Assessing the Impact of Transcranial Magnetic Stimulation on Speech Perception in Noise

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Abstract

■ Healthy aging is associated with reduced speech perception in noise (SPiN) abilities. The etiology of these difficulties remains elusive, which prevents the development of new strategies to optimize the speech processing network and reduce these difficulties. The objective of this study was to determine if sublexical SPiN performance can be enhanced by applying TMS to three regions involved in processing speech: the left posterior temporal sulcus, the left superior temporal gyrus, and the left ventral premotor cortex. The second objective was to assess the impact of several factors (age, baseline performance, target, brain structure, and activity) on post-TMS SPiN improvement. The results revealed that participants with lower baseline performance were more likely to improve. Moreover, in older adults, cortical thickness within the target areas was negatively associated with performance improvement, whereas this association was null in younger individuals. No differences between the targets were found. This study suggests that TMS can modulate sublexical SPiN performance, but that the strength and direction of the effects depend on a complex combination of contextual and individual factors. ■

INTRODUCTION

Normal aging is associated with increasing difficulties following conversations in complex auditory environments such as noisy backgrounds or group situations (e.g., Pichora-Fuller, 2003; Frisina & Frisina, 1997; Sommers, 1996; Helfer & Wilber, 1990; Working Group on Speech Understanding and Aging, 1988). These difficulties have initially been linked with presbycusis, an age-related decline in hearing sensitivity that has been associated with speech perception in noise (SPiN) performance (e.g., Eggermont, 2019; Gates & Mills, 2005; Humes et al., 1994; Souza & Turner, 1994). However, more recent investigations have revealed that age-related SPiN difficulties stem from a complex combination of changes in the peripheral and central auditory system, speech processing, and cognitive processes, including auditory attention and working memory (e.g., Pichora-Fuller, Alain, & Schneider, 2017; Tun, Williams, Small, & Hafter, 2012; Aydelott, Leech, & Crinion, 2010; Dubno et al., 2008; Humes, 2007). As background noise is ubiquitous in daily life, SPiN difficulties can hinder communication-mediated activities, such as family reunions or friends gathering (Sommers, 1996), and impact well-being (Yorkston, Bourgeois, & Baylor, 2010; Gates & Mills, 2005; Heine & Browning, 2002; Working Group on Speech Understanding and Aging, 1988). Processing speech is a remarkably challenging task, especially in the presence of speech noise, which increases the complexity of the auditory scene and consequently the cognitive demand to process speech (e.g., see Pichora-Fuller et al., 2016, 2017; Rönnberg, Rudner, Foo, & Lunner, 2008). In the presence of multiple talkers, for instance in social gatherings, listeners must separate the speech sounds from the rest of the auditory scene, but they also need to process each talker's specific characteristics (voice, accent, intonation) to correctly perceive speech despite the huge acoustical variability across talkers (Johnson & Sjerps, 2021). This process is referred to as "talker normalization" (Nusbaum & Magnuson, 1997). The presence of multiple talkers is known to slow down speech processing in young adults, reflecting an increase in processing demands for the listener (e.g., Magnuson, Nusbaum, Akahane-Yamada, & Saltzman, 2021; Choi, Hu, & Perrachione, 2018; Magnuson & Nusbaum, 2007; Green, Tomiak, & Kuhl, 1997).

Processing speech relies on an extended cerebral network that includes the primary auditory cortex, the superior (STC) and middle temporal cortex, the inferior parietal lobule, the motor (M1) and premotor (PM) regions, the inferior frontal gyrus (IFG), the arcuate fasciculus, and other regions involved in executive functions such as the insula and the cingulate cortex (Holt, Peelle, Coffin, Popper, & Fay, 2022; Alain, Du, Bernstein, Barten, & Banai, 2018; Eckert, Teubner-Rhodes, & Vaden, 2016; Vaden et al., 2013; Turkeltaub & Coslett, 2010; Hickok & Poeppel, 2007). Processing sublexical speech and speech in noise is associated with upregulation in the dorsal speech stream (e.g., Lankinen et al., 2023; Alain et al., 2018; Tremblay & Small, 2011; Turkeltaub & Coslett, 2010; Saur et al., 2008; Pulvermüller et al., 2006; Zatorre, Evans, Meyer, & Gjedde,

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1992), a network of regions that connect the temporal lobe (superior temporal gyrus [STG], posterior superior temporal sulcus [pSTS]), inferior parietal lobule, and ventrolateral frontal cortex (IFG and ventral PM cortex [PMv]; Hickok, 2012, 2022; Hickok & Poeppel, 2004, 2007; Scott & Johnsrude, 2003). The STG is involved in the acoustic analysis of speech, whereas the pSTS and PMv contain phonological and articulatory representations of speech (e.g., McGettigan & Tremblay, 2018; Skipper, Devlin, & Lametti, 2017; Saur et al., 2008; Hickok & Poeppel, 2007; Scott & Johnsrude, 2003). Aside from this core speech processing network, additional areas (e.g., the frontoparietal and cingulo-opercular networks) play a crucial role in processing speech, especially when perceiving speech in challenging listening situations (Peelle, 2018; Eckert et al., 2016; Pichora-Fuller et al., 2016; Rönnberg, 2003). These models suggest an ongoing interplay between external demand (e.g., task difficulty, stimulus complexity, and signal degradation) and individual resources, encompassing sensory processing, cognitive abilities, and motivation. Clearly, SPiN is a multifaceted behavior engaging numerous systems.

To clarify the mechanisms that underlie age-related SPiN decline, the relationship between SPiN performance in young and older adults and the structure/function of these regions has been investigated extensively (Tremblay, Brisson, & Deschamps, 2021; Rogers et al., 2020; Presacco, Simon, & Anderson, 2016, 2019; Tremblay, Perron, et al., 2019; Manan, Yusoff, Franz, & Mukari, 2017; Du, Buchsbaum, Grady, & Alain, 2016; Eckert et al., 2016; Peelle & Wingfield, 2016; Bilodeau-Mercure, Lortie, Sato, Guitton, & Tremblay, 2015; Vaden, Kuchinsky, Ahlstrom, Dubno, & Eckert, 2015; Erb & Obleser, 2013; Tremblay, Dick, & Small, 2013; Sheppard, Wang, & Wong, 2011; Wong, Ettlinger, Sheppard, Gunasekera, & Dhar, 2010; Wong et al., 2009; Hwang, Li, Wu, Chen, & Liu, 2007). Neuroimaging studies have shown positive correlations between activity within the dorsal stream and SPiN performance in older and younger adults (Fitzhugh, Schaefer, Baxter, & Rogalsky, 2021; Bilodeau-Mercure et al., 2015; Eckert et al., 2008). Furthermore, studies have reported a decreased gray matter and reduced BOLD signal in the STC for older adults performing SPiN tasks (Tremblay et al., 2021; Peelle & Wingfield, 2016; Sheppard et al., 2011; Harris, Dubno, Keren, Ahlstrom, & Eckert, 2009; Hwang et al., 2007). These studies, combined with studies showing evidence of degraded speech representations in the central auditory system (e.g., Presacco et al., 2016; Presacco, Jenkins, Lieberman, & Anderson, 2015; Tremblay, Piskosz, & Souza, 2003), suggest that age-related speech perception decline is associated with a reduced efficiency in early auditory processing mechanisms (Peelle, 2018; Peelle & Wingfield, 2016). However, most of the studies have not tested the relationship between SPiN performance and the structural and functional integrity of the STC in older adults; thus, causal conclusions cannot be drawn. It is expected that a decline in early sensory mechanisms, similarly to signal degradation contexts, would make the task more effortful and increase cognitive demand in older adults (e.g., Peelle, 2018; Pichora-Fuller et al., 2016, 2017; Eckert et al., 2016). Some studies have indeed shown elevated activation in regions involved in cognitive control in older adults (e.g., the insula and the cingulate cortex). Importantly, however, this enhanced activity did not correlate with a better SPiN performance (Bilodeau-Mercure et al., 2015; Erb & Obleser, 2013; Harris et al., 2009; Eckert et al., 2008; Sharp, Scott, Mehta, & Wise, 2006), suggesting a failed attempt to compensate for inefficient processing in areas involved in speech processing. On the other hand, enhanced recruitment of regions involved in attention (e.g., middle frontal gyrus, prefrontal gyrus) were found to be beneficial to SPiN performance in older adults, suggesting a higher-order compensation mechanism (Du et al., 2016; Erb & Obleser, 2013; Wong et al., 2009). Unfortunately, however, a unifying theoretical view of these different accounts is currently lacking, which hinders the development of strategies to optimally reduce or prevent SPiN difficulties in the elderly.

Given that some of the regions involved in SPiN are also involved in talker normalization, the ability to adjust to different talkers could also decline with aging. However, talker normalization has mainly been studied in young adults. In this population, alternating talkers during speech perception increases the activity in the bilateral STC, parietal areas (specifically the superior parietal lobule), and inferior frontal regions (Tremblay et al., 2021; Zhang et al., 2016; Chandrasekaran, Chan, & Wong, 2011; Wong, Nusbaum, & Small, 2004). The STC is involved in processing spectral and temporal properties of speech, whereas parietal areas and inferior frontal areas are involved in perceptual attention. Electrophysiological studies have found amplitude modulations in several auditory event-related components (N1, P2, and P3)—which are thought to reflect attention shifting toward the vocal features of the new talker—during talker normalization (e.g., Uddin, Reis, Heald, Van Hedger, & Nusbaum, 2020; Kaganovich, Francis, & Melara, 2006). Increased activity within these regions (STC, superior parietal, inferior frontal) is often observed in other challenging speech perception conditions (e.g., when the level of the noise is increased) and are thought to reflect an increase in processing demands.

The impact of aging on the talker normalization process is not currently understood. One study showed a greater accuracy decline from single to multiple talkers in a word identification in noise test for older compared with younger adults (Sommers, 1997), suggesting a less efficient talker normalization process in older adults. In a recent study from our group, we compared the talker normalization process in young and older adults (Tremblay et al., 2021). Our results showed that performance was poorer in the multiple talker condition for all the listeners, young and older. In the multiple talker condition, the BOLD signal difference between speech in noise and speech in quiet was larger in older compared with younger adults in the left parietal cortex and the left ventral postcentral gyrus and sulcus, but these differences did not predict

performance. More studies are thus required to clarify whether talker normalization is costlier in aging, and how differences in the brain structure/function might contribute to the decline or preservation of this ability in older adults. In summary, multiple questions remain regarding the mechanism of age-related SPiN decline, and the conditions that are most challenging to older adults, including social gatherings where multiple talkers are present. Understanding these mechanisms is essential for the development of new strategies to reduce—or potentially prevent—these difficulties.

