Title: On the role of the supramarginal gyrus in phonological processing and verbal working memory: evidence from rTMS studies.

Isabelle Deschamps\textsuperscript{1,2}, Shari R. Baum\textsuperscript{1,2}, Vincent L. Gracco\textsuperscript{1,2,3}

1. McGill University, Faculty of Medicine, School of Communication Sciences and Disorders, 1266 Avenue des Pins, Montreal, Quebec, H3G 1A8, Canada

2. Centre for Research on Brain, Language and Music, Rabinovitch House, McGill University, 3640 rue de la Montagne, Montreal, Quebec, H3G 2A8, Canada

3. Haskins Laboratories, 300 George St., Suite 900, New Haven, Connecticut, 06511, USA

Corresponding author:

Isabelle Deschamps

1266 avenue des Pins West, Montreal, Qc, Canada, H3G 1A8, Tel. 1-514-398-6998, Email: isabelle.deschamps@mail.mcgill.ca
Abstract

The supramarginal gyrus (SMG) is activated for phonological processing during both language and verbal working memory tasks. Using rTMS, we investigated whether the contribution of the SMG to phonological processing is domain specific (specific to phonology) or more domain general (specific to verbal working memory). A measure of phonological complexity was developed based on sonority differences and subjects were tested after low frequency rTMS on a same/different judgment task and an n-back verbal memory task. It was reasoned that if the phonological processing in the SMG is more domain general, i.e., related to verbal working memory demands, performance would be more affected by the rTMS during the n-back task than during the same/different judgment task. Two auditory experiments were conducted. The first experiment demonstrated that under conditions where working memory demands are minimized (i.e. same/different judgment), repetitive stimulation had no effect on performance although performance varied as a function of phonological complexity. The second experiment demonstrated that during a verbal working memory task (n-back task), where phonological complexity was also manipulated, subjects were less accurate and slower at performing the task after stimulation but the effect of phonology was not affected. The results confirm that the SMG is involved in verbal working memory but not in the encoding of sonority differences.

Keywords:

Transcranial magnetic stimulation; verbal working memory; phonological processing; supramarginal gyrus.
1. Introduction

Phonology represents the basic building blocks of all human languages. In order to comprehend speech, whether spoken or written, individuals must rely on phonological representations to establish a link between sounds or symbols and meaning. While phonological representations and phonological processing have been shown to recruit a widely distributed network of cortical and subcortical regions, one area that is often identified as an important network node is the inferior parietal lobule (IPL). More precisely, functional neuroimaging studies have identified the supramarginal gyrus (SMG), a region located in the most anterior part of the IPL, as an important component (node) in the phonological processing network. Observations that the SMG is recruited during various language tasks such as word processing (Howard, et al., 1992; R. L. Newman & Joanisse, 2011; Petersen, Fox, Posner, Mintun, & Raichle, 1988), nonword processing (S. D. Newman & Twieg, 2001; Wise, et al., 1991), and syllable processing (Dehaene-Lambertz, et al., 2005; Zatorre, Evans, Meyer, & Gjedde, 1992) and that it is preferentially activated when participants focus on the sound of a word as compared to when they focus on its meaning (Chee, O'Craven, Bergida, Rosen, & Savoy, 1999; Demonet, Price, Wise, & Frackowiak, 1994; Devlin, Matthews, & Rushworth, 2003; McDermott, Petersen, Watson, & Ojemann, 2003; C. J. Price, Moore, Humphreys, & Wise, 1997) underlie much of the support for the SMG as a major contributor to phonological processing. Similar results documenting the involvement of the SMG in phonological processing using different tasks and stimuli (serial recall with visually presented pseudowords (Kirschchen, Davis-Ratner, Jerde, Schraedley-Desmond, & Desmond, 2006), homophone judgments with visually presented words (Stoeckel, Gough,
Watkins, & Devlin, 2009), syllable counting with visual and auditorily presented words (Hartwigsen, Baumgaertner, et al., 2010) and, rhyming judgment with visually presented words (Sliwinska, Khadilkar, Campbell-Ratcliffe, Quevenco, & Devlin, 2012)), have been reported in TMS experiments although the type of effect (inhibitory, facilitatory) varied depending on stimulation parameters (rTMS versus single pulse).

Interestingly, apart from the evidence regarding the involvement of the SMG in tasks targeting phonological processing, there is also accumulating evidence from brain imaging studies that suggests that the SMG is also recruited during verbal working memory tasks (VWM) (for a review, please refer to Awh, Jonides, Shumacher, Koppe, & Katz, 1996; Barch & Csernansky, 2007; Jonides, et al., 1998; Kirschen, et al., 2006; Koelsch, et al., 2009; McKenna, Brown, Drummond, Turner, & Mano, 2013; Paulesu, et al., 1996; Salmon, et al., 1996; Smith & Jonides, 1999; Smith, Jonides, & Koeppe, 1996). While it is certainly plausible that the activation observed within the SMG during verbal working memory tasks can be attributed to phonological processing, given that in these experiments subjects were presented with either letters or words and that verbal working memory tasks were not directly contrasted with phonological tasks, it is not clear what the common process is. Although functional neuroimaging evidence is consistent with the SMG being involved in phonological processing and VWM, it is difficult to establish causal links without more direct manipulation of the SMG while engaging phonological processing.

