

available at www.sciencedirect.comwww.elsevier.com/locate/brainres

**BRAIN
RESEARCH**

Research Report

Contribution of the pre-SMA to the production of words and non-speech oral motor gestures, as revealed by repetitive transcranial magnetic stimulation (rTMS)

Pascale Tremblay^{a,b,*}, Vincent L. Gracco^{a,b,c}

^aMcGill University, Faculty of Medicine, School of Communication Sciences and Disorders, 1266 Avenue des Pins, Montreal, Canada

^bCentre for Research on Language, Mind and Brain, Canada

^cHaskins Laboratories, New Haven, Connecticut, USA

ARTICLE INFO

Article history:

Accepted 27 February 2009

Available online 12 March 2009

Keywords:

Response selection

Speech production

Motor system

Language

Medial frontal Cortex

Attention

ABSTRACT

An emerging theoretical perspective, largely based on neuroimaging studies, suggests that the pre-SMA is involved in planning cognitive aspects of motor behavior and language, such as linguistic and non-linguistic response selection. Neuroimaging studies, however, cannot indicate whether a brain region is equally important to all tasks in which it is activated. In the present study, we tested the hypothesis that the pre-SMA is an important component of response selection, using an interference technique. High frequency repetitive TMS (10 Hz) was used to interfere with the functioning of the pre-SMA during tasks requiring selection of words and oral gestures under different selection modes (forced, volitional) and attention levels (high attention, low attention). Results show that TMS applied to the pre-SMA interferes selectively with the volitional selection condition, resulting in longer RTs. The low- and high-attention forced selection conditions were unaffected by TMS, demonstrating that the pre-SMA is sensitive to selection mode but not attentional demands. TMS similarly affected the volitional selection of words and oral gestures, reflecting the response-independent nature of the pre-SMA contribution to response selection. The implications of these results are discussed.

© 2009 Elsevier B.V. All rights reserved.

1. Introduction

The fundamental role of the medial frontal cortex, and especially of the pre-SMA, in cognitive aspects of voluntary behaviors is becoming more and more apparent. Classically, the SMA has been defined as a single region corresponding to the medial aspect of Brodmann's area 6 (Penfield and Welch, 1951). Evidence is accumulating indicating that the SMA is divided into at least two functionally distinct regions: the pre-SMA and the SMA-proper. The pre-SMA is densely

interconnected with the prefrontal cortex, an important center for executive functions (Bates and Goldman-Rakic, 1993; Lu et al., 1994; Wang et al., 2005), and it has no direct connection with M1, the spinal cord or the cranial nerve motor nuclei (e.g. Dum and Strick, 1991; Luppino et al., 1993; Lu et al., 1994). Recent evidence shows that the pre-SMA receives input from the non-motor domain of the basal ganglia and cerebellum (Akkal et al., 2007). The SMA-proper, in contrast, has direct connection with M1 (e.g. Muakkassa and Strick, 1979; Luppino et al., 1993), the spinal cord (e.g.

* Corresponding author. 1266 avenue des Pins West, Montreal, QC, Canada H3G 1A8. Fax: +1 514 398 8123.

E-mail address: pascale.tremblay@mail.mcgill.ca (P. Tremblay).

Dum and Strick, 1991; Bates and Goldman-Rakic, 1993; Lu et al., 1994) and the cranial nerve motor nuclei (Morecraft et al., 2001). The input that it receives from the basal ganglia and cerebellum originates from motor domains of these regions (Akkal et al., 2007). These radically different connectivity patterns suggest that the pre-SMA is involved with high-order aspects of movements such as response selection, conflict monitoring/resolution and decision-making, while the SMA-proper is primarily concerned with the execution of movements.

Consistent with this hypothesis, the pre-SMA has been associated with the production of volitional movements (e.g. Deiber et al., 1996; Van Oostende et al., 1997; Ullsperger and Von Cramon, 2001; Lau et al., 2004, 2006; Nachev et al., 2005), including manual gestures, finger movements and saccades, as well as with tasks involving high response competition/conflict such as response and task switching (Rushworth et al., 2002; Derrfuss et al., 2004; Mars et al., 2007), flanker-type tasks (Ullsperger and Von Cramon, 2001; Nachev et al., 2005; Botvinick et al., 1999; Fan et al., 2007) and inhibition of manual gestures and speech (Xue et al., 2008). The pre-SMA is more strongly active for drawing geometrical shapes (internally driven) compared to tracing them (externally cued) (Gowen and Miall, 2007); it is also involved in cognitive tasks involving memory and decision-making (Donohue et al., 2008), verbal trail making test (Moll et al., 2002), and verbal *n*-back task, wherein participants have to determine whether a visually presented letter has been presented *n* trials earlier (Derrfuss et al., 2004).

The pre-SMA is also involved in a wide variety of overt language production tasks, from the most simple, such as syllable repetition (Kemeny et al., 2005) to more complex tasks such as word reading (Fiez et al., 1999), semantic-based word generation (Abrahams et al., 2003; Alario et al., 2006; Tremblay and Gracco, 2006), letter-based fluency (Abrahams et al., 2003), verb generation (Etard et al., 2000), word-stem completion (Palmer et al., 2001), text reciting (Bookheimer et al., 2000), sentence production (Kemeny et al., 2005; Haller et al., 2005) and even story telling, a complex and ecological form of spoken language production (Braun et al., 2001). The pre-SMA is also involved in covert noun or verb generation (Crosson et al., 2001; Persson et al., 2004). In general, volitional word production tasks are associated with a higher activation level than more automatic and more externally constrained tasks (Etard et al., 2000; Blank et al., 2002; Kemeny et al., 2005; Alario et al., 2006; Tremblay and Gracco, 2006). A recent study comparing the covert selection of verbs, nouns and adjectives, has shown that the SMA/pre-SMA is always active, regardless of the nature of the word (Blacker et al., 2006), suggesting a role for the pre-SMA in a general word selection process. The pre-SMA is also involved in the selection of simple oral gestures (Tremblay and Gracco, *in press*) and in the production of self-organized sequences of lip, jaw and tongue movements (Braun et al., 2001). Recent evidence indicates that the pre-SMA is also active in lexical decision tasks, especially when it involves unfamiliar words or pseudowords (Carreiras et al., 2006, 2007).

The clinical literature converges with the neuroimaging literature to support a role for the pre-SMA in response selection. A relatively large number of studies have shown that lesions to the SMA/pre-SMA often lead to a deficit with

spontaneous, volitional actions and speech, in the absence of a concomitant paralysis (e.g. Zentner et al., 1996; Peraud et al., 2002; Fontaine et al., 2002; Russel and Kelly, 2003; Pai, 1999; Mendez, 2004; Chainay et al., 2009). Importantly, externally triggered movements are either preserved or they recover relatively quickly. For example, results from a case study revealed persistent difficulty with verbal fluency in a patient who underwent surgical removal of the pre-SMA, while naming, repetition and reading were preserved (Deblieck et al., 2003). Together, neuroimaging studies on healthy volunteers and SMA patient studies suggest a broad role for the pre-SMA in cognitive neuroscience, one that is independent of the response modality (finger, eye, tongue) and task domain (language, memory, motor). The pre-SMA appears to be part of a network that is concerned with response selection in a broad sense.

Previous neuroimaging studies from our laboratory (Tremblay and Gracco, 2006; Tremblay and Gracco, *in press*) and others (Crosson et al., 2001; Alario et al., 2006) have shown that the pre-SMA is involved in volitional word selection compared to more constrained word selection tasks. However, since volitional selection usually requires a higher attention level than constrained selection, it is unclear whether the pre-SMA contribution is due to increased attention demands or increased selection demands, or both. While neuroimaging studies can identify the brain regions that are active during response selection, they cannot reveal which of these areas are essential for this process. Transcranial magnetic stimulation (TMS), in contrast, is an interference technique that can be used to establish, in healthy volunteers, the necessity of a circumscribed cortical region for a particular cognitive, motor or language task. TMS-induced “virtual lesions” recover in tenths of milliseconds, that is, too quickly to trigger compensatory changes in the brain, and therefore do not suffer the main caveats of patient studies (spatial resolution, lesion-induced brain plasticity). The primary goal of the present study was to establish, using TMS, whether the pre-SMA is causally related to the selection of words under three different selection modes: a three-alternative low-attention forced selection condition (baseline), a three-alternative high-attention forced selection condition and a three-alternative high-attention volitional selection condition. This set of experimental conditions allowed us to dissociate the effect of attention from the effect of selection. Based on the literature, we predicted that TMS-induced disruption would take the form of a slowing of the RT in the volitional selection condition, leaving the RT in the other conditions unaffected. More specifically, we expected a two-way interaction between TMS and selection mode, with the effect of TMS being the strongest in the volitional selection condition. In order to assess the specificity of any potential TMS-related effect in the pre-SMA, we added a control stimulation site, the SMA-proper. While we expected that TMS over the pre-SMA would lead to a TMS by selection mode interaction, we expected no such interaction for SMA-proper stimulation. The two stimulation sites are illustrated in Fig. 1.