TMS is a non invasive brain stimulation method that can induce short- and long-term plasticity TMS can have a beneficial impact on performance. Speech perception has been successfully modulated in healthy young adults through TMS applied to speech areas including the motor cortex (Berent, Fried, Theodore, Manning, & Pascual-Leone, 2023; Murakami et al., 2018; Bartoli et al., 2015; Smalle, Rogers, & Möttönen, 2015; Rogers, Möttönen, Boyles, & Watkins, 2014; D'Ausilio et al., 2009; Möttönen & Watkins, 2009), STC (Kennedy-Higgins, Devlin, Nuttall, & Adank, 2020; Ramos Nuñez, Yue, Pasalar, & Martin, 2020; Murakami, Kell, Restle, Ugawa, & Ziemann, 2015; Grabski, Tremblay, Gracco, Girin, & Sato, 2013; Krieger-Redwood, Gaskell, Lindsay, & Jefferies, 2013; Beauchamp, Nath, & Pasalar, 2010), posterior IFG (Deschamps, Courson, Dick, & Tremblay, 2020; Murakami, Restle, & Ziemann, 2012; Hartwigsen et al., 2010; Gough, Nobre, & Devlin, 2005), PM (Nuttall, Kennedy-Higgins, Devlin, & Adank, 2018; Grabski et al., 2013; Krieger-Redwood et al., 2013; Sato, Tremblay, & Gracco, 2009; Meister, Wilson, Deblieck, Wu, & Iacoboni, 2007), and supramarginal gyrus (Deschamps et al., 2020; Grabski et al., 2013; Hartwigsen et al., 2010). However, because aging is associated with changes in brain structure and function, the impact of TMS might be age dependent. Previous studies have shown that baseline cortical excitability is lower in older adults (Tang et al., 2019), but this measure might not be representative of the potential to induce plasticity using different protocols. Evidence of plasticity induction through paired-pulse or repetitive TMS protocols applied to the motor cortex varies according to the protocol used and the sample characteristics (Semmler, Hand, Sasaki, Merkin, & Opie, 2021; Freitas, Farzan, & Pascual-Leone, 2013). In addition to age, many factors have been identified as potential predictors of TMS outcomes, including scalp–cortex distance, coil orientation, brain region, baseline performance level, and initial state of the brain (structure, signal, connectivity, and plasticity; Liu et al., 2023; Siebner et al., 2022; Abellaneda-Pérez et al., 2019; Silvanto, Bona, Marelli, & Cattaneo, 2018; Stokes et al., 2007). A better comprehension of the factors that determine post-TMS outcomes is required for the development of new strategies to induce gains in performance through TMS-induced cerebral reorganization.

In a recent study from our team (Brisson & Tremblay, 2021), we used TMS to enhance cortical excitability in two speech-related brain regions (posterior STS and PMv) using an intermittent theta-burst (iTBS) protocol. The objective was to determine if iTBS can improve performance in a syllable-discrimination task presented in speech noise. The results revealed that applying TMS to the PMv was associated with more improvement than TMS to the STS, and baseline performance level predicted post-TMS difference scores (i.e., participants with lower accuracy or higher RTs at baseline showed the most improvement on these same measures after TMS). Importantly, the results also revealed no age effect on post-TMS performance differences. Together, these results suggest that TMS could be used to improve SPiN in adults of all ages, but more studies are needed to replicate and extend these findings.

Building from our prior work, the main objective of the present study was to confirm, using a completely independent sample, whether TMS applied to the PMv or STS can improve sublexical SPiN performance in adults in a more complex situation in which the talker varies from trial to trial. A related objective was to determine whether TMS to the left STG, which was not part of our prior work, can enhance SPiN performance. Our main hypothesis was that stimulating the PMv would lead to larger SPiN improvement compared with the STS, and that stimulation of the STG would lead to larger improvement when multiple talkers are involved, compared with the PMv and the STS. The second objective was to identify which factors (age, baseline performance, target, brain structure, and activity) can predict post-TMS SPiN improvement. We hypothesized that lower baseline performance would be associated with stronger improvement, consistent with our prior finding.

METHODS

Participants

A nonprobabilistic sample of 34 healthy right-handed healthy native Québec French speakers aged 21–78 years was recruited through emails sent to the university community and the *Centre intégré universitaire de santé et des services sociaux de la Capitale-Nationale*, posts on our laboratory website (www.speechneurolab.ca) and Facebook page (https://www.facebook.com/speechneurolab/), and flyers distributed in various institutions, including shops and retirement homes throughout Québec City, as well as from our laboratory participant database (Figure 1A). Four participants were excluded: One participant stopped returning our calls after the first visit, and three dropped out because they were uncomfortable during the TMS sessions, leaving 30 participants in the final sample. A previous study from our team with a similar sample size ($n = 34$), participants' characteristics, and data analyses showed sufficient statistical power to detect age, baseline performance, and target effects on baseline performance and improvement scores (Brisson & Tremblay, 2021). Furthermore, two studies have shown that pitch accuracy and repetition

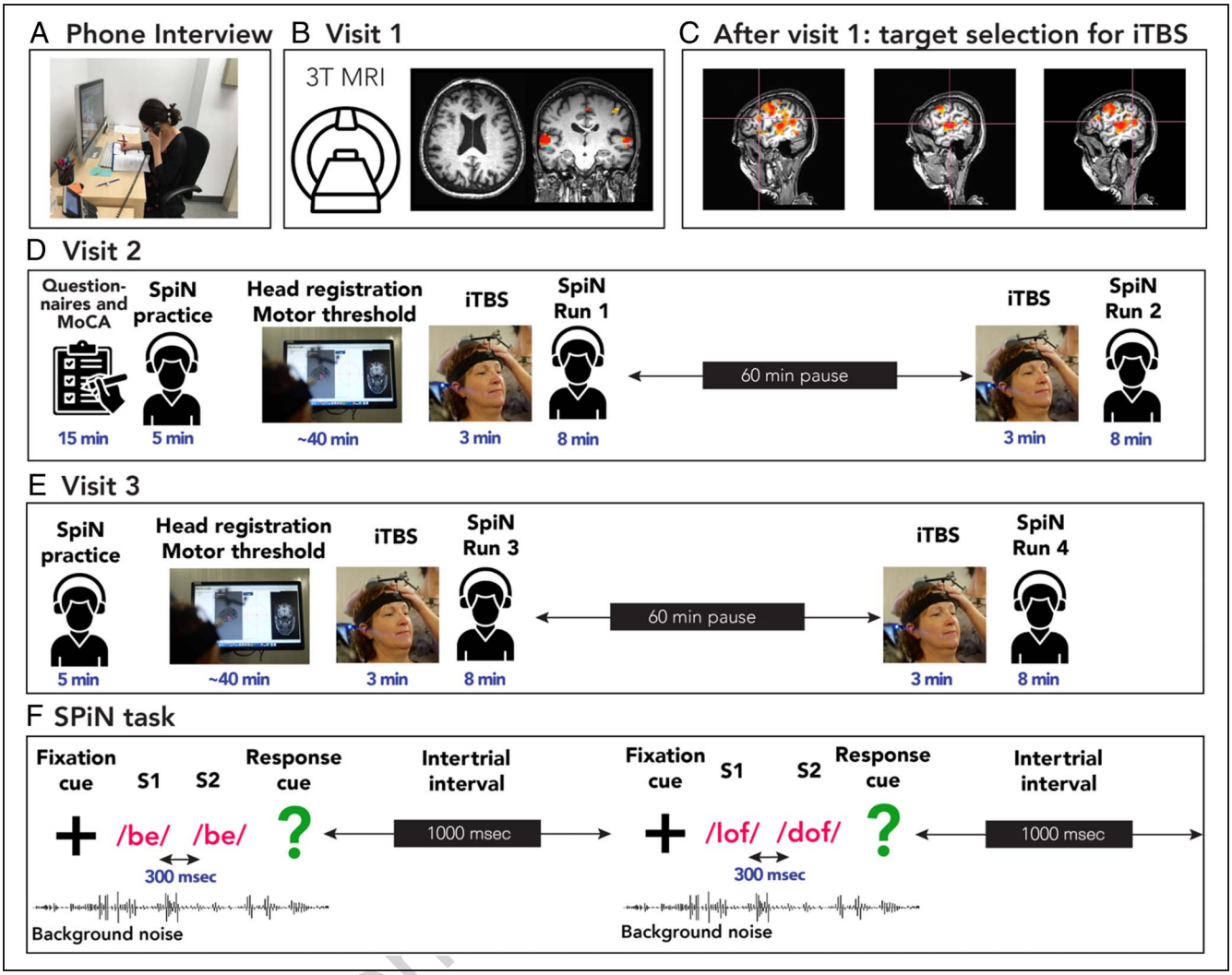

Figure 1. Experiment design (A–E) and details of the SPiN task (F). Each SPiN run was administered in the same order, but the order of the regions stimulated (sham, STG, STS, PMv) was counterbalanced across the participants.

accuracy could be improved by applying one session of iTBS to small groups of healthy young adults (n = 14 and n = 18, respectively; Finkel et al., 2019; Restle, Murakami, & Ziemann, 2012).

Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). Participants reported normal or corrected-to-normal vision; no history of language, neurological or psychiatric disorder; no hearing aids or cochlear implant; and no contraindication to MRI or TMS (Wassermann, 1998). The French version of the 30-item Geriatric Depression Scale (Yesavage et al., 1982) and the Geriatric Anxiety Inventory (Pachana et al., 2007) were used to assess depression and anxiety symptoms but were not used as exclusion criteria. Hearing was assessed using pure-tone audiometry (0.25, 0.5, 1, 2, 3, 4, 6, 8 kHz). Participant characteristics are presented in Table 1. The French version of the Montreal Cognitive Assessment (MoCA v8.1; Nasreddine et al., 2005) was used to assess participants' general cognitive level, but it was not used as an exclusion criteria.