In an attempt to clarify the contribution of the SMG during phonological processing, Romero and colleagues (2006) used online high frequency rTMS to inhibit the left SMG while subjects performed a phonological task (e.g. initial sound similarity and stress
assignment), a working memory task (e.g. a digit span task) or a control task (to rule out nonspecific TMS effects) with visually-presented stimuli. The application of rTMS to the left SMG had a significant effect on the mean RTs and accuracy for phonological processing, suggesting a contribution from the left SMG. However, as acknowledged by the authors, the phonological tasks were potentially confounded by verbal working memory. To exclude this possibility, the authors repeated the phonological tasks with a second group of subjects while attempting to minimize working memory by keeping words on the screen until judgment was completed. As previously observed, TMS applied to the left SMG disrupted phonological processing independent of working memory. However, orthographic presentation entails the recoding of orthographic form into phonological form, the rehearsal of the phonological form to access the short-term store and the “storage” of the phonologically recoded material (Henson, Burgess, & Frith, 2000). Thus, while keeping the visual stimuli on screen might lessen verbal working memory demands it certainly does not ensure that working memory was not recruited. In addition, while these studies were selectively designed to engage phonological processing or verbal working memory, the lack of control for phonological or verbal working memory processes does not allow for the association of specific functions to individual regions (for a similar discussion, refer to Poeppel, 1996).

Our goal in the present study was to address more directly the role of SMG in encoding phonological information during a speech perception and VWM task, using rTMS with stimuli that differed in terms of phonological complexity. The tasks were designed to: 1) modulate phonological complexity while minimizing working memory (e.g. same/different discrimination task) and (2) modulate both phonological complexity and
working memory (n-back task). Phonological complexity was manipulated by varying the sonority difference between the two first consonants of the initial syllable. Sonority reflects the acoustic energy being released in the production of a sound. In English, vowels are the most sonorous and stop consonants are the least sonorous (Dobrovolsky & Katamba, 1996). The sonority value is representative of perceptual salience and ease of production. In fact, higher sonority values are associated with more salient phonemes and easier articulation (i.e. more open vocal tract) (Lindblom, 1983; P. J. Price, 1981). In addition, the closer the sonority value of two consonantal segments, the higher the markedness of the CC—the harder their articulation and the lower their perceptual salience. Sonority differences between two phonemes (in our case consonants) can be calculated (Gierut, 2007), with smaller sonority differences between the consonants in a cluster associated with greater phonological complexity of the cluster (for more details, please refer to Steriade, 1990). We used auditory stimuli to directly access phonology.

We hypothesized that if the bilateral SMG is involved in the encoding of sonority differences, rTMS to the left and right SMG would affect both the n-back task and the same/different task, given that stimuli varying in phonological complexity were included in both tasks. However, if the bilateral SMG is involved in holding phonological codes in memory and not processing them per se (i.e. encoding), we hypothesized that the application of rTMS would only disrupt the n-back task, independent of complexity (as verbal WM demands were minimized in the same/different task).

2. Section: Materials and Method

2.1 Pilot experiment:
Our main experimental manipulation (i.e. sonority differences between the two consonants in the word-initial cluster) was selected largely on theoretical linguistic grounds. A pilot experiment was conducted to determine whether our manipulation would yield the expected results during a same/different judgment task (i.e. increased reaction times for more phonologically complex stimuli) (e.g. differences in sonority between consonants). Subjects made a same/different judgment after the presentation of pairs of stimuli with the same sonority ranking (2 or 5) that were either: (1) the same word presented twice, (2) a word and its corresponding pseudoword, (3) a pseudoword and its corresponding word, or (4) the same pseudoword presented twice. Identical words or words that differ on one item (i.e., the vowel in the word-pseudoword pair) are known to increase task difficulty and attention (Conrad, 1974; Murray, 1968). The results yielded faster reaction times for stimuli with lower complexity compared to stimuli with higher complexity (smaller sonority differences) (t=6.225, p=0.000), indicating that the participants were sensitive to the manipulation (see supplementary data). These stimuli were used in both studies with different tasks: i.e. same/different discrimination and n-back.

2.2 General Methods—Studies 1 and 2

2.2.1 Participants:

All participants were right-handed (mean = 91.1 ± 11.5) as assessed by the Edinburgh handedness inventory (Oldfield, 1971), had normal hearing and normal or corrected-to-normal vision as self-reported. None of the participants reported past or present speech, language or learning difficulties. None of the participants had any linguistic or phonetic training. Prior to the experimental session, all participants were screened for any relative
or absolute contraindication to TMS (Wasserman, 1998). Informed written consent was obtained from each participant.