In most studies of word production, response selection depends on semantic and phonological processing (e.g. word generation from a semantic category). As a result, it is unclear whether the pre-SMA contribution to these tasks is related to a

general selection mechanism, or whether it is related to the linguistic processes that accompany word production. The other aim of this study was therefore to provide direct evidence that the pre-SMA is involved in the selection of words, in a manner that is analogous to its role in the selection of any other response. In order to demonstrate that the pre-SMA contribution is independent from linguistic processes, we designed a word selection task that required no linguistic processing, but which relied instead on a set of arbitrary SR associations. In order to further demonstrate the generality of the selection process, we compared this non-linguistic word selection task to the selection of oral motor gestures (whistling, making a kissing gesture and a raspberry sound, see Table 1 for more details) involving the same set of effectors (mainly the lips). We predicted that the effect of TMS would be similar for the words and for the gestures, that is, that there would be no three-way interaction between TMS, selection mode and response modality, reflecting a role for the pre-SMA in a general (response-independent) selection process. Fig. 2 illustrates the experimental design. Refer to the [Experimental procedures](#) section for the specifics of the experimental manipulations.

2. Results

2.1. Response accuracy

Participants' performance reached ceiling with a mean \pm SD of $99.83\% \pm 0.03$ for the experimental group and $99.87\% \pm 0.04$ for the control group. The percentages of accurate responses for each experimental condition are listed in Table 2.

2.2. Volitional response generation

As indicated by the group contingency analyses in Table 3, TMS did not affect the manner in which volitional responses were selected. This was true for the majority of the experimental group (11/12) and, likewise, for the majority of the participants in the control group (11/12). The frequency of use of each word and each gesture, for each participant, is provided as [Supplementary material \(S1\)](#).

2.3. Reaction time

Table 4 presents the RT and response duration for all experimental conditions for the experimental group (pre-SMA). The repeated measure ANOVA (rANOVA) revealed a significant main effect of response MODALITY ($F_{(1,11)}=13.29$, $p=0.004$), with longer RTs for the oral gestures than the words. There was also a significant overall main effect of TMS ($F_{(1,11)}=13.38$, $p=0.004$), and a significant main effect of selection MODE ($F_{(2,22)}=35.34$, $p<0.001$). RTs for the forced choice (1.25 ± 0.07 s) and volitional (1.29 ± 0.069 s) conditions were significantly longer than for the baseline (0.81 ± 0.04 s) ($p \leq 0.05$, Bonferroni corrected) but did not differ from one another ($p=1.00$, Bonferroni corrected). As predicted, there was a significant two-way interaction between TMS and selection MODE ($F_{(2,22)}=4.69$, $p=0.02$), indicating that the effect of TMS was only significant for the volitional selection condition

($p \leq 0.05$, Bonferroni corrected). There was a 120 ms difference in RTs for the TMS trials (1.34 ± 0.07) compared to the SHAM trials (1.22 ± 0.06). This finding is illustrated in Fig. 3. As was also predicted, there was no three-way interaction between TMS, MODE and MODALITY ($F_{(2,22)}=2.37$, $p=0.12$). There was, however, a significant two-way interaction between TMS and response MODALITY ($F_{(1,11)}=9.99$, $p=0.009$), revealing a significant overall TMS effect for the gestures but not for the words. This finding is illustrated in Fig. 4.

Table 5 presents the RT and response duration for all experimental conditions for the control group (SMA-proper). The rANOVA revealed a significant main effect of response MODALITY ($F_{(1,11)}=133.52$, $p=0.00$). The RTs were longer for the oral gestures than for the words. The rANOVA also revealed a significant effect of selection MODE ($F_{(2,22)}=30.53$, $p<0.0001$). RTs for the forced choice (1.31 ± 0.10 s) and volitional (1.29 ± 0.12 s) conditions were significantly longer than RTs for the baseline condition (0.67 ± 0.06 s) ($p \leq 0.05$, Bonferroni corrected), but they did not differ from one another ($p=1.00$). There was also a significant main effect of TMS ($F_{(1,11)}=18.27$, $p=0.001$). As

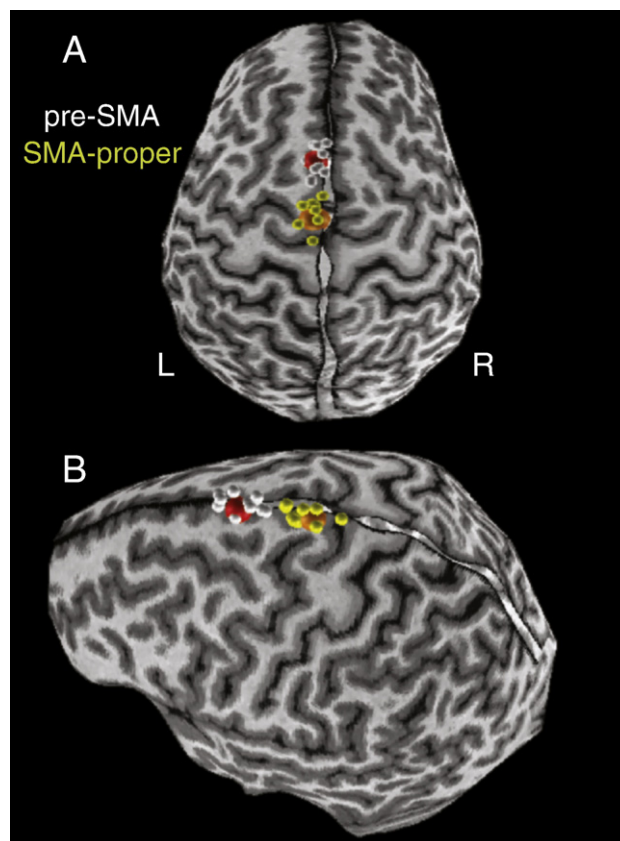


Fig. 1 – Dorsal (A) and left lateral (B) views of the stimulation sites, on a 3D reconstruction of a participant's MRI (Brainsight TMS, Rogue Research, Montréal, Canada). The small white spheres represent the individual stimulation sites for participants in the experimental group (pre-SMA TMS) and the larger red sphere represents the average stimulation site for that group. The small yellow spheres represent the individual stimulation sites for participants in the control group (SMA-proper) and the larger orange sphere represents the average stimulation site for that group.

Table 1 – Characteristics of the words and gestures used in the experiment.

Word	Gestures	Concret. ^a	Fam. ^b	KFRQ ^c	T-LFRQ ^d	Freq ^e	WFreq ^f	Phon. ^g	Syll. ^h	Artic. ⁱ
Wood	Whistling	606	574	55	620	N/A	N/A	3	1	Lips
Fish	Raspberry ^j	597	583	70	505	N/A	N/A	3	1	Lips
Pot	Kiss	584	548	35	597	N/A	N/A	3	1	Lips
Vue	Whistling	N/A	N/A	N/A	N/A	93	144	2	1	Lips
Fils	Raspberry	N/A	N/A	N/A	N/A	382	247	3	1	Lips
Point	Kiss	N/A	N/A	N/A	N/A	192	272	3	1	Lips

Note: words and gestures on the same row indicate pairing. Words #1 to 3 were used with the English participants and words #4 to 6 were used with the French speaking participants.

^a Concreteness rating (100–700) according to the MRC Psycholinguistic database (http://www.psy.uwa.edu.au/mrcdatabase/uwa_mrc.htm) (English words only).

^b Familiarity rating (100–700) according to the MRC Psycholinguistic database (English words only).

^c KFRQ: Kucera–Francis written frequency (>0) according to the MRC Psycholinguistic database (English words only).

^d T-LFRQ: Thorndike–Lorge written frequency (0–3,000,000) according to the MRC Psycholinguistic database (English words only).

^e Frequency rating based on a corpus of recent movie sub-titles containing 16.6 million words taken from 2960 movies (www.lexique.org) (French words only). The maximal frequency is 33,959.88 and the average is 64.83.

^f Written frequency rating based on a corpus of texts containing 14.7 million words taken from 218 books published between 1950 and 2000 (FranText; www.lexique.org) (French words only). The maximal frequency is 38,943.65 and the average is 48.37.

^g Number of phonemes.

^h Number of syllables.

ⁱ Main place of articulation.

^j Making a raspberry sound consists of blowing air out from the mouth while keeping the lips slightly approximated resulting in a sound that is reminiscent of flatulence. In the US it is also called a “Bronx cheer” and signifies derision.

predicted, there was no interaction between TMS and selection MODE ($F_{(2,22)}=2.79$, $p=0.83$), and no three-way interaction between TMS, MODE and MODALITY ($F_{(2,22)}=0.26$, $p=0.11$). There was, however, a marginally significant interaction between TMS and response MODALITY ($F_{(1,11)}=4.21$, $p=0.06$).