All participants gave their informed consent and received a monetary compensation. The study was approved by the *Comité d'éthique de la recherche sectoriel en neurosciences et santé mentale, Institut Universitaire en Santé Mentale de Québec* (#1495–2018 and #2015–98/369–2014 for the laboratory data bank BACH). Individual data (behavioral and MRI), as well as the speech stimuli and experimental materials) are publicly available on Borealis, The Canadian Dataverse Repository (https://doi.org/10.5683/SP3/3NBZLP).

Procedures

The project included three visits. As part of the first visit, MRI data were acquired. The second and third visits took place at the Speech and Hearing Neuroscience Laboratory in Québec City, Canada. During these visits, participants completed questionnaires and tests to evaluate hearing and

Table 1. Participants' Characteristics (n = 30, 15 F)

	M	*SD*	*Range*
Age (years)	52.63	17.50	21–78
Handedness[a]	95.67	7.51	80–100
Education (years)[b]	15.57	2.34	11–21
GDS (/30)[c]	2.97	2.85	0–9
GAI (/20)[d]	1.46	2.32	0–9
MoCA (/30)[e]	27.40	2.44	21–30
EVB (/62)[f]	9.47	5.48	0–22
Best ear PTA (dB)[g]	10.12	9.14	−3.33–40.83

N = number of participants; F = number of female participants; M = mean; SD = standard deviation.

[a] Handedness was measured from the Oldfield questionnaire. A score of 70 or more indicates that the participant is right-handed.

[b] Years of education were calculated according to the normal duration to complete the highest diploma achieved.

[c] Geriatric Depression Scale (30 questions). A score of 11 or more indicates possible depression.

[d] Geriatric Anxiety Inventory (20 questions). A score of 10 or more indicates possible anxiety disorder.

[e] MoCA (12 questions). A score of 25 or less indicates possible mild cognitive impairment.

[f] "*Entendez-vous bien*" (15 questions). This is an informal evaluation of a person's perceived hearing abilities. A consultation in audiology is recommended for those with scores ≥ 15.

[g] Best ear PTA. Thresholds were selected for the best ear at 0.25, 0.5, 1, 2, 3, 4, and 6 kHz, and then average, representing participants' optimal capacity in a dichotomous setting.

cognition and received two repetitive transcranial magnetic stimulation (rTMS) sessions per visit (Figure 1D and E).

Sublexical SPiN Task

The SPiN task consisted of a classic AX auditory syllable discrimination task. We chose to use a sublexical task because such tasks are associated with elevated activity in the speech dorsal network—the target of this investigation (e.g., Turkeltaub & Coslett, 2010; Rauschecker & Scott, 2009; Hickok & Poeppel, 2007). Furthermore, sublexical SPiN tasks can measure the ability to discriminate speech representations without lexical or context cues that can facilitate perception. Older adults are more sensitive to the presence of the cues during speech perception tasks, potentially reflecting a compensation strategy (Pichora-Fuller et al., 2017; Aydelott et al., 2010; Gordon-Salant, 2010). The use of these cues, although ecologically valid, could mask the extend of older adults' perceptual difficulties.

The stimuli were pairs of auditory syllables selected from SyllabO+, an open-source database of spoken Québec French (Bédard et al., 2017). Recording details are available in Appendix 1. One hundred thirty-six unique syllable pairs that differed by one feature (voice, place of articulation, manner of articulation, nasalization, vowel height or roundedness) were created. One hundred thirty-six identical syllable pairs were then created from the same syllable set. Half of the syllables had a consonant–vowel (CV) structure, and the other half had a CVC structure. These structures are the two most common in Québec French (Bédard et al., 2017). Stimuli were matched along four dimensions: structure, spoken frequency, lexicality, and duration (Appendices 2 and 3 for more details). A multitalker's babble noise (Perrin & Grimault, 2005) that consisted of four native French speakers (two male and two female individuals) aged 25–45 years, reading newspapers, was used as background noise. For the TMS runs, the noise file was normalized at an intensity of 73 dB SPL. The signal-to-noise ratio (SNR) was −3 dB (pressure signal / pressure noise). For the MRI task, the speech stimuli were normalized at an intensity of 85 dB SPL and the speech noise was normalized at an intensity of 75 dB (10 dB SNR). The resulting 272 pairs were divided into five runs: One run was administered during MRI acquisition (48 pairs), and the other four were administered after each TMS session (each contained 56 pairs, half different and half identical; see Appendices 2 and 3 for more details). The MRI run was divided in two lists: one with a single fixed speaker (low variability condition) and one with eight different speakers that varied within and across trials (high variability). These two lists were administered in a random order. The TMS runs each included four lists (two with a single speaker and two with multiple speakers). The order of the lists was randomized for each run, but the runs were administered in the same order across participants (Figure 1 and Appendix 3).

MRI Data Acquisition

The data were acquired on a whole-body Philips 3.0 Tesla Achieva TX at the Clinic IRM Québec-Mailloux in Québec City (Figure 1B). Structural magnetic response images were acquired with a 3-D T1-weighted magnetization prepared rapid gradient echo sequence (repetition time [TR] = 8.2 msec, echo time = 3.7 msec, field of view = 250 mm^2, flip angle = 8°, 256 mm × 256 mm matrix, 180 slices/volume, slice thickness = 1 mm^3, no gap).

One short run of 76 functional images was acquired with a sparse sampling parallel acquisition technique with parallel imaging (SENSE = 2.1; Gracco, Tremblay, & Pike, 2005; 45 interleaved axial slices, 3 mm^3 isotropic, no gap; TR = 7000 msec; acquisition time = 2399 msec, delay in TR = 4601 msec; echo time = 30 msec; field of view = 240 × 240 mm; 80 × 80 matrix; flip angle: 90°). The EPI run began with five dummy scans to allow the magnetization to stabilize to a steady state. Throughout the procedure, participants' head was immobilized using a set of cushions and pads. We have used a similar protocol to investigate speech perception mechanisms in older individuals (Tremblay et al., 2021; Bilodeau-Mercure et al.,

2015). During the fMRI sequence, participants completed a short SPiN task (syllable discrimination) that was used to select the TMS target. All stimuli were presented during the delay in acquisition using Presentation Software (Neurobehavioral System) through high-quality MRI-compatible stereo electrostatic earplugs (Nordic Neurolab), which provide 30 dB of sound attenuation. A baseline condition (rest) was included and interleaved with experimental (SPiN) trials. The order of the conditions and the number and duration of baseline trials were optimized using OPTseq2 (https://surfer.nmr.mgh.harvard.edu/optseq/). Task instructions were first delivered in a quiet environment through a PowerPoint presentation, immediately before the MRI session, and included nine audio examples of different or identical pairs presented in noise (10 dB SNR) with low or high variability.

TMS Experiment

Motor Threshold and TMS Protocol

Skin and brain reconstructions were individually generated using Brainsight 2 (Rogue Research). Eight anatomical landmarks were identified to register the position of the head for the neuro-navigating system (tip and bridge of the noise, corner of the eyes, anterior and intertragic notches of the left ear and right ear). After successful registration using an infrared tracking system (Polaris, Northern Digital), the active motor threshold (aMT) was determined using a single-pulse TMS session with a high-speed seven magnetic simulator (Rapid2, Magstim; Figure 1D and E). Surface electrodes were placed on the first dorsal interosseous (FDI) muscle of the right hand, and a ground electrode was placed on the right cubitus under the elbow. Participants were asked to produce three maximal voluntary contractions of the fist muscle to measure the average motor evoked potentials (MEPs) in the FDI. The maximal MEP value was measured during this contraction. Twenty percent of this value was then calculated and used as target during stimulation. Participants were asked to maintain a contraction that matched the target MEP value using visual feedback. Single pulses were then delivered by a 70-mm figure-of-eight coil held tangentially to the skull, on the hand knob of the left primary motor cortex. The area that elicited maximal MEPs was first identified. The initial intensity (50% of the simulator output) was increased in 5% steps until the amplitude of the MEPs reached at least 200 μV repeatedly. aMT was established as the minimal intensity of the simulator output needed to elicit MEPs at an amplitude of at least 200 μV, on 5 out of 10 consecutive stimulations, when the right FDI was contracted at 20% of maximal voluntary contraction, using visual feedback.

The coil was held tangentially to the skull by the experimenter (V.B.) and positioned on each target site (aSTG, pSTS, PMv, sham) using the tracking system. The head was immobilized manually by the second experimenter (P.T.). An iTBS paradigm was used to increase cortical excitability (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). This protocol consists of trains of three rapid pulses, presented at 50 Hz and repeated at a 5-Hz frequency for 2 sec, every 10 sec, for 190 sec (total of 600 pulses). Stimulation was applied at 80% of the aMT (Rossi, Hallett, Rossini, & Pascual-Leone, 2009), with a predetermined maximum of 50% of the stimulator output. Because the intensity of the stimulation is limited to 50% of the device capacity for iTBS and given that the intensity for iTBS is based on aMT (i.e., 80% of aMT), whenever a person's aMT was ≥ 62%, the intensity for iTBS was fixed at 50% of the stimulator output. For the sham stimulation, the same protocol was administered at a fixed intensity of 5% on the top of the head (vertex). The stimulation sessions were separated by 60 min to avoid carryover effects. The order of stimulation sites was counterbalanced across participants.

Post-TMS SPiN Task

The sublexical SPiN task was administered 5 min after each iTBS session. This delay allowed enough time for the participant to be installed in front of the computer and reminded of the instructions. The time frame in which the task was performed (5–12 min after the stimulation) is well within the period were iTBS effects have been found (20–30 min; Gedankien, Fried, Pascual-Leone, & Shafi, 2017; Huang et al., 2005). Participants were seated in a double-walled soundproof room (Génie Audio. Inc), 50 cm away from a 27-in. monitor (HP, E272q). The stimuli and responses were presented using Presentation Software 21.1 (NeuroBehavioural Systems Inc.) on a desktop computer running Windows 10 (64 bits). Each run took approximately 5 min to complete. At the beginning of each trial, a fixation cross appeared simultaneously with the speech noise in the middle of a black background. The first syllable was presented 1000 msec after the presentation of the noise and followed 300 msec later by the second syllable (Figure 1F); this delay was chosen to minimize working memory demands. Immediately after the second syllable, a green question mark was presented visually on the monitor to prompt participants to determine if the pairs were identical or different by pressing as quickly as possible a button on a response box (11 840, Cedrus Corporation) with their right hand. Trials were terminated immediately following a response or after 3 sec if no response was provided. The intertrial interval was set to 1000 msec. No feedback was provided during the task. Syllable pairs were played binaurally through high-quality headphones (DT 770 Pro, Beyer Dynamic Inc.), at an intensity that was comfortable to the participant.

