen et al., 1998). Based on this compelling evidence, we propose that efficiency in the neural connections might have lead to improvements in inhibitory control.

Next, we'll discuss the generalization of training effects, i.e. whether the training-induced improvements reported in Manuel et al. (2010, 2012c) might generalize to other untrained

stimuli and conditions, as well as their implication for the rehabilitation of inhibition-related disorders.

4.4 Generalization of the effect of learning

Throughout the previous chapters, we demonstrated that an important feature of the human brain is to reorganize and modify its activity and connections with training. The goal of training is not only to increase performance in the task being trained but rather in the cognitive ability being trained. Therefore, the effects of training on a specific task should generalize to similar tasks or situations and reinforce the intended cognitive function (Green and Bavelier, 2008). For instance, if a participant trains on a motor inhibition task, he would benefit from these improvements if the effects would transfer to other stimuli, inhibition tasks and to other real-life situations where inhibition is required. However, this is often not the case. Most of the studies report that the effects of training are specific to the trained stimuli, task or function, meaning that training-induced improvements on a specific perceptual or motor task often don't transfer to other stimuli, tasks or conditions (even if similar) (e.g. Mackrous and Proteau, 2007). For example, a recent study demonstrated that children improved significantly on the trained tasks (working memory and attentional tasks), but the effects of training did not generalize to non-trained tasks of either inhibition or other executive functions. In this example, effects were specific to the function trained; improvement in working memory but not in inhibitory control. Similarly, several studies pointed out evidence for modality and task-dependant activity in Go/NoGo and Stop Signal studies, likely indicating improvements only on the trained modality (Walther et al., 2010) or task (Swick et al., 2011).

That effects of training are specific constitutes a potential brake for rehabilitation protocols where the goal is to reinforce a general process and not only inhibitory control in a particular situation. In Manuel et al. (2010), neuroplastic changes manifested within parietal cortices over the very initial stages of sensory integration, indicative of the development of a stimulus-driven, low-level form of inhibition directly triggered by the NoGo stimuli (see also Shiffrin and Schneider, 1977; Verbruggen and Logan, 2008b). Although the development of automatic inhibition did improve performance, the effects were likely highly specific to the trained stimuli. Consequently, the training protocol in Manuel et al. (2010) has a very limited value

for rehabilitation where a generalization of the effect of training must be achieved to increase inhibitory control in everyday life and situations.

In Manuel et al. (2012c), training modified the high-level, fronto-basal inhibitory control network. We hypothesized that the effects of training would generalize to other task and conditions relying on the same fronto-basal network. Importantly, the fronto-basal network supporting improvements in inhibitory control in the SST study has been reported in many motor and non-motor inhibition processes. The network underlying training-induced improvements in inhibitory control also supports motor inhibitory control across various effectors; for example, inhibition of eye movements (Stuphorn and Shall, 2006; Chikazoe et al., 2007; Leung and Cai, 2007). Several studies reported an involvement of this brain circuit for inhibiting language related processes (Xue et al., 2006, 2008) or inhibitory control of thoughts, emotion and memory (Rubia et al., 2001; Dolcos and McCarthy, 2006; Depue et al., 2007; Dillon and Pizzagalli, 2007). Because the same network is involved for motor inhibition as for cognitive/affective inhibition, training-induced modification of this network in motor inhibition would likely transfer to untrained inhibitory processes. We hypothesize that SST training would offer a promising approach for the rehabilitation of various motor and non-motor disorders involving deficits of the fronto-basal inhibitory control network. Supporting this hypothesis, various studies reported abnormal SSRTs even if disorders don't show a prominently motor deficit (ADHD: Overtoom et al., 2002; Aron and Poldrack, 2005; obsessive compulsive disorders: Chamberlain et al., 2006; schizophrenia or addiction: Mulvihill et al., 1997; Fillmore and Rush, 2002; see Lipzyc and Schachar, 2010 or Liijfijit et al., 2005 for meta-analyses). However, additional studies are required to assess if the effects of training on the Stop signal task generalize to other tasks and conditions, and if they, hopefully, rehabilitate the intended disorder (e.g. addiction).

4.5 Towards the rehabilitation of inhibition-related pathologies

Understanding whether and how inhibitory control can be trained is crucial since it will improve the rehabilitation of inhibition-related pathologies by optimizing behavioral interventions and proposing targeted rehabilitation protocols.

Recent studies demonstrated that patients suffering from an inhibition-related disorder (addiction, ADHD) showed deficient inhibitory performance (e.g. slower SSRTs) on various tasks including the Go/NoGo and the Stop Signal tasks (Aron and Poldrack, 2005; Lijffijt et

al., 2005). In addition, neuroimaging and lesion studies consistently advance that an intact fronto-basal network is crucial for implementing proper inhibitory control (Aron, 2011; Whelan et al., 2012). Importantly, Manuel et al. (2012c) demonstrated that inhibitory control was subject to fast improvements as evidenced by shorter SSRTs and that training reinforced the fronto-basal network. Moreover, we reported that the change in response of the IFG across training predicted improvements in inhibitory control, indicating a functional association between activity in inferior frontal gyrus and improvements in inhibitory control.

How does training inhibitory control might contribute to the rehabilitation of psychiatric patients, for example in the case of substance abuse? We hypothesize that training inhibitory control might improve higher-level processes by reducing impulsive behavior and hence affecting acting out (e.g. drug consumption). Recent evidence indeed support this assumption. First, Houben and collegues (2011) trained heavy drinkers on a Go/NoGo task in which images of beer were either the Go stimuli or NoGo stimuli. The authors showed that repeatedly suppressing irrelevant responses toward alcohol-related stimuli significantly reduced subsequent alcohol intake up to one week after the experiment (the same results were shown with urges towards high-caloric food (Houben and Jansen, 2011). These results suggest that learned stimulus-response associations can indeed influence behavior by reducing substance abuse. Second, a new approach (neuroplasticity-based cognitive training) based on studies investigating the mechanisms underlying behavioral and neurophysiological plasticity in psychiatric patients, started to emerge in the last decade. This approach advances that appropriately targeting recovery by training and normalizing early perceptual processes will reinforce high-level cognitive functions (Adcock et al., 2009). For example, studies training auditory perception, auditory-verbal working memory tasks and verbal learning tasks in schizophrenic patients reported improvements in global cognitive processes, working memory and verbal learning (which are key symptoms in schizophrenia; Fisher et al., 2009, 2010; Subramaniam et al., 2012). Importantly, Subramaniam et al. (2012) reported that recovery of activity in the medial prefrontal cortex (which is disturbed in schizophrenic patients) predicted improved psychosocial functioning and quality of life for up to six months. Based on our results (Manuel et al., 2012c), we hypothesize that training on the SST task would improve high-level cognitive functions and reduce impulsive behavior and substance abuse. Additionally, modulation in the IFG could be used as a reliable index for guiding neuropsychological interventions in the recovery of patients showing deficits in inhibitory control. Although Manuel et al. (2012c) demonstrated that inhibitory control could be improved, future studies are needed to better assess how and if training is indeed efficient in rehabilitating inhibition-related pathologies and implementing better quality of life.

In the next chapter, we'll investigate which brain regions play a causal role in apraxia, a specific motor control pathology often present in brain-damaged patients. This approach allowed us to further refine the fronto-basal model.

4.6 Motor control in the case of ideomotor apraxia: a convergence with the fronto-parieto-basal inhibitory control network

In our Voxel-based Lesion-Symptom Mapping (VLSM) study entitled "Inter- and intra-hemispheric dissociations in ideomotor apraxia: a large-scale lesion-symptom mapping study in subacute brain-damaged patients" (Manuel et al., 2012b) we investigated motor control in a wider approach, namely motor control in brain-damaged patients. Our results revealed an intra-hemispheric dissociation between distinct lesion sites in different types of pantomime errors. Specifically, configural/spatial errors (CS) were associated with lesions of a left fronto-parietal network while Body part as object errors (BPO) were associated with lesions of superior and inferior frontal areas and underlying white matter tracts. The common lesion affecting both types of errors is the left inferior frontal gyrus. Interestingly the areas highlighting in this study are part of the inhibitory control network described through my thesis. We propose that a lesion in the fronto-basal network (Aron, 2011) may not only lead to deficits in inhibitory control, but also to deficits in motor control (i.e. here in the case of motor control of meaningful movements, pantomimes).

Parietal structures store knowledge about manipulation of objects and learned gestures required to perform adequately the pantomime; they store the concept of the movement (Wheaton and Hallett, 2007; Goldenberg, 2009). In contrast, inferior frontal regions (Goldenberg et al., 2007; Bohlhalter et al., 2011), are involved in the selection of task relevant gestures among a whole set of available gestures related to the object use; they modify the concept into a specific motor plan (Goldenberg et al., 2007; Weathon and Hallett, 2007).

These latter brain regions must communicate to successfully generate a motor plan. Literature supports that not only frontal and parietal regions are important in pantomiming but their respective connections as part as a network are necessary. They interact for the sensory guidance of movement and even be imperative for proper execution of motor

commands (Rizzolatti et al., 1998 ; Weathon and Hallett, 2007). Prefrontal and frontal motor areas, as well as parietal areas (which are reciprocally interconnected) send extensive projections to the basal ganglia (Alexander et al., 1986; Geyer et al., 2000; Glickstein, 2003). Yeterian and Pandya (1993) suggested that connections between parietal areas and basal ganglia may be involved in the preparation and coding of movements. Importantly, our results show that BPO errors were induced by white matter tracts lesions. Lesions to white matter tracts (superior longitudinal fasciculus, SLF) have been shown to induce apraxia by interrupting corticocortical and corticosubcortical connections and thus disconnecting parietal and frontal areas (Pramstaller and Marsden, 1996; Mori et al., 2002; Bartolomeo et al., 2007; Schmahmann, 2011). Disruption of the fronto-parietal circuit and their respective subcortical connections has been demonstrated to interfere with the transformation of sensory information into motor action, the sequencing and response selection and give rise to most of the apraxic errors (Leiguarda et al., 2001; Weathon and Hallett, 2007).

Our work put forward the importance of fronto-parietal interactions as part of a more global cortico-subcortical network (Manuel et al., 2010; 2012a; 2012c). According to the model we proposed, it seems conceivable that if either the frontal (IFG) or parietal areas, which both connect to basal ganglia, are lesioned, motor output will be disturbed and potentially lead to apraxia. Basal ganglia-thalamocortical circuits have been proposed to influence the selection (facilitatory) and suppression (inhibition) of competing responses (Alexander et al., 1990; Seiss and Pramstraa, 2004). Therefore, according to task demands, the basal ganglia can inhibit a motor response (likely in the case of our inhibitory control studies) or activate a motor response (likely in the case of pantomiming), through thalamocortical circuits connecting frontal motor areas to motor areas.

4.6.1 Towards the rehabilitation of apraxia

In our study on apraxic patients we reported an involvement of parietal areas in the absence of any additional spatial demands (as those induced by the scanner). We hypothesized that left parietal areas in pantomimes were revealed because we focused on the post-acute phase and not in the chronic state as for the majority of pantomimes studies (e.g. Dovern et al., 2011). Focusing on the post-acute phase might have revealed the specificity of the network before major plastic reorganization occurred (Witte et al., 2000; Adriani et al., 2003). Supporting our hypothesis, studies have reported that activity related to spatial processing in a patient with a left parietal lesion to shift to the right parietal lobe during spatial transformation, suggesting an underlying reorganization of brain areas supporting pantomiming (Zacks et al., 2004). However, the precise brain mechanisms underlying

recovery following apraxia remain unclear. Based on our own work, we could expect that rehabilitating one part of the network (e.g. training spatial processes to reinforce parietal brain areas) would influence activity in other modules of the network and strengthen connections since brain areas supporting pantomiming are closely connected.

Although speculative, another potential direction for the rehabilitation of disturbed fronto-parietal connections would consist in implementing errorless learning paradigms. This assumption relies on our findings for enhanced connections between frontal and parietal areas following correct responses but not after errors in inhibitory control paradigms (Manuel et al., 2012a). Errorless learning strategies have been proven to be beneficial in the rehabilitation of apraxia (Goldenberg and Hagmann, 1998; Jackson et al., 1999; Goldenberg et al., 2001; Buxbaum et al., 2008). They consist in training patients to complete the action of a whole gesture without any errors. Patients are guided and assisted through the different steps involved in the production until they perform the gesture adequately. The above mentioned studies report positive and lasting effects of errorless learning. Future studies are thus required to further test this hypothesis.

CHAPTER 5 CONCLUSION

Inhibitory control is a crucial executive function allowing the suppression of irrelevant information or inappropriate actions which would disrupt efficient behavioral actions or cognitive processes (Fillmore, 2003). Essentially, the importance of inhibitory control in everyday life is emphasized by patients showing extensive inhibitory deficits. Throughout our work, we aimed at better understanding the organization and plasticity of inhibitory control, to potentially develop simple rehabilitation regimen for inhibition-related pathologies.

We demonstrated that inhibitory control was subject to fast behavioral improvements and was accompanied by modulations of the underlying brain mechanisms (Manuel et al., 2010, 2012c). In Manuel et al. (2010) we showed that practicing on a Go/NoGo task improved inhibitory performance and modified parietal areas at an early-latency. The latency and localization of these effects suggest that with training automatic inhibition develops by shortcutting the need for controlled, top-down control once stimulus-response mapping rules are learned. With this study, we reveal for the first time that inhibitory control is not only engaged only by intentional control over prepotent responses along with modulations of a top-down fronto-basal network. Conversely, when stimulus-response mapping are inconsistent, as in the Stop Signal task, top-down control over prepotent responses is necessary to improve performance. Manuel et al. (2012c) indeed reported that training-induced improvements were associated with a reinforcement of late-latency fronto-basal network.

In Manuel et al. (2012a) we investigated how a stimulus is processed as a function of previous performance and how in turn it impacts subsequent behavioral adjustments accordingly. We showed that after error commission, participants shift from an automatic inhibition mode to a controlled form of inhibitory control which in turns slows subsequent responses to adapt consequently.

Our studies on inhibitory control and post-error behavioral adjustments allowed us to further refine an existing inhibitory control model relying on a fronto-basal network (Aron, 2011). We propose an additional pathway, namely the automatic inhibition pathway relying on parietal areas and short-cutting frontal brain regions (IFG, pre-SMA). Furthermore, we advance that the response mode in which participants are engaged can be dynamically modified according to previous performance.

The last study, (Manuel et al. 2012b) shed light on the intra-hemispheric dissociations between body-part-as-object errors and configural/spatial errors and revealed that BPO errors were associated with frontal deficits whereas CS errors involved parietal brain areas, resolving previous discrepancies in the apraxia literature. Interestingly, we reported that the lesions underlying apraxia were part of the fronto-parieto-basal network advanced in this thesis suggesting that this latter network may support inhibitory control and more generally motor control.

5.1 Future perspectives

Our knowledge on the effects of neuroplastic changes on the fronto-parieto-basal network supporting inhibitory control remain incomplete (Manuel et al., 2010; Aron, 2011; Manuel et al., 2012c). One line of research requiring further investigation concerns the long-term effects of inhibitory control training: i) what are the long-term effects of strengthening inhibitory control and ii) whether neuroplastic changes of fronto-basal network supporting performance improvement following a short training (30-60min) vs intensive training share the same neural mechanisms. Houben et al. (2011) showed evidence for an effect of Go/NoGo training on drinking behavior up to *one week* following the experiment, suggesting that strengthening inhibitory control may persist over time. Unfortunately, long-term follow-up of training effects were often not the focus of inhibitory control studies. Additional evidence is therefore needed to assess the long-term effects of inhibitory control, especially for developing effective training protocols for inhibitory-related pathologies. Based on our studies, we could expect that training on the Stop Signal task and thus reinforcing the high-level fronto-basal network might have long-lasting effects on inhibitory control.

Another possible avenue for exploring long-lasting neuroplastic effects of inhibitory control training on underlying brain structure lies in the expert population. Experts in executive functions, as for example elite athletes who underwent years of training in activities involving specific executive processes (fencing, martial arts), are more proficient in inhibitory control tasks than controls and show specific patterns of functional brain reorganization (Williams and Ericsson, 2005; Di Russo et al., 2006; Yarrow et al., 2009; Roberts et al., 2010). Based on the current evidence, we hypothesize that extensive training in executive function underwent by elite athletes may reinforce the fronto-basal network or modify brain connectivity between its subparts (Manuel et al., 2012c). If the effects of intensive sports training spread and manifest

outside the practice of their sports, at the level of inhibition related behaviors or personality (e.g. impulsivity), then it consists in a further argument in favor of a long-term reinforcement of the fronto-basal network and for the generalization of training effects to other tasks or conditions. This approach is currently being investigated.

A second line of research could focus on the control mode engaged for inhibiting responses. Most of the studies in laboratory settings investigating inhibitory control focus on the stimulus-driven, phasic, *reactive control* response mode, i.e. how individuals inhibit a response when instructed by an external signal (Aron, 2011; Braver, 2012). However, recent evidence advance that the reactive mode would not be sufficient in explaining the complexity of inhibition-related psychiatric disorders alone. Consequently, recent studies are beginning to investigate tonic, *proactive/intentional control* which is how a subject internally prepares to inhibit a forthcoming response (Jaffard et al., 2008; Jahfari et al., 2010; Aron, 2011). Zandbelt et al. (2011) recently demonstrated that proactive but not reactive inhibitory control was affected in schizophrenics, supporting the idea that proactive response mode might better explain inhibitory deficits in psychiatric disorders. Nevertheless, reactive and proactive response modes are not mutually exclusive, but rather interact to engage efficient inhibitory control (Criaud et al., 2012). Jahfari et al. (2010) investigated proactive control with a conditional stop paradigm in which participants, depending on their first button press (left of right), knew if they had to inhibit their response or not. With this setting, it is likely that participants will constantly engaged the fronto-basal network to implement anticipatory, sustained proactive control (Chikazoe et al., 2009; Aron, 2011). Interestingly, Jahfari et al. (2010) reported dorsolateral prefrontal cortex and striatum activations in proactive inhibition that likely reflect increases in working memory to continuously maintain internal task goals (Aron, 2011; Braver, 2012). If, for example, proactive inhibitory control can be trained on a conditional stop paradigm, it would open new opportunities for the rehabilitation of inhibitory-related psychiatric pathologies.

CHAPTER 6 REFERENCES

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CHAPTER 7 ARTICLES

Appendix A : Manuel et al. (2010)

Appendix B : Manuel et al. (2012a)

Appendix C : Manuel et al. (2012b)

Appendix D : Manuel et al. (2012c)

APPENDIX A

Manuel AL, Grivel J, Bernasconi F, Murray MM, Spierer L (2010) Brain dynamics underlying training-induced improvement in suppressing inappropriate action. J Neurosci 30:13670-13678.

Behavioral/Systems/Cognitive

Brain Dynamics Underlying Training-Induced Improvement in Suppressing Inappropriate Action

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Inhibitory control, a core component of executive functions, refers to our ability to suppress intended or ongoing cognitive or motor processes. Mostly based on Go/NoGo paradigms, a considerable amount of literature reports that inhibitory control of responses to "NoGo" stimuli is mediated by top-down mechanisms manifesting ~200 ms after stimulus onset within frontoparietal networks. However, whether inhibitory functions in humans can be trained and the supporting neurophysiological mechanisms remain unresolved. We addressed these issues by contrasting auditory evoked potentials (AEPs) to left-lateralized "Go" and right NoGo stimuli recorded at the beginning versus the end of 30 min of active auditory spatial Go/NoGo training, as well as during passive listening of the same stimuli before versus after the training session, generating two separate 2 × 2 within-subject designs. Training improved Go/NoGo proficiency. Response times to Go stimuli decreased. During active training, AEPs to NoGo, but not Go, stimuli modulated topographically with training 61–104 ms after stimulus onset, indicative of changes in the underlying brain network. Source estimations revealed that this modulation followed from decreased activity within left parietal cortices, which in turn predicted the extent of behavioral improvement. During passive listening, in contrast, effects were limited to topographic modulations of AEPs in response to Go stimuli over the 31–81 ms interval, mediated by decreased right anterior temporoparietal activity. We discuss our results in terms of the development of an automatic and bottom-up form of inhibitory control with training and a differential effect of Go/NoGo training during active executive control versus passive listening conditions.

Introduction

Inhibitory control is the ability to suppress intended or ongoing cognitive or motor processes and allows flexible adaptation to changing environmental contingencies (Aron et al., 2004, 2007). Investigations of inhibitory control principally rely on Go/NoGo paradigms requiring speeded responses to one class of stimuli ("Go") while withholding responses to another class of stimuli ("NoGo"). Convergent evidence indicates that the suppression of prepotent responses to NoGo and the monitoring of conflicts between divergent response requirements to Go and NoGo are prominently controlled by top-down mechanisms. Neuroimaging and lesion data report that inhibitory control involves brain regions traditionally associated with higher-order executive functions, including the inferior frontal cortex and temporoparietal areas (Rubia et al., 2001; Aron et al., 2004; Polich, 2007). Further corroborating the role of higher-order cognitive processes, event-related potential (ERP) studies of Go/NoGo tasks demonstrated that the suppression of prepotent responses manifests over processing stages subsequent to initial sensory functions at latencies of 150–400 ms after stimulus onset (NoGo–N2/P3 components peaking over frontocentral electrodes) (Pfefferbaum et al., 1985; Jodo and Kayama, 1992; Eimer, 1993; Schröger, 1993; Falkenstein et al., 1995, 1999; Kiefer et al., 1998; Kaiser et al., 2006).

Whether inhibitory control can be trained and the supporting neural mechanisms remain unresolved. Two alternative, nonexclusive hypotheses can be drawn about this issue. First, based on the compelling evidence that Go/NoGo proficiency relies on the engagement of top-down executive control (Aron et al., 2004; Dillon and Pizzagalli, 2007), one could hypothesize that improvement of inhibitory control would be solely supported by the reinforcement of these top-down processes. In line with this assumption, one ERP study demonstrated that Go/NoGo practice modulates responses to both Go and NoGo stimuli at 160–240 ms and to NoGo only at 240–320 ms (Schapkin et al., 2007). The authors interpreted this pattern of results in terms of changes in higher-order processes involving the comparison of the stimuli with a memory template and the subsequent inhibition of responses to NoGo stimuli.