3. Discussion

The process of selecting a response is an essential component in the planning of voluntary behaviors including language production. The main objective of this study was to examine the contribution of the pre-SMA to this process. Before discussing the results in more details, it is worth mentioning three intrinsic limitations of the TMS technique: 1) inter-subject anatomical differences, 2) nonspecific attentional and/

or sensory effects induced by the TMS stimulation, and 3) spatial resolution. In order to minimize inter-subject anatomical differences, the location of the stimulation site was done using frameless stereotaxy and individually adjusted based on participants' own anatomy. Although we did not perform fMRI to determine the specific part of the left SMA/pre-SMA involved in selecting words and oral gestures, our stimulation sites were consistent with peak activations in these regions during speech production, as reported in previous studies (e.g. Tremblay and Gracco, 2006; Alario et al., 2006). With regard to the second limitation, we believe that the selectivity of the current TMS interference, which only affected the volitional selection condition, argues against the possibility of a nonspecific TMS effect. As for the third potential limitation, spatial resolution, it might be argued that the size of the stimulator that was used (7 cm) limited our

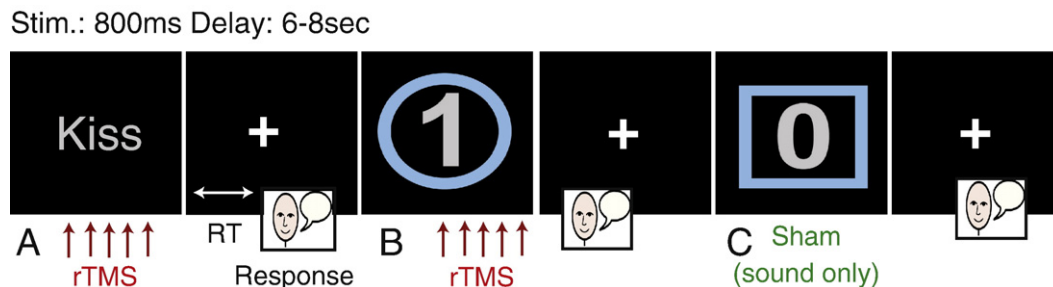


Fig. 2 – Examples of the visual stimuli used in the experiment. The faces represent the time during which the participant responded. RT=reaction time, which was calculated from stimulus offset to response onset. The red arrows indicate the time of application of the stimulation (rTMS, Sham). (A) Example of a low attention forced selection trial (baseline) with rTMS. In all conditions, stimulus presentation is always followed by the presentation of a crosshair fixation point, which remains on the screen until the next stimulus is presented 6–8 s later. (B) Example of a high-attention forced selection trial also with TMS. Geometrical shapes indicate the response modality (words, oral gestures), while numbers indicate the specific response (refer to the manuscript for more details). (C) Example of a volitional selection SHAM trial (no TMS). In these trials, the number zero is presented within a circle or a square.

Table 2 – Accuracy results.

Selection mode	Response modality	Stimulation level	Control group (mean %±SE)		Experimental group (mean %±SE)	
Baseline	Words	TMS	100.0	0.0	100.0	0.0
		Sham	100.0	0.0	100.0	0.02
Forced	Oral gestures	TMS	100.0	0.02	99.9	0.04
		Sham	99.9	0.06	100.0	0.03
	Words	TMS	99.8	0.07	99.7	0.11
		Sham	99.7	0.15	99.9	0.04
Volitional	Oral gestures	TMS	99.7	0.1	99.7	0.08
		Sham	99.6	0.1	99.7	0.1
	Words	TMS	99.9	0.05	100.0	0.02
		Sham	99.9	0.05	100.0	0.03
	Oral gestures	TMS	99.9	0.05	99.9	0.05
		Sham	99.9	0.03	99.9	0.03

Note: accuracy results (expressed in percentage of correct responses) for the different trial types (baseline=low attention forced selection; forced=high-attention forced selection; volitional=high-attention volitional selection), modalities (words, oral gestures) and stimulation levels (TMS, SHAM) for each of the groups: control (SMA-proper) and experimental (pre-SMA).

ability to dissociate the pre-SMA from the SMA-proper, due to their relative proximity (on average, 2.2. cm apart). This interpretation has the advantage of accounting for the present finding that the TMS-induced behavioral changes were qualitatively similar for the two groups. The finding of a tendency for TMS to interfere with volitional selection in the control group (SMA-proper) might have been caused by stimulation to the adjacent pre-SMA, or by spread of activation from the SMA-proper to the pre-SMA. It is important to mention, however, that our two stimulation sites were consistent with published guidelines for locating the face representation within the pre-SMA and the SMA-proper (Picard and Strick, 1996). In addition, the fact that the group results were quantitatively different suggests that our stimulation targets were distinct, at least to some extent, an interpretation that is consistent with a growing body of evidence suggesting that the effect of TMS is relatively focal (see for example Walsh and Pascual-Leone, 2003 for a review).

3.1. Neural implementation of response selection

The primary goal of the present study was to test, using an interference technique (TMS), whether the pre-SMA is causally related to the selection of words under different selection modes (forced and volitional), and attention levels (low and high). We predicted that TMS would interfere specifically with volitional selection, regardless of the response modality (words, gestures), in the experimental group (pre-SMA) only. Results showed that, in support of our predictions, pre-SMA TMS had no effect on low- and high-attention forced selection but did affect volitional selection RTs (with a 115 ms difference between TMS and sham trials). Two main conclusions can be drawn from these findings. First, the contribution of the pre-SMA to response selection is not related to attention, a factor that is frequently confounded with selection. This finding is consistent with two recent fMRI studies showing that when attention level is matched across selection modes, the

Table 3 – Group level distribution of observed and expected response frequencies along with the effect size (W) and chi-square (X²) value for the TMS and Sham trial.

Group	Stim.	Words								Gesture							
		Observed frequencies			Expected frequencies (H ₀ assumed)			W	X ²	Observed frequencies			Expected frequencies (H ₀ assumed)			W	X ²
		W1	W2	W3	W1	W2	W3			G1	G2	G3	G1	G2	G3		
EXP	Sham	178	138	147	167	137	160	0.13	3.58	164	169	116	170	170	109	0.08	1.41
	TMS	153	134	170	164	135	157	(small)	(p=0.17)	177	171	102	171	170	109	(small)	(p=0.49)
Control	Sham	155	148	161	157	144	163	0.03	0.263	166	178	124	155	192	120	0.06	0.971
	TMS	160	142	166	158	146	164	(small)	(p=0.87)	161	185	122	160	185	122	(small)	(p=0.62)

Note. EXP=experimental group (pre-SMA stimulation); Control group (SMA-proper stimulation). Stim=Stimulation level (TMS, Sham). H₀=null hypothesis (no association between stimulation level and the distribution of responses). The effect sizes (W) were calculated according to the formula by Cohen (1988):

$$W = \sqrt{\sum_{i=1}^{rk=6} (P_{oi} - P_{ei})^2 / P_{ei}}$$

where rk=the number of rows*the number of columns (2*3). P_{oi}=the proportion in cell i posited by H₀. P_{ei}=the observed proportion in cell i. In order to ensure that the group pattern was representative of single subject patterns, the same analysis was conducted for each participant. Results revealed that for all but two participants, there was no relationship between the stimulation level and the distribution of responses.

Table 4 – Descriptive statistics for the experimental group (pre-SMA stimulation).

Mode	Modality	Stim.*	RT		Duration	
			Mean	SD	Mean	SD
Baseline	Words	Sham	0.78	0.17	0.32	0.10
		TMS	0.76	0.15	0.32	0.11
	Gestures	Sham	0.82	0.18	0.35	0.26
		TMS	0.86	0.18	0.42	0.28
Forced	Words	Sham	1.18	0.30	0.32	0.10
		TMS	1.12	0.26	0.32	0.10
	Gestures	Sham	1.27	0.22	0.39	0.26
		TMS	1.40	0.28	0.34	0.26
Volitional	Words	Sham	1.14	0.22	0.32	0.10
		TMS	1.26	0.26	0.32	0.10
	Gestures	Sham	1.30	0.29	0.36	0.27
		TMS	1.42	0.32	0.32	0.27

* Stimulation condition.

activation level in the pre-SMA is modulated by selection mode (Lau et al., 2004; Tremblay and Gracco, in press).

The second main conclusion that can be drawn from these findings is that the pre-SMA is an important component in a response selection network, but only when selection is volitional. This result is consistent with previous neuroimaging experiments showing a stronger involvement of the pre-SMA for volitional selection compared to forced selection tasks (e.g. Deiber et al., 1996; Van Oostende et al., 1997; Hyder et al., 1997; Crosson et al., 2001; Ullsperger and Von Cramon, 2001; Lau et al., 2004, 2006; Tremblay and Gracco, 2006; Gowen and Miall, 2007; Tremblay and Gracco, in press). It is also consistent with a previous rTMS experiment, which showed that stimulation applied over the pre-SMA during a forced response selection task does not interfere with performance (Rushworth et al., 2002). The fact that, in the present study, rTMS applied during volitional selection did not result in a complete incapacity to perform the task, but only in delayed RT, is consistent with previous rTMS studies of the medial frontal cortex (e.g. Hadland et al., 2001; Rushworth et al., 2002, Kennerly et al., 2004). As pointed out by Walsh and Pascual-Leone (2003): “In its disruptive mode [...] TMS applied while a subject is trying to perform a task induces neural noise into the

signal-processing system” (p. 45). “Under most conditions, TMS adds only enough noise to delay the process, but if the task is difficult enough (i.e., in circumstances where internal noise is already high) errors may occur.” (p. 66). Hence, it is not necessary to produce a complete behavioral disruption to conclude that a cortical region is causally related to a task.

