Functional Differentiation Between the Left and Right Hemisphere for a Sub-Region of Wernicke's Area is Revealed with fMRI-Guided, Single-Pulse TMS.

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Abstract

Functional Differentiation Between the Left and Right Hemisphere for a Sub-Region of Wernicke's Area is Revealed with fMRI-Guided, Single-Pulse TMS.

by John J. Ferrera

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During the past two decades, studies of neural organization have been bolstered by the addition of functional and structural brain-imaging techniques capable of localizing and correlating brain activity to cognitive functions. With potential clinical applications abound, localizing language-related activity prior to neurosurgery is an interest shared by both neuroscientists and neuroradiologists who are interested in protecting essential language regions in neurosurgery candidates. Since imaging is correlative, however, it does not distinguish essential brain activity from supporting and associated activity and therefore cannot be used independently to determine hemispheric language dominance. Transcranial magnetic stimulation (TMS), on the other hand, is a non-invasive technique that stimulates targeted brain regions directly and can therefore inform causative structure/function relationships.

The goal of this study is to develop non-invasive techniques that definitively identify hemispheric language dominance. Functional Magnetic Resonance Imaging (fMRI) was used to locate language-related regions in 36 right-handed participants. In most participants, there were two clusters of activation within classic Wernicke's territory. We termed these dorsal and ventral Wernicke's areas. On a separate day, fourteen of the thirty-six participants returned to participate in a single-pulse TMS experiment which targeted dorsal and ventral Wernicke's areas and their right-sided homologues. Picture naming latency was decreased following TMS of left-sided dorsal and ventral Wernicke's areas as well as right-sided ventral Wernicke's homologue. No effect was observed following TMS of dorsal Wernicke's homologue.

These results highlight the advantages of using cross-modal imaging techniques by providing direct evidence in support of modern theories of neural language organization that propose a bilateral sub-region of Wernicke's area involved in phonological processing, and a unilateral left-sided component involved in integration and relay of semantic information to other cortical regions.

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Introduction

The modern-day functional neuroanatomy of speech and language has emerged from clinical reports of Paul Broca and Carl Wernicke, who identified patients with deficits resulting from neural damage to anterior and posterior perisylvian regions, respectively (Geschwind 1965). The clinical presentation of patients with Broca's and Wernicke's aphasia has helped to shape our views of the general functional neuroanatomy of the brain in addition to the specific organization of speech and language. Broadly speaking, Broca's patients are capable of comprehending both oral and written speech, but have difficulty with expressive speech. Wernicke's patients display the opposite pattern; they have fluent expressive speech with impaired comprehension of oral and written speech (Geschwind 1965). A picture began to emerge that placed speech production as a frontally-mediated task and speech comprehension as a temporally-mediated task.

Of course, no theory is without its caveats and there was early evidence that the neural organization of speech and language may be more complex than just a frontally-located production region and a temporally-located comprehension region. For instance, early direct cortical electrical stimulation (DCES) experiments conducted by Penfield and others revealed expressive language deficits even when temporal regions were stimulated (Penfield and Roberts 1959). In addition, neuropsychological evidence converged to reveal that the classic syndromes of Broca's and Wernicke's aphasia do not result from focal damage to Broca's and Wernicke's area per se, but instead from widespread damage to Broca's, Wernicke's and their surrounding regions (Mohr, Pessin et al. 1978;

Damasio and Geschwind 1984). Moreover, cases arose where damage to temporal language regions was linked to impaired production with spared comprehension, evidence that speech production recruits more than just frontal regions (Damasio and Damasio 1980).

More recently, functional neuroimaging has helped to identify a network of regions within both cerebral hemispheres involved in different aspects of speech and language. Language mapping studies employing functional magnetic resonance imaging (fMRI), Positron Emission Tomography (PET), and evoked potentials all reliably produce activation throughout Broca's and Wernicke's regions in both the dominant and non-dominant hemispheres (Binder, Frost et al. 1996; Ishai, Ungerleider et al. 2000; Haxby, Gobbini et al. 2001; Wise, Scott et al. 2001; Mechelli, Price et al. 2004; Price, Thierry et al. 2005; Hickok and Poeppel 2007). Nonetheless, the correlative nature of functional neuroimaging coupled with the difficulty of eliminating task effects have thus far precluded it from being a standalone measure to map essential language function. The correlative nature of functional imaging makes it impossible to know (without either a priori knowledge and/or an additional complementary technique) whether an activated area is necessary for the task at hand. Currently, the Wada procedure is the gold-standard by which functional neuroimaging is verified. An area may be active on an fMRI map because it is needed to complete the experimental task, not because it is related to the experimental construct. For instance, visual picture naming, one commonly used task for mapping language function, recruits primary and secondary visual areas in addition to language areas. Moreover, since the subject is actively participating in the task, the brain regions responsible for maintaining attention and oculomotor control, a fronto-parietal system, are also recruited (Nelles, de Greiff et al. 2009). In order to best interpret the data, therefore, one must be familiar with what is already known about the functional organization of visual and attentional functioning.