Analyses

Subject-level fMRI Data Analyses for TMS Target Selection

First, the MRI data were converted to the Nifti format using MRIcron and visually inspected for artifacts. The resulting

functional images were analyzed using Analysis of Functional NeuroImaging (AFNI). The time series were aligned to the first functional run, motion-corrected, slice time corrected, and despiked, and the resulting time-series were mean-normalized. Functional volumes acquired during excessive motion (> 1 mm) were excluded from the analyses. A 3-mm spatial filter was then applied. Following preprocessing, subject-level regression analyses were conducted using AFNI 3ddeconvolve program with a 2-parameter gamma basis function (AFNI model "SPMG2"). An ordinary least square regression approach was used to analyze subject data. One regressor was created for all experimental trials, including both the single and multiple talker conditions (all trials > rest). Additional regressors were the mean, linear, and quadratic trend components, and the six-motion parameters (*x, y, z*, and roll, pitch, and yaw).

Targets for the TMS sessions were selected based on each person's most robust brain activity (highest *t* value) during the SPiN task (section 2.4) within predefined anatomical regions (aSTG, pSTS, and PMv) based on visual inspection of the resulting activation map (Figure 2). For the aSTG, we selected the coordinates of the area with the most robust activity (highest *t* value) in the middle to anterior STG. To avoid stimulating the temporal pole, which is involved in semantic processing and high-order information processing (Herlin, Navarro, & Dupont, 2021), the selected area could not be more anterior than the intersection of the STG and TTG (transverse temporal gyrus), and it could not be more posterior than the TTG as observed on coronal view. For the pSTS, we selected the coordinates of the posterior area of STS with the most robust activity. The selected area had to be posterior to the TTG and anterior to the ascending ramus of the lateral sulcus. For the PMv, we selected coordinates of the ventral anterior area of the precentral gyrus with the most robust activity. The area selected had to be more ventral than the medial frontal gyrus. For the sham stimulation, the coil position was determined by selecting coordinates between the two hemispheres, at the level of the posterior pole of the corpus callosum, on the vertex of the skull. An estimation of the location, extent, and strength of the electrical field induced by the TMS sessions was computed using simNIBS. The results are shown in Figure 2, and the. The detailed method is available in Appendix 4.

Functional and Structural ROIs

Reconstruction of participants' cortical surface was carried out with the FreeSurfer image analysis suite (Version 7.2; Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999) on an iMac running Mac OS 10.14. The pipeline includes motion correction, intensity normalization, removal of non-brain tissue (skull and meninges stripping), segmentation of gray and white matter, followed by a triangular tessellation of the gray matter white matter boundary, automated topology correction, and surface deformation smoothing following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class.

Outputs were inspected by the two authors, and manual interventions were performed when required. Quality checks were then performed again by the two authors. Cortical thickness, defined as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl & Dale, 2000), was then extracted.

Next, for each participant, the cortical thickness (from Freesurfer) and functional maps (from AFNI) were exported and aligned in SUMA (Saad, Reynolds, Argall, Japee, & Cox, 2004). ROIs were defined as 5-mm spheres around the individual target coordinates in native AFNI format. BOLD signal and gray matter thickness were then extracted from the ROI files. The whole-brain thickness in the left hemisphere was also extracted to mean normalize the thickness measure for each ROI.

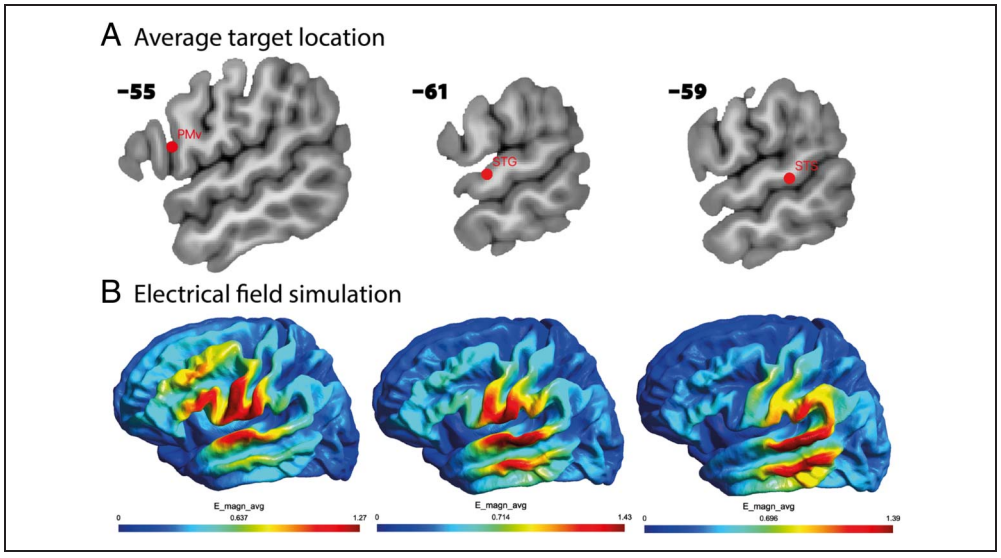

Figure 2. (A) The average targets are shown on sagittal views of the mni_icbm152_t1_tal_nlin_sym_09c.nii. The *x* coordinates for each view are provided in the MNI space. (B) Results of electrical field simulations. The estimated average magnitude (V/m) of the induced electrical field across subjects is illustrated on a normalized (fsaverage) cortical surface for each target.

Statistical Analyses

Pure-tone Averages

Pure-tone averages (PTAs) were calculated for each participant and each ear separately, for the following frequencies: 0.25, 0.5, 1, 2, 3, 4, and 6 kHz. The 8-kHz measure was excluded because the thresholds could not be measured for one participant (thresholds were > 90 dB SPL in both ears). The left ear PTA was not included for this same participant because the left ear threshold at 6 kHz was also beyond 90 dB SPL. A Spearman correlation revealed a strong association between participant's left and right PTA ($p < .01$, $\rho = 0.88$). To account for hearing thresholds in the following analyses, the thresholds of the best ear (i.e., lowest value) was selected for each frequency from 0.25 kHz to 6 kHz, and these values were then averaged for each participant.

SPiN Performance and Post-TMS Difference Scores (Linear Mixed Models)

Statistical analyses were computed using R and RStudio (RStudio Team, 2021; R Core Team, 2017). Outliers (3 *SD*s from the mean) were removed for each dependent variable. Linear mixed models were computed with the lme4 package. For each model, stepwise elimination was performed from the largest regression model that converges using the "Buildmer" package (Voeten, 2023). The model with the best fit, based on likelihood ratio tests or chi-square mixtures (for random effects), is selected from all the convergent models. Each model initially included participants and run order as random variables, and multiple covariates: sex, best ear PTA, the MoCA score. After the final model was selected, assumptions were verified, including multicollinearity (variation inflation factors < 3), and distribution of the residuals (Q-Q plots and histograms visual inspection). To interpret significant interactions with continuous variables, the Interactions package was used to plot the interactions and to compute simple slope analyses.

The first two analyses focused on accuracy and RTs from the SPiN our as dependent variables. This set of analyses addressed our general objective, which was to determine whether TMS can significantly improve performance compared with the sham stimulation. Independent variables were age, target (STG, STS, PMv, or sham), and talker variability (fixed or multiple). Interaction between target, age, and variability were included in the model as well. Covariates (sex, best ear PTA, MoCA score) and random variables (participants, order) were also entered into the initial model.

The second set of analyses addressed our second objective, to determine which variables predict benefits on SPiN performance. These analyses focused on performance change in accuracy and RT (post TMS performance − post sham performance). Independent variables were age, target (STG, STS, PMv), variability, cortical thickness, and BOLD signal. Interactions between age, target, variability, and the brain measures (thickness and BOLD) were included in the model as two 4-way interactions (Age × Target × Variability × Thickness, and Age × Target × Variability × BOLD). Baseline performance (accuracy or RT after the sham stimulation) was added as an independent variable in these models to control for potential baseline imbalance, and because studies have suggested that TMS outcome is associated with the baseline activation state, which is likely to interact with performance level (see Silvanto et al., 2018, for a review). Covariates (sex, best ear PTA, MoCA score) and random variables (participants, order) were also entered into the initial model. Interactions were decomposed using the "Interaction" package for the two-way interactions and the "Emmeans" package for the three-way interaction.

A set of additional analyses were included to specify the effects of baseline performance revealed by the second set of analyses. We tested whether lower and higher performers showed significant improvement scores (i.e.,

Table 2. SPiN Accuracy and Post-TMS Difference Scores (n = 30, 15 F)

	Fixed Talker		*Multiple Talkers*	
	M (SD)	*Range*	*M (SD)*	*Range*
STG raw score	80.91 (7.41)	60.71 to 92.86	71.19 (8.94)	46.47 to 89.29
STS raw score	74.17 (12.50)	46.43 to 92.86	70.71 (10.71)	53.57 to 89.29
PMv raw score	78.21 (10.99)	50.00 to 96.43	70.69 (10.16)	53.57 to 92.86
Sham raw score	76.19 (12.52)	42.86 to 92.86	69.05 (11.73)	35.71 to 92.86
STG difference score	3.33 (12.72)	−17.86 to 39.29	2.14 (10.00)	−21.43 to 25.00
STS difference score	−2.02 (15.49)	−32.14 to 32.15	1.66 (12.88)	−21.43 to 28.57
PMv difference score	2.02 (14.21)	−25.00 to 35.71	0.23 (11.37)	−21.43 to 28.57

Difference scores represent the difference between the performance score after the stimulation and the performance score after the sham stimulation (i.e., sham raw score) for each participant, and then averaged. A positive difference score indicates improved accuracy compared with the sham stimulation.