The finding that the pre-SMA is only causally related to volitional response selection raises the question of its role within the human action system. One possibility is that the pre-SMA is specifically involved in preparing volitional actions, perhaps in providing a motivational signal to bias the choice of one response, allowing selection to occur. Such motivational signal is not necessary during forced selection, so long as the learned stimulus–response (SR) associations can be accessed. The idea that the medial frontal cortex is involved in the preparation of volitional (willed) behaviors is longstanding, although not without controversy. In his seminal article, Goldberg (1985) suggested that the medial premotor area (SMA) is a central component in a willed action system (also comprising the basal ganglia and the cingulate motor area), which he described as spontaneous, anticipatory (intention driven), and sensitive to internal factors. This hypothesis, however, cannot account for the pre-SMA activation that is often observed during forced selection tasks (e.g. Sakai et al., 2000; Kemeny et al., 2006; Mueller et al., 2007, Tremblay and Gracco, in press). Another possibility, more consistent with these findings, is that the pre-SMA is involved in a general response selection process that can be bypassed when responses are selected based on SR associations, as in forced response selection. Put simply, selection in this context may be more automatic, and rely on cortical regions involved in activating a motor response based on a stimulus and less so on the pre-SMA. When a response is freely chosen, in contrast, response competition is high and selection cannot be accomplished in an automatic fashion. In other words, resolving response competition, rather than volition *per se*, may be one of the functional roles of the pre-SMA. A previous rTMS study by Jahanshahi and Dürmberger (1999) provides some evidence for this interpretation. Results of this study showed that rTMS applied over the left dorsolateral prefrontal cortex (DLPFC), but not over the medial frontal cortex, modifies the manner in which participants generate random sequences of numbers, suggesting a role for the DLPFC in biasing the choice of

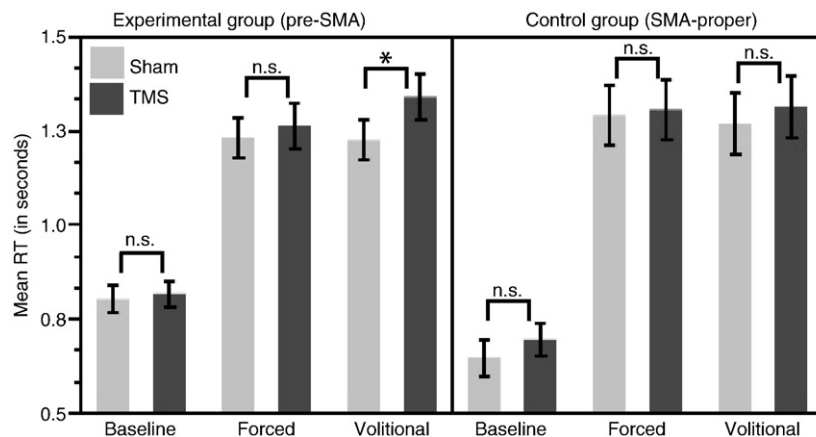


Fig. 3 – Mean reaction time, in seconds, for each of the selection mode (Baseline, Forced and Volitional) during the TMS trials and the sham trials, collapsed across response modalities, for the experimental group (left panel) and the control group (right panel).

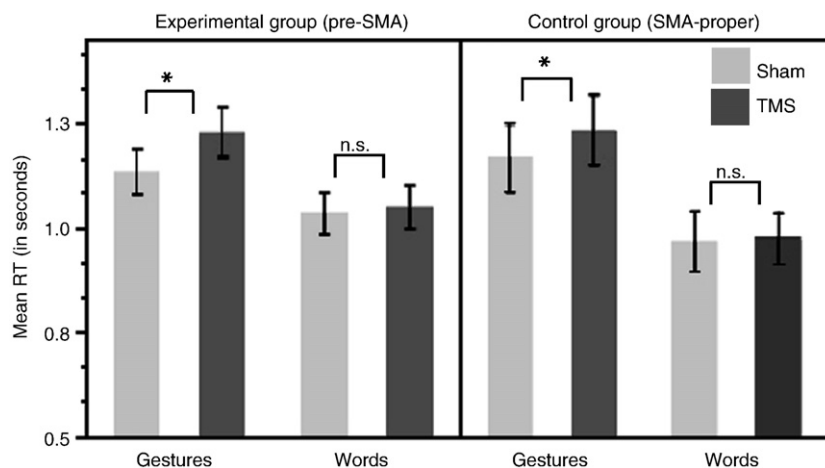


Fig. 4 – Mean reaction time, in seconds, for each of the response modality (words, oral gestures) during the TMS trials and the sham trials, collapsed across selection mode, for the experimental group (left panel) and the control group (right panel).

responses. In the present study, the contingency analysis revealed no such effect, consistent with Jahahanshi et al. In keeping with this study, hence, the current findings suggest that while the pre-SMA may be involved in resolving competition, the DLPFC may be providing a biasing signal toward one of the competing response alternatives, allowing for selection to occur.

3.2. Pre-SMA, SMA-proper and response selection

As was expected, only the pre-SMA exhibited sensitivity to selection mode. When applied to the SMA-proper, rTMS caused a general slowing of motor responses, in the order of 30 ms (TMS > SHAM trials). This effect did not differ statistically across selection modes. This is in contrast to the effect observed for the pre-SMA, which was specific to the volitional selection task. The finding of a functional dissociation between pre-SMA and the SMA-proper is consistent with the literature on non-human primates indicating a difference between these areas based on cytoarchitecture (Matelli et al., 1991; Geyer et al., 1998; Vorobiev et al., 1998), connectivity (e.g. Dum and Strick, 1991; Matelli and Luppino, 1996; Inase et al., 1999; Bates et al., 1993; Lu et al., 1994; Wang et al., 2005; Akkal et al., 2007), and excitability properties (Luppino et al., 1991). The connectivity pattern of the pre-SMA suggests that it is involved in supra-motor processes such as response selection, while the SMA-proper appears to be involved in movement execution (Rizzolatti et al., 1998; Luppino and Rizzolatti, 2000). In keeping with the known characteristics of the pre-SMA and SMA-proper, the present results further support the notion that the SMA-proper has a general motor or premotor function, while the pre-SMA is modulated by higher-order cognitive-motor factors such as selection mode. A previous rTMS study has shown that stimulation over the pre-SMA interferes with response switching, while stimulation over the SMA-proper during the same task had no observable effect, neither on response switching nor on response selection (Rushworth et al., 2002). Our results concur with those of Rushworth et al. (2002) demonstrating that the pre-SMA, but not the SMA-proper, is concerned with higher-order cognitive-

motor processes such as volitional response selection and response switching.

3.3. Selection across response modalities

The pre-SMA is activated for tasks involving linguistic-based response selection, such as word generation (Etard et al., 2000; Crosson et al., 2001; Chung et al., 2005; Alario et al., 2006; Tremblay and Gracco, 2006), verbal fluency (Abrahams et al., 2003; Schlosser et al., 1998; Basho et al., 2007), and even propositional speech (Braun et al., 2001; Blank et al., 2002). However, one question that has not been addressed previously is whether the pre-SMA contributes directly to the linguistic operations such as semantic or phonemic-based search, morphological or syntactic encoding or contributes in a more language-independent way to any kind of response selection. In the present study, selection of words and

Table 5 – Descriptive statistics for the control group (SMA stimulation).

Mode	Modality	Stim. *	RT		Duration	
			Mean	SD	Mean	SD
Baseline	Words	Sham	0.59	0.24	0.34	0.13
		TMS	0.62	0.20	0.37	0.14
	Gestures	Sham	0.70	0.24	0.32	0.19
		TMS	0.77	0.21	0.35	0.18
Forced	Words	Sham	1.16	0.36	0.34	0.12
		TMS	1.12	0.31	0.34	0.12
	Gestures	Sham	1.42	0.40	0.36	0.18
		TMS	1.49	0.40	0.30	0.18
Volitional	Words	Sham	1.16	0.40	0.34	0.12
		TMS	1.27	0.40	0.33	0.12
	Gestures	Sham	1.37	0.40	0.32	0.19
		TMS	1.44	0.45	0.30	0.17

* Stimulation condition.

gestures was never contingent upon semantic or phonological processing; instead, it relied on a set of arbitrary SR associations. Results clearly demonstrate that even in the absence of linguistic processing, volitional word selection is affected by rTMS applied over the pre-SMA; likewise for the oral gestures. These results have important theoretical implications for the modeling of language production, indicating that a task-general process is involved during language production, especially when language is produced spontaneously and volitionally. Contemporary models of speech and language (e.g. Indefrey and Levelt, 2004; Hickok and Poeppel, 2007; Guenther et al., 2006; Riecker et al., 2005) usually focus on language-specific processes (e.g. lexical selection, morpho-phonological code retrieval, phonetic encoding) providing no information about the manner and extent to which language production is bound to the production of other behaviors, and relies on domain-general neural resources. A more global understanding of brain processes requires a thorough understanding of the manner in which systems supporting different behaviors overlap one another functionally. Further studies are needed to understand how a general response selection process interacts with language-specific processes allowing contextually appropriate language to emerge.