2.2.2 Stimuli:

Initial word lists containing common two-syllable trochaic nouns, six to eight letters in length, with onsets utilizing all legal two consonant clusters of English were developed using the UWA Psychology: MRC Psycholinguistic Database (Coltheart, 1981). Word-initial consonant clusters were classified by sonority ranking (Steriade, 1990) calculated by measuring the absolute distance in sonority between the two consonants in the word-onset cluster. Words with a sonority ranking of two or five were chosen because each of these two rankings contributed an ample number of words while being substantially distinct with respect to sonority. Based on these words, pseudowords were created by substituting the nucleus of the second syllable of the word with each of the vowels of English (e.g. clinic, clinac). A pseudoword was rejected if the vocalic orthography change resulted in a real word. Words and pseudowords were then compared for bigram frequency to ensure that the pseudowords were legal and equally frequent combinations in English orthography and phonology as their corresponding words (Balota, et al., 2007; Solso & Juel, 1980). Words and pseudowords in each sonority category were matched on the number of orthographic neighbours and mean bigram frequency (Balota, et al., 2007). Words in each sonority category were also matched on frequency of occurrence in verbal language, printed familiarity rating, concreteness (UWA Psychology: MRC Psycholinguistic data base; (Colheart, 1981) and phonological neighbours (Balota, et al., 2007).
Stimulus recordings were made (at a 44 kHz sampling rate) with a headset microphone directly connected to a computer, using PRAAT (Boersma & Weenink, 2011) as a recording platform. All words and pseudowords were recorded by a female native English speaker in a sound-treated room. To increase task difficulty in both studies, a degradation of the auditory stimuli was introduced by combining recorded stimuli in PRAAT with a 100-Hz square wave. A 100-Hz square wave was used instead of noise (based on a pilot experiment) in order to ensure that subjects could perceive acoustically the difference between the words and pseudowords—which was a change in the nucleus (i.e. vowel) of the second syllable. The intensity of the square wave and the recorded stimuli were normalized to 80 dB before combination.

2.2.3 Procedure:
Participants were seated in a padded armchair in front of a laptop with their head held in place comfortably by a headrest. The auditory stimuli were presented on a Dell laptop computer controlled by Presentation® Software (Version 14, www.neurobs.com). Prior to the experimental session, presentation volume was adjusted to each subject’s comfort level.

2.3 TMS
A high-resolution T1-weighted anatomical MRI scan was obtained for all participants. The MRI scans were imported into BRAINSIGHT 2 software (Rogue Research, Montreal, Canada) and a MRI-to-head co-registration was performed to guide coil placement during rTMS stimulation.

2.3.1 Resting motor threshold (RMT):
Motor evoked potentials were obtained from surface electrodes (10mm) placed over the first dorsal interosseus muscle (FDI) using BRAINSIGHT 2 software (Rogue Research, Montreal, Canada). For each subject, stimulation was performed with a high-speed magnetic stimulator producing short duration biphasic pulses (Magstim Rapid 1400, Wales, U.K.) through a 70-mm figure-of-eight coil. The coil was held tangentially to the skull. Single pulses were delivered to the motor cortex and the intensity of the stimulation was adjusted until the motor evoked potential (MEP) in the right FDI was observed in 5 of 10 trials with an amplitude of at least 50 μV (Rossini, et al., 1994). Adjustments were made in order to locate the maximum excitable hand area. Due to technical difficulties with the EMG recording software (n=16), visual inspection of finger twitches was used to determine resting motor threshold. Previous studies have established that there is a high correlation between the resting motor threshold estimates determined by means of visual inspection and EMG (Balslev, Braet, McAllister, & Miall, 2007; Pridmore, Fernandes Filho, Nahas, Liberatos, & George, 1998). Accordingly, we included subjects regardless of the method used to determine resting motor threshold.

**rTMS stimulation:** Off-line low-frequency (1 Hz) rTMS was used to induce a longer lasting suppression and to avoid nonspecific concurrent effects associated with online TMS (behavioral and attentional effect) (Bolognini & Ro, 2010) during task performance. Previous studies have shown that the time-course of the induced neural suppression during offline protocols lasts for at least half the time of the stimulation length (Eisenegger, Treyer, Fehr, & Knoch, 2008; Fitzgerald, Fountain, & Daskalakis, 2006; Robertson, Theoret, & Pascual-Leone, 2003). The stimulation parameters were well within TMS safety guidelines (Wasserman, 1998). The application of low frequency (1
Hz) repetitive TMS was controlled through Presentation software (Version 14, www.neurobs.com) installed on a Dell Precision M60 laptop computer. The laptop computer was connected to the Magstim Rapid unit through a NIDAQ DI/O card (National Instruments, Austin, Tx, USA).

Stimulation intensity was set to 110% of the participant’s RMT. The stimulation duration of 10 minutes (600 pulses) was within the time frame of the experiment (9 minutes). During the experiment, the coil was held tangentially to the skull with adjustable clamps. The position of the coil was monitored online and adjustments were made if the stimulation point drifted more than 1mm away from the target. For the first experiment, the rTMS intensity ranged from 55-83% of the stimulator output (mean = 68%), and for the second experiment, the intensity ranged from 64-83% (mean = 73%).