Alternatively, some evidence for modality-dependent NoGo inhibition (e.g., inhibition-related activity within supratemporal

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Figure 1. Experimental design. Each participant completed one training session (active Go/NoGo training) as well as two sessions of passive listening before and immediately after the training sessions (passive pretraining and posttraining sessions).

plane in auditory but not visual Go/NoGo) (Walther et al., 2010) suggested a role for bottom-up and lower-order sensory-cognitive processes in Go/NoGo proficiency, challenging the view that inhibitory control involves solely top-down inputs from higher-order executive modules. In support, recent psychophysical models advanced that fast, feedforward, and automatic forms of inhibitory control develop with Go/NoGo practice that are driven by repeated associations between NoGo stimuli and response withholding (Shiffrin and Schneider, 1977; Logan, 1988; Verbruggen and Logan, 2008).

To identify the spatiotemporal brain mechanisms underlying training-induced plasticity in inhibitory control, we contrasted electrical neuroimaging analyses of auditory evoked potentials (AEPs) to Go and NoGo stimuli at the beginning versus the end of an auditory spatial Go/NoGo training. These analyses differentiate effects attributable to topographic modulations from those attributable to changes in response gain, allowing for a better description of likely neurophysiologic mechanisms. To test whether the training impacted preattentive, task-independent stimulus representation rather than solely top-down executive control, we further investigated how training modified AEPs to the trained stimuli presented during passive listening.

Materials and Methods

Participants. Eleven healthy volunteers participated in the study (all male, all right-handed using the Edinburgh questionnaire) (Oldfield, 1971), aged 22–39 years (mean ± SD, 29.36 ± 1.56 years). Each participant provided written, informed consent to participate in the study. No participant had a history of neurological or psychiatric illness, and all reported normal hearing. All procedures were approved by the Ethics Committee of the Faculty of Biology and Medicine of the Vaudois University Hospital Center and University of Lausanne.

Stimuli. Auditory stimuli were 150 ms noise bursts (200–500 Hz band-pass filtered; 5 ms rise/fall; 44.1 kHz sampling; generated using Adobe Audition 1.0; Adobe Systems), lateralized by means of a right- or left-ear leading interaural time difference of 770 μs, which led to perceived lateralization of ~80° from the central midline (Blauert, 1997). The sounds were presented via insert earphones (ER-4P; Etymotic Research) at a level judged comfortable by the participant (~85 dB sound pressure level, measured using a CESVA SC-160 sound pressure meter).

Procedure and task. Each participant completed one training session that we refer to as "active Go/NoGo training," as well as two sessions of passive listening before and immediately after the training sessions (Fig. 1). Throughout the experiment, participants were seated in an electrically shielded and sound-attenuated booth in front of a 19 inch liquid crystal display screen. Stimulus delivery and response recording were controlled using E-prime 2.0.

Active Go/NoGo training. The training session consisted in an auditory spatial Go/NoGo task in which participants had to respond as quickly as possible using the forefinger of the right hand via a manual response-box button to left-lateralized sounds (Go stimuli, hereafter termed LG) and to withhold responses to right-lateralized sounds (NoGo stimuli, termed RNG). The stimulus–response mapping was straightforward, and the LG and RNG sounds were easily discriminated. Respectively, these features minimize confounding effects of either learning the rules of the task or learning to discriminate between the spatial positions of the sounds on the Go/NoGo performance improvement. Each trial started with the presentation of a visual cue (centrally presented gray cross on a black background) of a randomly determined duration ranging from 1000 to 1900 ms. At the same time that the cross was turned off, the LG and RNG sounds were presented and response was recorded.

In the Go conditions, a feedback was provided immediately after the response (see below). To avoid that any differences between ERPs to LG and RNG trials followed from differences in relative novelty or presentation frequency, they were presented with an equal probability of 0.5. This balance further ensured that, during the passive listening portion, pretraining versus posttraining difference in EEG responses to LG and RNG stimuli were not attributable to differences in the number of intervening stimulus presentations.

The active Go/NoGo training was divided into three experimental sessions. Each session started with a calibration block of 16 randomly presented trials (eight LG and eight RNG), followed by two test blocks each of 80 randomly presented trials (40 LG and 40 RNG). The calibration blocks were used to individually adjust the task difficulty and to maintain time pressure across the whole experiment. This was accomplished in the following way. During each calibration phase, the mean response time (RT) to LG trials was calculated online and used to determine the individual participant's RT threshold (RTt), which was set slightly below current response speed (i.e., calculated as 80% of the mean RT from the calibration block). During the test block, a Go response RT was considered as correct if it was below the 80% RTt of the immediately preceding calibration phase. Otherwise, a feedback screen indicating "too late!" was displayed immediately after the Go response (slow hit). On each trial, feedback on global accuracy was displayed (mean percentage of correct trials, including fast hit and correct rejection). Participants were not informed about this thresholding procedure. Except the global accuracy, no visual feedback was displayed after fast hits or false alarms (FAs) (i.e., a response to a NoGo stimulus) (for a similar procedure, see Vocat et al., 2008). The whole Go/NoGo training session included a total of 528 stimuli [(160 stimuli in the test block + 16 stimuli in the calibration block) × 3 sessions = 528 stimulus] and lasted for a total of ~35 min. After the completion of each session, a rest period of 10 min was provided to participants.

Passive pretraining and posttraining sessions. Pretraining and posttraining passive sessions consisted of six blocks of passive listening. In each block, the stimuli were presented in a pseudorandom order with a random interstimulus interval (ISI) ranging from 700 to 900 ms. The ISIs were reduced in the passive listening part of the study compared with the active Go/NoGo training session in which the ISI ranged from 1000 to 1900 ms. ISIs were reduced to increase the number of presented stimuli (and thereby the signal-to-noise ratio) while keeping the experiment as short as possible for participants. A corresponding reduction of ISI was not applicable in the active task, because the presentation of the cue, the recording of participant's response, and the presentation of the feedback were included between the presentations of the two stimuli. We would note that in the differences in ISIs between active and passive conditions could constitute a potential confounds when comparing the results of the two tasks. The blocks were randomized across pretraining and posttraining sessions and across subjects. In each block, the same LG and RNG stimuli as in the active Go/NoGo training were presented (69 LG and 69 RNG per block). Seven other additional sounds were presented in the framework of another experiment focusing on the generalization of the effects of the Go/NoGo training and were not analyzed in the present study. Each participant completed three blocks before and three blocks after the training tasks while watching a muted film; they were instructed to ignore the auditory stimuli. The pretraining and posttraining session lasted for ~30 min each.

EEG acquisition and preprocessing. Continuous EEG was acquired at 1024 Hz though a 128-channel Biosemi ActiveTwo system referenced to the common mode sense/driven right leg ground (which functions as a feedback loop driving the average potential across the montage as close as possible to the amplifier zero). Before group averaging, data at artifact electrodes from each participant were interpolated (Perrin et al., 1987). EEG epochs from 100 ms before to 452 ms after stimulus onset (i.e., 102 data points before and 463 data points after stimulus onset) were averaged, for each participant, for LG and RNG trials from the two first ("beginning" condition) and two last ("end" condition) blocks of the active training session and from the three pretraining and three posttraining sessions during passive, generating separate 2×2 within-subject designs for the active training and passive listening portions of the experiment with factors of section (beginning and end of the active training; "pre" and "post" training in the case of the passive listening portion) and stimulus (LG and RNG). In addition to a ± 80 μV artifact rejection criterion, EEG epochs containing eye blinks or other noise transients were removed after visual inspection. Data were baseline corrected using the 100 ms prestimulus period, bandpass filtered (0.18–40 Hz), and recalculated against the average reference.

During active training, the average $\pm$ SEM number of accepted epochs was 75 ± 2 for the beginning LG, 72 ± 3 for the beginning RNG, 71 ± 5 for the end LG, and 62 ± 5 for the end RNG conditions. A 2×2 repeated-measures ANOVA with factors of section and stimulus (as performed for the ERP analyses) revealed a main effect of section ($F_{(1,10)} = 5.72$, $p = 0.03$). Neither the main effect of stimulus nor the interaction term were significant.

During passive listening, the average $\pm$ SEM number of accepted epochs was 170 ± 8 for the pre LG, 170 ± 9 for the pre RNG, 182 ± 6 for the post LG, and 180 ± 8 for the post RNG conditions. These values did not statistically differ.

EEG analyses and source estimations. Because of the leftward shift of RTs with training and the fact that participants responded to Go but not NoGo stimuli, confounding stimulus $\times$ section interactions could have occurred as a result of difference in the latency of the activity related to response button press. Therefore, in the analyses of ERPs from active training, we considered only effects occurring over a window limited to the first 100 ms after stimulus onset, i.e., before the minimal latency of response initiation in the motor cortex occurring ~100 ms before the execution of the button press (the shortest mean RTs measured in our study were ~200 ms) (Thorpe and Fabre-Thorpe, 2001). Consequently, the N2/P3 complex occurring 150–400 ms after onset will not be analyzed here. Plus, because of the large psychophysical distance and the equal probability of presentation between the Go and NoGo stimuli in our study, large N2/P3 responses would not be expected (Nieuwenhuis et al., 2003, 2004). In our ERP analyses, we do not provide details on effects of block nor main effect of stimuli because they can be attributed to, respectively, unspecific effects of stimulus repetition and psychophysical differences between left-lateralized Go and right-lateralized NoGo stimuli, both effects being outside the scope of the present study. Main effects of stimulus could also be explained in terms of spatial attention, because Go stimuli were always left-lateralized. Thus, any differences could reflect participants' ability to deploy their attention rather than to response inhibition per se. Such effects of attention have been observed as modulations of the N2/P3 responses (i.e., after ~200 ms after stimulus onset) (Schröger, 1993). As will be clear below in Results, however, the present effects occur within the initial 100 ms after stimulus onset and follow from interactions between stimulus type and block.

Topographic analyses (implemented in Cartool software developed by D. Brunet, Functional Brain Mapping Laboratory, Geneva, Switzerland) were performed to determine whether the configuration of intracranial generators changed across either or both factors (i.e., section and stimulus). These methods have been detailed previously and have many analytical and interpretational benefits over canonical AEP waveform analyses (Murray et al., 2008). We provide only the essentials here. Major impetuses for the use of the present analyses were the ability to circumvent interpretational issues attributable to the reference-dependent nature of AEPs and to differentiate effects arising from topographic modulations from effects resulting from changes in response strength. Moreover, the analyses used here require minimal experimenter selection of either the electrodes or time periods of interest, which are two major sources of potential bias in AEP investigations.

Hierarchical clustering based on an atomize and agglomerate approach was performed to identify the pattern of predominating topographies (maps) in the cumulative group-averaged data (Murray et al., 2008). In this approach, the number of clusters initially equals the number of data points in the concatenated group-averaged dataset (i.e., 565 in the present study). This number is then sequentially reduced by identifying the cluster with the lowest global explained variance (GEV) with respect to all other clusters (for a recent publication of formulae, see Murray et al., 2008). The data from this cluster are then reassigned to one of the surviving clusters. The optimal number of clusters to describe the dataset is identified using a modified Krzanowski–Lai criterion (Tibshirani et al., 2005) (for an approach based on a modified cross-validation criterion, see Pascual-Marqui et al., 1995). These steps are all a hypothesis generation tool that is then statistically evaluated using single-subject data. Differences in the pattern of maps observed between conditions in the group-averaged data were tested by calculating the spatial correlation between these "template" maps from the group-averaged data and each time point of single-subject data from each experimental condition (referred to as "fitting"). For each participant, we calculated the GEV of each template map within the single-subject AEPs. In colloquial terms, GEV can be understood as the average (over the fitted time period) spatial correlation between a given template map and an individual's data from a specific condition that is weighted by the global field power at each time point over the averaged time period. In this way, GEV provides a measure across participants of how well a given template map accounts for a given condition over a specific time period.

We estimated the sources in the brain using a distributed linear inverse solution and the local autoregressive average (LAURA) regularization approach (Grave de Peralta Menendez et al., 2001; Grave-de Peralta et al., 2004) (for a comparison of inverse solution methods, see Michel et al., 2004). LAURA selects the source configuration that better mimics the biophysical behavior of electric fields (i.e., activity at one point depends on the activity at neighboring points according to electromagnetic laws). Homogenous regression coefficients in all directions and within the whole solution space were used. The solution space is based on a realistic head model and included 3005 nodes selected homogeneously distributed within the gray matter of the average brain of the Montreal Neurological Institute (courtesy of R. Grave de Peralta Menendez and S. Gonzalez Andino, University Hospital of Geneva, Geneva, Switzerland). The results of the above topographic pattern analysis defined time periods of stable topography for which intracranial sources were estimated and statistically compared at each node level between conditions using the same section $\times$ stimulus within-subject design as in the topographic pattern analysis. A spatial criterion of minimum 36 contiguous points was applied in the statistical parametric mapping procedure.

Results

Behavioral results

Participants completed a 35 min Go/NoGo training session during which they were instructed to respond as quickly as possible to left-lateralized sounds (LG stimuli) while withholding responses to right-lateralized sounds (RNG stimuli). We indexed behavioral performance by RTs to Go stimuli, the percentage of hits (responded Go stimuli) and FAs (NoGo errors). As for the EEG analyses, behavioral data were separately averaged for the beginning and end conditions (i.e., two first and two last blocks of the training session, respectively). RTs significantly decreased with training (mean $\pm$ SEM, beginning, 274 ± 28 ms; end, 228 ± 15 ms; $t_{(10)} = 4.673$; $p < 0.001$). Because participants were required to respond with their right hand to the left-lateralized Go stimuli, the speeding of response time may be partly attributable to a reduction of the Simon effect with training (Proctor and Shao, 2010). The mean percentage of hits was at ceiling from the beginning of the training and did not modulate across sections of the training session (beginning, $98.9 \pm 0.3\%$; end, $98.5 \pm 0.4\%$;

$t_{(10)} = 0.69$; $p = 0.50$). The mean percentage of FAs significantly increased with training (FA beginning, 7.5 ± 0.8%; FA end, 14.3 ± 1.1%; $t_{(10)} = -3.90$; $p < 0.001$). However, we are reluctant to interpret the increase in commission errors as reflecting a decrease in Go/NoGo proficiency. Because of the implementation of the auto-adaptative thresholding of the minimal RTs at which a response was reported as correct, a strong time pressure was maintained constantly across the training session, even when participants had reached their maximal response speed (i.e., ~200 ms). At the end of the training, participants were unable to continue accelerating their responses to Go stimuli. As a result, they committed more FAs (for discussion on this issue, see Falkenstein et al., 2000). Further arguing against the same training-induced mechanisms for decrease in RT and the increase in FA with training, speed–accuracy tradeoff analyses revealed no relation between the modulation in RT and in FA with training ($r_{(9)} = 0.14$; $p = 0.67$).

Electrical neuroimaging results

Active Go/NoGo training session

Hierarchical clustering was performed on the AEPs to identify the pattern of predominating topographies (maps) of the electric field at the scalp in the cumulative group-averaged data. The output of the topographic pattern analysis of the collective data during active training is displayed in Figure 2*a* [see also AEP waveforms at a vertex electrode (Cz)]. The GEV of the results of the cluster analysis was 96.96%. This topographic pattern analysis identified the same sequence of stable maps for trials from the beginning and end conditions and LG and RNG trial types, with the exception of the 61–104 ms after stimulus. Over this time period, these maps were differentially observed across sections and stimuli.

Using the single-subject data from each condition, the GEV of each of the maps identified over period of topographic modulation in the group-averaged AEPs was then calculated to obtain a quantitative estimate of how well they accounted for individual participants' AEPs over the same time interval (Fig. 2*b*).

There was a significant interaction between section, stimulus, and map ($F_{(1,10)} = 5.672$, $p = 0.039$). Follow-up ANOVAs were therefore conducted for each stimulus separately. There was a significant interaction between section and map for the RNG but not LG stimuli as a function of training section (section × map interaction; LG, $F_{(1,10)} = 0.087$, $p = 0.774$; RNG, $F_{(1,10)} = 11.27$, $p = 0.007$). Over the same time period, there was a significant interaction between section and map ($F_{(1,10)} = 6.263$, $p = 0.031$), indicating an unspecific effect of training on topographic responses to both RNG and LG stimuli. LAURA distributed source estimations were calculated over the 61–104 ms poststimulus period (Fig. 2*c*), i.e., when the topographic pattern analysis showed significant interaction between factors section, stimulus, and map. To do so, AEPs for each participant and each experimental condition separately were first averaged across the above mentioned time period to generate one data point per participant and experimental condition. Source estimations were then calculated, and the scalar value of each solution point was submitted to a 2 × 2 repeated-measures ANOVA with section and stimulus as within-subject factors. There was a significant main effect of section over right temporoparietal areas ($F_{(1,10)} > 4.965$, $p < 0.05$). The main effect of stimuli included frontoparietal regions bilaterally ($F_{(1,10)} > 4.965$, $p < 0.05$). This is consistent with models of auditory spatial processing and spatial attention that implicate frontoparietal circuits (Spierer et al., 2007, 2008, 2010). The fact that both frontal and parietal regions were synchronously observed over this time window is suggestive of a degree of parallel processing. However, we cannot exclude the possibility of directionality at a finer temporal scale, because data were first averaged in time across the 61–104 ms period.

Of particular relevance to the goals of the present study, there was a significant interaction between these factors in a left temporoparietal cluster ($F_{(1,10)} > 4.965$, $p < 0.05$) (Fig. 2*d*). Follow-up statistical tests were performed to determine the basis for this interaction. The scalar values of the solution points comprised within the region of interest (ROI) showing the section × stimuli interaction were extracted and averaged for each subject and condition. The resulting values were compared across sections for LG and RNG stimuli separately. These analyses revealed a significant decrease in the activation strength of the temporoparietal ROI between beginning and end conditions for the RNG, but not for LG, stimuli ($t_{(10)} = 4.621$, $p < 0.01$ and $t_{(10)} = 1.045$, $p = 0.321$, respectively) (Fig. 2*e*).

Correlational analysis performed between scalar values of the ROI showing the section × stimulus interaction and behavioral performance revealed that training-induced modulations in response strength to RNG within the temporoparietal ROI (beginning–end) negatively correlated with modulations in RT (beginning–end; solution point showing the maximal correlation within the ROI, $r_{(9)} = -0.67$; $p < 0.03$) (Fig. 2*f*). The more activity decreased within this region across training blocks, the more the speed of performance improved.

Passive pretraining and posttraining session

The topographic pattern analysis identified the same sequence of stable maps for trials from the pretraining and posttraining conditions and LG and RNG trial type, with the exception of two poststimulus intervals. The output of the topographic pattern analysis of the collective data from the passive listening portions is displayed in Figure 3*a* [see also AEP waveforms at an exemplar electrode (Cz)]. The GEV of the results of the cluster analysis was 90.87%.

Two maps were identified in the group-averaged data over the 31–81 ms interval, and these were differentially observed across sections and stimuli. There was a significant interaction between factors section, stimulus, and map over the 31–81 ms poststimulus period ($F_{(1,10)} = 9.003$, $p = 0.013$). Follow-up ANOVAs were therefore conducted for each stimulus separately. There was a significant interaction between section and map for the LG but not RNG stimuli as a function of training section (section × map interaction; LG, $F_{(1,10)} = 6.145$, $p = 0.033$; RNG, $F_{(1,10)} = 0.609$, $p = 0.453$). This pattern of results indicates that the intervening training session modulated topographically responses to passively presented LG but not RNG stimuli (Fig. 3*b*). Over the 248–350 ms interval, there was a significant interaction between stimulus and map ($F_{(1,10)} = 5.264$, $p = 0.045$), indicating that distinct topographic patterns accounted for responses to the two stimuli. This differential processing of the two stimuli likely followed from the psychophysical differences between the left- and right-lateralized sounds (for corresponding findings, see Schröger, 1993; Spierer et al., 2007).