Another important finding of the current study is that RT in both the experimental and control groups exhibited a TMS by modality interaction. This interaction revealed a stronger overall TMS interference effect on the oral gesture condition. One possible interpretation is that the oral gestures were associated with a greater (motor) difficulty level than the words, and hence were more vulnerable to interference. Alternatively, this vulnerability of the gestures may be related to a frequency/familiarity effect rather than a difficulty effect *per se*. Reports of familiarity effects on RTs are abundant in the literature. For example, word familiarity is known to affect word recognition times (e.g. Howes and Solomon, 1951; Gibson et al., 1970; Forster and Chambers, 1973; Scarborough et al., 1977), lexical decision times (Bradshaw and Nettleton, 1974; Gerhand and Barry, 1999; Morrison and Ellis, 1995), word naming (Gerhand and Barry, 1998; Morrison and Ellis, 2000), and object/picture naming (Barry et al., 1997; Ellis and Morrison, 1998). Interestingly, recent evidence suggests that the SMA/pre-SMA region is sensitive to motor and non-motor familiarity effects. For example, it has been shown that word frequency modulates activation in the SMA/pre-SMA region, with greater activation for lexical decisions involving low frequency words than high frequency words, and for reading aloud low frequency words compared with reading aloud high frequency words (Carreiras et al., 2006). More recently, it was shown that activation in the SMA/pre-SMA region is greater for pseudoword reading compared with word reading, and for lexical decision involving pseudowords compared with words (Carreiras et al., 2007). In keeping with these findings, the current results demonstrate that the production of unfamiliar, perhaps more difficult responses, is more vulnerable to stimulation of the SMA/pre-SMA region. Based on these findings, we predict that the use of more familiar gestures would preclude modality effects. This is, however, entirely speculative and this hypothesis will have to be tested directly in future experiments.

4. Conclusions

The present research addressed the issue of the role of the pre-SMA in response selection and provides new insights into the functions of this region. It appears that the pre-SMA is causally related to volitional selection, but not for forced selection, even when the attention levels are matched. Importantly, the study also demonstrates the response-independent (general) nature of the response selection process. A global understanding of brain functioning requires a thorough understanding of the extent to which neural systems supporting different behaviors overlap with one another; this knowledge is essential to broaden current understanding of the basic brain operations that are used to produce language and eventually develop clinical interventions that will take advantage of these cross-systems interactions (for a more thorough discussion on this issue, see McFarland and Tremblay, 2006).

5. Experimental procedures

5.1. Participants

A total of twenty-six healthy (26) right-handed adults participated in this study. One participant was excluded due to excessive head movement (≥ 10 mm) during the stimulation resulting in inaccurate localization, and one was excluded because of inadequate behavioral performance, leaving twenty-four participants in the study (11 males, mean age 25, SD 4.5 years), divided into two groups (experimental, control) each comprising 12 participants. The experimental group received stimulation over the pre-SMA, while the control group received stimulation over the SMA-proper. Average right-handedness score was $89 \pm 6\%$ according to the Edinburgh Handedness Inventory (Oldfield, 1971). The mean number of years of education was 16 ± 2 years. All participants scored normal (or above) on the Montreal Cognitive Assessment (Nasreddine et al., 2003) and had normal or corrected-to-normal vision, no speech, language or learning difficulty, past or present. Participants were screened for any relative or absolute contraindication to TMS (Wasserman, 1998) before their arrival at the laboratory (phone interview), and again upon arrival. Informed written consent was obtained from each participant.

5.2. Study procedure

Participants were seated in a padded armchair in front of a computer monitor, with their head held in place comfortably by a customized headrest. The experiment involved participants producing either single words or single oral gestures following the presentation of a stimulus cue. All trials began with a stimulus cue displayed on a computer monitor for 800 ms. Cues consisted of a word, or a single digit number (0 to 3) presented within a geometrical shape (a circle or a square). Fig. 1 illustrates the stimuli used and the associated responses. Following the removal of the cue, participants produced the cued response as quickly as possible. A long

inter-trial interval (6.5 ± 1.5 s) was chosen to allow participants enough time to respond, and to preclude carry-over effects.

Words and oral gestures were produced under three different conditions controlling for selection, attention level, and number of response alternative: a three-alternative low-attention forced selection condition (baseline), a three-alternative high-attention forced selection condition (forced choice) and a three-alternative high-attention volitional selection condition (volitional). In the baseline condition, the cue was the required response (word or oral gesture). For example, the word WOOD cued the production of the word WOOD, and the word WHISTLE cued whistling. Responses in the baseline condition are unambiguously specified by the cue, and selection required minimal attention. This task was chosen as the baseline because previous results have demonstrated that forced response selection is not associated with significant activation in the pre-SMA (Tremblay and Gracco, 2006). For the three-choice high-attention forced condition, a number (1, 2 or 3) was presented within a geometrical shape (a circle or a square). The geometrical shape specified the response modality (word or oral gesture) while the number specified the response within the category. For half the subjects, circles were paired with oral gestures while squares were paired with words. For the other half, the assignments were reversed. For the volitional condition, the number 0 was presented on the screen, within a circle or a square. The circle or square specified the category (word or oral gesture) while the 0 specified that any of the responses within the category could be chosen. Participants were asked to respond as spontaneously as they could on the volitional selection trials. The high-attention forced and volitional conditions differed only along one dimension, the selection mode; all other aspects of the tasks were comparable: the working memory load, the required attention level (sustained), the motor planning and motor output and the complexity of the visual stimuli used. The presentation of the conditions was pseudo randomized. The same experimental condition never occurred on more than two consecutive trials.

This experimental design resulted in twelve conditions (i.e. three selection modes*two response modalities*two stimulation intensities (TMS, sham)), which were pseudo randomly presented within eight blocks of sixty trials each, resulting in a total of four hundred eighty trials (240 TMS and 240 sham), resulting in forty trials per condition. To avoid fatigue and prevent overheating of the stimulator, 5–10 min breaks were inserted in between each block. Stimulation never occurred on more than three consecutive trials.

5.3. Stimuli and responses

To accommodate the native language of the participants, we constructed two sets of comparable words, one in French and one in English. All participants were native speaker of one of these languages. The words were all highly familiar and none of the oral gestures was novel to any of the participants. The words and oral gestures were matched on several dimensions: each response was short, articulated mainly with the lips, and required the production of a word or an audible noise (oral gesture) with the same articulator and using a related action. For example, the word “wood” was paired with

a whistle since each requires bilateral protrusion of the lips. Table 1 presents the characteristics for the words and oral gestures.

5.4. Electromyographic (EMG) and acoustic recordings

Muscle activity was obtained from surface electrodes (10 mm diameter) placed over the first dorsal interosseous (FDI) muscle of the right hand and the upper and lower lip muscles. The FDI recording was used to determine each participant's resting motor threshold (RMT) while the lip muscle activity was used to ensure that the stimulation did not induce motor evoked potentials during the experiment. The EMG signals were band-passed filtered (30 Hz to 3 KHz), digitized at 10 KHz with 12-bit precision onto a lab computer for offline analysis.

A unidirectional condenser microphone (Sennheiser, Wedemark, Germany) was used to record participants' responses (words and oral gestures). The acoustic signal was pre-amplified, digitized at 44 KHz with 16-bit precision and stored on an Apple IMac G5 computer for offline analysis. The acoustic recordings were used to calculate participants' accuracy and reaction times (RTs).

5.5. TMS

5.5.1. MRI acquisition and co-registration

A high-resolution T1-weighted MRI scan was obtained for all participants. For fourteen (14) participants, an MRI scan was acquired on a 1.5 T Siemens Vision scanner (matrix 256×256 mm, 176 slices, $1 \times 1 \times 1$ mm, no gap) at the Montreal Neurological Institute. The remaining 10 participants were scanned with a 3 T Siemens Trio scanner (same acquisition parameters) as part of another research protocol from our laboratory. Although the higher field strength of a 3 T scanner compared with 1.5 T scanner provides significantly greater signal-to-noise (e.g. Schick, 2005), and therefore better spatial resolution (for a review of the advantages of 3 T vs. 1.5 T, see for example Willinek and Schild, 2008), it is nevertheless possible to acquire good quality structural MRI images of the brain with a 1.5 T scanner. Moreover, it has been shown that MRI field strength (0.5 vs. 1.5 T) does not correlate with localization accuracy (Kondziolka et al., 1992). More recently, Scheid et al. (2007) have shown that although 3 T scanner provides superior images, both 1.5 and 3 T scanner are capable of detecting traumatic microbleeds in the brain (Scheid et al., 2007). Finally, gray-to-white matter contrasts on T1-weighted images appear to be better at 1.5 than 3 T (Schmitz et al., 2005). Hence, despite an overall inferior spatial resolution at 1.5 T, it is nevertheless possible to obtain good quality structural data at both signal strengths. In line with the literature, we were able to localize the supplementary motor area in each participant, regardless of the scanner that was used (1.5 T or 3 T).