Table 3. SPiN Reaction Times (in seconds) and Post-TMS Difference Scores (n = 30, 15 F)

	Fixed Talker		*Multiple Talkers*	
	M (SD)	*Range*	*M (SD)*	*Range*
STG raw score	0.57 (0.22)	0.34 to 1.14	0.62 (0.23)	0.35 to 1.30
STS raw score	0.55 (0.16)	0.25 to 0.90	0.62 (0.16)	0.31 to 0.94
PMv raw score	0.56 (0.14)	0.37 to 0.94	0.66 (0.22)	0.31 to 1.22
Sham raw score	0.58 (0.19)	0.33 to 1.05	0.63 (0.16)	0.33 to 0.94
STG difference score	−0.02 (0.15)	−0.36 to 0.38	−0.00 (0.16)	−0.20 to 0.43
STS difference score	−0.03 (0.18)	−0.48 to 0.23	−0.04 (12.88)	−0.27 to 0.23
PMv difference score	−0.02 (0.15)	−0.35 to 0.31	0.04 (0.14)	−0.21 to 0.34

Difference scores represent the difference between the performance score after the stimulation and the performance score after the sham stimulation (i.e., sham raw score) for each participant, and then averaged. A positive difference score indicates increased RT compared with the sham stimulation.

different from 0) through one-sample t tests. For each talker condition and each dependent variable (accuracy and RT improvement), participants were divided into two groups based on their baseline performance (e.g., 50% fastest participants in the multiple talker condition). The classification of participants was done independently for each dependent variable and task condition; thus, participants could be included in different performance groups for different analyses.

RESULTS

Descriptive results for the SPiN task and post-TMS difference scores by target and variability condition are presented in Tables 2 and 3.

Predictors of Raw Accuracy

For accuracy, the model estimates are illustrated in Table 4. The final model included Variability and Hearing Thresholds as fixed variables, and participants and order as random variables. The results revealed a Main Effect of Variability: Accuracy was lower in the multiple talker condition (b = −6.89, 95% CI [−9.02, −4.77]). Hearing Thresholds also influenced accuracy: Participants with higher PTA values had lower accuracy (b = −0.69, 95% CI [−0.85, −0.54]).

For RT, a logarithmic transformation was first applied to the data to correct for a nonnormal distribution of the residuals in the raw data. The model estimates are illustrated in Table 5. The final model included Age, Variability, and the Age × Variability as fixed variables, and

Table 4. Results for the Analysis of SPiN Accuracy

	Accuracy (% correct)		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	84.11	[80.20, 88.01]	**<.001**
Variability [Multiple]	−6.89	[−9.02, −4.77]	**<.001**
Best ear PTA	−0.69	[−0.85, −0.54]	**<.001**
Random Effects			
σ^2	69.32		
$\tau_{00\ Participants}$	5.42		
$\tau_{00\ Order}$	10.18		
ICC	0.18		
N_{Order}	4		
$N_{Participants}$	30		
Observations	238		
Marginal R^2 / conditional R^2	0.357 / 0.475		

σ^2 = random effect variance; τ_{00} = random intercept variance; ICC = intraclass correlation coefficient; N = number of random effects groups.

Table 5. Results for the Analysis of SPiN RTs (logRT)

	log(RT)		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	6.11	[5.82, 6.40]	**<.001**
Age	0.00	[−0.00, 0.01]	.211
Variability [Multiple]	−0.01	[−0.16, 0.13]	.863
Age × Variability [Multiple]	0.00	[−0.00, 0.01]	.051
Random Effects			
σ^2	0.03		
$\tau_{00\ SID}$	0.05		
$\tau_{00\ Order}$	0.00		
ICC	0.65		
N_{SID}	30		
N_{Order}	4		
Observations	240		
Marginal R^2 / conditional R^2	0.109 / 0.684		

participants and order as random variables. Main effects (Age, Variability) were not significant. There was a near significant Age × Variability interaction: Older adults showed longer RTs in the multiple talker condition (p = .051; Figure 3). A simple slope analysis revealed a significant Age effect for the multiple talker condition only (b = 0.01, t = 2.23, p = .03).

Predictors of Post-TMS Differences

For accuracy change, the model estimates are detailed in Table 6. The final model included Age, Thickness, Age × Thickness, Variability, Baseline Accuracy, and MoCA Score as fixed variables, and order as a random variable. Greater improvement in accuracy was found in the fixed talker condition compared with the multiple talker condition (multiple talker: b = −5.19, 95% CI [−8.05, −2.33]). Lower baseline performance predicted greater accuracy improvement (b = −0.76, 95% CI [−0.89, −0.63]). Higher MoCA scores were associated with greater accuracy improvement (b = 0.93, 95% CI [0.28, 1.58]). The Age × Thickness interaction revealed an age-dependent thickness effect on accuracy improvement (b = −0.29, 95% CI [−0.56, −0.02]). Specifically, for older adults (mean age + 1 *SD*), thinner cortex was associated with greater accuracy improvement (b = −6.33, t = −2.02, p = .05), whereas no significant association was revealed for middle-aged and young adults (mean age or mean age – 1 *SD*; mean age: b = −1.36, t = −0.66, p = .51, mean age – 1 *SD:* b = 3.62, t = 1.14, p = .25; Figure 4A).

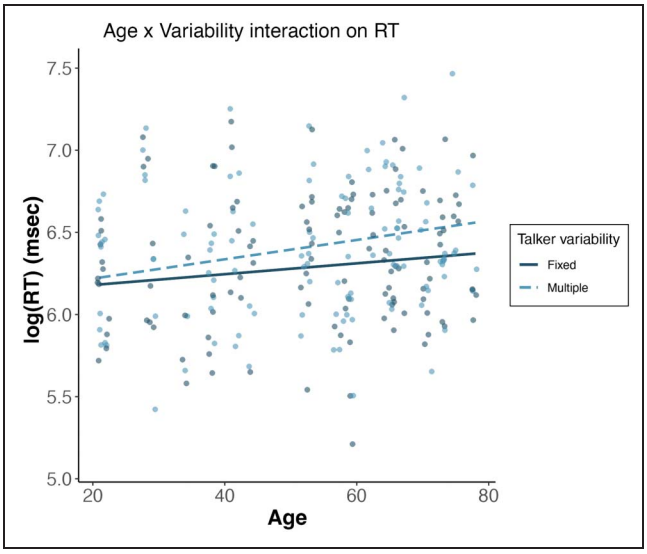

Figure 3. This figure illustrates the Age × Talker Variability interaction on log(RT).

For RT change, the model estimates are available in Table 7. The final model included baseline RT, age, Variability, Thickness, and all the interactions between Age, Variability, and Thickness as fixed variables. The factor Participants was also included as a random variable. Slower baseline performance predicted greater RT improvement, that is, larger RT reduction (b = −0.51, 95% CI [−0.69, −0.32]). There was also a significant Age × Variability × Thickness interaction on the RT change. In the fixed talker condition, the effect of Age on cortical thickness was weakly negative (b = −2.46, p = .37) whereas it was moderately positive in the multiple talker condition (b = 4.47, p = .10; Figure 4B). The slopes for each age subgroup were not significantly different from zero in the fixed talker

Table 6. Predictor of Post-TMS Accuracy Differences (TMS –Sham)

	Accuracy Difference		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	32.07	[6.15 to 57.99]	**.016**
Age	0.03	[−0.15 to 0.22]	.714
Variability [Multiple]	−5.19	[−8.05 to −2.33]	**<.001**
Thickness	13.84	[−1.14 to 28.81]	.070
Baseline accuracy	−0.76	[−0.89 to −0.63]	**<.001**
MoCA	0.93	[0.28 to 1.58]	**.005**
Age × Thickness	−0.29	[−0.56 to −0.02]	**.038**
Random Effects			
σ^2	84.51		
$\tau_{00\ Order}$	14.68		
ICC	0.15		
N_{Order}	4		
Observations	180		
Marginal R^2 / conditional R^2	0.414 / 0.501		

condition (mean age −1 *SD:* $b = 13.12$, $t = 0.20$, $p = .84$, mean age: $b = -29.44$, $t = -0.71$, $p = .48$, mean age + 1 *SD:* $b = -72.00$, $t = -1.20$, $p = .23$), nor in the multiple talker condition (mean age −1 *SD:* $b = -103.61$, $t = -1.59$, $p = .11$, mean age: $b = -26.40$, $t = -0.65$, $p = .52$, mean age + 1 *SD:* $b = 50.81$, $t = 0.88$, $p = .38$; Figure 4B). Nevertheless, when the slopes are compared by thickness subgroups instead of age subgroups, a significant positive age effect is found for subgroups with mean thickness and higher thickness in the multiple talker condition (mean thickness: $b = 2.75$, $t = 2.24$, $p = .03$, mean thickness + 1 *SD:* $b = 4.32$, $t = 2.78$, $p = .01$; not illustrated). Figure 4B accordingly shows a differentiation between the age subgroups when thickness is high: A RT decrease is observed in the younger group whereas a RT increase is observed in older adults in this condition.