LAURA distributed source estimations were calculated over the 31–81 ms poststimulus period (Fig. 3*c*), i.e., when the topographic pattern analysis showed a significant interaction between factors of section, stimulus, and map. There was a significant interaction between section and stimulus in a cluster including anterior parietal and superior temporal regions ($F_{(1,10)} > 4.965$, $p < 0.05$) (Fig. 3*d*) but no main effect of stimuli or section. Follow-up statistical tests were performed to better understand

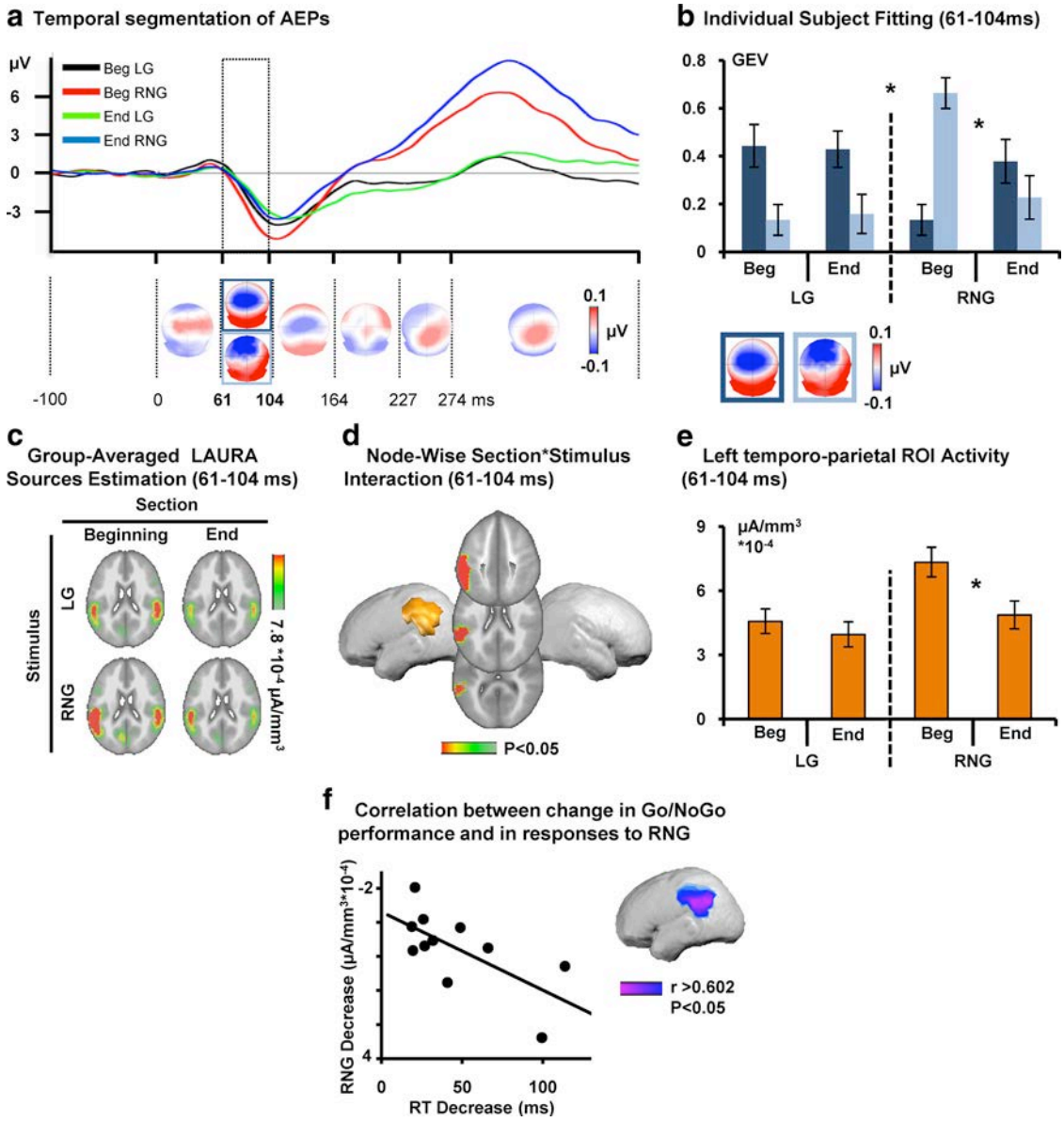

Figure 2. Active Go/NoGo training: electrical neuroimaging results. ***a***, The AEP in response to the beginning for Go (LG, black trace) and NoGo (RNG, red) and end for Go (green) and NoGo (blue) of the experiment are displayed in microvolts as a function of time for the Cz electrode. Topographic pattern analyses identified six time periods of stable electric field topography across the collective 452 ms poststimulus period. All topographies (i.e., maps) are shown with the nasion upward and left scalp leftward. For one of these time periods (61–104 ms), multiple maps were identified in the group-averaged AEPs. These maps are framed in blue. ***b***, The reliability of this observation at the group-averaged level was then assessed at the single-subject level using a spatial correlation fitting procedure. The GEV of each template map provides a measure across subjects of how well a given template map accounts for a given condition over the 61–104 ms time period (see Materials and Methods). Over the 61–104 ms period after stimulus, different maps (framed in dark and light blue) described AEPs in response to the Go and NoGo stimuli as a function of training (beginning/end). There was a significant three-way interaction between section, stimulus, and map. Error bars indicate SEM. ***c***, Group-averaged distributed linear source estimations were calculated over the 61–104 ms poststimulus period for each experimental condition (scale indicated), when AEPs analyses revealed a significant topographic modulation across conditions. ***d***, Node-wise section × stimulus ANOVA on source estimation over the 61–104 ms interval revealed significant section × stimuli interactions within a left temporoparietal cluster. ***e***, Follow-up analyses on the mean scalar value of the ROI revealed a decrease in the left temporoparietal cortex for the NoGo stimuli as a function of training. ***f***, Node-wise correlations between response time to Go stimuli and the activity within the cluster showing the significant section × stimulus interaction revealed that the more performance improved, the more response strength to NoGo stimuli decreased within the left temporoparietal ROI.

the basis of the interaction, revealing a significant decrease in the activation strength of the right anterior temporoparietal ROI between pretraining and posttraining conditions for the LG but not RNG stimuli ($t_{(10)} = 3.100$, $p < 0.02$ and $t_{(10)} = -0.337$, $p = 0.743$, respectively) (Fig. 3*e*).

Discussion

We identified the spatiotemporal brain dynamics underlying training-induced plasticity in inhibitory control. The processes engaged for responding to Go stimuli while withholding responses to NoGo were subject to facilitation; RTs significantly decreased to Go stimuli during the course of active training. Brain mechanisms associated with such plasticity in inhibitory control were first identified by applying electrical neuroimaging analyses to AEPs in response to Go and NoGo stimuli recorded at the beginning versus the end of 35 min active auditory spatial Go/NoGo training. Then, we applied the same contrast to EEG responses recorded during passive listening of the Go and NoGo stimuli immediately before and after the active training session. The collective findings support a model wherein learning-

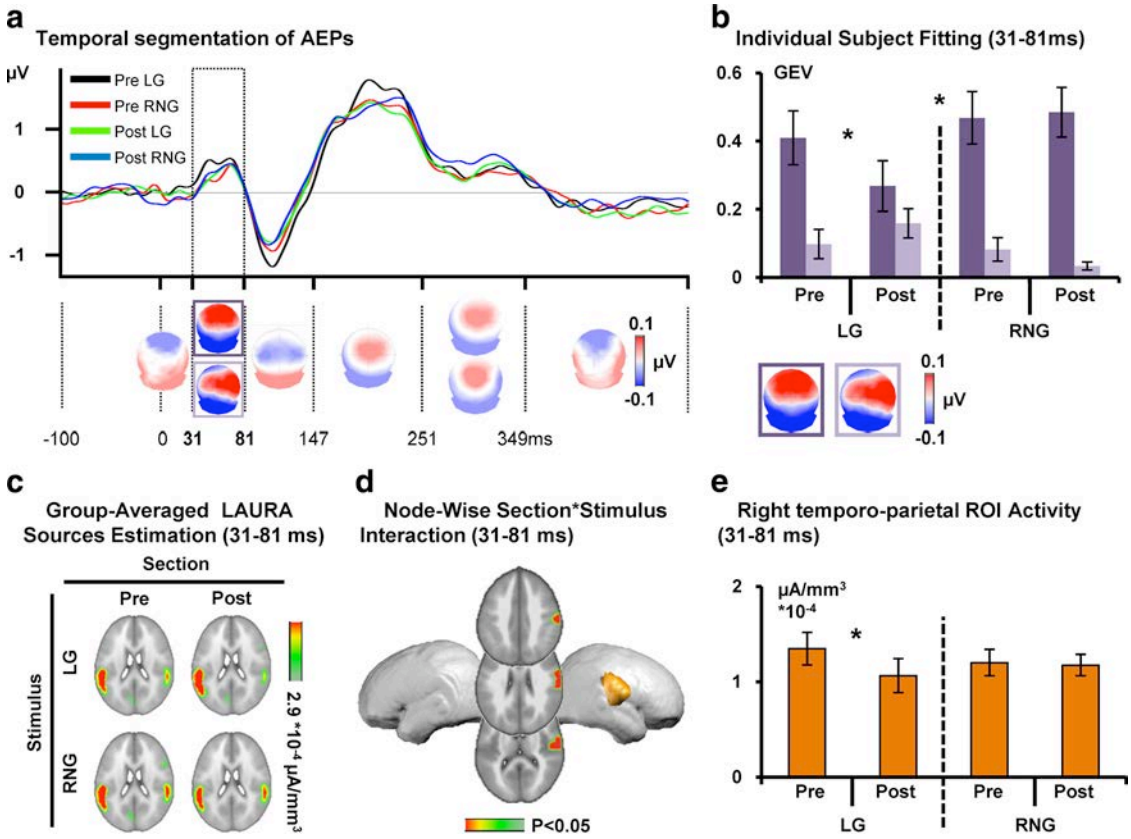

Figure 3. Pretraining and posttraining passive listening: electrical neuroimaging results. ***a***, The AEP in response to the pretraining Go (LG, black trace) and NoGo (RNG, red) and posttraining Go (green) and NoGo (blue) stimuli are displayed in microvolts as a function of time for the Cz electrode. Topographic pattern analyses identified six time periods of stable electric field topography across the collective 452 ms poststimulus period. All topographies (i.e., maps) are shown with the nasion upward and left scalp leftward. For the 31–81 ms period, multiple maps were identified in the group-averaged AEPs. These maps are framed in purple. ***b***, The reliability of this observation at the group-averaged level was then assessed at the single-subject level using a spatial correlation fitting procedure. The GEV of each template map provides a measure across subjects of how well a given template map accounts for a given condition over the 61–104 ms time period (see Materials and Methods). Over the 31–81 ms period after stimulus, different maps (framed in dark and light purple) described AEPs in response to the Go and NoGo stimuli as a function of training (pre/post). There was a significant three-way interaction between section, stimulus, and map. Error bars indicate SEM. ***c***, Group-averaged distributed linear source estimations were calculated over the 31–81 ms poststimulus period for each experimental condition (scale indicated), when AEPs analyses revealed a significant topographic modulation across conditions. ***d***, Node-wise section × stimulus ANOVA on source estimation over the 31–81 ms interval revealed significant section × stimuli interactions within a right temporoparietal cluster. ***e***, Follow-up analyses on the mean scalar value of the ROI revealed a decrease in the right temporoparietal cortex for the Go stimuli as a function of training.

induced plasticity in inhibitory control manifests during early, low-level stages, affects prepotent responses to stimuli, and extends beyond training to impact passive listening of previously behaviorally relevant stimuli.

Responses to NoGo but not Go stimuli during active training modulated the AEP topography over the 61–104 ms poststimulus onset interval, indicative of the engagement of distinct configurations of intracranial generators. Source estimations revealed that this modulation followed from decreased activity within left temporoparietal cortices in response to NoGo stimuli that in turn correlated with the extent of RT facilitation to Go stimuli during active training. This correlation supports a functional role for left parietal structures in the plasticity of inhibitory control to NoGo stimuli (at least in the case of the present paradigm). No AEP effects were observed with Go stimuli during active training.

The specificity of the AEP effects, i.e., that only NoGo and not Go trials were affected, and their correlation with RT facilitation are not readily explained in terms of simple motor or procedural learning. If either of these were the case, AEPs from Go trials would likely have modulated, too. Plus, the fact that source activity significantly decreased argues against a straightforward explanation in terms of enhanced attention to one type of stimulus or one region of space, both of which would be predicted to enhance responses after training. Instead, our pattern of results is consistent with low-level inhibitory control over prepotent responses to NoGo stimuli (although another potentially concurrent possibility is that these effects reflect changes in decision criterion).

Both the main effect of section and also the evidence for frontal activity that was modulated as a function of stimulus would suggest that top-down control processes are likely playing a more general role during active training. Still, additional experiments akin to those by Schröger (1993) would be required to better disentangle effects of spatial processing from response mapping in the present study.

The latency of our effect (i.e., 61–104 ms) suggests that training-induced plasticity in inhibitory control occurs during relatively early sensory processing stages. In this regard, it is worthwhile to situate the timing of the present effects with respect to general auditory processing as well as to spatial processing (Murray and Spierer, 2009; Spierer et al., 2010). Primary auditory cortices respond to sounds at ~15 ms

(Liégeois-Chauvel et al., 1994) with propagation along the superior temporal cortex within the subsequent 3–10 ms (Howard et al., 2000). Likewise, auditory-driven responses in frontal (Liasis et al., 2001) and even occipital (Romei et al., 2007, 2009) regions have been observed within the initial 30–60 ms after stimulus onset. Thus, although effects over the 61–104 ms poststimulus interval are indeed earlier than reported previously, they are unlikely reflecting exclusively feedforward or stimulus-driven activity, particularly in the temporoparietal regions identified by our source estimations (Inui et al., 2006).

The present findings over the 61–104 ms poststimulus interval are substantially earlier than what has been typically reported. Previous studies suggest that inhibition of prepotent responses to NoGo stimuli relies on top-down control involving frontoparietal networks over the 150–400 ms poststimulus onset interval (Schröger, 1993; Botvinick et al., 2001; Rubia et al., 2001; Aron et al., 2004; Polich, 2007). We therefore hypothesize that our effects during active training reflect the development of a low-level form of inhibition, mediating Go/NoGo performance improvement that may act in concert with top-down, consciously controlled, inhibitory processes. Accordingly, Verbruggen and Logan (2008) advanced that decreases in response time induced by Go/NoGo practice relies on the emergence of fast bottom-up suppression signals mediated by an increase in the strength of association or mapping between the stimulus and stop response (Shiffrin and Schneider, 1977; Logan, 1988). The parietal localization of the present source estimations provides an additional line of support to the proposition that inhibitory control develops based on the recurrence of consistent mappings of stimuli onto motor response withholding rules (Shiffrin and Schneider, 1977; Logan, 1988). Parietal structures are suitable candidates for comprising learned associations between stimuli and behavioral responses. On the one hand, parietal structures have been implicated in the control of motor planning (Watanabe et al., 2002), in the coordinate transformations required to convert sensory signals into motor commands (Andersen et al., 1997), as well as in the preparation for movements (Deiber et al., 1991, 1996; Decety et al., 1992). On the other hand, previous studies demonstrated the involvement of left (contralateral) temporoparietal networks in the integration of spatial information differentiating the Go and NoGo stimuli in our study (Spierer et al., 2007, 2008). Together, the evidence for a role of parietal structures in both sensorimotor interactions and auditory spatial processing suggest that the effect of Go/NoGo training revealed in the present study might reflect the labeling of right-lateralized NoGo stimuli with signals yielding motor response inhibition. This hypothesis is further supported by the significant correlation between RTs to Go stimuli and the decrease in left parietal response strength.

In contrast to the effect of training manifesting when participants were engaged in the active Go/NoGo task [i.e., modifications of responses to NoGo (right) but not Go stimuli], in the context of passive listening, the effect of training manifested as topographic modulations of AEPs to left (Go) but not right (NoGo) stimuli over the 31–81 ms interval. Source estimations performed over this period revealed a decrease in response strength to left stimuli (Go) within right temporal and anterior parietal areas.

Participants were trained to respond to left-lateralized stimuli, which presumably increased their behavioral relevance. We hypothesize that the training sessions modified responses to Go but not NoGo stimuli during the passive listening portion because, under passive listening (or other task-irrelevant) contexts, there is a functional advantage of nonetheless detecting stimuli that were recently behaviorally relevant. This would not be the case for behaviorally irrelevant (NoGo) stimuli. Supporting this hypothesis, our effect occurred at a latency and locus corresponding to the P50, a component associated with sensory gating mechanisms by which the auditory system prevents irrelevant and/or redundant sensory information from the environment accessing and overwhelming higher-order representations (Hsieh et al., 2004; Kisley et al., 2004; Lijffijt et al., 2009; Yadon et al., 2009). The decrease in response strength of P50 generators associated with learning to respond to Go stimuli may reflect facilitated access for these stimuli to reach higher processing stages. Several studies demonstrated associations between the strength of P50 and performance on attention or detection tasks (Wan et al., 2008; Thomas et al., 2010). P50 has also been shown to play a role in the maintaining of auditory attentive state (Wan et al., 2008). The findings during passive listening are consistent with the hypothesis that Go/NoGo training modified low-level stimulus representations.

Several putative mechanisms could account for suppressed responses to NoGo stimuli during active training. One possibility is that conflicts between Go and NoGo response requirements are reduced (Nieuwenhuis et al., 2003). Another possibility is that, during the course of training, brain responses become more selective or otherwise refined. Training has been proposed to result in the exclusion of irrelevant neural activity and thus in the increase in the selectivity and efficiency of neural activity (Schoups et al., 1998; Schiltz et al., 1999; Song et al., 2002; Kelly and Garavan, 2005). Accordingly, the recurrent mappings of NoGo stimuli onto inhibition rules could have reduced the activity involved in triggering motor responses to NoGo stimuli. Alternatively, recurrent inhibition of response to NoGo while executing speeded responses to Go stimuli could have modulated the attentional or cognitive demand required to apply the (NoGo) response rule to the NoGo stimuli (Hill and Schneider, 2006). With regard to evidence that unattended and task irrelevant stimuli are processed more slowly and less reliably in the brain (Kanwisher and Wojciulik, 2000; Kastner and Ungerleider, 2000; Lamme and Roelfsema, 2000), the decrease in response strength to NoGo stimuli could reflect training-induced lessening in the behavioral relevance attributed to right-lateralized stimuli, which in turn helped decrease response prepotency. In turn, during passive listening, this extended to effects on Go stimuli because of their high behavioral relevance during the task.

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APPENDIX B

Manuel AL, Bernasconi F, Murray MM, Spierer L (2012a) Spatio-temporal brain dynamics mediating post-error behavioral adjustments. J Cogn Neurosci 24:1331-1343.

Spatio-temporal Brain Dynamics Mediating Post-error Behavioral Adjustments

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Abstract

■ Optimal behavior relies on flexible adaptation to environmental requirements, notably based on the detection of errors. The impact of error detection on subsequent behavior typically manifests as a slowing down of RTs following errors. Precisely how errors impact the processing of subsequent stimuli and in turn shape behavior remains unresolved. To address these questions, we used an auditory spatial go/no-go task where continual feedback informed participants of whether they were too slow. We contrasted auditory-evoked potentials to left-lateralized go and right no-go stimuli as a function of performance on the preceding go stimuli, generating a 2 × 2 design with "preceding performance" (fast hit [FH], slow hit [SH]) and stimulus type (go, no-go) as within-subject factors. SH trials yielded SH trials on the following trials more often than did FHs, supporting our assumption that SHs engaged effects similar to errors. Electrophysiologically, auditory-evoked potentials modulated topographically as a function of preceding performance 80–110 msec poststimulus onset and then as a function of stimulus type at 110–140 msec, indicative of changes in the underlying brain networks. Source estimations revealed a stronger activity of prefrontal regions to stimuli after successful than error trials, followed by a stronger response of parietal areas to the no-go than go stimuli. We interpret these results in terms of a shift from a fast automatic to a slow controlled form of inhibitory control induced by the detection of errors, manifesting during low-level integration of task-relevant features of subsequent stimuli, which in turn influences response speed. ■

INTRODUCTION

Rapid and flexible adaptation to environmental requirements is critical for optimal goal-directed behaviors. Behavioral adjustments are typically driven by the detection of inappropriate responses, potentially yielding negative consequences (e.g., MacDonald, Cohen, Stenger, & Carter, 2000). The impact of error detection on subsequent behavior typically manifests as a slowing down of RTs following errors as reported in various paradigms including the Stroop task (Egner & Hirsch, 2005), stop signal task (Li et al., 2008), or go/no-go tasks (e.g., Hester, Simoes-Franklin, & Garavan, 2007). Whereas the neural underpinnings of error detection have been the focus of extensive investigations, how it impacts the processing of subsequent stimuli and in turn shapes behavior remains unclear.

Error detection processes have been repeatedly found to involve the ACC (Garavan, Ross, Murphy, Roche, & Stein, 2002) as notably evidenced by higher activity within ACC, following errors than correct responses (e.g., Ullsperger & von Cramon, 2004). ERP studies further revealed that error-related components generated within ACC peak 50–100 msec postresponse onset when the inappropriateness of a response is detected (Dikman & Allen, 2000; Gehring, Goss, Coles, Meyer, & Donchin, 1993). Although still debated, current views hold that error-related activity is elicited by comparison mechanisms between the expected versus actual response outcome (Carter & van Veen, 2007).

Prominent models suggest that, in the case of an error, performance monitoring mechanisms supported by ACC trigger the engagement of antero-lateral prefrontal regions, notably including the dorsolateral pFC (DLPFC). In turn, these areas would mediate behavioral adjustments (e.g., Botvinick, Braver, Barch, Carter, & Cohen, 2001; see also Kerns et al., 2004). Supporting the role of ACC–DLPFC interactions in behavioral adjustment, the activity of ACC has been found to predict both the magnitude of subsequent pFC involvement and the extent of post-error slowing (PES; Kerns et al., 2004; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004).

A recent account for PES effects assumes that response speed decreases because participants need to refocus attention to the task following the distraction (Nunez Castellar, Kuhn, Fias, & Notebaert, 2010; Notebaert et al., 2009) or the increase in arousal induced by the occurrence of infrequent, unexpected error trials (Carp & Compton,

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2009; Taylor, Stern, & Gehring, 2007). Alternative, nonexclusive hypotheses advance that PES merely reflects a switch to more conservative response modes, increasing the probability of making a correct response on subsequent trials by favoring accuracy over response speed (Holroyd, Yeung, Coles, & Cohen, 2005; Botvinick et al., 2001). Compatible with these assumptions, converging evidence documents the involvement of DLPFC in modulating the allocation of attention (MacDonald et al., 2000) and in modulating the level of top–down executive control engaged in resolving a task (Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004).

The studies reviewed above demonstrate that errors impact behavioral responses to the subsequent stimulus mediated by interaction between error detection mechanisms comprised within ACC and the consequent increase in executive control or attentional modulation driven by the DLPFC. However, how these processes act on the neurophysiological processing of subsequent stimuli to shape behavior remains unclear.

Recent models of inhibitory control suggest that participants adopt an automatic, controlled response mode once stimulus–response mapping rules are learned. Automatic response mode concerns both responses to go trials and inhibition of motor responses to no-go trials (engagement of no-go goals) and involves a feedforward control of stimulus–response mapping by parieto-prefrontal executive networks over the very initial stages of sensory integration (Manuel, Grivel, Bernasconi, Murray, & Spierer, 2010; Verbruggen & Logan, 2008; Logan, 1988; Shiffrin & Schneider, 1977). As it does not rely solely on slow top–down inputs from frontal executive modules, an automatic response mode allows optimal go/no-go performance consisting in reduced RT to go stimuli while keeping low the rate of false alarms (FAs; Kenner et al., 2010; Manuel et al., 2010). According to this model, it could be predicted that the detection of errors would induce a switch from automatic to more controlled forms of inhibition and increase the level of top–down executive control, in turn slowing down responses.