Once obtained the anatomical MRI was incorporated into BrainSight TMS (Rogue Research) to guide coil placement. For each participant, an MRI-to-head co-registration was performed using Brainsight software (Rogue Research, Montreal, Canada). The position of three anatomical landmarks (tip of the nose, bridge of the nose, superior-lateral edge of the tragus of left and right ears), previously identified on participant's MRI, was assessed using an infrared tracking system (Polaris,

Northern Digital, Waterloo, Canada). Upon successful co-registration, infrared tracking was used to monitor the position of the coil with respect to the participant's brain.

5.5.2. Resting motor threshold (RMT)

For all TMS stimulation, a 70-mm figure-of-eight coil was used, which was driven by a high-speed magnetic stimulator producing short duration biphasic pulses (Magstim Rapid 1400, Wales, U.K.). The stimulator was controlled through Presentation software (Neurobehavioral Research) installed on a Dell Precision M60 laptop computer connected to the Magstim Rapid unit through a NIDAQ DIO card (National Instruments, Austin, TX, USA).

For the determination of each subject's RMT, the TMS coil was placed over the participant's left motor cortex hand area with the coil held tangentially to the skull, with the handle pointing posterior and down. Single pulses were delivered to the motor cortex, with the intensity of the stimulation adjusted until a muscle evoked potential (MEP) in the right hand was observed on the EMG recording in 5 out of 10 trials with an amplitude of at least 50 μ V (Rossini et al., 1994). The location of the stimulation was adjusted to locate the maximally excitable hand area.

5.5.3. rTMS stimulation

The intensity of the stimulation was set at 110% of subjects' RMT, which ranged from 55–78% of the output capacity of the stimulator, with a mean of 64%. The coordinates of stimulation sites were determined individually for each participant using Brainsight TMS (Rogue Research, Montreal, Canada) software. First, we identified, on subjects' anatomical MRI, the anterior commissure and a vertical line passing through this point was drawn (i.e. the VAC line). For the experimental (pre-SMA) group, we selected a point that was approximately 10 mm anterior to this line, on the medial most portion of the left superior frontal gyrus. The mean coordinates, in MNI space, were $-4\ 9\ 55$ (Talairach: $-4\ 11\ 50$)¹. This stimulation site was based on previous results from our laboratory (Tremblay and Gracco, in press), showing strong pre-SMA activation 10 mm anterior to the VAC line in the medial frontal gyrus associated with the selection verbal motor responses. For the control group (SMA-proper), the stimulation site was located approximately midway between the VAC line and the anterior edge of the precentral gyrus, on the medial most portion of the superior frontal gyrus. The mean coordinates, in MNI space, were $-3\ -13\ 59$ (Talairach: $-3\ -10\ 55$), thus leading to an average of 2.2 cm between the stimulation sites. The location of these two SMA stimulation sites is illustrated in Fig. 1. It should be noted that these SMA locations are consistent with published anatomical representations of the face muscles within the pre-SMA and SMA-proper (Picard and Strick, 1996).

Stimulation was applied in trains of five pulses delivered at a rate of 10 Hz for 0.4 s. Stimulation started 200 ms after the beginning of the trial, corresponding to the response prepara-

tion interval. This time-window was selected based on the meta-analysis of language experiments conducted by Indefrey and Levelt (2004). In the sham trials (control trials), a tape-recorded sample of the stimulator clicking sound was presented through small computer speakers located close to the participant to control for the TMS noise. Each trial was followed by 7-second (± 1 s) inter-trial interval. This long inter-trial interval was chosen to allow participants to respond, and to prevent any carry-over effect from the stimulation.

Each participant received 1200 pulses during the whole session, which lasted approximately 3 h. During the experiment, the coil was held tangentially to the skull, with the handle pointing backwards and secured by a system of multi-joint clamps (Rogue Research, Montreal, CAN). The coil position was monitored online and adjusted following any head movements resulting in displacement of more than 2 mm in any direction.

5.6. Data analysis

5.6.1. Response accuracy

The acoustic recordings were evaluated and transcribed by a research assistant naïve to the study. The percentage of errors was calculated for each experimental condition for each subject. Errors included both misses (no response) and incorrect responses, including the production of a word instead of an oral gesture or vice versa, or the production of the incorrect word or oral gesture. This second type of error only occurred in the forced choice condition.

5.6.2. Volitional response generation

For each participant, the frequency distributions of the words and the oral gestures in the volitional selection condition were examined to determine whether it was contingent upon the presence of TMS. In order to test the null hypothesis (H_0) of no relationship between stimulation level and response distribution, we used 2×3 contingency (chi-square) analyses with TMS level (Sham, TMS) and response (word1, word2, word3; gesture1, gesture2, gesture3) as the variables. This analysis was performed separately for the words and the oral gestures, at the group level. In order to assess whether the group results really reflected the individual patterns, the same analysis was also run at the single subject level.

5.6.3. Reaction time

The reaction time was defined as the time from the stimulus offset to the onset of the subject's response. Response onsets were identified manually from the acoustic signal using MATLAB® (The MathWorks Inc., Natick, MA, USA), but blindly to the experimental condition. RTs that were three standard deviations above or below the mean for each participant and each condition were removed from the analysis. Incorrect responses and misses were also excluded from the RT analysis. Data were then entered in a three-way factorial ANOVA with repeated measurements (rANOVA) using SPSS 16 (SPSS Inc., Chicago, IL). The factors were the selection MODE (baseline, forced, volitional), the TASK (words, oral gestures) and the TMS level (TMS, sham). Each group was analyzed separately. Bonferroni corrected two-tailed paired t-tests were used for post hoc comparisons.

¹ The conversion of MNI to Talairach coordinates was obtained using a non-linear coordinate transformation Matlab routine (mni2tal.m) available freely at <http://imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/mni2tal.m>. These coordinates are only an approximation of Talairach coordinates.

Acknowledgments

We would like to acknowledge Laura Lewis and Marc Sato for their help collecting the data, Douglas Shiller for helping develop MATLAB tools to analyze the reaction time data, and the reviewers for their comments on previous versions of this manuscript. We are also grateful to Isabelle Deschamps for her comments on a previous version of this manuscript, and to all the participants. This work was supported by a Canada Graduate Scholarship to P. Tremblay from the Canadian Institute of Health Research (CIHR), and from research grants to V. Gracco from the Natural Science and Engineering Research Council of Canada (NSERC) and the Center for Research on Language on Language, Mind and Brain (CRLMB).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.brainres.2009.02.076](https://doi.org/10.1016/j.brainres.2009.02.076).