Functional brain imaging has come a long way and imaging researchers have developed various ways to circumvent its limitations. One way to overcome these issues is to add a complementary technique, such as transcranial magnetic stimulation (TMS). TMS is an investigational medical procedure capable of stimulating the cortex non-invasively via electromagnetic induction. Unlike functional neuroimaging, which is a passive process that takes snapshots of neural activity over time, TMS directly affects cortical functioning and can therefore yield causative results.

Early TMS studies sought to replicate DCES by producing expressive speech deficits via stimulation of Broca's region, but were unsuccessful (Pascual-Leone, Gates et al. 1991; Jennum, Friberg et al. 1994; Michelucci, Valzania et al. 1994). In many of these studies, the incidence of bilateral language representation was over-diagnosed when compared to studies conducted with Wada and DCES. Later studies revealed that in many early TMS studies, the location reported as Broca's area was in fact the motor-mouth area (Epstein, Meador et al. 1999), which is a bilateral representation of the mouth located adjacent to Broca's area (Brown, Laird et al. 2009). More recent TMS studies have managed to produce significant effects on speech and language functioning (Drager, Breitenstein et al. 2004; Martin, Naeser et al. 2004; Nixon, Lazarova et al. 2004; Andoh, Artiges et al. 2005; Aziz-Zadeh, Cattaneo et al. 2005; Holtzheimer, Fawaz et al. 2005; Niyazov, Butler et al. 2005; Thiel, Habedank et al. 2005; Thiel, Haupt et al. 2005; Andoh, Artiges et al. 2006; Cappelletti, Fregni et al. 2007; Luber, Kinnunen et al. 2007). Most relevant to the present study, reaction-time was found to decrease (i.e., naming was facilitated) when left-sided Wernicke's area was stimulated, whereas TMS of Brocas area had no effect. TMS of Broca's area had no effect (Topper, Mottaghy et al. 1998; Sparing, Mottaghy et al. 2001). The facilitation effect disappears when high-intensity stimulation is used. In this case, the intensity of stimulation refers to the overall magnitude of stimulator output. It is thought that TMS is effective because it pre-activates the underlying language network, subsequently reducing the amount of time it takes to respond.

An open question that still remains is why doesn't high-intensity TMS of Broca's and Wernicke's areas produce the same disabling effect as DCES? One explanation could be that the intended targets are out of reach, because the TMS coil is oriented at a less than optimal angle to the target, preventing the pulse from reaching the intended destination, and/or the coil is placed in the incorrect location. Since it is known that functional brain organization and scalp topography vary across individuals, it is very likely that some subjects in TMS studies are not being stimulated at the intended target. One way to eliminate these confounds is to use structural and/or functional neuroimaging to locate TMS targets. In recent years, the efficacy of TMS has been bolstered by the addition of MRI and fMRI to help pinpoint TMS targets on a subject-by-subject basis (Fierro, Brighina et al. 2005; Kammer, Puls et al. 2005; Niyazov, Butler et al. 2005; Andoh, Artiges et al. 2006). Prior to this, TMS studies most often used the 10-20 EEG system to estimate the location of target regions. Since the 10-20 EEG system is an estimate, it does not account for individual variation in neuroanatomy as well as structural and/or functional MRI. One recent study on the degree of precision of different localization methods indicates that using fMRI activation maps to locate TMS targets provides the highest level of precision (Sparing, Buelte et al. 2008). Accordingly, the present study employs functional imaging to locate TMS targets.