Most of the previous studies focused on the neural correlates of error detection (i.e., processes related to the commission of the error) and correlated it with subsequent performance and behavioral adjustments (e.g., Kerns et al., 2004; Ridderinkof, Ullsperger, et al., 2004). Consequently, previous literature did not directly distinguish between error detection mechanisms and subsequent behavioral adjustments (e.g., Fiehler, Ullsperger, & von Cramon, 2004; Garavan et al., 2002). For example, Garavan et al. (2002) assessed the brain mechanisms of behavioral adjustments but did not directly focus on how the following stimulus was processed. As another example, Fiehler and colleagues (2004) aimed at distinguishing between error detection and correction. Participants were separated in two groups and were asked to either immediately correct their errors or not. Because they were asked to immediately correct their errors and because error detection precedes error correction in both cases, it seems difficult to evaluate the specific network implicated in behavioral adjustments. However, to our knowledge, only few functional studies on the neural correlates of post-error behavioral adjustment directly addressed how the detection of error affects the processing of subsequent stimuli. Using a stop signal task, Li et al. (2008) examined the brain responses to go trials as a function of the performance to a previous stop stimulus. Their results suggest a role for prefrontal areas, notably the right ventrolateral prefrontal area, in PES. Reinforcement learning studies have also pointed out associations between activity in prefrontal areas and associative learning (Brown & Braver, 2005; Nieuwenhuis, Holroyd, Mol, & Coles, 2004; Holroyd & Coles, 2002), and more specifically, this literature reported associations between error-related activity in pFCs and immediate changes in post-error behavior (Hester, Murphy, Brown, & Skilleter, 2010; Hester, Barre, Murphy, Silk, & Mattingley, 2008; Frank, Woroch, & Curran, 2005; Frank, Seeberger, & O'Reilly, 2004). However, the low temporal resolution of fMRI technique used in their study did not allow for disentangling the precise dynamics of brain mechanisms underlying post-error behavioral adjustments.

To resolve how errors impact the processing of subsequent stimuli to shape behavior, we contrasted electrical neuroimaging analyses of auditory-evoked potentials (AEPs) to stimuli as a function of response performance to the preceding go stimulus recorded during the completion of a speeded auditory spatial go/no-go task, generating a 2×2 design with "preceding performance" (fast hit [FH], slow hit [SH]) and stimulus type (go, no-go) as within-subject factors.

EEG investigations of error-related processes are typically analyzed using response-locked ERPs, notably because error detection processes manifest in time relative to the error commission rather than to the stimulus presentation. Most of the literature focusing on error detection provides convergent evidence for the importance of response-locked error processes during the postresponse period including, for example, the error-related negativity (ERN), N2/P3 components (Dimoska, Johnstone, & Barry, 2006; Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Falkenstein, Hoormann, & Hohnsbein, 1999; Falkenstein, Koshlykova, Kiroj, Hoormann, & Hohnsbein, 1995; Gehring et al., 1993). The preresponse period has also been shown to comprise indices of FA, indicating that error-related processes manifest before the actual error commission (Pourtois, 2011). However, this study does not focus on error-related processes per se but in how error detection impacts the processing of subsequent stimuli and in turn shapes behavioral adjustments. Therefore, we time-locked the ERP to stimulus onset.

We expect SHs to be processed as error and induce behavioral adjustments for three reason: (i) emphasis was explicitly put on response speed over accuracy, (ii) participants were continuously informed of whether they were too slow by a negative feedback following SHs, and (iii)

SHs were considered as error in the calculation of the global accuracy provided to participants after each trial. In addition, we assessed whether SH induced the typical ERN by averaging response-locked ERP to SH and FH. The former condition indeed showed an ERN, further supporting that SH can be considered as errors in our study. This assumption will be controlled by evaluating if SHs induce PES, that is, the typical post-error behavioral adjustment pattern.

METHODS

Participants

Ten healthy volunteers participated in the study (all men, all right-handed; Oldfield, 1971), aged 22–39 years (mean = 30.10 years, *SD* = 1.53 years). Each participant provided written, informed consent to participate in the study. No participant had a history of neurological or psychiatric illness, and all reported normal hearing. All procedures were approved by the ethics committee of the Faculty of Biology and Medicine of the CHUV and University of Lausanne.

Stimuli

Auditory stimuli were 150 msec noise bursts (200–500 Hz band-pass filtered, 5 msec rise/fall, 44.1 kHz sampling) lateralized by means of a right- or left-ear leading interaural time difference of 770 μsec, which led to perceived lateralization of ca. 80° from the central midline (Blauert, 1997). The sounds were presented via insert earphones (ER-4P; Etymotic Research, Elk Grove Village, IL) at a level judged comfortable by the participant.

Procedure and Task

This study is based on a reanalysis of the data reported in Manuel et al. (2010). Participants underwent an auditory spatial go/no-go task, in which they had to respond as fast as possible via a manual response box button to left-lateralized sounds (go stimuli, hereafter termed LG) and to withhold responses to right-lateralized sounds (no-go stimuli, RNG).

Throughout the experiment, participants were seated in an electrically shielded and sound-attenuated booth in front of a 19-in. LCD screen. Stimulus delivery and response recording were controlled using E-Prime 2.0 (Psychology Tools, Inc., Pittsburgh, PA). Each trial started with the presentation of a visual cue (centrally presented gray cross on a black background) of a randomly determined duration ranging from 1000 to 1900 msec. At the same time that the cross was turned off, the LG or RNG sounds were presented and the time window during which response were recorded was open. LG and RNG trials were presented with an equal probability of .5.

The go/no-go task was divided into three experimental sessions. Each session started with a calibration block of 16 randomly presented trials (8 LG and 8 RNG), followed by two test blocks each of 80 randomly presented trials (40 LG and 40 RNG). The calibration blocks were used to individually adjust the task difficulty and to maintain time pressure across the whole experiment. This was accomplished in the following way. During each calibration phase, the mean RT to LG trials was calculated on-line and used to determine the participant's RT threshold, which was set slightly below current response speed (i.e., calculated as 80% of the mean RT from the calibration block). During the test block, a go-response RT was considered as correct if it was below the 80% RT threshold of the immediately preceding calibration phase (FH). Otherwise, a feedback screen indicating "too late!" was displayed immediately after the go-response (SH). The instructions emphasized the speed of response over accuracy. SHs and FA were considered as errors in the calculation of the global feedback on performance displayed continuously on the top of the screen, such that the participants were also aware when they responded correctly. The global feedback indexing mean performance consisted of the cumulated accuracy expressed in percent correct. The index of mean performance was updated during the intertrial interval, immediately after the feedback on response speed for SH trials. No visual feedback on response speed was displayed after FHs or FAs (i.e., a response to a no-go stimulus; see Vocat, Pourtois, & Vuilleumier, 2008, for a similar procedure).

Participants were not informed about this thresholding procedure. The whole go/no-go training session included 528 stimuli ([160 stimuli in the test block + 16 stimuli in the calibration block] × 3 sessions = 528 stimuli) and lasted for ca. 35 min. After the completion of each session, a rest period of 10 min was provided to participants.

EEG Acquisition and Preprocessing

Continuous EEG was acquired at 1024 Hz through a 128-channel Biosemi ActiveTwo system (Biosemi, Amsterdam, Netherlands) referenced to the CMS-DRL ground (which functions as a feedback loop driving the average potential across the montage as close as possible to the amplifier zero). EEG data preprocessing and analyses were conducted using Cartool (sites.google.com/site/fbmlab/Cartool.htm; Brunet, Murray, & Michel, 2011). EEG epochs from 146 msec prestimulus to 146 msec poststimulus onset (i.e., 150 data points before and 150 data points after stimulus onset) were averaged, for each participant, for go and no-go trials following performance at preceding go stimuli, generating a 2 × 2 within-subject design with factors of "Preceding Performance" (SH, FH) and "Stimulus" (go vs. no-go; Figure 1). As we were interested in the processing of the stimulus as a function of previous performance, we locked the ERPs and focus our analyses to the stimulus and not to the response. Moreover, because processes occurring after 150 msec post-S2 onset were differentially contaminated by the initiation of the motor response as a function of factor stimulus (go but not no-go stimuli

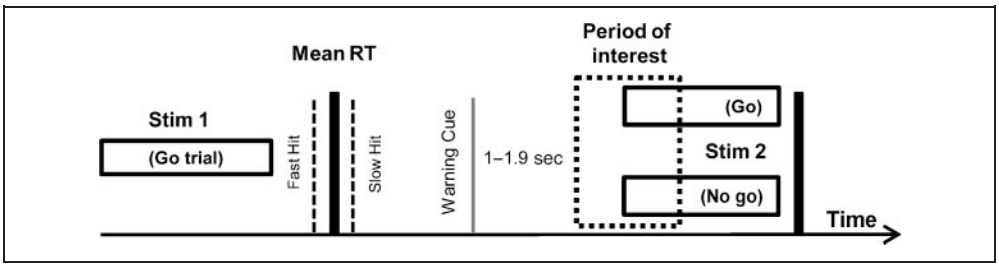

Figure 1. Experimental design. Each participant completed a 35-min go/no-go task. The period of interest comprises the processing of Stimulus 2 as a function a preceding performance (fast or slow).

were followed by a motor responses), we restricted our analyses with the initial 146 msec poststimulus onset period (mean RT was ca. 260 msec in our study [see Results section] and minimal latency of response initiation in the motor cortex occurs ca. 100 msec before the execution of the button press [Thorpe & Fabre-Thorpe, 2001]). We would note, however, that several lines of evidence report that response-related cortical motor activity already manifest 200–500 msec before response onset as, for example, the lateralized readiness potential, a measure of selective response preparation (Gratton, Coles, Siveraag, Ericksen, & Donchin, 1988; Kutas & Donchin, 1980). Although motor-related activity could have occurred during our period of interest, restraining our analyses to the first 150 msec lowered the probability of a contamination of our effects by motor responses. In addition, such contamination would have modulated the main effect of stimulus but not the main effect of preceding performance or the interaction term. In turn, this possible confound would not invalidate our results.

In addition to a ±80 μV artifact rejection criterion, EEG epochs containing eye blinks or other noise transients were removed after visual inspection. Before group averaging, data at artifact electrodes from each participant were interpolated using 3-D splines (Perrin, Bertrand, & Pernier, 1987). Data were band-pass filtered (0.18–40 Hz) and recalculated against the average reference. By removing slow drifts at the single epoch level, the low-pass filter resulted in a baseline correction on the whole epoch. Because one factor involved performance preceding stimulus onset, prestimulus differences could have been expected. Therefore, we did not apply a prestimulus baseline correction on our data.

The average number (±*SEM*) of accepted epochs was 57 ± 5.3 for the go preceded by an SH, 53.6 ± 5.5 for the go preceded by an FH, 62 ± 5.6 for the no-go preceded by an SH, and 53.3 ± 4.9 for the no-go preceded by an FH conditions. These values did not statistically differ ($p > .16$), ruling out that our effects followed from differences in signal-to-noise ratios across conditions.

Topographic Patterns Analyses

Topographic analyses were performed to determine whether the configuration of intracranial generators changed across either or both factors (i.e., preceding performance and stimulus type). These methods have been detailed elsewhere and have many analytical and interpretational benefits over canonical AEP waveform analyses (Tzovara, Murray, Michel, & De Lucia, in press; Murray, Brunet, & Michel, 2008). We provide only the essentials here. Major impetuses for the use of the present analyses were the ability to circumvent interpretational issues because of the reference-dependent nature of AEPs and to differentiate effects arising from topographic modulations from effects owing to changes in response strength. Moreover, the multivariate analyses used here require no selection either of the electrodes or periods of interest which are two major sources of potential bias in the statistical analysis of ERPs (Tzovara et al., in press). Still, we would be remiss to not acknowledge that a period of interest was defined by the experimenters during the act of epoching the continuous EEG into peristimulus intervals for signal averaging and ERP calculation. Likewise, parameters such as filtering and artifact rejection criteria were likewise selected by the experimenters.

The most dominant scalp topographies appearing in the AEPs of the group-averaged ERPs from each condition over time were identified with a *k*-means cluster analysis (Pascual-Marqui, Michel, & Lehmann, 1995). This approach is based on the observation that evoked potential topographies do not change randomly but rather remain for a period in a certain configuration and then switched to a new stable configuration (e.g., Murray et al., 2008; Michel et al., 2004). The optimal number of clusters to describe the data set is identified using a modified Krzanowski–Lai criterion (Tibshirani, Walther, Botstein, & Brown, 2005). These steps are all a hypothesis generation tool that is then statistically evaluated using single-subject data. Differences in the pattern of maps observed between conditions in the group-averaged data were tested by calculating the spatial correlation between these "template" maps from the group-averaged data and each time point of single-subject data from each experimental condition (referred to as "fitting"). For this fitting procedure, each time point of each AEP from each subject was labeled according to the map with which it best correlated spatially (see Murray et al., 2008; Brandeis, Lehmann, Michel, & Mingrone, 1995). The output of fitting is a measure of relative map presence in milliseconds, which indicates the amount of time over a given interval that each map that was identified in the group-averaged data best accounted for the response from a given individual subject and condition.

Electrical Source Estimations

We estimated the sources in the brain using a distributed linear inverse solution and the local autoregressive average (LAURA) regularization approach (Grave de Peralta, Gonzalez-Andino, & Gomez-Gonzalez, 2004; Grave de Peralta, Gonzalez-Andino, Lantz, Michel, & Landis, 2001; also Michel et al., 2004, for a comparison of inverse solution methods). LAURA selects the source configuration that better mimics the biophysical behavior of electric fields (i.e., activity at one point depends on the activity at neighboring points according to electromagnetic laws). Homogenous regression coefficients in all directions and within the whole solution space were used. For the lead field calculation, the Spherical Model with Anatomical Constrains method was applied (Spinelli, Andino, Lantz, Seeck, & Michel, 2000). This method first transforms the individual MRI to the best-fitting sphere using homogeneous transformation operators. It then determines a regular grid of 3005 solution points in the gray matter of this spherical MRI and computes the lead field matrix using the known analytical solution for a spherical head model with three shells of different conductivities as defined by Ary, Darcey, and Fender (1981).

To confirm and extend the above-described topographic analyses in the sensor space, we conducted a parallel analysis in the brain space independently to the topographic pattern analyses. Intracranial sources were estimated for each participant and condition and then statistically compared at each node level between conditions using the same within-subject design as in the topographic pattern analysis. Time-point wise 2 × 2 ANOVAs were computed with factors Preceding Performance and Stimulus for the 3005 solution points. A spatial criterion of a minimum of eight contiguous points and a duration criterion of 11 time samples was applied in the statistical parametric mapping procedure.

RESULTS

Behavioral Results

The performance with go stimuli was analyzed as a function of the performance on the preceding stimulus (S1), yielding two conditions for responses to go S2: those preceded by an SH or FH response to S1. We calculated PES effects as the number of SH following FH versus the number of SH following SH. Whether a given RT to go stimuli was considered as an SH or FH depended on its value relative to the RT threshold calculated during the RT calibration block that participants underwent before each test block. Because the threshold was determined for each participant individually and adjusted dynamically for each block of trials, we assume that the RT relative to individually determined response speed threshold is not the most sensitive index of response speed in our study. The mean absolute RTs for SH and FH occurrence for the four possible types of stimulus sequence (FH–FH, SH–FH, FH–SH, SH–SH) are displayed in Table 1. According to classical PES formula (difference between postcorrect trial RT and post-error trial RT), we report the differences in RT. RT for FH following FH or SH did not significantly differ ($t(9) = -0.63, p = .54$) nor did RT for SH following FH or SH differ ($t(9) = 0.59, p = .56$). However, as stated above, because of the individual calibration procedure implemented in our study and the separation of the RTs in FH and SH groups, the most relevant index of PES in our experimental paradigm is the relative number of FH and SH following accuracy at Stimulus 1.

The feedback "too late" was provided to the participants following SH. After an SH, participants committed more SH than FH ($t(9) = 4.16; p < .005$), replicating well-established PES effects (e.g., Ridderinkhof, Ullsperger, et al., 2004) and supporting that SH were indeed considered as error in our paradigm. After FHs, participants tended to commit more FH than SH, although not in a significant way ($t(9) = 1.66; p = .13$). These additional data are provided in Table 2.

The performance on no-go stimuli was analyzed as a function of the performance to the preceding stimuli. The percentage of FAs after an FH or after an SH did not statistically differ (6.39 ± 1.03% [7/109.4] and 6.75 ± 1.68% [8.5/125.9], respectively; $t(9) = -0.20; p = .84$). The absence of significant differences in FA as a function of the preceding performance likely followed from the fact that emphasis was put on speed over accuracy.

Electrical Neuroimaging Results

Topographic Pattern Analysis

K-means clustering was performed on the AEPs to identify the pattern of predominating topographies ("maps") of the electric field at the scalp in the cumulative group-averaged data. The output of the topographic pattern analysis is displayed in Figure 2A (see also exemplar AEP waveforms (C3 electrode)). The global explained variance of the results of the cluster analysis was 92.84%. This topographic pattern analysis identified the same sequence of stable maps for trials from the correct and error conditions and LG and RNG trial types with the exception of two

Table 1. Detailed Behavioral Effects of SH and FH Commission: RTs

Go1 Type–Go2 Type	*Go1 (msec)*	*Go2 (msec)*
FH–FH	213.4 ± 15.5	217.6 ± 16.6
FH–SH	211.6 ± 17.5	302.5 ± 27.9
SH–FH	316.6 ± 23.6	214.3 ± 19.2
SH–SH	301.6 ± 29.5	307.9 ± 32.5

Mean and *SEM* of RTs before and following SH or FH commission (in msec).

Table 2. Detailed Behavioral Effects of SH and FH Commission

Preceding Go Stimuli	*FH (n)*	*SH (n)*
FH	32.1 ± 4.5	24.7 ± 2.2
SH	17.1 ± 1.1	42.2 ± 5.5

Mean number and *SEM* of SHs or FHs as a function of previous performance.

periods. Over these periods, distinct sets of maps were observed first as a function of preceding performance and then as a function of the stimulus. The fitting procedure was then applied to the single-subject data from each condition to calculate the number of time points for each of the maps identified over the periods of topographic modulation observed in the group-averaged AEPs. This generated a quantification of how well each map accounted for an individual participant's AEPs over a given time interval. In the first time window (76–111 msec), there was a significant interaction between preceding performance and map ($F(1, 9) = 11.74$; $p < .01$; Figure 2B). In the second time window (113–146 msec), a significant interaction between stimulus and map was observed ($F(1, 9) = 4.84$; $p < .05$; Figure 2C). No other main effects or interactions were statistically reliable over either period.

Although several studies showed prestimulus differences as a function of accuracy (Pourtois, 2011; Hajcak, Nieuwenhuis, Ridderinkhof, & Simons, 2005), we did not take into account performance at the trial following FH or SH, representing a possible confound in the interpretation of our results. We did not sort trials as a function of performance because go and no-go stimuli were taken in account for the factor stimulus and that performance on these two trial types cannot not be assessed similarly (e.g., error to no-go trial are FA and error for go trials are too slow), the same rejection criterion based on performance cannot be applied to both trials type. Thus, the absence of effect during the prestimulus period could have resulted from a differential activity before successful versus unsuccessful trial that was not controlled in our study.

Source Estimations

A timeframe wise 2 × 2 ANOVA, with factors of Preceding Performance (SH, FH) and Stimulus (LG, RNG) was performed for each of the 3005 solution points. This analysis revealed a significant ($p < .05$) main effect of the Preceding Performance over the 104–126 msec period ($F(1, 9) > 5.12$; $p < .05$) and a main effect of Stimulus over the 122–146 msec interval ($F(1, 9) > 5.12$; $p < .05$), but no interaction between these factors at any point in time. These periods and the sequence of main effects corresponded to those observed in the above analyses of the surface-recorded AEPs. The slight differences between the period of the effects revealed by the topographic and sources analyses could follow from the fact that data were reduced in time by the clustering procedure applied during the temporal segmentation of the ERPs but not during the time-wise analyses of the inverse solutions (e.g., Murray et al., 2008). The topographic pattern analyses thereby relied on a reduced number of periods of stable

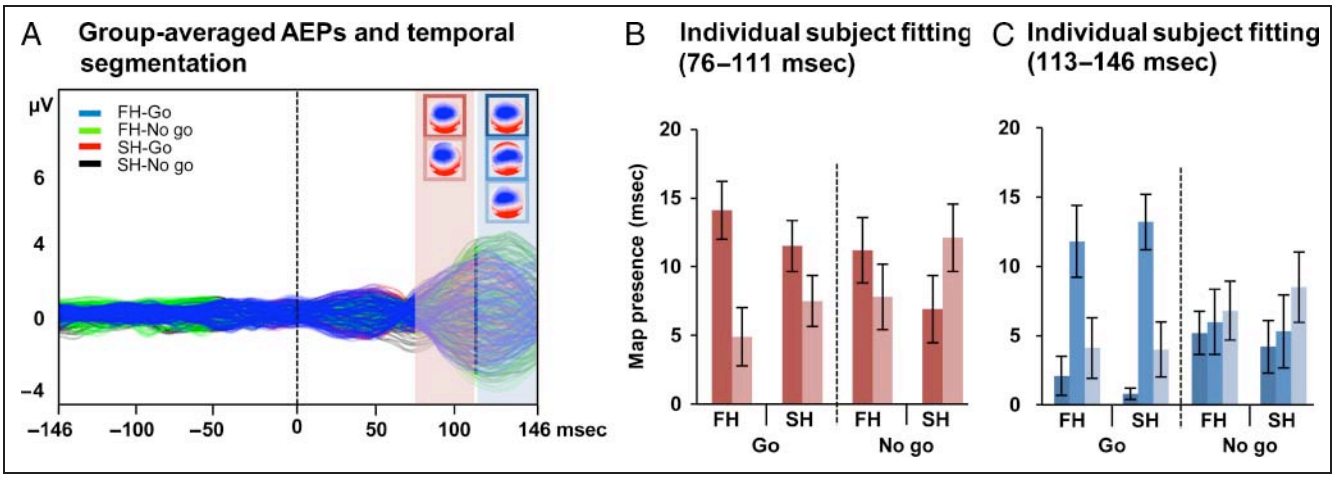

Figure 2. (A) The AEP in response to go (blue trace) and no-go (black) stimuli preceded by SHs and go (red) and no-go (green) preceded by FHs are displayed in microvolts as a function of time. Topographic pattern analyses in the group-averaged AEPs identified two periods of stable electric field topography where multiple maps were differentially engaged as a function of the experimental conditions: 76–111 msec (framed in red) and 113–146 msec (framed in blue). All topographies (i.e., maps) are shown with the nasion upward and left scalp leftward. The reliability of this observation at the group-averaged level was then assessed at the single-subject level using a spatial correlation fitting procedure (see Methods). (B) Over the 76–111 msec poststimulus period, different maps (framed in dark and light red) described AEPs in response to stimulus (go/no-go) as a function of preceding performance (FH/SH). There was a significant main effect of Preceding Performance. Error bars indicate *SEM*. (C) Over the 113–146 msec poststimulus period, different maps again (framed in dark and light blue) described AEPs in response to stimulus (go/no-go) as a function of preceding performance (FH/SH). Results showed a significant main effect of factor Stimulus. Error bars indicate *SEM*.