2.3.2 rTMS location:

For each participant, the coordinates of the stimulation sites (left and right supramarginal gyrus) were determined using BRAINSIGHT 2 software (Rogue Research, Montreal, Canada). On each subject’s anatomical MR scan, the anterior portion of the supramarginal gyrus, an area that is sensitive to phonological processing according to various neuroimaging studies (Petersen, et al., 1988; C. J. Price, et al., 1997) was identified (See Fig. 1) corresponding to a point located approximately 3-5mm rostrally and 5-7mm ventrally from the end of the lateral fissure. The mean coordinates in Talairach space for the left SMG were -53 -36 24 and 51 -30 27 for the right SMG in the first experiment. For the second experiment, the mean coordinates in Talairach space for the left SMG were -54 -37 26 and 51 -29 26 for the right SMG.

2.3.4 rTMS Procedure:
Each participant underwent four experimental blocks, consisting of either stimulation applied to the left or right SMG or SHAM stimulation applied over the same site. The two real TMS blocks were separated by at least 40 minutes to minimize plasticity effects in the excitability of the stimulated region. Because the two real TMS blocks had to be at least 40 minutes apart, the serial ordering of the TMS blocks (real and SHAM) was: one real TMS block, two SHAM TMS blocks and one real TMS block. The order of the two TMS blocks (i.e. left and right hemisphere stimulation) as well as the order of the two SHAM blocks were fully counterbalanced across subjects.

During the SHAM stimulation, the coil was positioned over either the left or right SMG using the same localization procedure as in the rTMS session. However, during the SHAM stimulation, the coil was placed away from the surface of the scalp as to ensure that no current was induced in the brain. During the SHAM stimulation, the stimulator was also on to replicate as much as possible the settings of the real TMS stimulation (e.g. clicking noise from stimulation, and noise from the cooling system).

2.4. Data analysis

2.4.1 Response accuracy:

The percentage of correct answers was calculated for each experimental condition for each subject. Errors were defined as either missed trials (no response) or incorrect response. The accuracy data were transformed to the natural logarithm of odds (i.e. \( \ln(p/1-p) \)) because binomially distributed data violate the assumption of normality (for more details, please refer to Jaeger, 2008). For the first experiment, transformed data were entered into a repeated measures ANOVA (rANOVA) with three factors: (1) TMS, (2) Hemisphere and (3) Complexity and one between subject factor: Group using SPSS.
19 (SPSS Inc., Chicago, IL). We included the Group factor to investigate whether the order of stimulation (left or right hemisphere) had any effect on behavior. For the second experiment, data were entered into two separate rANOVAs, one for each n-back task. The two n-back tasks were entered into separate rANOVAs because the 0-back task was only included to test for non-specific effects of TMS on behavior, and given that subjects responded to a tone interspersed among words there was no effect of complexity. For the 2-back task, three within subjects factors were included: (1) TMS, (2) Hemisphere, (3) Complexity and one between subject factor was included: (1) Group. In the 0-back task, as aforementioned, only two within subject factors were defined: (1) TMS and (2) Hemisphere and one between subject factor was defined: (1) Group. For post hoc comparisons, Bonferroni-corrected two-tailed paired t-tests were used.

To ensure that the two tasks (same/different judgment and 2-back) were equivalent in difficulty, we conducted a separate rANOVA on the SHAM blocks with two within subject factors (1) Complexity and (2) Hemisphere and one between subject factor (1) Task. By including task as a between subject factor we were able to systematically investigate whether accuracy data differed significantly between the tasks.

2.4.2 Reaction times

For the first experiment, reaction time was defined as the time from the second stimulus onset to the onset of the subject’s response. In the second experiment, the reaction time was defined from the onset of the stimulus to the onset of the subject’s response. Latencies were log-transformed to reduce skewness before removing outliers. RTs that were three standard deviations above or below the mean for each participant in each
condition were removed from the analysis. The RT data were analyzed using the same statistical procedure as the accuracy data.

2.5 Experiment 1: Phonological complexity and the supramarginal gyrus

2.5.1 Participants:
Sixteen adult speakers of Canadian English (5 males, mean age = 23.3 ± 4 years) participated in this experiment. Data from one subject were excluded due to excessive movement during the rTMS block.

2.5.2 Procedure:
Subjects performed a same/different judgment to pairs of auditory stimuli following either a block of real stimulation or a block of SHAM stimulation. The stimuli were divided equally into four blocks of fifty trials. Within each block, there were twenty-five pairs requiring a “different” judgment (i.e. word-pseudoword, pseudoword-word) and twenty-five pairs requiring a “same” judgment (i.e. word-word, pseudoword-pseudoword). Each block also contained twenty-five pairs of stimuli with a small sonority difference (i.e. more difficult decision—high complexity) and twenty-five pairs of stimuli with a large sonority difference (i.e. less difficult decision—low complexity).