REFERENCES

- Abrahams, S., Goldstein, L.H., Simmons, A., Brammers, M.J., Williams, S.C.R., Giampietro, V.P., Andrew, C.M., Leigh, P.N., 2003. Functional magnetic resonance imaging of verbal fluency and confrontation naming using compressed image acquisition to permit overt responses. *Hum. Brain Mapp.* 20, 29–40.
- Akkal, D., Dum, R.P., Strick, P.L., 2007. Supplementary motor area and presupplementary motor area: targets of basal ganglia and cerebellar output. *J. Neurosci.* 27, 10659–10673.
- Alario, F.X., Chainay, H., Lehericy, S., Cohen, L., 2006. The role of the supplementary motor area (SMA) in word production. *Brain Res.* 1076, 129–143.
- Barry, C., Morrison, C.M., Ellis, A.W., 1997. Naming the Snodgrass and Vanderwal pictures: effects of age of acquisition, frequency, and name agreement. *Quarterly Journal of Experimental Psychology: Human Experimental Psychology* 50A, 560–585.
- Bates, J.F., Goldman-Rakic, P.S., 1993. Prefrontal connections of medial motor areas in the rhesus monkey. *J. Comp. Neurol.* 336, 211–228.
- Basho, S., Palmer, E.D., Rubio, M.A., Wulfeck, B., Müller, R., 2007. Effects of generation mode in fMRI adaptations of semantic fluency: paced production and overt speech. *Neuropsychologia* 45, 1697–1706.
- Blank, S.C., Scott, S.K., Murphy, K., Warburton, E., Wise, R.J., 2002. Speech production: Wernicke, Broca and beyond. *Brain* 125, 1829–1838.
- Blackler, D., Byrnes, M.L., Mastaglia, F.L., Thickbroom, G.W., 2006. Differential activation of frontal lobe areas by lexical and semantic language tasks: a functional magnetic resonance imaging study. *J. Clin. Neurosci.* 13, 91–95.
- Botvinick, M., Nystrom, L.E., Fissell, K., Carter, C.S., Cohen, J.D., 1999. Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature* 402, 179–181.
- Bookheimer, S.Y., Zeffiro, T.A., Blaxton, T.A., Gaillard, P.W., Theodore, W.H., 2000. Activation of language cortex with automatic speech tasks. *Neurology* 55, 1151–1157.
- Bradshaw, J., Nettleton, N., 1974. Articulatory interference and the MOWN-DOWN heterophone effect. *J. Exp. Psychol.* 102, 88–94.
- Braun, A.R., Guillemain, A., Hosey, L., Varga, M., 2001. The neural organization of discourse: an H2 15O-PET study of narrative production in English and American sign language. *Brain* 124, 2028–2044.
- Carreiras, M., Mechelli, A., Price, C.J., 2006. Effect of word and syllable frequency on activation during lexical decision and reading aloud. *Hum. Brain Mapp.* 27, 963–972.
- Carreiras, M., Mechelli, A., Estevez, A., Price, C.J., 2007. Brain activation for lexical decision and reading aloud: two sides of the same coin? *J. Cogn. Neurosci.* 19, 433–444.
- Chainay, H., Francois-Xavier, A., Alexandre, K., Hugues, D., Laurent, C., Emmanuelle, V., Stephane, L., 2009. Motor and language deficits before and after surgical resection of mesial frontal tumour. *Clinical Neurology and Neurosurgery* 111, 39–46.
- Chung, G.H., Han, Y.M., Jeong, S.H., Jack Jr., C.R., 2005. Functional heterogeneity of the supplementary motor area. *AJNR Am. J. Neuroradiol.* 26, 1819–1823.
- Cohen, J. 1988. *Statistical Power Analysis for the Behavioral Sciences*, second ed. Lawrence Erlbaum Associates.
- Crosson, B., Sadek, J.R., Maron, L., Gökçay, D., Mohr, C., Auerbach, E.J., Freeman, A.J., Leonard, C.M., Briggs, R.W., 2001. Relative shift in activity from medial to lateral frontal cortex during internally versus externally guided word generation. *J. Cogn. Neurosci.* 13, 272–283.
- Deblieck, C., Pesenti, G., Scifo, P., Fazio, F., Bricolo, E., Lo Russo, G., Scialfa, G., Cossu, M., Bottini, G., Paulesu, E., 2003. Preserved functional competence of perilesional areas in drug-resistant epilepsy with lesion in supplementary motor cortex: fMRI and neuropsychological observations. *Neuroimage* 20, 2225–2234.
- Deiber, M.P., Ibanez, V., Sadato, N., Hallett, M., 1996. Cerebral structures participating in motor preparation in humans: a positron emission tomography study. *J. Neurophysiol.* 75, 233–247.
- Derrfuss, J., Brass, M., von Cramon, D.Y., 2004. Cognitive control in the posterior frontolateral cortex: evidence from common activations in task coordination, interference control, and working memory. *Neuroimage* 23, 604–612.
- Donohue, S.E., Wendelken, C., Bunge, S.A., 2008. Neural correlates of preparation for action selection as a function of specific task demands. *J. Cogn. Neurosci.* 20, 694–706.
- Dum, R.P., Strick, P.L., 1991. The origin of corticospinal projections from the premotor areas in the frontal lobe. *J. Neurosci.* 11, 667–689.
- Etard, O., Mellet, E., Papathanassiou, D., Benali, K., Houde, O., Mazoyer, B., Tzourio-Mazoyer, N., 2000. Picture naming without Broca's and Wernicke's area. *Neuroreport* 11, 617–622.
- Ellis, A.W., Morrison, C.M., 1998. Real age-of-acquisition effects in lexical retrieval. *J. Exp. Psychol. Learn. Mem. Cogn.* 24, 515–523.
- Fan, J., Kolster, R., Ghajar, J., Suh, M., Knight, R.T., Sarkar, R., McCandliss, B.D., 2007. Response anticipation and response conflict: an event-related potential and functional magnetic resonance imaging study. *J. Neurosci.* 27, 2272–2282.
- Fiez, J.A., Balota, D.A., Raichle, M.E., Petersen, S.E., 1999. Effects of lexicality, frequency, and spelling-to-sound consistency on the functional anatomy of reading. *Neuron* 24, 205–218.
- Fontaine, D., Capelle, L., Duffau, H., 2002. Somatotopy in the supplementary motor area: evidence from correlation of the extent of surgical resection with the clinical patterns of deficit. *Neurosurgery* 50, 297–303.
- Forster, K.I., Chambers, S.M., 1973. Lexical access and naming time. *J. Verbal Learn. Verbal Behav.* 12, 627–635.
- Gerhard, S., Barry, C., 1998. Word frequency effects in oral reading are not merely age-of-acquisition effects in disguise. *J. Exp. Psychol.* 24, 267–283.
- Gerhand, S., Barry, C., 1999. Age of acquisition and frequency effects in speeded word naming. *Cognition* 73, B27–B36.
- Geyer, S., Matelli, M., Luppino, G., Schleicher, A., Jansen, Y., Palomero-Gallagher, N., Zilles, K., 1998. Receptor

- autoradiographic mapping of the mesial motor and premotor cortex of the macaque monkey. *J. Comp. Neurol.* 397, 231–250.
- Gibson, E.J., Shurcliff, A., Yonas, A., 1970. Utilization of spelling patterns by deaf and hearing subjects. In: Levin, H., Williams, J.P. (Eds.), *Basic studies on reading*. Basic Books, New York.
- Goldberg, G., 1985. Supplementary motor area structure and function: review and hypothesis. *Behav. Brain Sci.* 8, 567–616.
- Gowen, E., Miall, R.C., 2007. Differentiation between external and internal cuing: an fMRI study comparing tracing with drawing. *Neuroimage* 36, 396–410.
- Guenther, F.H., Ghosh, S.S., Tourville, J.A., 2006. Neural modeling and imaging of the cortical interactions underlying syllable production. *Brain Lang.* 96, 280–301.
- Haller, S., Radue, E.W., Erb, M., Grodd, W., Kircher, T., 2005. Overt sentence production in event-related fMRI. *Neuropsychologia* 43, 807–814.
- Hadland, K.A., Rushworth, M.F., Passingham, R.E., Jahanshahi, M., Rothwell, J.C., 2001. Interference with performance of a response selection task that has no working memory component: an rTMS comparison of the dorsolateral prefrontal and medial frontal cortex. *J. Cogn. Neurosci.* 13, 1097–1108.
- Hickok, G., Poeppel, D., 2007. The cortical organization of speech processing. *Nat. Rev. Neurosci.* 8, 393–402.
- Howes, D.H., Solomon, R.L., 1951. Visual duration threshold as a function of word-probability. *J. Exp. Psychol.* 41, 401–410.
- Hyder, F., Phelps, E.A., Wiggins, C.J., Labar, K.S., Blamire, A.M., Shulman, R.G., 1997. “Willed action”: a functional MRI study of the human prefrontal cortex during a sensorimotor task. *Proc. Natl. Acad. Sci. U.S.A.* 94, 6989–6994.
- Inase, M., Tokuno, H., Nambu, A., Akazawa, T., Takada, M., 1999. Corticostriatal and corticosubthalamic input zones from the presupplementary motor area in the macaque monkey: comparison with the input zones from the supplementary motor area. *Brain Res.* 33, 191–201.
- Indefrey, P., Levelt, W.J.M., 2004. The spatial and temporal signatures of word production components. *Cognition* 92, 101–144.
- Jahanshahi, M., Dirnberger, G., 1999. The left dorsolateral prefrontal cortex and random generation of responses: studies with transcranial magnetic stimulation. *Neuropsychologia* 37, 181–190.
- Kemeny, S., Ye, F.Q., Birn, R., Braun, A.R., 2005. Comparison of continuous overt speech fMRI using BOLD and arterial spin labeling. *Hum. Brain Mapp.* 24, 173–183.
- Kemeny, S., Xu, J., Park, G.H., Hosey, L.A., Wettig, C.M., Braun, A.R., 2006. Temporal dissociation of early lexical access and articulation using a delayed naming task—an fMRI study. *Cereb. Cortex* 16, 587–595.
- Kennerley, S.W., Sakai, K., Rushworth, M.F., 2004. Organization of action sequences and the role of the pre-SMA. *J. Neurophysiol.* 91, 978–993.
- Kondziolka, D., Dempsey, P.K., Lunsford, L.D., Kestle, J.R., Dolan, E.J., Kanal, E., Tasker, R.R., 1992. A comparison between magnetic resonance imaging and computed tomography for stereotactic coordinate determination. *Neurosurgery* 30, 402–406 discussion 406–7.
- Lau, H.C., Rogers, R.D., Ramnani, N., Passingham, R.E., 2004. Willed action and attention to the selection of action. *Neuroimage* 21, 1407–1415.
- Lau, H., Rogers, R.D., Passingham, R.E., 2006. Dissociating response selection and conflict in the medial frontal surface. *Neuroimage* 29, 446–451.
- Lu, M.T., Preston, J.B., Strick, P.L., 1994. Interconnections between the prefrontal cortex and the premotor areas in the frontal lobe. *J. Comp. Neurol.* 341, 375–392.
- Luppino, G., Matelli, M., Camarda, R.M., Gallese, V., Rizzolatti, G., 1991. Multiple representations of body movements in mesial area 6 and the adjacent cingulate cortex: an intracortical microstimulation study in the macaque monkey. *J. Comp. Neurol.* 311, 463–482.
- Luppino, G., Matelli, M., Camarda, R., Rizzolatti, G., 1993. Corticocortical connections of area F3 (SMA-proper) and area F6 (pre-SMA) in the macaque monkey. *J. Comp. Neurol.* 338, 114–140.
- Luppino, G., Rizzolatti, G., 2000. The organization of the frontal motor cortex. *News Views* 15, 219–224.
- McFarland, D.H., Tremblay, P., 2006. Clinical implications of cross-system interactions. *Semin. Speech Lang.* 27, 300–309.
- Mars, R.B., Piekema, C., Coles, M.G., Hulstijn, W., Toni, I., 2007. On the programming and reprogramming of actions. *Cereb. Cortex* 17, 2972–2979.
- Matelli, M., Luppino, G., Rizzolatti, G., 1991. Architecture of superior and mesial area 6 and the adjacent cingulate cortex in the macaque monkey. *J. Comp. Neurol.* 311, 445–462.
- Matelli, M., Luppino, G., 1996. Thalamic input to mesial and superior area 6 in the macaque monkey. *J. Comp. Neurol.* 372, 59–87.
- Mendez, M.F., 2004. Aphemia-like syndrome from a right supplementary motor area lesion. *Clin. Neurol. Neurosurg.* 106, 337–339.
- Moll, J., de Oliveira-Souza, R., Moll, F.T., Bramati, I.E., Andreiuolo, P.A., 2002. The cerebral correlates of set-shifting: an fMRI study of the trail making test. *Arq. Neuropsiquiatr.* 60, 900–905.
- Morrison, C.M., Ellis, A.W., 1995. Roles of word frequency and age of acquisition in word naming and lexical decision. *J. Exp. Psychol. Learn. Mem. Cogn.* 21, 116–133.
- Morrison, C.M., Ellis, A.W., 2000. Real age of acquisition effects in word naming and lexical decision. *Br. J. Psychol.* 91 (Pt. 2), 167–180.
- Morecraft, R.J., Louie, J.L., Herrick, J.L., Stilwell-Morecraft, K.S., 2001. Cortical innervation of the facial nucleus in the non-human primate: a new interpretation of the effects of stroke and related subtotal brain trauma on the muscles of facial expression. *Brain* 124, 176–208.
- Muakkassa, K.F., Strick, P.L., 1979. Frontal lobe inputs to primate motor cortex: evidence for four somatotopically organized ‘premotor’ areas. *Brain Res.* 177, 176–182.
- Mueller, V.A., Brass, M., Waszak, F., Prinz, W., 2007. The role of the preSMA and the rostral cingulate zone in internally selected actions. *Neuroimage* 37, 1354–1361.
- Nachev, P., Rees, G., Parton, A., Kennard, C., Husain, M., 2005. Volition and conflict in human medial frontal cortex. *Curr. Biol.* 15, 122–128.
- Nasreddine, Z.S., Chertkow, H., Hillips, N., Bergman, H., Whitehead, V., 2003. Sensitivity and specificity of the Montreal Cognitive Assessment (MoCA) for detection of mild cognitive deficits. *Can. J. Neurol. Sci.* 30.
- Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 97–113.
- Pai, M.C., 1999. Supplementary motor area aphasia: a case report. *Clin. Neurol. Neurosurg.* 101, 29–32.
- Palmer, E.D., Rosen, H.J., Ojemann, J.G., Buckner, R.L., Kelley, W.M., Petersen, S.E., 2001. An event-related fMRI study of overt and covert word stem completion. *Neuroimage* 14, 182–193.
- Penfield, W., Welch, K., 1951. The supplementary motor area of the cerebral cortex; a clinical and experimental study. *AMA Arch. Neurol. Psychiatry* 66, 289–317.
- Persson, J., Sylvester, C.Y., Nelson, J.K., Welsh, K.M., Jonides, J., Reuter-Lorenz, P.A., 2004. Selection requirements during verb generation: differential recruitment in older and younger adults. *Neuroimage* 23, 1382–1390.
- Peraud, A., Meschede, M., Eisner, W., Ilmberger, J., Reulen, H.J., 2002. Surgical resection of grade II astrocytomas in the superior frontal gyrus. *Neurosurgery* 50, 966–975.