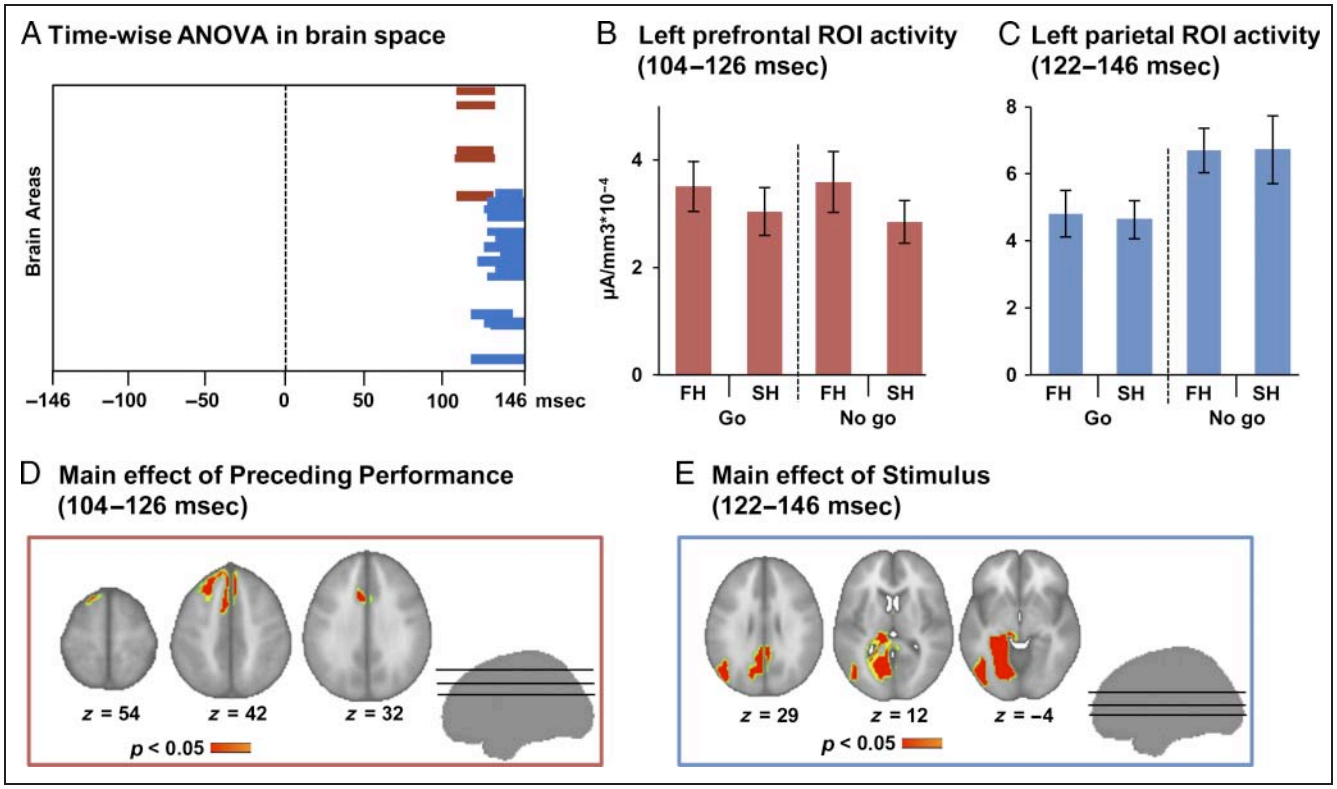

Figure 3. (A) Time-wise ANOVA in brain space is displayed as a function of time. The *y* axis shows the brain space merged in 80 ROIs (AAL space), organized from frontal (top) to occipital (bottom) brains areas. Red bars indicate significant main effect of Preceding Performance. Blue bars represent a significant main effect of Stimulus. (B) Follow-up analyses on the mean scalar value of the prefrontal ROI revealed a decrease in left pFCs following an SH relative to an FH. (C) Follow-up analyses on the mean scalar value of the parietal ROI revealed a decrease in left parietal cortices for the processing of go stimulus relative to no-go. (D) The main effect of preceding performance included a prefrontal cluster comprising the ACC and the DLPFC. (E) The main effect of stimuli included a parietal cluster comprising the precuneus, the posterior cingulate cortex, the parahippocampal gyrus, the fusiform gyrus, the lingual gyrus, the middle and inferior occipital gyri, the middle temporal gyrus, and the angular gyrus. Brain slices are displayed in *z*-coordinates in the MNI space.

microstate as compared with the source analyses, which was performed at each time frame. Figure 3A displays LAURA distributed source estimations averaged over the post-stimulus period when the timeframe wise ANOVA showed significant main effects of factor Preceding Performance and factor Stimulus. To facilitate the visualization of the temporal dynamics of the effects in Figure 3A, we down-sampled the 3005 solution points into the 80 ROIs of the AAL space (Tzourio-Mazoyer et al., 2002). The AAL ROIs are arranged from anterior (up) to posterior (down) regions along the *y* axis. The brain regions showing the main effect of factor Preceding Performance comprised ACC and DLPFC (Figure 3D) and the main effect of Stimuli at the left parietal cluster comprising the precuneus, the posterior cingulate cortex, the parahippocampal gyrus, the fusiform gyrus, the lingual gyrus, the middle and inferior occipital gyri, the middle temporal gyrus, and the angular gyrus (Figure 3E).

To determine the direction of these effects, AEPs for each participant and each experimental condition separately were first averaged across the period of interest to generate one data point per participant and experimental condition. Source estimations were then calculated, and the scalar value of each solution point comprised within the ROI, showing the main effect of Preceding Performance as well as Stimulus, were extracted and averaged separately for each subject and condition. The main effect of Preceding Performance followed from a significant decrease in the activation strength of the left prefrontal ROI for SH as compared with FH followed either by a go or no-go stimulus type (Figure 3B). The main effect of Stimulus followed from a lower activation of the left parietal ROI for go than no-go stimuli in both FH and SH conditions (Figure 3C).

To determine whether and how the prefrontal and parietal ROIs were functionally coupled, we performed a correlational analysis. The correlations were performed between factor Preceding Performance (FH or SH) and factor Stimulus irrespective of stimulus type, that is, activity of the parietal ROI were averaged between the go and no-go condition before the calculation of the correlations. This analysis revealed a significant correlation between prefrontal cluster and parietal clusters when the preceding performance was FH ($r(8) = 0.72$, $p < .02$). There was only a nonsignificant tendency for such a correlation in the SH condition ($r(8) = 0.58$, $p = .07$). The activity of prefrontal and parietal clusters is functionally coupled after FH, but not after the participant made an SH.

Correlational analysis showed significant negative correlations between the parietal ROIs activity and log-transformed RT both at FH and SH ($r(8) = -0.67, p < .05$; $r(8) = -0.65$, $p < .05$, respectively). These results indicate that the more the parietal ROI was active after an FH or an SH, the more the participants slowed down their responses.

DISCUSSION

Behaviorally, we replicated previous evidence for PES effects (e.g., Li et al., 2008). As compared with FH, SHs, considered as errors in our paradigm, induced a significant increase in the number of SH. We contrasted electrical neuroimaging responses to go and no-go stimuli as a function of the performance to the preceding stimuli. Our results showed that AEPs modulated topographically as a function of whether participants made an error or not on the preceding trial 70–110 msec post-onset, indicative of the engagement of distinct configurations of intracranial generators. Then AEP modulated topographically as a function of stimulus type 110–150 msec. A second level of time-wise statistical analyses conducted in the brain space independently to the topographic pattern analyses revealed an identical sequence of effects. Source estimations revealed a significantly stronger activity within prefrontal regions to go and no-go stimuli following FH than SH trials over the 100–120 msec poststimulus onset. This effect was followed by a stronger response of parietal areas to the no-go than go stimulus type 120–140 msec independently of preceding performance. This pattern of results suggests that errors in a speeded go/no-go task modulate early, low-level integration of the following stimuli, in turn influencing subsequent inhibitory proficiency. By capitalizing on prior but not current performance to contrast brain activity to trial processed with low versus high inhibitory proficiency, we were able to assess the effect of factor "stimulus type" in our design, that is, including no-go trials for which no behavioral responses were measured. This approach allowed to assess the effect of inhibitory proficiency in conditions where responses had to be elicited or not.

As go/no-go performance on a given trial determines inhibitory proficiency at the subsequent trial (i.e., response speed decrease following errors; Lawrence, Luty, Bogdan, Sahakian, & Clark, 2009; Rabbit, 1966), by contrasting AEPs to the auditory stimuli as a function of the preceding performance, we actually contrasted brain responses to the stimuli in a situation in which efficient versus inefficient inhibitory control processes were engaged. Accordingly, we hypothesize that the main effect of preceding performance at 120 msec poststimulus onset reflects distinct response modes, allowing either fast or slow inhibitory control.

Recent models of inhibitory control suggest that optimal go/no-go performance is achieved by adopting an automatic form of inhibition, involving a feedforward control of stimulus–response mapping by parieto-prefrontal executive networks over the very initial stages of sensory integration (Manuel et al., 2010; Verbruggen & Logan, 2008; Logan, 1988; Shiffrin & Schneider, 1977). An automatic response mode would allow for increasing the speed of go/no-go decisions by shortcutting inputs from slow, controlled top–down executive modules (Kenner et al., 2010; Manuel et al., 2010). We would note that the term "automaticity" as used here not only refers to automatic responses to go stimuli because of the response prepotency induced by task instruction but also to the fact that no-go goals consisting in inhibiting motor response are no more solely supported by controlled processes once stimulus–response mapping rules are learned. Because the stimulus–response mapping rule was straightforward in our study and that emphasis was put on speed rather than on accuracy (negative feedback was provided after two SHs, and the later trials were counted as errors), participants were likely engaged in such automatic response mode during most of the trials. Further supporting that participants actually responded on the basis of speed rather than accuracy, response speed but not accuracy was modulated by practicing the go/no-go task in this study (Manuel et al., 2010). RTs for FH corresponded to the minimal physiological response speed in such tasks (Manuel et al., 2010) corresponding to asymptotic RT of approximately 200 msec.

However, the detection of errors would have broken down the engagement of automatic inhibition and increased the level of top–down executive control, in turn slowing down responses.

Supporting this hypothesis, we showed that the effect of preceding performance manifesting as topographic modulation over the 100–120 msec poststimulus onset followed from lower activity within prefrontal regions after SH than FH. This finding fits well with traditional views holding that error detection modulates dorsomedial pFCs comprising top–down executive mechanisms involved in subsequent behavioral adjustment (e.g., Li et al., 2008; Kerns et al., 2004; Ridderinkhof, van den Wildenberg, et al., 2004; Botvinick et al., 2001). For instance, Kerns et al. (2004) showed that the greater pFC was activated following errors, the greater were PES effects. In addition, animal data indicate that DLPFC activity reflects conflict level and maintain information about previous conflict in memory (Mansouri, Buckley, & Tanaka, 2007).

However, the direction of our effect contrasts with previous evidence for an increased prefrontal activity accompanying the engagement of top–down executive control following error detection (Kerns et al., 2004; Garavan et al., 2002). This apparent discrepancy might follow from differences in the period of interest examined in these studies. Our effect manifested during the processing of the subsequent stimuli and not immediately after the detection of the error, as investigated in previous literature (Ullsperger & von Cramon, 2001; Falkenstein et al., 2000). Supporting this explanation, differential activation patterns of pFC during error detection and subsequent processing have indeed been shown when these

phases were analyzed as separate within-trial processes. For instance, Chevrier and Schachar (2010) showed deactivation of medial pFC during error detection but increased activity in the same regions during subsequent PES. Activity within these structures was also found to decrease during cognitive tasks requiring mental effort or goal-directed behaviors (Tomasi, Ernst, Caparelli, & Chang, 2006; Greicius & Menon, 2004; Raichle et al., 2001). Alternatively, medial versus lateral pFCs have been shown to dynamically adjust their relative activity, depending on task demand, which could explain discrepancies between activation versus deactivation patterns of these areas between previous literature and our results. Medial pFC consistently shows increased activity during rest or low-demand across a wide range of tasks, compared with high demanding tasks (Mazoyer et al., 2001; Shulman et al., 1997; see also Hester & Garavan, 2004, for a deactivation in the left medial frontal gyrus before stopping in a response inhibition task). This default mode network is typically inversely correlated with lateral prefrontal regions, suggesting there to be a "dynamic equilibrium" between medial and lateral prefrontal regions (Greicius, Krasnow, Reiss, & Menon, 2003). The engagement in complex cognitive processes would be supported by a reallocation of neural resources from default mode medial areas to lateral prefrontal regions (Greicius & Menon, 2004).

The issue of a hemispheric specialization of the brain mechanisms supporting inhibitory processes and post-error behavioral adjustment remain debated. Kerns et al. (2004) reported post-error behavioral adjustments to be associated with activity in the right DLPFC. Further evidence also pointed the right DLPFC might contribute to on-line behavioral adjustments by amplifying task-relevant features (King, Korb, von Cramon, & Ullsperger, 2010; Egner & Hirsch, 2005). By contrast, several studies document a role for the left pFC in behavioral adjustment (Garavan et al., 2002; Kiehl, Liddle, & Hopfinger, 2000) and suggest that the left DLPFC would support maintenance of task sets (MacDonald et al., 2000). Garavan et al. (2002) further proposed the left pFC to be mostly activated by tonic inhibitory tasks in which inhibition processes must be sustained over a period rather than phasic inhibitory tasks such as the go/no-go task. Although top–down attentional processes are commonly associated to the left DLPFC (MacDonald et al., 2000), recent research revealed an essential role of the right DLPFC in task preparation (Vanderhasselt, De Raedt, Baeken, Leyman, & D'haenen, 2006; Brass & von Cramon, 2004). A recent review by Vanderhasselt, De Raedt, and Baeken (2009), suggest that the left DLPFC is activated when attentional adjustments are required regarding the processing of upcoming stimulus. Whereas the left DLPFC does not seem to be activated in the presence of conflict in the Stroop task, the right DLPFC is activated in conflict-driven cognitive control. Finally, basic task parameters could also participate in the lateralization of the effects related to behavioral adjustment and inhibitory control. For instance, in our task, the left lateralization of the main effect of Preceding Performance might also follow from the fact that participants responded with their right hand, which could have required the engagement inhibitory processes comprised within the same hemisphere as the motor areas solicited during the task.

That pFCs modulated at a latency of 100–120 msec poststimulus onset as a function of inhibitory proficiency further supports that it may reflect the differential involvement of early-stage forms of inhibition. Previous ERP studies of go/no-go tasks indeed demonstrate that the suppression of prepotent responses by top–down executive modules manifests over processing stages subsequent to initial sensory encoding, around 150–400 msec (Kaiser et al., 2006; Falkenstein et al., 1999; Kiefer, Marzinzik, Weisbrod, Scherg, & Spitzer, 1998).

According to recent hypotheses on the mechanisms mediating PES, the switch between automatic to top–down executive control could have been caused by an attentional modulation. PES has been advanced to follow from the need to refocus attention to the task following distraction induced by the infrequent error trials (orienting hypothesis: Nunez Castellar et al., 2010; Notebaert et al., 2009; Taylor et al., 2007) or error-related increase in arousal (Carp & Compton, 2009). Similarly, King et al. (2010) reported that PES could be because of the interference of the OR with task preparation and stimulus processing. Arguing against this hypothesis, we did not find evidence for modulation in attention-related areas during the prestimulus period (Brass, Derrfuss, Forstmann, & von Cramon, 2005). However, the prestimulus period analyses here were perhaps too short, which prevented to reveal the role of attention in the switch between the automatic versus controlled response mode. In addition, our analyses would not have caught nonphase locked attention-related processes manifesting at the level of oscillatory activity. Previous evidence indeed suggest that modulations in attention, supporting, for example, the anticipation of forthcoming stimuli manifest as an increase in the power of oscillation in the alpha frequency band in the hemisphere contralateral to the attended hemispace (Rihs, Michel, & Thut, 2009; Romei et al., 2008; Thut, Nietzel, Brandt, & Pascual-Leone, 2006). Because go stimuli were always presented in the left hemispace, the participants possibly learned to attend to the left for increasing response speed, yielding a main effect of stimuli during the prestimulus period in oscillatory activity.

Errors constitute a strong negative reinforcement learning signal; in this regard, the effect of error in the processing of subsequent stimuli is interpretable in terms of reflecting changes in associative learning. Interestingly, recent evidence shows that modifications in learned stimulus–response mapping associations depend on error-related activity within medial pFCs when feedback is provided to participants (Hester et al., 2010). This finding indicates that processes related to monitoring and reweighting of

a behavior's value parallel those related to increases in executive control within prefrontal areas following errors; both mechanisms impacting how subsequent stimuli are handled. Because they shape stimulus–response mapping rules, feedback-related learning mechanisms likely participate to plastic brain mechanisms underlying the development of automatic feedforward forms of inhibitory processes developing with go/no-go training as observed in Manuel et al. (2010; see also Verbruggen & Logan, 2008).

Go and no-go stimuli were differentially processed within parietal structures in the period immediately following the main effect of factor Preceding Performance, 120–140 msec poststimulus onset. Importantly, the activity within this parietal cluster positively correlated with the prefrontal clusters following FH but not SHs. We interpret this finding in terms of a facilitation of stimulus–response mapping processes occurring within parietal areas by prefrontal areas supporting fast inhibitory control. The stimulus–response mapping would directly depend on prefrontal areas during automatic response mode, but not in the top–down executive control engaged following errors.

Fronto-parietal circuits have been repeatedly implicated in action planning and initiation, with the degree of interaction between these areas modulating as a function of participants' control over responses (e.g., Pesaran, Nelson, & Andersen, 2008). These reports are in line with our hypothesis for a role of attention in switching between automatic to top–down response modes following errors. When no errors are committed, automatic control of response inhibition would be engaged and supported by a functional coupling between prefrontal and parietal areas. Following errors, however, top–down control would be engaged and this functional interaction would break down. Consistently, Prado, Carp, and Weissman (2010) linked reduced functional connectivity between the prefrontal and parietal cortices with increases in RT during a selective attention task, suggesting that, mediated by attention, the communication between these regions would facilitate response selection (Rushworth, Buckley, Behrens, Walton, & Bannerman, 2007) and action planning (Andersen & Cui, 2009).

Medial parietal regions, notably the precuneus, play a critical role in shifting attention toward relevant stimulus–response associations (Corbetta & Shulman, 2002; Rushworth, Paus, & Sipila, 2001). Moreover, stimulus–response mapping repertoires have been advanced to preactivate within parietal cortices (Barber & Carter, 2005; Ridderinkhof, van den Wildenberg, et al., 2004). Accordingly, during the prestimulus anticipatory period, parietal structures would send signals for increasing alertness and preactivating relevant stimulus–response associations (Barber & Carter, 2005; Astafiev et al., 2003; Rushworth et al., 2001).

Parietal structures are a suitable candidate for comprising stimulus–response mapping mechanisms involved in initiating or inhibiting motor responses based on the spatial attributes of the auditory go and no-go stimuli. Relative to the mean RT in our study, the 120–140 msec interval when main effect of stimulus type manifested corresponds to the period of motor response initiation (at ca. 130 msec post S2 onset, 130 msec before the mean RT (Thorpe & Fabre-Thorpe, 2001). On one hand, parietal structures have been involved in the interfacing between sensory signals and motor command (Andersen, Snyder, Bradley, & Xing, 1997), in the response preparation processes including control of motor planning (Ruge et al., 2005; Brass & von Cramon, 2004) or preparation for movements (Deiber, Ibanez, Sadato, & Hallett, 1996). Supporting these results, we recently demonstrated that parietal areas support learned associations between stimuli and behavioral responses early in the processing of a stimulus in a go/no-go task (Manuel et al., 2010). On the other hand, parietal structures are also involved in discriminating the spatial attributes of the stimuli (Spierer, Murray, Tardif, & Clarke, 2008; Spierer, Tardif, Sperdin, Murray, & Clarke, 2007). Accordingly, we would note that in our study go stimuli were always presented on the left and no-go on the right hemispace. These acoustic differences, coupled with the well-established functional lateralization of auditory spatial processing, could have biased the main effect of stimuli and thus limit the related interpretations. Furthermore, we cannot rule out from our data that participant paid more attention to the left hemispace from where go stimuli came and therefore that the main effect of stimuli reflected differential attention to go and no-go stimuli in addition to their acoustic difference. Further investigations, involving control of acoustic differences between go and no-go stimuli by, for example, reversing the SR mapping rule in half of the experiment would be necessary to disentangle this issue.

Collectively, our results support a model of executive control wherein either feedforward/automatic or top–down/controlled forms of inhibition can be engaged to resolve go/no-go tasks. In the former, stimulus response mapping is directly dependent on the activity of prefrontal executive module activated over the initial stage of cortical integration of the stimuli, allowing for fast response inhibition to no-go stimuli and in turn, fast RT to go stimuli. More consciously controlled top–down form of inhibition would instead involve higher-order executive modules activated by attention following error or in situation of new or complex stimulus–response mapping rules (Verbruggen & Logan, 2008). According to this model, PES would reflect a switch from automatic to controlled form of inhibition induced by errors.