Subjects were instructed to answer as promptly as possible after the presentation of each pair. Each block began with the visual presentation of instructions to attend followed by a fixation cross for 1000ms followed by the presentation of a pair of stimuli requiring a same or different judgment. Items were presented for 1000ms with an inter-item interval of 250ms. A question mark appeared 200ms after the presentation of the second word in a pair, cuing the response and remained on the screen for 1500ms. The inter-trial interval was 2050ms yielding a total duration of each trial of 7000ms (see Fig.
2. Responses were given via keyboard; the keys for “same” and “different” were switched for half of the participants to counterbalance dominant hand use. Reaction times (RTs) and accuracy data were recorded. The RTs were calculated from the onset of the second item in each pair. The presentation of the experimental blocks was systematically rotated across participants and TMS stimulation blocks. The total duration of each block was about 7 minutes, well within the 10 min window of effect for the rTMS stimulation (for a review, please refer to Fitzgerald, et al., 2006).

2.5.3 Results

Three trials from each block were removed due to a coding error. The total number of trials was forty-seven per block.

2.5.3.1 Response accuracy: The percentage of accurate responses is listed in Table 1 for each condition. Participants responded near ceiling level for all conditions with a mean of 98.1\% ± 2.9. In the rANOVAs, no significant main effects, two-way interactions or four-way interactions were found. However, a significant three-way interaction between TMS*Hemisphere*Complexity was found (F\(_{(1,13)}\)=8.939, p=0.010). In order to investigate the source of the three-way interaction, two-way interactions were computed. A significant spurious two-way interaction between Hemisphere*Complexity (F\(_{(1,14)}\)=4.62, p=0.050) was found only during the SHAM blocks\(^1\).

\(^1\) We determined that the two-way interaction observed is a spurious effect, a common problem associated with ordinal measurements (Kang & Waller, 2005). The source of the spurious effect is related to the SHAM trials, in which the hemisphere factor is of no interest, as it does not represent any meaningful experimental manipulation. It is a factor that is fully balanced across subjects. The source of the two-way interaction as established by post-hoc t-tests was only observed when a differential score for the level of complexity (HPC-LPC) was tabulated and compared between the two hemispheres.
2.5.3.2 Reaction Time:

Fig. 3 illustrates the mean reaction times (RT) for each experimental condition. As expected, the rANOVA revealed a main effect of Complexity ($F_{(1,14)}=54.55$, $p<0.00$). RTs for stimuli in the high complexity conditions ($=1.23s \pm 0.18$, collapsed across TMS conditions) were significantly longer than RTs for the low complexity conditions ($=1.17s \pm 0.19$) ($p < 0.05$ Bonferroni-corrected). There were no significant interactions.

2.6 Experiment 2: Working memory and the supramarginal gyrus

2.6.1 Participants:

Fifteen adult speakers of Canadian English (6 males, mean age = 23.5 ± 3 years) participated in the second experiment. Ten of the fifteen subjects had participated in the first experiment. Testing sessions were separated by a minimum of three months and a maximum of five months. Participants were subjected to the same exclusion and screening criteria as in experiment one. Data from three subjects had to be excluded from the analyses; one subject failed to do the task as instructed, and two subjects had too few trials due to technical difficulties associated with excessive movement during the rTMS block. Informed written consent was obtained from each participant.

2.6.2 Procedure:

Subjects performed two blocks of a 2-back and two blocks of a 0-back working memory task. In both tasks (for more details regarding the nature of the task, please see section below) each block differed in terms of complexity (based on sonority differences) and followed either a block of real stimulation or a block of SHAM stimulation. A subset of

(p=0.052). In addition, after correcting for multiple comparisons using a Bonferroni correction, this is effect is no longer significant.
the auditory stimuli used in Experiment 1 was used to create four blocks of a 2-back task containing stimuli with a low sonority difference (i.e. more complex) and four blocks of a 2-back task containing stimuli with a high sonority difference (i.e. less complex), for a total of eight blocks. For the 0-back task, we also created four blocks with a high sonority difference and four blocks with a low sonority difference. The total duration of each n-back block was 2.0 minutes, for a total of 8 minutes of experimental conditions after each TMS block (real or SHAM). The same testing procedures (i.e. instructions prior the experiment, seating, etc.) as for Experiment 1 were used.

For both 2-back and 0-back blocks, each block started with the presentation of visual instructions and a fixation cross, identical to the procedure in Experiment 1. For the 2-back task, each block contained forty-eight stimuli presented every 1000ms after the offset of the previous stimulus (refer to Fig. 2). Short-to-medium interstimulus interval (ISI) were used to increase difficulty and avoid ceiling effects and minimize cognitive strategies (for a review, please refer to Hancock, Leonard, Stierwalt, Bourgeois, & Zwann, 2007).

For the 2-back task, subjects were instructed to press a keyboard button every time an item was the same as that presented two trials back. For the 0-back task, subjects were instructed to press a keyboard button every time a tone was presented among the words and pseudowords. Participants were instructed to respond as quickly as possible. The presentation of the n-back blocks was randomized across participants and TMS blocks (real or SHAM).