Additional analyses were conducted to confirm that participants with initial difficulties significantly improved

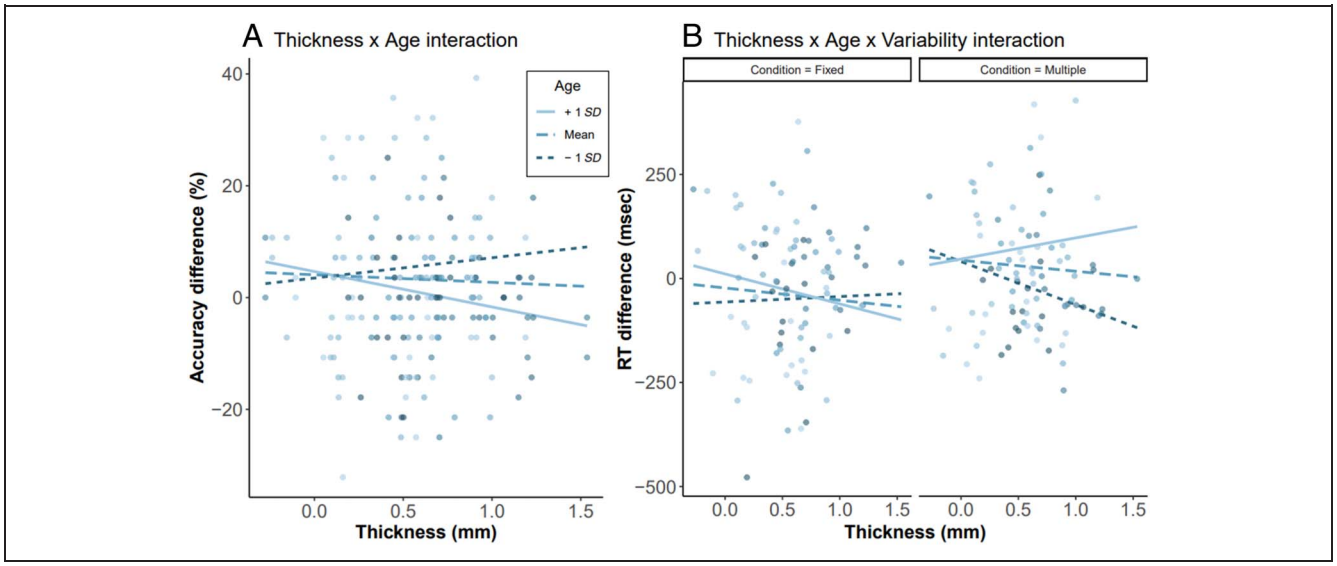

Figure 4. Main interactions for post TMS difference scores. (A) The plot illustrates the Thickness × Age interaction on accuracy difference scores, (B) The plot illustrates the Variability × Thickness × Age interaction on RT difference scores.

Table 7. Predictors of Post-TMS RT Differences (TMS –Sham)

	RT Difference		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	180.77	[−62.99 to 424.52]	.145
Age	1.95	[−1.91 to 5.82]	.320
Variability [Multiple]	160.04	[−85.17 to 405.24]	.199
Thickness	100.10	[−200.46 to 400.65]	.512
Baseline RT	−0.51	[−0.69 to −0.32]	**<.001**
Age × Variability [Multiple]	−1.78	[−5.96 to 2.40]	.402
Age × Thickness	−2.46	[−7.85 to 2.92]	.367
Variability [Multiple] × Thickness	−361.50	[−720.41 to −2.59]	**.048**
(Age × Variability [Multiple]) × Thickness	6.94	[0.41 to 13.46]	**.037**
Random Effects			
σ^2	13042.19		
$\tau_{00\ Participants}$	8252.68		
ICC	0.39		
$N_{Participants}$	30		
Observations	179		
Marginal R^2 / conditional R^2	0.289 / 0.565		

following TMS. Participants were split in two equal groups according to their baseline accuracy or RT (50% highest and 50% lowest performance), for each variability condition separately. One-sample *t* tests were performed to determine whether the difference scores of each group differed from 0, that is, whether improvement was significant. For two analyses, the Wilcoxon signed-ranks exact test was used because the normality assumption was violated (Shapiro–Wilk test with $p < .05$). The results are illustrated in Table 8. Accuracy analyses revealed that for both variability conditions, there was a significant increase (in % correct) from 0 in low performers (fixed talker average: +8.25%, multiple talker average: + 6.11%) and a significant decrease from 0 in high performers (fixed talker average: −6.03%, multiple talker average: −3.41%). RT analyses revealed a significant decrease (in RT) from 0 in low performers (average: −95.86 msec) and a significant increase from 0 in higher performers (average: + 9.12 msec), for the fixed talker condition only.

DISCUSSION

This study aimed at confirming that sublexical SPiN capacity can be enhanced in healthy adults by applying an iTBS protocol on regions involved in speech perception and at exploring the factors that influence post-TMS SPiN improvement (age, baseline performance, target, brain structure, and activity). The main findings of the study are: (1) There is a larger processing cost in the multiple talker condition in older adults compared with young adults (on RT); (2) successful SPiN enhancement depends on individual and contextual factors, including baseline performance, cortical thickness, and task condition, but not target; and (3) age and cortical thickness interact on

Table 8. Performance Improvement in Low and High Performers after TMS

Group	*Mean Accuracy Difference (% Correct)*		*Mean RT Difference (msec)*	
	Fixed Talker	*Multiple Talker*	*Fixed Talker*	*Multiple Talker*
High performers	**−6.03 (9.75)**	**−3.41 (8.98)**	**9.12 (111.13)**	14.29 (131.48)
Low performers	**8.25 (14.46)**	**6.11 (11.61)**	**−95.86 (175.89)**	9.75 (175.36)

Bold indicates data that were statistically different from zero ($p < .05$). Standard deviations are indicated in parentheses for each mean value.

accuracy and RT difference scores. These findings are discussed below.

Age Effects on SPiN Performance and Talker Normalization

In this study, we used a task condition that included multiple talkers to investigate the process of talker normalization in aging and to determine whether TMS would differentially impact performance when the acoustic environment is variable. As expected, accuracy was lower in the multiple talker condition, in line with several studies showing reduced speech perception performance when acoustic variability increases (e.g., Magnuson et al., 2021; Tremblay et al., 2021; Stilp & Theodore, 2020; Choi et al., 2018; Green et al., 1997). Moreover, a recent study revealed that young adults show consistent performance costs in the presence of multiple talkers, even when the voices are familiar (Magnuson et al., 2021).

The results also revealed an age effect on SPiN RT in the multiple talker condition, suggesting a larger performance cost for older adults compared with young adults when talker normalization is required, in line with a previous study that investigated this process in healthy older adults (Sommers, 1996). Unfortunately, the mechanisms that underlie this proportionally costlier processing in older adults are unknown. It is possible that these increased difficulties in older adults stem from a reduced capacity to process talker's voice. For instance, one study reported that older adults are less able to identify talkers during SPiN, suggesting they might be less efficient at processing the acoustic characteristics of each talker's voice (Best et al., 2018). Another possibility is that the multiple talker condition increased cognitive demand, thus increasing the likelihood of observing age differences in performance. The attentional resources required to process multiple talkers could, indeed, be less efficient in older adults because these resources are already overloaded. Alternatively, neural processing may be diminished.

A recent study revealed differences in BOLD signal in young compared with older adults in a syllable discrimination task during which talker variability was manipulated (Tremblay et al., 2021). Although age differences were not observed in the high variability condition, a lower signal in the bilateral STC was associated with lower performance (i.e., lower sensitivity and higher RTs) in the older group. Importantly, the older adults showed higher signal than younger adults in the left parietal lobe and right cingulate gyrus, two regions involved in the attention component of talker normalization (Tremblay et al., 2021). The results suggest that older adults show more difficulty with the acoustical analyses of the voices and increase attentional resources to perform talker normalization adequately. Additional neuroimaging studies are needed to clarify the mechanisms involved in this process in older adults, and to address whether lower performance from older adults in high variability conditions is associated with specific difficulties in the talker normalization process or if they reflect a general decrease in performance when the speech perception tasks become increasingly difficult. Understanding the aging of talker normalization is important, as this process is key to navigate a variety of daily social situations (e.g., recreative group activities, group discussions, and family reunions), and its decline could hinder social communications.

Our results revealed that SPiN accuracy was not predicted by age, but by hearing (higher hearing thresholds were associated with lower accuracy). In our prior work (Brisson & Tremblay, 2021), hearing was not predictive of lower SPiN accuracy, but it was predictive of SPiN RT. These differences may be explained by differences in the stimuli used. The first experiment of our prior work included only a fixed talker and CVC syllable pairs only. The SNR was −3 dB SPL, a noise-level that was found to be sensitive to age (Brisson & Tremblay, 2021). In the current study, because we used a multiple talker condition that we predicted would be more challenging, the SNR was set to 0 dB SPL to avoid floor effects in older adults' performance. In addition, to avoid repetitions and learning effects, we included both CVC and CV syllables. Increasing the SNR made the task slightly easier in the fixed talker condition (mean performance was of 76.19% compared with 73.07% in our prior work). Although the average age of participants was similar across the two experiments (~53 years), in our prior work, there were three adults of 83 and 85 years old, whereas the oldest adult of the current sample was 79. One study has shown that the relative contribution of age to SPiN performance increases at older ages (e.g., Dubno, 2015). These small differences in the task and sample could have reduced the task's sensitivity to age. Hearing measures were included in addition to age to control for this performance-related variables in the following analyses on difference scores.

Predictors of Post-TMS Outcomes

Analyses of SPiN difference scores did not reveal differences in the magnitude of the TMS-induced gain among the targets, which is in contrast to prior findings from our prior study, in which PMv stimulation was associated with greater gain in accuracy compared with STS stimulation (Brisson & Tremblay, 2021). It is possible that a single stimulation session enhanced the activity in more than one region given that our targets were adjacent (see Figure 2B), or indirectly through functional connectivity within the dorsal speech stream. Results of the raw data analyses revealed no significant effect of the target (STG, STS, PMv) on SPiN accuracy or RT. Our data and analyses reveal minor differences between the baseline and target conditions, and a high variability across participants difference scores (post-TMS –baseline). These results could be partially explained by interactive effects of a prior stimulation in the same visit, although we attempted to minimize the

influence of order by including a 60-min pause between the stimulation sessions, counterbalancing the order of the targets and by including order as a covariate in the analyses. Despite these results, group SPiN performance scores were almost always better after real stimulation compared with the sham (Table 2: e.g., mean accuracy difference scores varied from −2.02% to 3.33% in the fixed talker condition and 0.24% to 2.14% in the multiple talker condition). One potential explanation is that our sample size was insufficient to reveal significant post-TMS behavioral changes. However, when participants were divided by their initial performance, the results revealed significant differences from 0 in the subgroups and larger effect sizes. These results indicate that the strength and direction of the stimulation outcome are sensitive to individual characteristics. This is a crucial finding that has an important implication for future studies. One possibility would be to screen out those with high performance and apply iTBS only to those who actually need a performance boost. This could reduce the variability in the effect of iTBS.