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APPENDIX C

Manuel AL, Radman N, Mesot D, Chouiter L, Clarke S, Annoni JM, Spierer L (2012b) Inter- and intra-hemispheric dissociations in ideomotor apraxia: a large-scale lesion-symptom mapping study in subacute brain-damaged patients. Cerebral Cortex, *in press.*

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Inter- and Intrahemispheric Dissociations in Ideomotor Apraxia: A Large-Scale Lesion–Symptom Mapping Study in Subacute Brain-Damaged Patients

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Pantomimes of object use require accurate representations of movements and a selection of the most task-relevant gestures. Prominent models of praxis, corroborated by functional neuroimaging studies, predict a critical role for left parietal cortices in pantomime and advance that these areas store representations of tool use. In contrast, lesion data points to the involvement of left inferior frontal areas, suggesting that defective selection of movement features is the cause of pantomime errors. We conducted a large-scale voxel-based lesion–symptom mapping analyses with configural/spatial (CS) and body-part-as-object (BPO) pantomime errors of 150 left and right brain-damaged patients. Our results confirm the left hemisphere dominance in pantomime. Both types of error were associated with damage to left inferior frontal regions in tumor and stroke patients. While CS pantomime errors were associated with left temporoparietal lesions in both stroke and tumor patients, these errors appeared less associated with parietal areas in stroke than in tumor patients and less associated with temporal in tumor than stroke patients. BPO errors were associated with left inferior frontal lesions in both tumor and stroke patients. Collectively, our results reveal a left intrahemispheric dissociation for various aspects of pantomime, but with an unspecific role for inferior frontal regions.

Keywords: frontal, ideomotor apraxia, lesion, pantomime, parietal, voxel-based lesion–symptom mapping

Introduction

Pantomime of object or tool use is the act of pretending to use an object by adopting the same limb configurations and producing the same sequences of movements as if the object were actually held and used. Pantomime of object or tool use is the act of pretending to use an object by adopting the same limb configurations and producing the same sequences of movements as if the object were actually held and used. Within the model of praxis by Rothi et al. (1991, 1997), pantomime to verbal command is distinguished from other types of motor productions based on the fact that it neither requires a visual analysis of the gesture to be produced nor a comparison between the visual input with a lexicon of action (as would be the case for, e.g., imitation of new or familiar gestures). Rather, the analysis of the auditory/verbal command is directly followed by the selection of the spatiotemporal attributes of the gesture to be performed from an action output lexicon and the programming and implementation of the motor action (see also Peigneux and Van der Linden 2000). Because the production of pantomimes involve semantic, executive, and spatial/configural level of motor processing (to respectively understand the gestures, select the relevant movements representing the action, and represent accurately the relationships between the body parts involved in the movement and of how they interact with the object (Goldenberg 2009)), pantomime constitutes a sensitive task to detect ideomotor apraxia following a brain lesion (Heilman and Rothi 1993). In the current article, we refer to "ideomotor apraxia" using the definition proposed by Rothi et al. (1991, 1997): "an impairment in the timing, sequencing, and spatial organization of gestural movements" (Rothi et al. 1991).

Starting from the seminal hypotheses of Liepmann (1908) in stroke patients, most prominent models of praxia advance that left parietal areas store the motor representations of tool use guiding action and therefore predict that these structures play a central role in pantomime (Moll et al. 2000; Peigneux et al. 2004). Functional neuroimaging studies corroborate these models by consistently observing correlations between left parietal areas activity and pantomiming (Vingerhoets, Acke et al. 2012, Vingerhoets, Vandekerckhove et al. 2011; see Lewis (2006) for a meta-analysis of activation studies).

In contrast, lesion studies report that accurate pantomime depends on the integrity of left inferior frontal areas (Goldenberg et al. 2007) and less consistently of parietal areas (Kertesz and Ferro 1984; Goldenberg and Hagmann 1997; Peigneux et al. 2000). Although not directly for pantomimes, parietal areas have been involved in ideomotor apraxia (Basso et al. 1985; Haaland et al. 2000; Buxbaum et al. 2007) or coordination of arm movements in ideomotor apraxia (Mutha et al. 2010). Therefore, lesion studies conclude that pantomime critically depends on the selection of a limited, task-relevant set of features among the many features involved in the actual tool use to be mimed (Goldenberg et al. 2007; Goldenberg 2009; Bohlhalter et al. 2011). The disparity between the findings of neuroimaging and lesion approaches about the involvement of parietal regions has been hypothesized to follow from the pantomimes being realized under different conditions in each type of study. Because of the constraints induced by the scanner on participant's movements, the pantomimes require additional spatial transformations of movements to unusual reference frames, which in turn increase the involvement of parietal structures (Andersen et al., 1997; Goldenberg et al., 2007). Rumiati et al. (2004), however, reported an involvement of left parietal areas for the pantomiming of visually presented objects in patients with deficit in the organization of sequences relative to tool use (ideational apraxia), suggesting that these structures might trigger tool use-related motor programs. Pantomime are globally sensitive to left hemisphere lesions (Bickerton et al.

2012), but have been found to be sensitive to lenticular stroke and associated to impaired working memory, suggesting that correct pantomime execution necessitates an efficient lexical route but also a dedicated workplace subserved by subcortical structures (Bartolo et al. 2003). Of note, electroencephalography studies manipulating the production of pantomimes in naturalistic conditions showed evidence for parietal activation in preparing tool-use movements, suggesting that this region is not only involved in spatial transformation, but also in planning tool-related motor actions (Wheaton, Shibasaki et al. 2005; Wheaton, Yakota et al. 2005). During the neuropsychological assessments, the patients produce the movements within a natural body-centered reference frame and with visual feedback (Goldenberg et al. 2007; Goldenberg 2009), which involves only routine support from parietal areas.

However, several other hypotheses could account for the discrepancy between the results of functional and lesion studies. The contribution of parietal structures to pantomime might have been underestimated in previous lesion studies due to the assessment having been conducted in chronic patients, that is, more than 1 month after lesion onset (Goldenberg 2003a, 2003b; Dovern et al. 2011). Specificity of networks may indeed be revealed in the postacute phase only, after the resorption of the ischemic penumbra (Witte et al. 2000) and before the occurrence of major plastic anatomofunctional reorganizations (Adriani et al. 2003; Rey et al. 2007). The type of evaluation (conceptual vs. production components) may be more sensitive to parietal or to frontal lesions (Halsband et al. 2001). Furthermore, previous neuropsychological studies included only a limited number of patients with lesions covering only limited portion of the brain (Goldenberg 2003a, 2003b), patients selected based on a priori hypotheses on the region of interest (Dovern et al. 2011; Hanna-Pladdy et al. 2001) or patients with aphasia (Goldenberg et al. 2007). Finally, previous studies dichotomized behavioral data on apraxia (with vs. without apraxia) instead of considering the scores as continuous data, leading to a loss of power and reduced effect sizes (Cohen 1983). Collectively, these potential caveats could have lead to false-negative results in current lesion data on pantomime, potentially concerning the involvement of parietal areas.

In addition, attempts to find common substrates for different types of pantomime errors and the rarity of some kinds of errors motivated researchers to collapse together various types of error in neuropsychological scoring of pantomime. As lesions to distinct areas may induce distinct types of error (Rumiati and Humphreys 1998; Halsband et al. 2001; Hanna-Pladdy et al. 2001; Rumiati et al. 2001), the use of compound scores might have in turn contributed to obscure putative intrahemispheric dissociations for different types of pantomime errors. For instance, body-part-as-object (BPO) pantomime errors, consisting in representing objects with a part of the body rather than pretending to use an "invisible" object as specified in the test instructions (Goodglass and Kaplan 1963) have been suggested to depend on frontal but not parietal components (Peigneux and Van der Linden 1999; Arzy et al. 2006). The study of BPO errors could thus help to further reveal intrahemispheric dissociations between frontal and parietal contributions to pantomime.

To test these hypotheses, we conducted large-scale retrospective voxel-based lesion–symptom-mapping analyses (VLSM; Bates et al. 2003) on a group of subacute, unselected, hemispheric brain-damaged patients and pantomime scores differentiating the typical spatial/configural (CS) and BPO pantomime error types. We used highly selective inferential statistical analyses of lesion–symptom mapping based on continuous scores rather than descriptive comparisons between lesion patterns of patients' groups defined by behavioral cutoffs (i.e., with or without apraxia). Because the inclusion of tumor and stroke patients in VLSM analyses might yield different results, we analyzed separately these 2 types of brain-damaged patients (e.g., Karnath and Steinbach 2011).

Methods

Patients

One hundred and fifty right-handed patients with a first right or left unilateral hemispheric lesion (demographic data in table 1) were selected retrospectively from consecutive in-patients admitted to the Neuropsychology and Neurorehabilitation Service of the Centre Hospitalier Universitaire Vaudois or the Hôpitaux Fribourgeois between 2007 and 2011. Patients with bilateral lesions were excluded to facilitate the interpretability of our results in terms of hemispheric specialization of pantomime. On average, the pantomime assessment was conducted 2.3 ± 6.9 weeks (mean ± SD) after the lesion onset or tumor diagnosis or removal and was part of the formal neuropsychological assessment carried out by experienced psychologists specialized in neuropsychology. All patients met the following criteria: 1) first unilateral hemispheric lesion without damage to the brain stem or cerebellum documented by CT-scan and/or MRI; 2) no prior neurological illness; 3) no psychiatric illness; 4) good cooperation and absence of major behavioral or attentional problems; 5) sufficient understanding of the instructions; and 6) assessment of at least 4 pantomimes. Inclusion in the study was neither determined by the lesion characteristics nor by the pattern of behavioral deficit. The study was carried out in agreement with the recommendations of the Ethics Committee of the Faculty of Biology and Medicine, Lausanne. Data were handled according to Swiss-Federal law on data protection.

Neuropsychological Assessment of Pantomime

The production of pantomime on verbal command was assessed by asking the patient to mime the use of an imaginary tool. In the case of hemiparesis, the patient was asked to use only the nonparetic ipsilesional hand. The evaluation of paresis was based on the Medical Research Council Scale for Muscle Strength (e.g., Pizzi et al. 2009). In the present study, if the patient's strength was below 3, the nondominant (left) hand was used. Pantomimes were tested with items of the

Table 1
Demographic data of the 150 patients included in the study

	N = 150 Patients
Age, mean (±SD)	60.5 (±15.3), 16–89 years
Gender	
Female	68
Male	82
Damaged hemisphere	
LBD	84 (38 with aphasia: 32 patients with fluent aphasia and 6 with nonfluent aphasia)
RBD	66
Etiology	
Stroke (LBD, RBD)	81 (42, 39)
Tumor (LBD, RBD)	69 (42, 27) (44 before and 25 after surgery)
Postlesion delay (weeks ± SD)	2.3 (±6.9)

LBD, left brain-damaged; RBD, right brain-damaged.

screening batteries by Peigneux and Van der Linden (2000) or Mahieux-Laurent et al. (2009). The former included 4 items: brushing the hair with a comb; brushing the teeth with a toothbrush; planting a nail with a hammer; and sawing a branch of wood (Peigneux and Van der Linden 2000). The latter included 5 items: planting a nail with a hammer, tearing a piece of paper in two, lighting a match, brushing the hair with a comb, and drinking a glass (Mahieux-Laurent et al. 2009). On average 4.3 ± 0.5 (mean ± SD; range 4–5) items were probed for the assessment of pantomimes.

Two different types of errors were documented and analyzed in the present study: First, CS errors refer to inaccurate limb configurations during pantomiming at the level of the sequencing, timing, and/or amplitude of the gestures, and of the relationships between the different body parts engaged in the movements. CS errors result in imprecise or unrecognizable gestures. For example, if the patient mimed brushing his hair with an imaginary comb with one hand but placed the imagined comb far away from his head, the pantomime was considered as incorrect. The second type of errors consisted in the use by the patients of their body parts as the object (BPO errors). BPO were considered as errors only when the patients did not correct it after reinstruction from the examiner. The patient was reinstructed after every BPO error. This reinstruction condition was implemented because BPO are common among healthy controls, but neurologically healthy population correct BPO after being reinstructed (Heilman and Rothi 1993; Raymer et al. 1997; Peigneux and Van der Linden 1999). For example, for combing the hair, if the patient used his fist as the comb and brushed his hair with it, the examiner reinstructed him to pretend he was holding an imaginary comb in his hand rather than using his forelimb as the comb. If the patient did not correct the error and continued to use his limb as the object, the BPO was considered as pathological and counted as a BPO error (Heilman and Rothi 1993; Raymer et al. 1997). We would note that because the present study was based on a retrospective analysis of data collected during routine neuropsychological assessments, the scoring of pantomime was not as precise and controlled as what could have been obtained with a specifically designed prospective study. For this reason, not all possible error types [including, e.g., semantic content errors (Rumiati and Humphreys 1998); sequence or conceptual errors (Rumiati et al. 2001); or parapraxic errors (Halsband et al. 2001)] were analyzed separately. However, the pantomime errors were scored by trained and experienced specialists in neuropsychology, according to strict published procedures (Peigneux and Van der Linden 2000; Mahieux-Laurent et al. 2009). Because each patient did not have to produce the same number of pantomimes (4 items for Peigneux's battery and 5 items for Mahieux-Laurent's battery), the scores used in the VLSM were the standardized numbers of BPO and CS pantomime error types (%). Pantomime scores obtained with Peigneux's battery or Mahieux-Laurent's battery did not statistically differ, neither for BPO errors ($t(148) = -0.43$; $P = 0.66$) nor for CS errors ($t(148) = 0.56$; $P = 0.57$).

Voxel-Wise Statistical Analysis of Lesion–Symptom Mapping

Brain lesions were manually reported on axial slices of the standard Montreal Neurological Institute's (MNI) brain template using the MRIcro software (Rorden and Brett 2000), according to previously described methods (Karnath et al. 2004; Spierer et al. 2009). Lesions were reported on the template brain by trained assistants naive to the clinical profiles of the patients (Fiez et al. 2000). These normalized lesions were then submitted to statistical mapping analyses using VLSM algorithms implemented in the MRICroN and NPM softwares (Rorden et al. 2007) to determine brain areas where damage yielded each type of pantomime errors. Because each patient did not have to produce the same number of pantomime, the scores used in the VLSM were the standardized numbers of BPO and CS pantomime error types (%). The *t*-tests on the continuous CS and BPO scores were performed on a voxel-by-voxel basis to compare performance in patients with versus without a lesion in each voxel, only testing voxels damaged in at least 4 patients. The results of the *t*-tests were then color-coded and mapped on the MNI template brain using the software package (Rorden and Brett 2000). Only voxels surviving a conservative false discovery rate (FDR) corrected significance threshold of $P < 0.05$ were considered in the results (though a threshold of 0.01 was applied for the analyses of the tumor and stroke patients collapsed together presented in the Fig. 1 because we reached a much larger sample size, see the Results and discussion section).

The overall distribution of lesion among our patient sample is depicted in Supplementary Figure S1a.

Results

We conducted the VLSM analyses on the groups of stroke and tumor patients separately (see Table 1 for demographic information of each subgroup).

In stroke patients, CS pantomime error types were associated with lesions to a network centered on inferior frontal and temporal areas, with sparse evidence for a role of parietal areas (Fig. 1*b*). In tumor patients, CS error types were associated with lesions to a more posterior network extending from inferior frontal to parietal areas, mostly including parietal white matter (Fig. 1*e*).

In stroke patients, BPO pantomime errors were associated with lesions to the left middle and inferior frontal gyri, the rolandic and inferior frontal opercula, and the underlying white matter, mainly including the superior longitudinal fasciculus (Fig. 1*c*). In tumor patients, BPO errors were associated with the same network, but extending higher to the supplementary motor area (Fig. 1*f*; see Supplementary Fig. S2 for the double dissociation between CS and BPO errors).

We also conducted the same VLSM analyses as above with stroke and tumor patients collapsed together. CS pantomime error types were associated with lesions to the left inferior parietal and angular gyri, postcentral and supramarginal gyri, and portions of the underlying white matter (Supplementary Fig. S1c). BPO pantomime errors were associated with lesions to the left middle and inferior frontal gyri, the rolandic and inferior frontal opercula, and the underlying white matter, mainly including the superior longitudinal fasciculus (Supplementary Fig. S1d) (see Supplementary Fig. S2 for the double dissociation between CS and BPO errors). Comparison between the results of the analyses of the lesions associated with CS and BPO errors revealed that the left inferior frontal regions predicted the occurrence of both types of error (Supplementary Fig. S1cd). We further tested putative effects of lesion size on the occurrence of CS and BPO errors. Lesion size differed between patients with versus without CS errors ($P < 0.05$, uncorrected) but not for patients with versus without BPO errors ($P = 0.29$, uncorrected). However, there was no evidence for correlations between the CS or BPO errors and the size of lesions ($r(26)$=0.16; $P = 0.40$; $r(11) = -0.10$; $P = 0.74$, respectively).

The incidence of the different patterns of error (CS, BPO, or CS + BPO) across patients is displayed in Table 2. The relationship between impaired pantomiming and aphasia is depicted in Figure 2. There were more apraxic patients in the group "left hemispheric with aphasia" than in the group "left hemispheric without aphasia" and in the group "right-hemispheric." The analysis of the incidence of at least 1 pantomime error in these 3 groups of patients further reveal that very few patients show both CS and BPO errors (Supplementary Fig. S3).

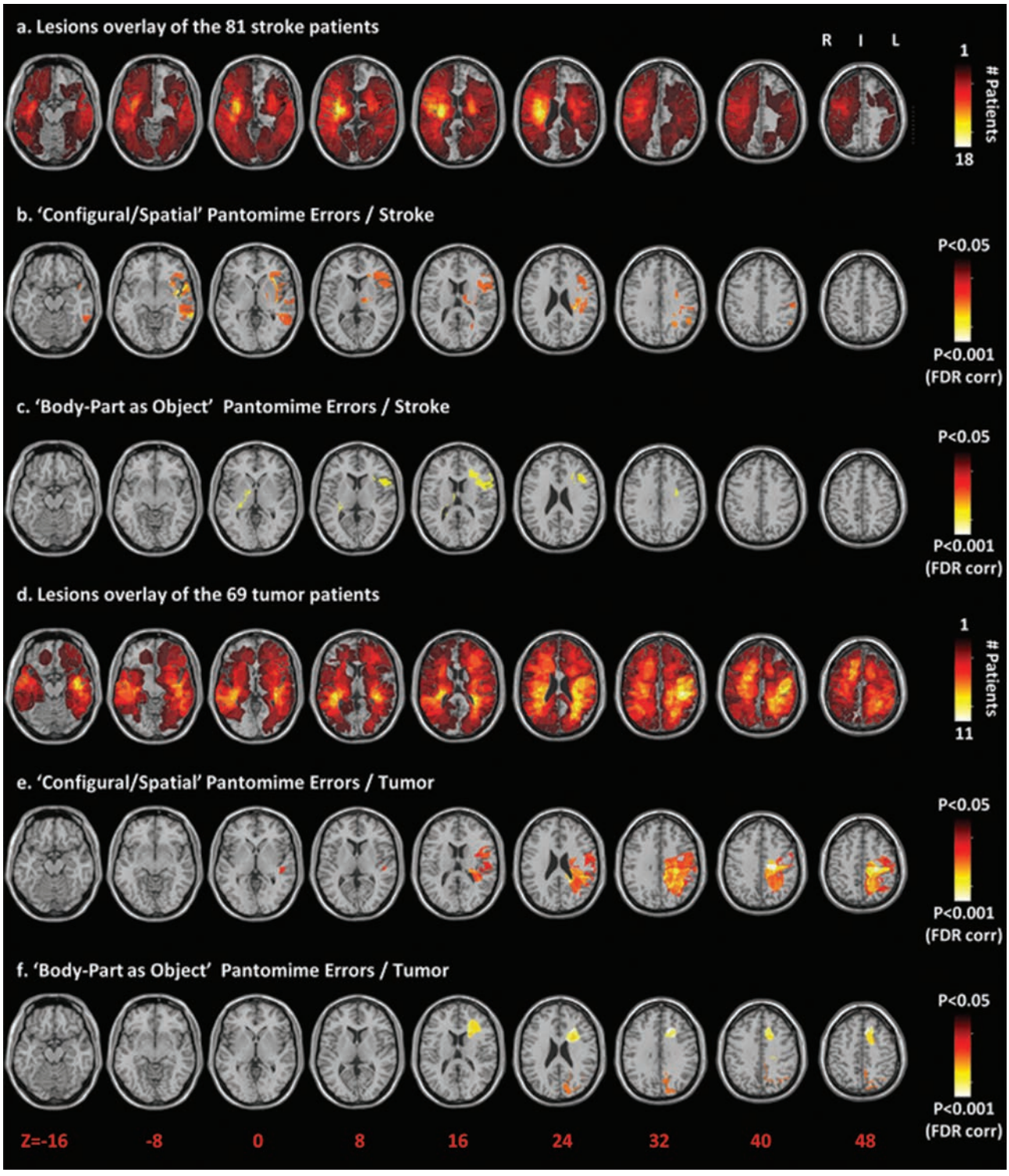

Figure 1. Voxel-based lesion–symptom mapping on the stroke patients and tumor patients separately shows the relationship between performance in pantomime and brain lesions. (**a**) Overlap lesion plot of the 81 stroke patients. The number of overlapping lesions is coded with colors ranging from dark red (n = 1) to light yellow (n = 18 patients). (**b**) Only voxels significant at P<.05 FDR corrected are color-coded ranging from red to white. Configural/ spatial errors were associated with lesions to a network centered on left inferior frontal and temporal areas, with sparse evidence for a role of left parietal areas. (**c**) Body-part-as-object errors were associated to lesions of the left middle and inferior frontal gyri and the rolandic inferior frontal opercula, and the underlying white matter mainly including the superior longitudinal fasciculus. (**d**) Overlap lesion plot of the 69 tumor patients. The number of overlapping lesions is coded with colors ranging from dark red (n = 1) to light yellow (n = 11 patients). (**e**) Only voxels significant at P<.05 FDR corrected are color-coded ranging from red to white. Configural/ spatial errors were associated with lesions to the left inferior frontal and inferior and superior parietal gyri, angular gyrus, postcentral and supra marginal gyri, largely including the underlying white matter. (**f**) Body-part-as-object errors were associated to lesions of the left middle and inferior frontal gyri and the underlying white matter mainly including the superior longitudinal fasciculus. Brain slices are displayed from z-coordinates −16 to 48 of the MNI space, with the left hemisphere on the right side.