2.6.3 Results

2.6.3.1 Response accuracy:
The percentage of accurate responses is listed in Table 2 for each condition for the 0-back task. Participants responded at ceiling level for all conditions with a mean of 99.8% ± 0.8. As expected, no significant main effects or interaction was found. Fig. 4 illustrates the accuracy results for the 2-back task for each group collapsed across phonological complexity. The rANOVA yielded a significant main effect of TMS (F(1,10)=10.733, p=0.008). Response accuracy was higher in the SHAM blocks (90.8% ± 10.8) than in the TMS blocks (82.9% ± 14.8). A significant two-way interaction between Hemisphere*Group was found (F(1,10)=10.653, p=0.009). Paired sample t-tests revealed that subjects in Group 1 (real stimulation to left hemisphere first) were significantly more accurate during right hemisphere stimulation (real and SHAM) than during left hemisphere stimulation (real or SHAM) (T=-4.650, p ≤ 0.05 Bonferroni corrected). A significant three-way interaction between TMS*Hemisphere*Group was also found (F(1,10)=6.839, p=0.026). In order to investigate the source of the three-way interaction, interaction effects were computed for each level of the Group factor. For Group 1, a two-way interaction between TMS*Hemisphere was observed (F(1,6)=7.53, p=0.03). Paired sample t-tests revealed that subjects were less accurate when real TMS was applied to the left hemisphere as compared to SHAM TMS to the same hemisphere (T=-4.30, p ≤ 0.05 Bonferroni corrected) and a significant difference was also observed between the two real TMS blocks. Subjects’ accuracy was significantly lower when real TMS was applied to the left hemisphere than the right hemisphere (T=-5.687, p ≤ 0.05 Bonferroni corrected). For Group 2, no significant two-way interaction was observed. No other interactions reached significance.
To look for potential interactions among serial order of stimulation and hemisphere, we investigated the source of the three-way interaction by comparing hemispheric differences between the two groups at each level of the TMS factor (real and SHAM). The only significant difference was observed for real TMS blocks after the left SMG stimulation. Participants who received TMS to left hemisphere during the second block of real TMS stimulation were more accurate than participants who received real TMS to the left hemisphere during the first block (T=-4.32, \( p \leq 0.05 \) Bonferroni corrected).

To rule out the possibility that cortical modulation associated with the first TMS block affected the accuracy data of subsequent blocks, we conducted a rANOVA on the behavioral data obtained from the two SHAM blocks with two within subject factors: Hemisphere (left and right) and Complexity (high and low) and one between subject factor: Group (real TMS to the left hemisphere first or real TMS to the right hemisphere first). The rANOVA yielded no significant two-way or three-way interactions (\( p<0.1 \)) and no significant linear trends that would indicate that the groups differed.

To investigate whether the two tasks differed in complexity, a rANOVA was conducted on the accuracy data of the same/different task and the 2-back task. The rANOVA yielded no significant two-way or three-way interactions.

**2.6.3.2 Reaction time:**

The reaction times for the 0-back task are listed in Table 3. For the 0-back task, the rANOVA revealed no significant effects. Fig. 5. illustrates the RT for each experimental condition for the 2-back task for each group collapsed across phonological complexity. For the 2-back task, the rANOVA revealed a main effect of TMS (\( F_{(1,10)}=11.698, \)
p=0.007). Mean RTs for real TMS blocks were significantly longer (1.02s ± 0.13) than for SHAM TMS blocks (0.98s ± 0.09) (p ≤ 0.05 Bonferroni corrected). Also, as predicted, there was a significant effect of complexity (F(1,10)=7.896, p=0.02) but no main effect of hemisphere. The RTs for stimuli in the high complexity conditions (1.02 ± 0.09) were significantly longer than RTs in the low complexity conditions (0.98 ± 0.12) (p ≤ 0.05 Bonferroni corrected). The only significant two-way interaction was observed between Group*Hemisphere (F(1,10)=11.987, p=0.006). Paired sample t-tests revealed that for Group 1, the RT for the left hemisphere was significantly longer than the RT for the right hemisphere (t=4.736, p ≤ 0.05 Bonferroni corrected). A significant three-way interaction between TMS*Hemisphere*Group was found. In order to investigate the source of the three-way interaction, interaction effects were computed for each level of the Group factor. For Group 1, a significant two-way interaction between TMS*Hemisphere was found (F(1,7)=9.256, p=0.02). Paired sample t-tests revealed that RTs in TMS trials were significantly longer than for SHAM trials only for the left hemisphere (t=3.083, p ≤ 0.05 Bonferroni corrected) and that the RTs for TMS trials were significantly longer for the left hemisphere than the right hemisphere (t=4.774, p ≤ 0.05 Bonferroni corrected). For Group 2, no significant two-way interaction was observed. Only a significant effect of TMS was observed. Paired-sample t-tests revealed that TMS trials were significantly longer than SHAM trials (t=2.769, p ≤ 0.05 Bonferroni corrected). Fig. 5 illustrates the three-way interaction between TMS*Hemisphere*Group. No other interactions reached significance.