Although it has been shown that rTMS effectively induce plasticity in the human brain (Siebner et al., 2022), behavioral outcomes are often highly variable across individuals, resulting in nonsignificant or small differences compared with baseline values (Minkova et al., 2019; Hinder et al., 2014; López-Alonso, Cheeran, Río-Rodríguez, & Fernández-del-Olmo, 2014). In this study, for each target and variability condition, approximately half of the sample improved from TMS. This result could reflect random fluctuations, but it is also plausible that rTMS could offer benefits only within certain contexts or for individuals with specific characteristics. For instance, rTMS or TBS protocols have been recognized as efficient strategies to alleviate depressive symptoms, although the number of responders in the samples often approaches 50% (e.g., Rossi et al., 2021; Lefaucheur et al., 2020). Investigating potential predictors of post-TMS difference scores, in terms of contexts of application as well as beneficiaries' characteristics, is thus essential to accurately predict behavioral outcomes and assess potential clinical applications.

The multiple talker variability predicted lower raw scores, and lower post-TMS enhancement compared with the fixed talker condition. This effect could be attributed to very low performance in the most difficult condition (close to the 50% chance level) for some of the participants (see the performance range in Table 2), possibly reflecting floor effects and thus reducing potential for improvement. Yet, initial performance level (performance after the sham stimulation) inversely predicted difference scores, that is, individuals with lower accuracy or higher RTs improved the most from TMS. These results are consistent with our initial hypothesis and with prior finding (Brisson & Tremblay, 2021). Additional analyses confirmed that participants with low accuracy at baseline (the low performer group had an accuracy of less than 79% for the fixed condition and less than 72% in the multiple condition at baseline) showed a significant increase in accuracy in both variability conditions. Participants with higher RT at the baseline in the fixed talker condition (higher than 0.55 sec) showed significant decrease in RT after real stimulation. This result indicates that when a task is more challenging for a person, there might be more room for improvement. A possible explanation for these conflicting patterns is that individuals who experience greater initial difficulties are more likely to improve after TMS, but there may be a cutoff point, meaning that the extent of this benefit diminishes in very challenging listening environments when performance is at floor level.

Analyses of high performers revealed a decrease in accuracy in both variability conditions, as well as an increase in RT in the fixed condition. These results are consistent with a study that investigated the effect of single-pulse TMS during a visual perceptual task, in which initial performance was found to be negatively associated with different improvement outcomes: Facilitation was observed in low performers, and inhibition was observed in high performers (Silvanto et al., 2018).

This baseline performance effect could be associated with differences in brain activity patterns in target regions between low and high performers. Recent evidence suggests that a brain stimulation outcome is state dependent, that is, the intensity and direction (facilitation or inhibition) of the stimulation are influenced by the initial cell activation/plasticity state, which can be modulated through priming and adaptation paradigms (e.g., Fung & Robinson, 2014; Müller-Dahlhaus & Ziemann, 2015; Silvanto & Pascual-Leone, 2008). Therefore, the relationship found between baseline performance and TMS outcome might reflect the relationship between brain state and TMS facilitation/inhibition, in which individuals with lower brain activity are more likely to perform more poorly and to improve. Nevertheless, a study from Silvanto and colleagues (2018) found that baseline performance and task context were both significant predictors of TMS outcome, suggesting that baseline performance effects are at least partially independent from brain state effects and that combining these factors would lead to more precise predictions on TMS outcome. To better understand the relationship between baseline performance, brain state, and TMS outcome, we included cortical thickness and BOLD signal within the target regions as potential predictors of SPiN difference scores.

The results revealed that BOLD signal was not predictive of TMS outcome. Although it is possible that brain activity within the target regions is not a predictor of post-TMS outcome, an alternative explanation is that brain activity might still be a predictor of post-TMS improvement, but that the brain signal during the TMS experiment was different from the brain signal measured during MRI acquisition. Studies that found evidence of a relationship between initial cortical excitability and TMS behavioral outcome used online protocols, in which participants

were stimulated while performing the task (e.g., Silvanto et al., 2018; Grabski et al., 2013; Tremblay, Sato, & Small, 2012). In the present study, we measured the BOLD signal when participants performed the task in the MRI scanner and applied the stimulation offline on a later day. Activating the SPiN network during TMS administration (e.g., by sending auditory stimuli) would have reproduced the conditions in which these state-dependent effects were found and might have revealed a similar relationship with TMS outcomes (e.g., lower activity in the targeted region might be more likely to induce facilitating effects). The recent development of TMS-compatible EEGs represents an interesting avenue to clarify the neurobiological mechanisms that underlie TMS effects, as well as the relationship between changes in brain excitability and induced changes in behavior (Tremblay, Rogasch, et al., 2019). Nevertheless, our results suggest that individuals with initial difficulties can benefit from iTBS independently of the functioning of their speech-processing network, a desirable outcome for future clinical applications given the cost of MRI, but one that needs replication.

Although the BOLD signal did not predict the TMS outcome, our analyses did reveal an age-dependent effect of regional cortical thickness on post-TMS difference scores. To the best of our knowledge, the present study is the first to reveal such a relationship in healthy adults using a TMS protocol with facilitation aftereffects. In our previous study, which did not include BOLD signal or cortical thickness measurements, no age effects were found on difference scores, suggesting that individuals could improve from TMS independently of their age (Brisson & Tremblay, 2021). In the present study, we found a significant negative relation between cortical thickness and SPiN accuracy difference scores in older adults (+1 *SD*), adding nuance to our initial interpretations. Moreover, observation of the interaction plots suggests reversed patterns of improvement between young and older adults with thicker cortex. Specifically, older adults with thinner cortex in the target areas exhibited significantly higher TMS-induced gains in terms of accuracy, whereas middle-aged and younger adults did not show a significant relationship between thickness and post-TMS improvement. Moreover, in the multiple talker condition, an age effect was observed in adults with thicker cortex in terms of RT difference scores: The older age group showed increased RT (no benefit) whereas the younger age group showed decreased RT after TMS (Figure 4B). These results suggest that the nature of the relationship between thickness and TMS improvement is age dependent. Further investigation is needed to clarify the nature of this relationship for different age subgroups.

Evidence regarding the relation between cortical thickness and TMS outcome is scarce. One paired associative stimulation (PAS) study involving young adults showed that larger cortical thickness in the left sensorimotor cortex was associated with larger facilitating effects (Conde et al., 2012). Another study in which PAS was administered to healthy older adults showed a positive correlation between M1 cortical thickness and resting motor threshold values, but no significant relationship between thickness and PAS-induced changes in cortical excitability (List et al., 2013). A separate study involving older adults with or without mild cognitive impairment showed that cortical thickness was a poor predictor of PAS-induced responses (Minkova et al., 2019). The relationship between cortical thickness and behavioral outcome after repetitive TMS has been investigated in clinical studies with populations with mood disorders including depression, bipolarity, and early phase psychosis (Harika-Germaneau et al., 2022; Lu et al., 2022; Baeken, van Beek, Vanderhasselt, Duprat, & Klooster, 2021; Francis et al., 2019; Boes et al., 2018), with most studies showing positive associations (i.e., higher thickness predicting better treatment response). However, it is difficult to determine from these studies whether this association was specific to the TMS treatment. For instance, one study showed that thickness predicted the clinical response in both the TMS and control groups (Baeken et al., 2021). These studies suggest that thicker cortex might predict better TMS outcomes, but more studies are required to confirm this relationship within different contexts and across different sample characteristics.

The results of the present study revealed a negative association between cortical thickness and post-TMS SPiN improvement in older adults, whereas a null association was found for younger adults. Importantly, this negative association was independent of baseline performance; hence, this association cannot be explained by a poorer initial performance in older adults with a thinner cortex. Moreover, it was found that older adults with a higher MoCA score were also more likely to benefit more from the stimulation applied on the dorsal stream regions. As mentioned previously, SPiN abilities stem from a complex and dynamic interplay between peripheral and central mechanisms, encompassing both sensory (low-level), perceptual (speech), and cognitive (high-level) processes. Although some researchers attribute SPiN decline in older adults mainly to sensory deficits, others emphasize the independent impact of cognitive decline, such as working memory, processing speed, and selective attention (e.g., Peelle, 2018; Pichora-Fuller et al., 2016, 2017; Eckert et al., 2016; Akeroyd, 2008). The diversity in findings across previous studies might be because of the heterogeneous nature of the aging process. Comparable SPiN difficulties among older adults do not necessarily imply a common etiology. For certain older adults, these difficulties could be primarily linked to hearing loss or central sensory decline, whereas for others, they might relate more strongly to changes in the speech processing network or to a broader cognitive decline. Our findings align with this perspective. Notably, older adults scoring higher on the cognitive test showed greater benefits from TMS sessions, suggesting that their initial SPiN difficulties might be more related to speech specific or early sensory mechanisms than reduced cognitive abilities. Furthermore, enhancing

cortical excitability of the dorsal speech network had a more positive impact on older adults with thinner cortex in the stimulated regions, suggesting that the SPiN difficulties faced by these older individuals might be closely associated with structural decline within this speech processing network. Unfortunately, this study does not yield definitive explanations regarding the precise mechanisms that determine the effectiveness of TMS administration. However, our findings highlight the significance of considering individual characteristics that contribute to SPiN difficulties in older adults before determining the most effective strategy. Further research is needed to elucidate the relationship between SPiN enhancement and potential contributors to SPiN difficulties, including peripheral and central hearing abilities, cognitive skills, brain structure, and brain activity during SPiN tasks.

Finally, contrary to our initial hypothesis, there was no interaction between target and talker variability on TMS outcome, suggesting that all targets influenced performance similarly for the two talker conditions. It is possible that TMS did not specifically improve the talker normalization process, but SPiN performance more generally, as all three regions are engaged during speech perception, especially in challenging environments. Although the PMv has not been shown to contribute directly to talker normalization, there is evidence that motor representations of speech can actively participate in the early phases of the speech perception process, when talker normalization is most likely to occur (e.g., see Liebenthal & Möttönen, 2018, for a review). It is thus possible that activating the PMv, which is structurally and functionally connected to the STC, might also have activated the regions that are required for talker normalization, including the STG and STS. Future investigations focusing on speech perception in the absence of background noise could potentially confirm whether there are differences in TMS-induced outcomes across these targets. In such a context, the PMv might be less strongly solicited compared with the STG and STC, allowing for a clearer understanding of the effects of the PMv stimulation in the context of multiple talkers.