Table 2
Incidence and range of each error type

Error (≥1)	Total (n = 150), %	Mean % of error (± SD) + range
No error	76	–
CS only	15	36.6 ± 18.0% (10–75%)
BPO only	6	45.4 ± 16.6% (20–75%)
CS + BPO	3	CS: 43.8 ± 24% (25–75%) BPO: 31.3 ± 12.5% (25–50%)

CS, configural/spatial error; BPO, body-part-as-object error.

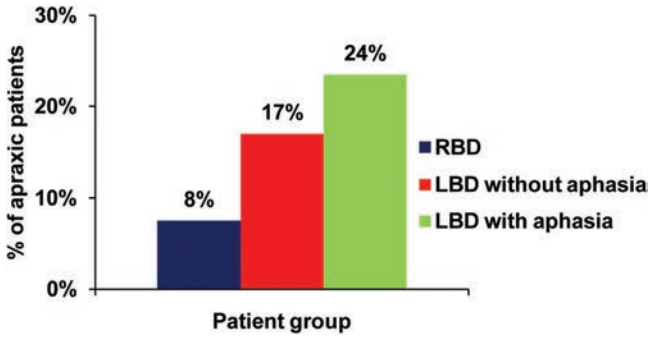

Figure 2. Distribution of apraxic patients as a function of the damaged hemisphere and aphasia. Right brain-damaged (RBD) patients are reported in blue, left brain-damaged patients (LBD) without aphasia are reported in red, and LBD with aphasia are reported in green.

Discussion

We conducted VLSM analyses based on a large cohort of 150 unselected patients with unilateral left or right hemispheric brain damage and their continuous scores in BPO and CS errors types in a classical neuropsychological assessment of pantomime. Our results reveal that distinct lesion sites within the left hemisphere predicted the occurrence of CS and of BPO pantomime error types. Both types of error were associated with damage to left inferior frontal regions in tumor and stroke patients. CS errors were associated with lesions of left inferior parietal areas, whereas BPO errors were associated with lesions extending from left superior to inferior frontal gyri and a large portion of the underlying white matter in both tumor and stroke patients. Of note, we put forward a differential pattern of deficits according to etiology for CS errors: CS errors were less associated with parietal areas in stroke than in tumor patients, and temporal areas were less associated with CS errors in tumor than stroke patients.

Most of the previous investigations of pantomime in brain-damaged patients included only left brain-damaged patients and/or samples selected based on the presence of aphasia (Schnider et al. 1997; Hanna-Pladdy et al. 2001; Goldenberg 2003a, 2003b; Goldenberg et al. 2007; Dovern et al. 2011). In contrast, our study includes unselected consecutive patients sustaining both left and right unilateral brain damage. Our finding for a left hemispheric dominance in pantomime thus provides robust lesion evidence for the prominent involvement of left but not right hemispheric structures in pantomime and corroborates functional imaging studies documenting a left hemispheric specialization for pantomime (Hermsdorfer et al. 2007; Vingerhoets, Acke et al. 2012, Vingerhoets, Vandekerckhove et al. 2011). A limitation of our results in this regard is that because we included only right-handed patients, the present study cannot disentangle potential interactions between handedness, the hand used for the pantomime and the side of the lesion. However, our results are consistent with previous evidence for a left lateralization in pantomimes in both left- and right-handed individuals (Vingerhoets, Acke et al. 2012) and for a similar left lateralization in studies comparing left- and right-hand pantomimes in right-handed participants (Moll et al. 2000; Choi et al. 2001). Of note, the VLSM analysis revealed the brain regions inducing the "more severe" pantomime impairments (Fig. 1, Supplementary Fig. S1), which does not rule out that other regions play a role in pantomime. Although the left parieto-frontal network revealed in our results is the region which, when damaged, induces the most robust increase in the number of pantomime errors, right-hemispheric brain regions (or left nonfrontal, nonparietal regions) might be involved in praxis as well. Indeed, impaired pantomiming manifest in 8% of the right brain damaged patients (Fig. 2) and the lesion overlap of patients showing a deficit in pantomime reveals associations between right hemispheric lesions and apraxia (see Supplementary Fig. S2b).

A separated VLSM analysis of the lesion sites associated with the commission of distinct types of pantomime errors revealed a left intrahemispheric dissociation between the contribution of parietal and frontal areas to CS and BPO error types, respectively.

In tumor patients, our finding for a role of left parietal areas in CS pantomime errors is in line with findings from functional imaging approaches (Moll et al. 2000; Hermsdorfer et al. 2007; Vingerhoets, Acke et al. 2012, Vingerhoets, Vandekerckhove et al. 2011). These studies interpreted the left parietal activity during pantomime as supporting the storage of knowledge about manipulation of familiar objects and learned gestures, both mechanisms being specific to praxia and necessary for accurate pantomime. Damage to this region is thus conceivably at the origin of the CS error types we observed (Buxbaum et al. 2007; Vingerhoets, Acke et al. 2012, Vingerhoets, Vandekerckhove et al. 2011). However, our analyses revealed a critical role for the parietal white matter in pantomime in tumor patients, suggesting that a disruption of the functional interactions between the subparts of the fronto-parietal network involved in pantomime would yield even more CS errors than focal damage to their constitutive regions (Peigneux et al. 2001; Wheaton, Shibasaki et al. 2005; Wheaton, Yakota et al. 2005). In line with this finding, fronto-parietal and basal ganglia damage induced by corticobasal degeneration have been shown to induce severe apraxic symptoms (Leiguarda et al. 2000).

In contrast to these activation studies and to our finding in tumor patients, lesion data so far mostly report that the integrity of left frontal but less consistently parietal areas are necessary for pantomime (Goldenberg et al. 2007; see also Bohlhalter et al. 2011 for supporting Transcranial Magnetic Stimulation data). Moreover, sparse evidence from single case reports describe patients with left parietal damage but preserved pantomime (Goldenberg and Hagmann 1997; Peigneux et al. 2000). These lesion data have been interpreted in terms of the involvement of inferior frontal regions in the selection of task relevant gestures among all gestures possibly related to a given tool or object use (Goldenberg et al. 2007). Goldenberg et al. (Goldenberg et al. 2007; Goldenberg 2009)

advanced that the disparities between the findings of functional and lesions studies on the role of parietal regions in pantomime could follow from the gestures being realized under different conditions in the scanners when compared with during neuropsychological assessments. In the scanner, more spatial transformation would be required because the movements have to be performed with constrained limb positions, within unusual portions of space and without visual feedback. These additional demands would have artificially increased the involvement of the parietal structure supporting spatial processing and transformations into coordinates (Sack 2009; though see Rumiati et al. 2004 for evidence of parietal activity even when participant were not instructed to perform the gestures in the scanner). However, our result for a parietal involvement in the absence of any extra demand on spatial transformation calls for additional accounts for the lack of associations between parietal damage and CS pantomime errors observed in previous lesion studies. The following hypotheses could be put forward in this regard. First, previous studies included only stroke patients; our results for a much stronger association between CS errors and parietal areas in the tumor than in the stroke group suggest that the etiology of the lesion might play a role in their functional consequences on apraxia. While some evidence suggest that stroke and tumor results in the same deficits (Haaland and Delaney 1981), other pointed out that these 2 etiologies could yield distinct patterns of deficits, even if lesion size and location is controlled (Anderson et al. 1990). Our results suggest that lesion location associated with pantomime errors might differ depending on whether the VLSM analyses are based on stroke versus tumor lesions. Lesion–symptom mapping based on tumoral lesions has been argued to induce different patterns as when stroke lesions are analyzed. A possible reason for these discrepancies could be that in tumor patients, infiltrations could yield functional loss while being invisible to the MRI or CT scans used to delineate the lesion loci during the lesion reconstruction, in turn confounding the mapping between lesion and symptoms (for discussion, see Anderson et al. 1990; Karnath and Steinbach 2011; Shallice and Skrap 2011). Interestingly, in line with the previous lesion data reviewed above (e.g., Goldenberg et al. 2007), the result for a parietal involvement in CS error almost vanished when analyses were conducted in stroke patients only. However, we would note that specifically designed studies should be conducted to elucidate the differential role of lesion versus tumor patients (Duffau 2011). The results of VLSM analyses are indeed highly dependent on the spatial distribution of the lesion because it not only determines where in the brain the VLSM tests are actually conducted, but also the distribution of the statistical power of the statistical tests conducted at each voxel between the behavioral scores of lesioned versus intact patients (Kimberg et al. 2007; see Method section). This factor possibly account for our differential pattern of results in the 2 groups of patients as evident from the difference in the lesion overlap in Figure 1*a*,*d* showing that lesion location are not strictly identical in stroke and tumor patients.

In this regard, the fact our study included a large cohort considerably increased the statistical power of our analyses and the portion of the brain covered by lesions. This factor could also explain why, in contrast to previous lesion studies, we reveal a parietal involvement in pantomime (though mostly in tumor patients). The inclusion of both left and right brain-damaged patients in the VLSM further strengthened the sensitivity of our statistical tests by increasing the number of data-points (i.e., the behavioral scores) in the groups of the intact and lesioned patients compared at each voxel. We also analyzed continuous data instead of dichotomizing the scores into normal versus impaired based on behavioral cutoffs, thereby taking into account the severity of pantomime impairment in the VLSM and maximizing the statistical power of the analyses (Cohen 1983).

Finally, although the following reasoning only applies to stroke patients where the association between parietal areas and CS error was weak, our results might have revealed a parietal involvement because pantomime was assessed during the subacute phase and not during the chronic phase as in most previous studies. In the literature so far, pantomime scores were collected at postlesion delays of about 28 weeks (Goldenberg 2003a, 2003b); 20 weeks (Goldenberg et al. 2007); or 4 weeks (Schnider et al. 1997). In contrast, pantomime scores in our study were collected on average 2 weeks after lesions onset, a period corresponding to the subacute phase. The specificity of parietal networks for pantomime was possibly revealed in the present study because pantomime was assessed after—or at least during—the release of areas surrounding damaged regions from ischemic penumbra (Witte et al. 2000), but before major plastic anatomo-functional reorganization took place (Adriani et al. 2003). Although highly speculative, parsimonious explanations for the fact that the functions subserved by parietal but not frontal areas recovered in chronic patients would be that 1) parietal mechanisms could be hierarchically subordinated to frontal selection processes and more specific to the pantomime task; and/or 2) the largely acquired and mnesic nature of parietal movement representations could be more prone to be recovered and taken over by other areas than frontal executive selection mechanisms. We would note, however, that our interpretation of the results on the influence of the postlesion delay is not made by directly comparing subacute versus chronic patients but in the light of previous literature. Consequently, the present study does not allow drawing definitive conclusions on the influence of postlesion delay functional recovery in pantomime, but rather calls for further investigations specifically designed to disentangle the precise influence of this factor.

The results of the VLSM revealed a role of temporal regions in CS error, mostly in stroke patients. This finding is in line with models positing that the knowledge on tool use required to perform accurate pantomime on verbal command as in the current study depends on the semantic memory, notably instantiated within temporal areas (Kellenbach et al. 2003; Lewis 2006; Frey 2007; Canessa et al. 2008; Goldenberg and Spatt 2009). Our analyses further reveal that left frontal but not parietal lesions correlated with BPO error type. This finding is consistent with previous lesion studies reporting higher rates of BPO in left than right brain damaged patients (Mozaz et al. 1993). We also observed that lesions predicting BPO extended largely to the white matter underlying inferior and middle frontal cortices, including the superior longitudinal fasciculus (SLF). This finding substantiates the observations by Hanna-Pladdy et al. (2001) of more BPO after left subcortical than cortical damage and evidence that lesions to the SLF induce severe apraxia (Mori et al. 2002; Schmahmann

and Pandya 2011). Lesions to frontal white matter tracks have been interpreted as inducing apraxia by disconnecting parietal and frontal motor areas (Pramstaller and Marsden 1996).

Several candidate mechanisms have been advanced to explain BPO errors. First, because BPO are considered as errors only when they persist after reinstruction, they could be interpreted as perseveration and be accounted for by mere executive dysfunctions. A neighbor hypothesis by Peigneux and Van der Linden (1999) assumes that BPO could follow from difficulties in inhibiting automatic activations of often used emblematic gestures (e.g., using his hand to represent the handset to signify a phone call). Supporting the hypothesis that BPO are due to a lack of inhibitory control, healthy elderly individuals with weaker inhibitory control also show more BPO errors than young and healthy adults (Peigneux and Van der Linden 1999). However, if BPO errors resulted from perseveration only, they should manifest in both left and right frontal damaged patients and not selectively in left hemispheric patients as in our results (Freedman et al. 1998).

Alternatively, BPO could be committed due to a pathological embodiment of the tool in the patient's limbs, echoing phenomenon occurring during the rubber hand illusion (Botvinick and Cohen 1998). Kondo et al. (2009) further advanced that the inability to precisely form finger postures to perform the gesture follows from the contamination of the motor command by the information concerning the shape of the objects. Such effect could possibly follow from damage to frontal regions (Arzy et al. 2006; Kondo et al. 2009).

A third candidate mechanism for BPO is advanced by Raymer et al. (1997), who suggests that BPO errors could be linked to difficulties of representing and/or selecting the appropriate object features necessary to produce the correct hand postures used to hold the object. In turn, such deficits would make the patients portraying the object itself instead of imagining it and adapting their gestures accordingly. In this regard, BPO would be in an attempt to circumvent the task difficulty by using limbs as a concrete rather than as an abstract representation of the object (see also Bartolo et al. 2003).

Of note, the overlap between patients' lesions show that 5 of the 9 patients with only BPO errors are right-brain damaged, suggesting that right hemispheric structures might also play a role in BPO errors (Supplementary Fig. S2b). Because our study includes only unilateral patients, this result might explain the very limited number of patients showing both BPO and CS errors. However, the role of right-hemispheric structures in BPO error does not appear in the VLSM where the severity of the deficits (i.e., the number of BPO) and the patients with both CS and BPO errors are taken into account. Further studies including bilateral patients are required to investigate this question.

Another limitation of the present study is that because it was based on a retrospective approach, only information on CS and BPO error types were available. Previous neuropsychological investigations of pantomime deficits identified several other types of error, which revealed other types of mechanisms involved in pantomime. For instance, investigation of the relationships between pantomime and actual tool use or tool recognition showed that these 2 processes correlated to a certain extent (Bartolo et al. 2003; Rumiati et al. 2004 for discussion), suggesting that pantomime deficits may not solely follow from semantic processing impairments but also from deficits of the output lexicon (Cubelli et al. 2000).

Taken together, our findings reveal that pantomime is subserved by a distributed, left-lateralized, frontoparietal network and that lesions to subparts of this network induce distinct error types. Furthermore, the results point out that the postlesion delay and the etiology of the brain damage might be important to consider in the study of apraxia in brain-damaged patients.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

Notes

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APPENDIX D

Manuel AL, Bernasconi F, Spierer L (2012c) Spatio-temporal brain mechanisms of training-induced neuroplastic reinforcement of inhibitory control. *In revision*.

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Abstract: Introduction. Inhibitory control refers to our ability to suppress ongoing motor, affective or cognitive processes and depends on a fronto-basal brain network. Inhibitory control deficits have been shown to participate in the emergence of several prominent psychiatric disorders, including attention deficit/hyperactivity disorder or addiction. The rehabilitation of these conditions might therefore benefit from training-based behavioral interventions aiming at improving inhibitory control proficiency and normalizing the underlying neurophysiological mechanisms. The development of efficient inhibitory control training regimen first requires determining whether and how inhibitory control can be trained.

Methods. We addressed these questions by contrasting behavioral and electrical neuroimaging analyses of auditory evoked potentials recorded in human at the beginning vs. the end of one hour of training on a stop-signal task involving to withhold responses when a stop signal was presented during a speeded auditory discrimination task.

Results. Our results indicate that a short training improved inhibitory control proficiency. Electrophysiologically, AEPs modulated topographically at 200msec post-stimulus onset, indicative of the engagement of distinct brain network with training. Source estimations localized this effect within the inferior frontal gyrus, the pre-SMA and basal ganglia. Critically, the modulation of the activity within IFG during the training predicted the behavioral improvements.

Conclusion. Our collective results indicate that inhibitory control is subject to fast plastic changes and provide evidence that high-order fronto-basal executive networks can be reinforced. Moreover, our results indicate that modulations in the activity of the inferior frontal gyrus could be used to index the efficiency of rehabilitation protocol of inhibition-related disorders.

Journal section:
Notes

Title:
Spatio-temporal brain mechanisms of training-induced neuroplastic reinforcement of inhibitory control

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ABSTRACT

Introduction. Inhibitory control refers to our ability to suppress ongoing motor, affective or cognitive processes and depends on a fronto-basal brain network. Inhibitory control deficits have been shown to participate in the emergence of several prominent psychiatric disorders, including attention deficit/hyperactivity disorder or addiction. The rehabilitation of these conditions might therefore benefit from training-based behavioral interventions aiming at improving inhibitory control proficiency and normalizing the underlying neurophysiological mechanisms. The development of efficient inhibitory control training regimen first requires determining whether and how inhibitory control can be trained.

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Keywords:

Inhibitory control; EEG; source estimation; Inferior frontal gyrus; Stop-signal task

1. INTRODUCTION

Inhibitory control refers to the ability to suppress ongoing cognitive, affective or motor processes (Dillon and Pizzagalli, 2007) and rely on a fronto-striato-basal network (Aron, 2011). Structural and functional deficits within the inhibitory control network have been repeatedly advanced as constituting a causal factor, or at least as being associated with prominent psychiatric disorders, including for example attention deficit/hyperactivity disorder (Overtoom et al., 2002), obsessive-compulsive disorders (Chamberlain et al., 2006) and addiction (Fillmore and Rush, 2002).

The rehabilitation of inhibition-related conditions might therefore benefit from behavioral interventions aimed at improving inhibitory control with targeted training regimen. Similar approaches have for instance proven helpful for the remediation of impaired reality monitoring in psychotic patients, which in turn decreased the severity of clinical symptoms and improved social functioning (Subramaniam et al., 2012). More germane, Houben and colleagues (2011a; b) provided psychophysical evidence that inhibitory control training using Go/NoGo tasks helped to decrease high-caloric food consumption and alcohol drinking, respectively. However, the development of optimal neuroplasticity-based rehabilitation strategies of inhibitory control first requires determining whether and how this function could be improved with training in healthy populations and the supporting brain mechanisms. While inhibitory control has been extensively studied (Chambers et al., 2009; Aron, 2011), these two questions remain largely unresolved.

Manuel et al. (2010) demonstrated that training on a Go/NoGo task improved inhibitory control performance, but that the behavioral improvement was not supported by a modification of the global fronto-basal inhibitory control network. Rather, neuroplastic changes manifested within temporo-parietal cortices over the initial stages of the stimuli processing, indicative of the development of a stimulus-driven, feed-forward form of inhibition directly triggered by the NoGo stimuli (Manuel et al., 2010; Shiffrin and Schneider, 1977). Although the development of automatic inhibition did improve performance, its effects were likely highly specific to the trained stimuli. Consequently, the training regimen in Manuel et al. (2010) has a very limited value for rehabilitation purposes where a massive transfer of the effects of training should be achieved.

In the current study, we hypothesized that the global fronto-basal inhibitory control network could be reinforced by training inhibitory control with a Stop-Signal task (SST). Stop-Signal task consists in a speeded discrimination task in which responses to the stimuli have to be

canceled when a stop signal is presented (Logan and Cowan, 1984). Because stimulus-response mappings are inconsistent in the SST task (each Go stimulus is associated with activation or with inhibition goals), automatic inhibition would unlikely develop and the global fronto-basal inhibitory control network would be constantly involved during the training (Verbruggen et al., 2008a). In turn, this global inhibitory network should be reinforced.

To test this hypothesis, we contrasted inhibitory control performance and electrical neuroimaging analyses of auditory evoked potentials (AEPs) to Go stimuli recorded at the beginning versus the end of a Stop-Signal training, a typical inhibitory control task shown to be a reliable marker on inhibition deficits in clinical populations.

2. MATERIALS AND METHODS

2.1. Participants

Thirteen right-handed volunteers participated in the study (7 male, mean age 23.9y). No participant had a history of neurological or psychiatric illness and all reported normal hearing. Each participant provided written, informed consent to participate in the study. All procedures were approved by the local Ethics committee.

2.2. Stimuli

Auditory stimuli were 75msec band-pass noise bursts (410-470Hz (Go1), 592-652 Hz (Stop) and 850-910Hz (Go2); 5 msec rise/fall time; 44.1kHz sampling) presented via ER-4P-Etymotic earphones.

2.3. Procedure and task

Participants underwent an auditory Stop Signal Task (Logan and Cowan, 1984) in which they had to discriminate between the pitch of two stimuli (Go1, low pitch, button 1; or Go2, high pitch, button 2) as fast and accurately as possible via a manual response-box button, unless immediately followed by the stop signal stimuli (Stop). Participants were seated in an electrically-shielded and sound-attenuated booth in front of a 19" LCD screen. Stimulus delivery and response recording were controlled using E-prime 2.0. All trials began with an inter-trial interval (ITI) varying randomly from 2000 to 3000msec followed by the Go stimulus (either Go1 or Go2). During the ITI, a fixation cross was presented at the center of the screen. At the end of the ITI, the cross was turned off, the Go1 or Go2 sounds were presented and the time window during which response were recorded was open. On 33% of

the trials, a stop signal tone (Stop) was presented shortly after the Go stimulus which indicated that participants were to inhibit their response (see Figure 1). These trials are referred to as “Stop signal trials” in contrast to the 66% of “Go trials” during which the response had to be executed to its end. On stop trials, the delay between the Go and the Stop stimulus (Stop Signal Delay, SSD) was initially set at 300msec and adjusted continuously throughout each block with a tracking procedure allowing to obtain a probability of successfully stopping of 0.5 (Verbruggen and Logan, 2009): When participants managed to stop their response during a Stop signal trial, the SSD increased automatically by 50msec; when they responded on a Stop signal trial, SSD decreased by 50msec. The Stop Signal task was divided in ten blocks containing each 102 randomly presented trials: 68 Go stimuli (34 Go1, 34 Go2) and 34 Stop signal trials. The whole Stop signal training session included a total of 1020 stimuli and lasted for a total of about 1 hour.