To look for potential interactions among serial order and hemisphere within the RT data, we also investigated the source of the three-way interaction by comparing at
each level of the TMS factor (real and SHAM) hemispheric differences between the two groups. The only significant difference was observed for the real TMS to the right SMG. Participants who received TMS to right hemisphere during the second block of real TMS stimulation were significantly faster than participants who received TMS to the right hemisphere during the first block of real TMS ($T=4.62$, $p \leq 0.05$ Bonferroni corrected).

To rule out the possibility that cortical modulation associated with the first TMS block affected the reaction time data of subsequent blocks, we conducted the same rANOVA described above. The rANOVA yielded no significant two-way or three-way interactions ($p<0.1$) and no significant linear trends that would indicate that the groups differed.

The rANOVA that was conducted to investigate task difficulty differences yielded no significant two-way or three-way interaction between groups.

2.7 General Discussion

The present experiment was designed to address the involvement of the SMG in encoding phonological information relative to verbal working memory. From functional MRI and TMS studies of the nature of the involvement of the left and right SMG in language related tasks, the functional role of this region is unclear. Brain imaging studies have associated the left and right SMG with phonological processing (Chee, et al., 1999; Demonet, et al., 1994; Devlin, et al., 2003; C. J. Price, et al., 1997) and verbal working memory (Awh, et al., 1996; Barch & Csernansky, 2007; Jonides, et al., 1998; Kirschen, et al., 2006; Koelsch, et al., 2009; McKenna, et al., 2013; Paulesu, Frith, & Frackowiak, 1993; Paulesu, et al., 1996; Salmon, et al., 1996; Smith & Jonides, 1999; Smith, et al., 1996), while TMS studies have provided evidence regarding the involvement of the left
and right SMG during phonological processing (Hartwigsen, Baumgaertner, et al., 2010; Romero, et al., 2006; Stoeckel, et al., 2009), but based on these studies, the possibility that the experimental tasks used also recruited verbal working memory processes cannot be discounted. To gain a better understanding of the role of the left and right SMG in both verbal WM and phonological processing, we conducted two TMS experiments to test hypotheses regarding the contribution of the left and the right SMG to phonological encoding and verbal WM separately.

2.7.1 Phonological processing and the supramarginal gyrus

Surprisingly, the results from experiment one revealed that processing sonority-based manipulation was unaffected by TMS stimulation to either the left or the right SMG. While this finding suggests that these two regions are not directly involved in processing changes in sonority between consonants (affecting the phonological complexity of the onset of a syllable), and might seem at odds with results from previous TMS experiments (Hartwigsen, Price, et al., 2010; Romero, et al., 2006; Stoeckel, et al., 2009), it is not. There are several differences in tasks, stimuli and stimulation sites that can explain the discrepancy in results between our study and previous studies. The most noticeable difference is that unlike other studies that have used rhyming tasks, we used a phonological metric to recruit regions involved in phonological processing. Thus, rhyming judgments might tax different phonological processes than same/different judgments with stimuli that vary in terms of phonological complexity. Stimulus modality is another factor that may explain the differences in our results compared to previous TMS results. While most previous studies have used auditory and visual stimuli, we relied on auditory stimuli to eliminate orthographic-phonological transformations that
might recruit additional VWM. In the presence of direct phonological manipulation, the present results suggest that anterior SMG is not directly involved in the processing of sonority differences. Thus, the effects observed in previous TMS studies appear to be related to the transformation of orthographic codes into phonological representations. This interpretation is consistent with phonological tasks such as rhyming or syllable judgments using visually presented stimuli, wherein an emphasis is put on both the recoding of the visual input into phonological representations and holding that information in memory in order to perform the task. Recent fiber dissection, DTI tractography and functional resting-state connectivity studies have identified an anterior segment of the superior longitudinal fasciculus connecting the poster portion of the STG and the SMG to the precentral gyrus (Catani, Jones, & Fytche, 2005; Makris, et al., 2005; Martino, et al., 2012; Xiang, Fonteijn, Norris, & Hagoort, 2010). Hence, the SMG might serve as one node in a local, distributed network between the STG and the precentral gyrus in which phonological information is kept in memory once it has been phonologically encoded. This hypothesis leads to the prediction that in tasks in which both VWM and phonological complexity are manipulated, stimulation to the SMG should lead to a main effect of TMS on VWM tasks independently of the complexity of the stimuli. This is the hypothesis that we sought to address in the second experiment. Another factor that cannot be disregarded is the fact that stimulation sites vary from study to study. Differences in stimulation sites coupled with the observation that the supramarginal gyrus includes several sub-regions that differ in terms of cytoarchitecture and receptor architectonics (Caspers, et al., 2008; Caspers, et al., 2012), suggest that the SMG encompasses more than one functional field. Thus very different processes might
recruit sub-regions within the SMG. In fact, a fairly recent fMRI study by Ravizza and colleagues (2004) has shown that the ventral SMG was sensitive to the type of information (verbal or non-verbal) whereas the dorsal SMG was sensitive to the memory load. With regards to previous TMS studies, some of the stimulation sites were located more dorsally (Hartwigsen, Baumgaertner, et al., 2010; Stoeckel, et al., 2009) than our stimulation site. However, other studies reported stimulation sites that were very similar to ours (Romero, et al., 2006). Thus, at this point it is hard to tease apart the effects of different factors (i.e. tasks, modality of stimulus presentation, stimulation site). In order to address this issue, we used the same stimulation site for the second experiment using a task that clearly involved verbal working memory processes and phonological processing.