Conclusions

The present study shows that older adults encounter a greater performance cost when talker variability is high, which may be associated with increased communication challenges in everyday situations that involve more than one talker. Further research is needed to assess the process of talker normalization in older adults and its influence on communication and social interactions, both in the presence and absence of noise. Importantly, individuals with lower initial speech processing performance were more likely to improve after TMS independently of their age or the target region, a promising finding for future clinical applications. When participants were split based on their initial performance, there was a significant improvement in both accuracy and RT after TMS. Cortical thickness was found, for the first time, to be associated with sublexical SPiN improvement after TMS under certain conditions. Together, these results offer nuanced insights into the factors that influence post-TMS outcome, and suggest that although TMS can lead to SPiN enhancement, the strength and direction of the outcome are influenced by a complex combination of factors, including the listening context and individual characteristics including cortical thickness. A better understanding of how different people can improve in different listening environments will guide future strategies to reduce SPiN difficulties in aging and could also clarify the neurobiological mechanisms that underlie successful speech perception in young and older adults.

APPENDIX 1: STIMULI RECORDING

The syllables were recorded in a double-walled soundproof room (Génie Audio. Inc.) by four male and four female speakers of Québec French trained in linguistics. Each syllable was recorded through a high-quality headset microphone (Microflex Beta 53, Shure) connected to a USB audio interface (Quartet, Apogee Electronics). The recording was made using sound Studio Software (v 4.8, Felt Tip Software) for Mac, at a sampling rate of 44.1 kHz with 16 bits digitization. Each syllable was produced within a carrier sentence "Maintenant je dis _____" (Now I say _____) to ensure a constant descending (neutral) intonation. Three to five repetitions were obtained for each stimulus. The amplitude of the stimuli was normalized using Praat v 6.0 (Boersma & Weenink, 2011) at a mean intensity of 70 dB SPL. Syllables were segmented using Praat. The selected syllables were listened to by a linguistics student to validate the phonemes and the quality of the recording.

APPENDIX 2: MRI SPiN TASK

Forty-eight syllable pairs were presented (12 at low variability and 12 at high variability). The same number of CV and CVC syllables were distributed in each variability condition (see Figure A2).

The syllable pairs were matched across conditions on three other factors: spoken frequency, lexicality, and duration. For spoken frequency, a two-way ANOVA was performed to ensure that the average spoken frequency of the syllables did not differ between the Talker Variability conditions (low or high variability) and Types of Pair (identical or different). The dependent variable was the average frequency of the pair, which was multiplied by itself (exponential transformation) to obtain equality of error variances (Levene's test: $p > .05$). No effect of Talker Variability, $F(1) = 0.27, p = .606$, Type of Pair, $F(1) = 1.69, p = .200$, or interaction, Variability × Type of Pair: $F(1) = 0.52$, $p = .474$, were significant. Because some of the syllables were meaningful one-syllable words, we ensured that the number of words was similar across all talker variability. To control for lexicality, a binary logistic

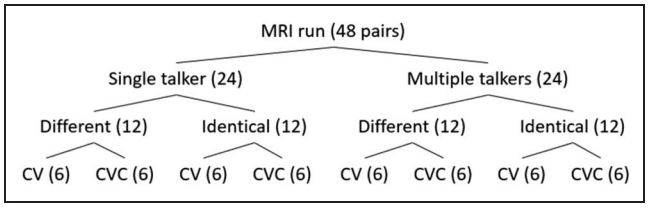

Figure A2. Number of pairs in the SPiN task during MRI acquisition (one run).

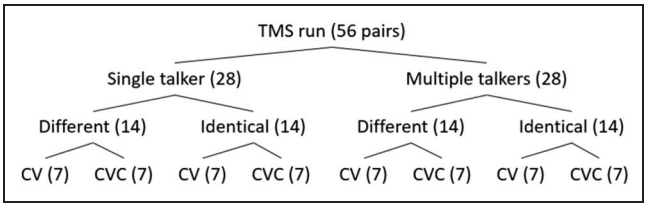

Figure A3. Number of pairs in the SPiN task after TMS administration (four runs).

regression was performed with the syllable pair category (containing no words or containing at least one word) as the dichotomous dependent variable, and the variability condition and type of pair (identical or different) as categorial independent variables. The results showed no effect of talker variability ($\beta = -0.85, p = .606$) or type of pair ($\beta = -0.85, p = .664$), and no interactions between both these variables ($\beta = 0.09, p = .941$). Finally, to control for duration, a three-way ANOVA was performed. Talker Variability (low or high variability) and Types of Pair (identical or different) were the main factors. The structure of the syllable pairs (CV or CVC) was included as a covariate because the duration of the CV syllables was systematically shorter than the CVC syllables. Levene's test confirmed equality of error variances ($p > .05$). The results revealed a structure effect, $F(1) = 78.36$ $p < .001$, with the CVC syllables being longer than the CV syllables, but no effect of Variability condition, $F(1) = 1.88, p = .177$, or Type of Pair, $F(1) = 0.29, p = .594$, and no interaction, Variability × Type of Pair: $F(1) = 0.17, p = .678$.

APPENDIX 3: TMS SPiN TASK

The main task included four runs of 56 pairs, each presented following a TMS session (see Figures 1 and A3). Each run was divided in four lists. In two of the lists, all stimuli were spoken by the same speaker (low variability), whereas in the other two lists, the stimuli were spoken by different speakers, with eight different speakers (high variability). There were 28 trials per talker variability (low variability, high variability). The order of the lists was different across the runs (Table A3).

A three-way ANOVA was performed to ensure that the average spoken frequency of the syllables did not differ across the four runs. The between-subject factors were the Run, the Talker Variability (low or high variability), and the Type of Pair (identical or different). The dependent variable was the average frequency of the pairs. To obtain equality of error variances, frequency was multiplied by itself (exponential transformation; Levene's test: $p > .05$). No effect of Run, $F(3) = 0.35, p = .790$; Talker Variability, $F(1) = 0.01, p = .919$; Type of Pair, $F(1) = 0.37$, $p = .545$, nor any two-way or three-way interactions were significant ($p > .66$).

In addition, because some of the syllables were meaningful one-syllable words, we ensured that the number of words was similar across all talker variability. Logistic regressions were performed with the syllable pair category (containing no words or containing at least one word) as the dichotomous dependent variable, and the run, talker variability, and type of pair (identical or different) as categorial independent variables. The results showed no effect of Run ($\beta = -0.75, p = .236$), Talker Variability ($\beta = -1.21, p = .276$), or Type of Pair ($\beta = -2.62, p = .267$), nor any two-way or three-way interaction ($p > .35$). Hence, the average frequency and the number of syllable pairs containing at least one word were matched across the four TMS runs.

A three-way ANOVA was performed to ensure that the average duration of the syllables did not differ across the four runs. The between-subject factors were the Run, the Talker Variability (low or high variability), and the Type of Pair (identical or different). Because the duration of the CV syllables was systematically shorter than the CVC syllables, the structure of the syllable pairs (CVC or CV) was included as a covariate. Equality of error variances was verified (Levene's test: $p > .05$). As we predicted, the structure had a significant impact on average duration, $F(1) = 124.72, p < .001$. However, no effect of Run, $F(3) = 0.56, p = .645$; Talker Variability, $F(1) = 0.02$, $p = .898$; Type of Pair, $F(1) = 0.59, p = .445$; nor any two-way or three-way interactions were observed ($p > .61$).

APPENDIX 4: ESTIMATION OF THE MAGNETIC FIELDS INDUCED BY TMS

The location, extent, and magnitude of the electric field induced by TMS for each individual and each target was estimated using the SimNIBS software Version 4.0 (Thielscher, Antunes, & Saturnino, 2015). Individual head models were generated based on the individual T1-weighted images using the segmentation and meshing pipeline *charm* (Puonti et al., 2020). The quality of the head reconstructions was visually inspected. One participant was excluded from the subsequent steps because of spurious segmentation, after failed attempts to fix the affine registration.

The individual TMS simulations were run from the graphical user interface. The rate of change of the coil current was set at 1 A/μs, and the distance between the coil and the skin was fixed at 4 mm. Targets were identified from the individual coordinates, and the coil orientation

Table A3. Organization of the Lists for Each Run

Run 1	*Run 2*	*Run 3*	*Run 4*
Single	Multiple	Multiple	Multiple
Multiple	Single	Multiple	Single
Multiple	Multiple	Single	Single
Single	Single	Single	Multiple

Each list included one type of syllable (CV or CVC), and 50% of the syllables for each list were different.

was automatically oriented to be orthogonal to the local scalp surface. The magnitude of the electric field (V/m) was extracted for each TMS session. The subject's electrical field was mapped to the fsaverage space for group analyses, which were run from the Python interpreter. The final images were visualized in *Gmsh*, a 3-D mesh generator (Geuzaine & Remacle, 2009; Figure 2B in the main article).

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Data Availability Statement

Individual data (behavioral and the MR images), as well as the speech perception materials (all stimuli and experiment files) are publicly available on Borealis, The Canadian Dataverse Repository (https://doi.org/10.5683/SP3/3NBZLP).

Author Contributions

Valérie Brisson: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Visualization; Writing—Original draft. Pascale Tremblay: Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Writing—Review & editing.

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Diversity in Citation Practices

Retrospective analysis of the citations in every article published in this journal from 2010 to 2021 reveals a persistent pattern of gender imbalance: Although the proportions of authorship teams (categorized by estimated gender identification of first author/last author) publishing in the *Journal of Cognitive Neuroscience* (*JoCN*) during this period were M(an)/M = .407, W(oman)/M = .32, M/W = .115, and W/W = .159, the comparable proportions for the articles that these authorship teams cited were M/M = .549, W/M = .257, M/W = .109, and W/W = .085 (Postle and Fulvio, *JoCN*, 34:1, pp. 1–3). Consequently, *JoCN* encourages all authors to consider gender balance explicitly when selecting which articles to cite and gives them the opportunity to report their article's gender citation balance. The authors of this paper report its proportions of citations by gender category to be: M/M = .432; W/M = .221; M/W = .137; W/W = .211.

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