2.4. EEG acquisition and pre-processing

Continuous EEG was acquired at 1024Hz through a 128-channels Biosemi ActiveTwo system referenced to the CMS-DRL ground. EEG data pre-processing and analyses were conducted using Cartool software (http://sites.google.com/site/fbmlab/cartool; Brunet et al., 2011). EEG epochs from 100msec pre- to 300msec post-stimulus onset were averaged, for each participant, for all Go stimuli and separately for the first 4 blocks (Beginning condition, BEG) and the 4 last blocks (End condition, END) of the SST task. This epoch of interest was chosen to avoid any contamination of the ERP to the Go stimuli by activity related to the stop signals. A ±80 µV automatic artifact rejection criterion was applied to exclude artifact epochs. Prior to group averaging, data at artifact electrodes from each participant were interpolated using 3D splines (mean 5.8% interpolated electrodes; Perrin et al., 1987). Data were band-pass filtered (.18-40 Hz) and recalculated against the average reference. A baseline correction was then applied to the whole epoch. We did not sort trials as a function of performance or of whether it was followed by a stop signal or not because the type of trial (Go or Stop trial could not be predicted and our period of interest did not include the Stop stimuli in Stop trials). The average number (±SEM) of accepted epochs was 382±6 for the Go trials at the BEG and 364±9 for the Go trials in the END condition. These values did not statistically differ ($p>0.05$).

2.5. Topographic patterns analyses

A topographic pattern analysis was applied to the AEPs to determine whether the configuration of intracranial generators changed between the beginning and the end of the training (e.g. Michel et al., 2004; Murray et al., 2008; Manuel et al., 2010; Manuel et al, 2012). This approach is based on evidence that the ERP map topography does not vary randomly across time, but remains quasi-stable over 20-100msec functional microstates before rapidly switching to other stable periods (Lehmann and Skrandies, 1980; Britz & Michel, 2011). Because a change in the topography of the scalp-recorded electric field necessarily follows from a change in the configuration of the underlying brain's active generators, topographic modulations can be directly interpreted as the engagement of distinct brain networks (e.g. Lehmann, 1987). This method is independent of the reference electrode and is insensitive to pure amplitude modulations across conditions (topographies of normalized maps are compared; Tzovara et al., 2011 for discussion).

The sequence of predominating topographies (template maps) in the cumulative group-averaged data was identified using a hierarchical clustering based on an atomize and agglomerate approach. The optimal number of clusters to describe the dataset is identified using a modified Krzanowski–Lai criterion (Tibshirani et al., 2005). Differences in the pattern of topographic maps observed between conditions in the group-averaged data are tested by calculating the spatial correlation between these template maps from the group-averaged data and each time-point of single-subject data from each experimental condition. For this fitting procedure, each time point of each AEP from each subject was labeled according to the map with which it best correlated spatially. The output of fitting is a measure of relative map presence in milliseconds, which indicates the amount of time over a given interval that each map that was identified in the group-averaged data best accounted for the response from a given individual subject and condition. These values are then submitted to a repeated measure ANOVA with factors of condition (BEG; END) and map (e.g. Murray et al., 2008 for details on the procedure).

2.6. Electrical source estimations

Electrical sources estimations were calculated using a distributed linear inverse solution and the local autoregressive average (LAURA) regularization approach (Grave de Peralta et al., 2001, 2004). The results of the above topographic pattern analysis defined time periods of topographic modulations over which intracranial sources were estimated and statistically compared between the BEG vs. END conditions.

3. RESULTS

3.1. Behavioral Results

We indexed behavioral performance by median Go RTs, SSDs (stop signal delays) and SSRTs (stop signal reaction times). SSRT is calculated by subtracting the median SSD from the median RT (Band et al., 2003; Verbruggen and Logan, 2009). In line with previous literature, we consider the SSRT as the critical variables because it indexes the time needed to inhibit a response once the stop signal occurs, i.e. the latency of the stop process (Verbruggen and Logan, 2008b). As for the EEG analyses, behavioral data were separately averaged for the Beginning (BEG) and End (END) conditions. SSRT decreased significantly between the beginning and the end of the training (BEG: median±SEM = 177.5±7.2msec; END: 146.6±7.8msec; $t_{(12)}$=2.72; p=0.018). Go RTs, SSD, the percentage of successful stopping and of misses did not significantly differ with training (Go RT: BEG: 756.3±28.6msec; END: 778.3±30.9msec; $t_{(12)}$=-0.72; p=0.483; SSD: BEG: 578.8±28.4msec; END: 631.7±32.8msec; $t_{(12)}$=-1.85; p=0.088; percent success stop: BEG: 61.76±1.38%; END: 63.34±1.67%; $t_{(12)}$=-0.90; p=0.386 and percent misses: BEG: 0.30±0.09%; END: 0.63±0.17%; $t_{(12)}$=-1.22; p=.243).

3.2. Electrical Neuroimaging Results

3.2.1. Topographic Pattern Analysis

The output of the topographic pattern analysis is displayed in Figure 2.a (the butterfly plot of the AEP to the Go stimuli is provided to help evaluating the signal quality and to situate the present effect according to typical AEP waveform components). The global explained variance of the Hierarchical Clustering analysis was 97.8%. This topographic pattern analysis identified the same sequence of stable topographic maps for trials from the BEG and END conditions, except for the 185-213msec post-stimulus onset time period. Over this period, different maps were observed for the BEG vs. END conditions. The reliability of this observation at the group-averaged level was then assessed at the single-subject level using a spatial correlation fitting procedure (see Method section). The individual-subject fitting procedure revealed that over the 185-213msec period, the light blue map was more frequent for the BEG and the dark blue map for the END condition ($t_{(12)}$=-2.23, p=0.045), indicative of the engagement of distinct configuration of intracranial generator in response to Go stimuli presented at the beginning vs. the end of the training (Fig. 2.b).

3.2.2. Electrical Source Estimations

LAURA distributed source estimations revealed a significant decrease of activation between the BEG and END conditions within right inferior frontal gyrus (IFG) as well as in pre-supplementary motor area (SMA), SMA, primary motor area (M1) and basal ganglia ($t_{(12)}$>3.05; p<0.01; Fig. 3). Correlational analysis performed between the current density (i.e. the scalar values of the source estimation) of the IFG and behavioral performance revealed that the difference in response strength between the beginning and the end of the training within the right inferior frontal gyrus cluster positively correlated with the decrease in SSRT between the beginning and the end of the training ($r_{(11)}$=0.60; p=0.027). The more activity in the right IFG decreased with training, the more the latency of inhibition decreased. We found no such correlation with the other cluster (p<0.05).

4. DISCUSSION

We showed that inhibitory control proficiency improves rapidly with training and we identified spatio-temporal brain mechanisms of the supporting neuroplastic changes. Behaviorally, Stop Signal Reaction Time (SSRT) decreased over the course of the Stop-Signal Task training, indicating that the training reduced the speed of response inhibition. The contrast between electrical neuroimaging responses to Go stimuli recorded at the beginning versus the end of the SST training showed that AEPs modulated topographically as a function of training at a latency of 200ms post-stimulus onset, indicative of changes in the underlying intracranial generators. The statistical analysis of electrical source estimations showed that this effect followed from a decrease in the activity of the right inferior frontal gyrus as well as of the pre-SMA, primary motor cortex and basal ganglia. Importantly, the decrease in activity of the inferior frontal gyrus positively correlated with the behavioral improvement in inhibitory control.

Our behavioral results corroborate previous psychophysical evidence for a increase in inhibitory control proficiency SSRT with SST training (Fillmore et al., 2001; Turner et al., 2004; though see Cohen and Poldrack, 2008). This finding suggests that inhibitory control proficiency increases with SST practice. Because it takes into account both the SSD and GoRT, the SSRT is generally considered as being independent on changes in responses strategies and thus to constitute a reliable index of inhibitory control proficiency (Congdon et al., 2012). However, SSRT have been shown to depend on several factors unrelated to inhibitory control including e.g. the probability or salience of stop-trials (van den Wildenberg

et al., 2002; van der Schoot et al., 2005) or the motivational context (Leotti and Wager, 2010), suggesting it may not forcibly reflect genuine inhibition performance. Although negative results should be interpreted with caution, the change in SSRT unlikely followed from a change in strategy in the current study because there was no evidence of a change in the proportion of missed Go or of Stop success across training blocks. We detected a change in SSRT and thus if there was any undetected change in the other dependent variables due to a lack of statistical power, the effect size would likely be lower than the change in SSRT.

At the electrophysiological level, the effects of training manifested as a topographic modulation over the 185-213msec post-stimulus onset. The latency of our effect is in line with previous literature on the temporal dynamic of inhibitory control reporting that inhibition-related ERP components peak around 200msec post-stimulus in Go/NoGo (Falkenstein et al, 1999) and SST paradigms (Schmajuk et al., 2006).

Source estimations revealed that the topographic modulation followed from the change in the activity of the right inferior frontal gyrus and pre-SMA, primary motor cortex and basal ganglia. This result is highly consistent with previous functional, transcranial magnetic stimulation (TMS) and lesion studies showing a specific involvement of the right IFG, pre-SMA and basal ganglia in inhibitory control. Numerous studies indeed pointed out this right-lateralized fronto-basal network as the core network of inhibitory control of motor action (in SST task, see Aron and Poldrack, 2006; Verbruggen and Logan, 2008b; Aron, 2011). TMS over the right IFG (but not the left IFG or right middle frontal gyrus) has been shown to impair stopping performance (Chambers et al., 2006). Likewise, lesions in the right IFG or in the right pre-SMA lead to impairments in the stopping performance (Aron et al., 2003). Our finding for training-induced activity in the basal ganglia is in line with fMRI studies reporting activation in the subthalamic nucleus (STN) and striatum during inhibitory control tasks (e.g. Aron and Poldrack, 2006). Similarly, lesion or deep-brain stimulation of the STN influences SSRT during SST (van den Wildenberg et al., 2006; Eagle et al., 2008).

The inhibitory control of motor action across various effectors and critically, of non-motor, cognitive and affective functions relies on the same fronto-basal network (and latency) as the network that was modified with our training regimen. Indeed, the 200msec time period has been shown to correspond to processing stage when non-motor types of inhibition manifest, suggesting that effectors- and functions- aspecific inhibitory processes take place over this time window (e.g. Jackson et al., 2001). Moreover, the pre-SMA, IFG and STN are also recruited for inhibiting or stopping eye movements (Chikazoe et al., 2007), speech (Xue et

al., 2008) or other language-related processes (Xue et al., 2006). Growing evidence also report the involvement of this fronto-basal network in the inhibitory control of thoughts, memory or emotion (Jonides et al., 1998; Depue et al., 2007; Dillon and Pizzagalli, 2007). Although speculative, because the same fronto-basal network supports motor inhibitory control as trained in the current study and the inhibition of other cognitive processes, a modification of this network would likely impact the inhibitory control of other untrained functions. In turn, one could hypothesize that the proposed training regimen might help recovering pathologies involving either structural or functional deficits of the fronto-basal network. This hypothesis requires direct empirical testing, but it is further supported by evidence that even if inhibition-related pathologies are not functionally characterized by motor deficits, their clinical profiles include abnormal SSRT (ADHD: Overtoom et al., 2002; obsessive compulsive disorders: Chamberlain et al., 2006; addiction: Fillmore and Rush, 2002; or schizophrenia: Enticott et al., 2008; see Lipszyc and Schachar, 2010 for a meta-analysis). Moreover, recent evidence pointed that motor inhibitory control training reduced risky behavior during subsequent gambling tasks (Verbruggen et al., 2012). While further studies are needed to elucidate the question of the generalization of our effects to other tasks and conditions, the current results suggest that using SST training for the remediation of complex inhibition-related psychiatric conditions involving functional and structural deficits of the inhibitory fronto-basal network might constitute a viable option.

Importantly, the change in activity within the prefrontal cluster with training correlated with the improvement in inhibitory control proficiency. This result not only supports the functional role of the observed electrophysiological effects of training, but also that the change in the IFG response constitute reliable indexes of behavioral improvements and might thus serve to monitor functional recovery in inhibition-related diseases.

Most of previous studies show increased activity in the right prefrontal areas to be associated with shorter Stop Signal Reaction Times (Aron and Poldrack, 2006; Rubia et al., 2007; though see Chao et al., 2009). By contrast, we show that improvement in inhibitory efficiency was correlated with a decrease in activity in the right IFG. A putative neurophysiological mechanism accounting for our effect is that training yielded to an exclusion of irrelevant neural activity to increase the selectivity and in turn the efficiency of neural activity (Kelly and Garavan, 2005). Supporting our results, decreases in frontal activity have typically been reported following training on high-order executive function tasks as the one used in the current study (Beauchamp et al., 2003; Hempel et al., 2004), whereas increased activity in task-relevant brain regions were observed in lower-level motor or sensory training tasks (Kelly et al., 2006). However, as mentioned above, we cannot rule out

that change in response strategies or in motivation during the training impacted the SSRT and could thus also be reflected in the decrease in rIFG activity. Further studies would be necessary to elucidate this question.

Of note, the inhibitory control training regimen used in the current study modified high-order, late-latency fronto-basal executive mechanisms. This pattern contrasts with previous evidence for the development of automatic, feed-forward forms of inhibition induced by training with a Go/NoGo task (Manuel et al., 2010). This difference in the effect of training with a SST vs. a Go/NoGo task likely follow from the fact that in SST task, Go stimuli are inconsistently associated with Go and NoGo goals, whereas in Go/NoGo task, repeated associations between NoGo stimuli and NoGo goals enable stimulus-driven inhibition to develop (Shiffrin and Schneider, 1977; Verbruggen and Logan, 2008a).

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FIGURE LEGENDS:

Figure 1. Experimental design. Each participant completed a one-hour training session on the Stop Signal Task. The Stop Signal Delay (SSD) varied according to participants' performance.

Figure 2. Topographic pattern analyses of the auditory evoked potential. **a**. The Auditory Evoked Potential (AEPs) in response to the beginning (BEG; red) and the end (END; black) of the SST training are displayed in microvolts as a function of time. Topographic pattern analysis identified one period of stable electric field topography where two maps were differentially accounted for the two conditions: 185-213msec post-stimulus onset. **b**. The reliability of this observation at the group-averaged level was then assessed at the single-subject level using a spatial correlation fitting procedure. Over the 185-213msec period, different maps (framed in light and dark blue) described AEPs as a function of training (BEG/END). Results showed a significant interaction between training session and map. Error bars indicate SEM.

Figure 3. Electrical source analyses. **a**. Node-wise t-test over the 185-213msec post-stimulus onset period revealed significant differences between the beginning vs. the end of SST training in the right inferior frontal gyrus (rIFG) and the pre-supplementary motor area (SMA), SMA, and basal ganglia. **b**. There was a decrease in the activity of the inferior frontal gyrus and **c**. in pre-SMA and basal ganglia as a function of training.

Figure 1
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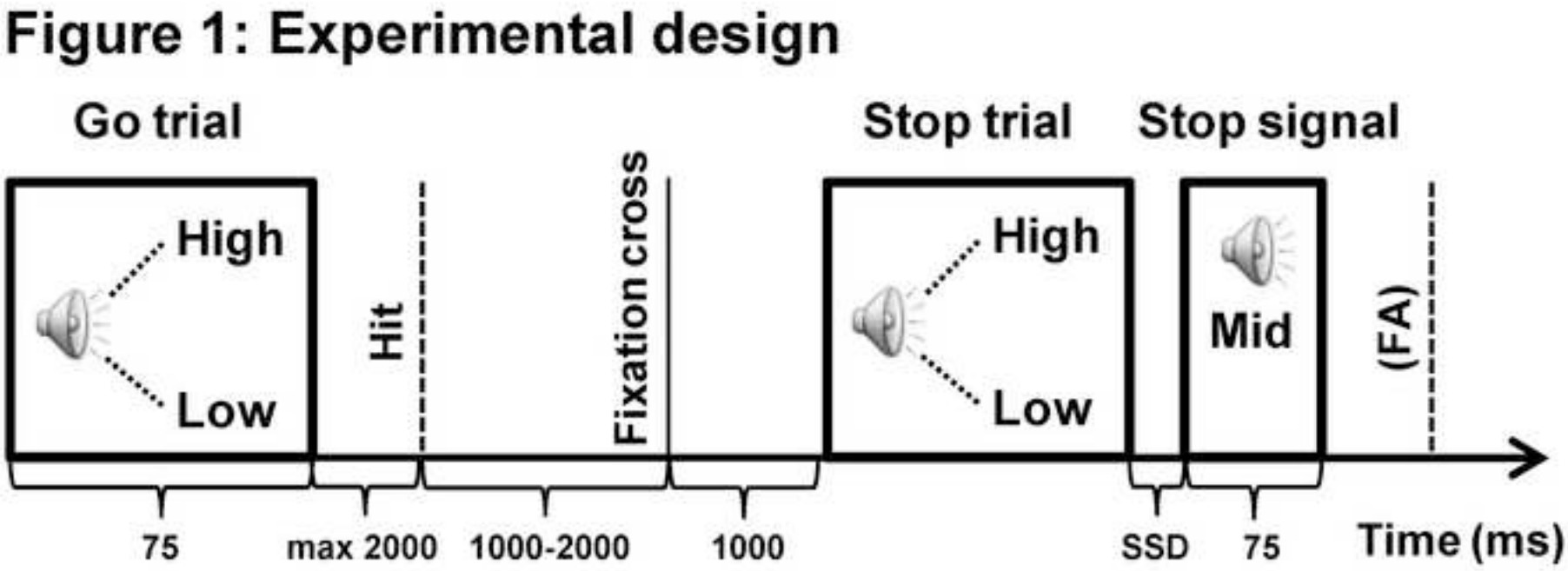

Figure 2
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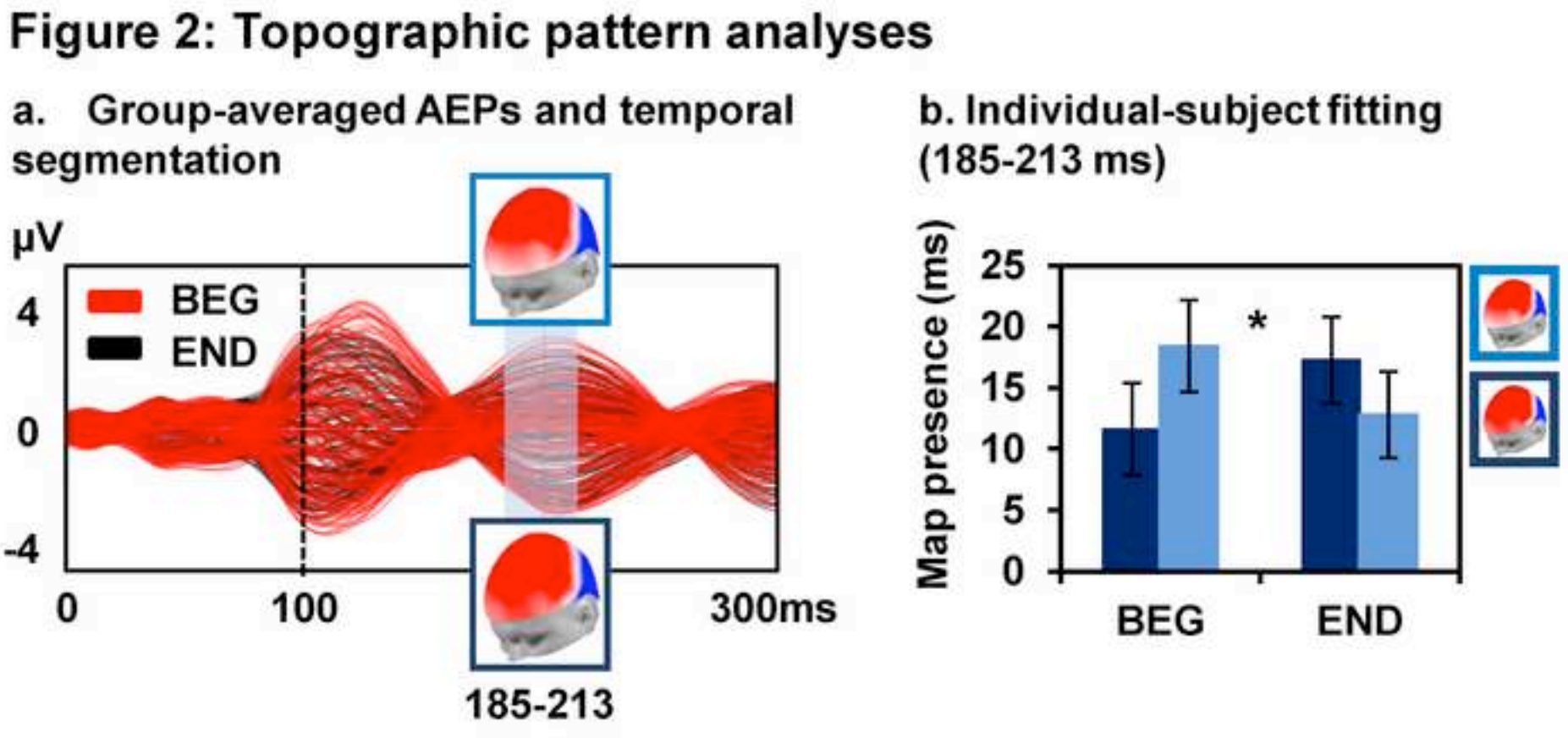

Figure 3
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