2.7.2 Verbal working memory and the supramarginal gyrus

The goal of the second experiment was to examine the possible contribution of the same cortical region to verbal working memory. The same stimuli as in Experiment 1 were used but in two n-back working memory tasks (2-back, 0-back). While TMS applied to either the left or right SMG had no effect on the processing of sonority differences, TMS to the same locations resulted in consistently slower performance in the 2-back task. In the 2-back task, no significant two-way interaction between TMS and Complexity emerged, further confirming that the SMG is not involved in the processing of sonority differences. The results from the second experiment do suggest, however, that the bilateral SMG is involved in VWM independent of processing phonological complexity. Thus, it is likely that unlike the pSTG, the anterior SMG is not involved in decoding/encoding phonological information, a process common to both VWM and speech production tasks.
An interesting finding that emerged is the apparent effect on reaction time of the ordering of the hemispheric stimulation. More precisely, an effect of TMS stimulation for both hemispheres only emerged when the right SMG was stimulated first. If the left SMG was stimulated first, TMS to the right hemisphere during the second stimulation block had no disruptive effect. However, if the right hemisphere was stimulated first and the left hemisphere second, a main effect of TMS stimulation was observed for both hemispheres. Although unexpected, this finding illustrates a complex hemispheric interaction and suggests an impact of order of hemispheric stimulation on the level of recruitment for VWM. One possibility is that the hemispheric interaction reflects a cortical modulation or carryover effect. However, this explanation was addressed by comparing the SHAM blocks across both groups. The lack of significant differences between the groups suggest, that the effect observed is not the results of the cortical modulation from previous TMS stimulation to the opposite hemisphere. Moreover, previous studies have shown changes in cortical activity in regions associated with VWM with short amounts of training (e.g. 30 minutes) (for a review, refer to Klingberg, 2010; Olesen, Westerberg, & Klingberg, 2004). Given that RT was affected by the timing of the stimulation to the different hemispheres, it suggests that interspersing the two SHAM blocks between real stimulation may have provided the subjects enough practice to induce a change in the contribution of the hemispheres to VWM. The hypothesis that training effects can account for a different hemispheric involvement of the SMG during VWM tasks is strengthen by two additional findings: (1) subjects who received real TMS stimulation to the left SMG during the first block were less accurate than subjects who received real TMS stimulation to the left SMG during the last block and (2) subjects who
received real TMS stimulation to the right SMG during the first block were slower than subjects who received real TMS stimulation to right SMG during the last block. Thus, without prior practice, both hemispheres contributed to verbal working memory and TMS to both left and right hemispheres disrupted performance. However, following practice on the verbal working memory task (during the SHAM trials), the network became more left lateralized as seen by the absence of TMS modulation following right hemisphere stimulation. As a result, only left hemisphere stimulation disrupted performance. In addition, it is also possible, that overall the effect of right SMG stimulation is weaker than left SMG stimulation; therefore performance is only disrupted following right SMG stimulation in the absence of training effects (first block) whereas performance is disrupted for the left SMG stimulation regardless of training effects (first and second block). It appears that the left hemisphere is crucial to working memory and that the right hemisphere is not capable of compensating for reduced function of the left hemisphere.

In sum, the results from both experiments demonstrate that the SMGa is a node within a distributed network involved in VWM. The SMGa might serve to maintain a verbal memory trace (Henson, et al., 2000) after being phonologically encoded. This hypothesis is consistent with a recent review by Buchsbaum and colleagues (2008), in which the authors present evidence suggesting that the encoding of information is not accomplished within the SMG but rather within a region near the junction of the temporal and parietal lobe. In the current experiments, both the same/different task and the 2-back task involved VWM components. In the case of the same/different judgments, in order to make a decision, subjects had to encode the first auditory stimuli, hold it temporarily in memory (storage and rehearsal) until the second stimuli was presented. The 2-back task
involved greater storage and rehearsal components of VWM in comparison to the same/different judgments.

2.8 Conclusion

The results from these two studies demonstrate involvement of the bilateral SMG in verbal working memory. More specifically, the findings from both experiments suggest that the anterior region of the supramarginal gyrus is involved in more domain-general VWM processes but not in domain-specific processing of sonority information, a finding consistent with VWM being involved in storing phonological representations rather than processing them (Baddeley, 1990, 2007).

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