- Picard, N., Strick, P.L., 1996. Motor areas of the medial wall: a review of their location and functional activation. *Cerebral Cortex* 6, 342–353.
- Riecker, A., Mathiak, K., Wildgruber, D., Erb, M., Hertrich, I., Grodd, W., Ackermann, H., 2005. fMRI reveals two distinct cerebral networks subserving speech motor control. *Neurology* 64, 700–706.
- Rizzolatti, G., Luppino, G., Matelli, M., 1998. The organization of the cortical motor system: new concepts. *Electroencephalogr. Clin. Neurophysiol.* 106, 283–296.
- Rossini, P.M., Barker, A.T., Berardelli, A., Caramia, M.D., Caruso, G., Cracco, R.Q., Dimitrijevic, M.R., Hallett, M., Katayama, Y., Lucking, C.H., et al., 1994. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalography and Clinical Neurophysiology* 91, 79–92.
- Russell, S.M., Kelly, P.J., 2003. Incidence and clinical evolution of postoperative deficits after volumetric stereotactic resection of glial neoplasms involving the supplementary motor area. *Neurosurgery* 52, 506–516.
- Rushworth, M.F., Hadland, K.A., Paus, T., Sipila, P.K., 2002. Role of the human medial frontal cortex in task switching: a combined fMRI and TMS study. *J. Neurophysiol.* 87, 2577–2592.
- Sakai, K., Hikosaka, O., Takino, R., Miyauchi, S., Nielsen, M., Tamada, T., 2000. What and when: parallel and convergent processing in motor control. *J. Neurosci.* 20, 2691–2700.
- Scarborough, D.L., Cortese, C., Scarborough, H.S., 1977. Frequency and repetition effects in lexical memory. *J. Exp. Psychol. Hum. Percept. Perform.* 3, 1–17.
- Schlosser, R., Hutchinson, M., Joseffer, S., Rusinek, H., Saarimaki, A., Stevenson, J., Dewey, S.L., Brodie, J.D., 1998. Functional magnetic resonance imaging of human brain activity in a verbal fluency task. *J. Neurol. Neurosurg. Psychiatry* 64, 492–498.
- Schick, F., 2005. Whole-body MRI at high field: technical limits and clinical potential. *Eur. Radiol.* 15 (5), 946–959.
- Scheid, R., Ott, D.V., Roth, H., Schroeter, M.L., von Cramon, D.Y., 2007. Comparative magnetic resonance imaging at 1.5 and 3 Tesla for the evaluation of traumatic microbleeds. *J. Neurotrauma* 24, 1811–1816.
- Schmitz, B.L., Gron, G., Brausewetter, F., Hoffmann, M.H., Aschoff, A.J., 2005. Enhancing gray-to-white matter contrast in 3 T T1 spin-echo brain scans by optimizing flip angle. *AJNR Am. J. Neuroradiol.* 26, 2000–2004.
- Tremblay, P., Gracco, V.L., 2006. Contribution of the frontal lobe to externally and internally specified verbal responses: fMRI evidence. *Neuroimage* 33, 947–957.
- Tremblay, P., Gracco, V.L., in press. On the selection of linguistic and non-linguistic motor responses: evidence of a response-independent fronto-parietal network. *Cortex*. doi:10.1016/j.cortex.2009.03.003.
- Ullsperger, M., von Cramon, D.Y., 2001. Subprocesses of performance monitoring: a dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *Neuroimage* 6, 1387–1401.
- Van Oostende, S., Van Hecke, P., Sunaert, S., Nuttin, B., Marchal, G., 1997. FMRI studies of the supplementary motor area and the premotor cortex. *Neuroimage* 6, 181–190.
- Vorobiev, V., Govoni, P., Rizzolatti, G., Matelli, M., Luppino, G., 1998. Parcellation of human mesial area 6: cytoarchitectonic evidence for three separate areas. *Eur. J. Neurosci.* 10, 2199–2203.
- Walsh, V., Pascual-Leone, A., 2003. *Transcranial Magnetic Stimulation: A Neurochronometrics of Mind*. MIT Press, Boston, MA.
- Wang, Y.I.M., Matsuzaka, Y., Shma, K., Tanji, J., 2005. Prefrontal cortical cells projecting to the supplementary eye field and presupplementary motor area in the monkey. *Neurosci. Res.* 53, 1–7.
- Wasserman, E.M., 1998. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. *Electroencephalogr. Clin. Neurophysiol.* 108, 1–16.
- Willinek, W.A., Schild, H.H., 2008. Clinical advantages of 3.0 T MRI over 1.5 T. *Eur. J. Radiol.* 65 (1), 2–14.
- Xue, G., Aron, A.R., Poldrack, R.A., 2008. Common neural substrates for inhibition of spoken and manual responses. *Cereb. Cortex*.
- Zentner, J., Hufnagel, A., Pechstein, U., Wolf, H.K., Schramm, J., 1996. Functional results after resective procedures involving the supplementary motor area. *J. Neurosurg.* 85, 542–549.