1.1 ***Language Mapping: Clinical Utility***

Currently, because of their ability to reliably detect the language-dominant hemisphere, DCES and the Wada procedure are the preferred methods for determining hemispheric language dominance (Kloppel and Buchel 2005; Petrovich, Holodny et al. 2005). The Wada procedure consists of a series of intracarotid injections of a paralyzing agent (usually amytal) into each hemisphere. Each injection, whose effects last at their peak for approximately 5 minutes and then taper off for the following 10 minutes, is followed by a series of speech and memory tests designed to assess the functioning of each hemisphere (Binder, Swanson et al. 1996; Kloppel and Buchel 2005). While the Wada test provides a useful index of language laterality, it is invasive and potentially traumatic to the patient, and is not able to provide more detailed information about the localization of specific language skills that are known to be distributed variably, both within and between the hemispheres. As a result, there is much research dedicated to finding a safer, non-invasive alternative to the Wada procedure (Pascual-Leone, Gates et al. 1991; Binder, Swanson et al. 1996; Epstein, Woodard et al. 2000; Woermann, Jokeit et al. 2003; Kloppel and Buchel 2005). Because of its ability to localize functioning brain areas with millimeter precision spatial resolution, fMRI became an ideal tool for the job.

However, because of the limitations mentioned above, fMRI remains an ancillary technique during brain surgery. Nonetheless, fMRI is now routinely used to assist in identifying essential language regions during pre-surgical language mapping, a procedure that was recently approved for reimbursement by health insurance (AMA CPT code 70555, effective January 1, 2007). One of the most widely used tasks for eliciting speech and language related activity while subjects are in the scanner is visual picture naming. Visual picture naming, also called confrontation naming, is considered optimal for speech and language mapping because it involves the core functions of perception (i.e. recognizing an object), symbolic association (i.e. attaching a word-label to a referent), and speech output (Hirsch, Ruge et al. 2000; Hirsch J. 2001; Clements, Rimrodt et al. 2006; Wilke, Lidzba et al. 2006; Ojemann 1991). Accordingly, visual picture naming leads to widespread activation across various cortical regions, including both the opercular and triangular subregions of Broca's area as well as areas along the superior temporal gyrus that fall within Wernicke's territory (Ruge 1999; Hirsch, Ruge et al. 2000; Hirsch J. 2001; Catani, Jones et al. 2005; Petrovich, Holodny et al. 2005).

Visual picture naming is an essential component of the presurgical mapping battery used at the Columbia University fMRI Center (Ruge 1999; Hirsch, Ruge et al. 2000). The presurgical mapping battery consists of four tasks aimed at localizing the primary sensory, motor and visual cortices in addition to eloquent cortex, or those areas involved in the receptive and expressive components of speech and language. All tasks are delivered in a block paradigm, which averages activity acquired during multiple successive naming trials and compares the result to activity acquired during rest (Ruge 1999; Hirsch, Ruge et al. 2000).

Laboratory results using fMRI visual picture naming reliably produce large clusters of activity across the posterior temporal region typically defined as Wernicke's area. On the left side, there usually exists two main clusters that are located on the superior and inferior aspects of the superior temporal gyrus, respectively. When individual language maps are averaged across groups of individuals, these regions become more evident. For the purposes of this study, we term these areas ventral and dorsal Wernicke's areas (see Figures 1 and 8 for examples of dorsal and ventral Wernicke's areas). In the right hemisphere, there is usually only one temporally-located cluster on the superior aspect of the middle temporal gyrus that is analogous to the left-sided ventral Wernicke's cluster. This pattern of language-related activity is consistent with other functional neuroimaging studies and with recent theories of speech and language organization (Binder, Frost et al. 1996; Ishai, Ungerleider et al. 2000; Haxby, Gobbini et al. 2001; Wise, Scott et al. 2001; Mechelli, Price et al. 2004; Price, Thierry et al. 2005; Hickok and Poeppel 2007).

1.2 ***Transcranial Magnetic Stimulation (TMS)***

TMS is a non-invasive way to stimulate neural tissue. The TMS coil is placed on the scalp and connected to a stimulator to produce a rapidly-alternating magnetic field that traverses the skull and stimulates the cortex by inducing an electrical current. To generate the magnetic pulse, high-intensity current is rapidly turned on and off within the coil, resulting in a time-varying magnetic field that lasts approximately 200 microseconds. The magnetic field strength is strongest (about 1.5 Tesla, depending on the stimulator) at the surface of the coil, and drops off exponentially with distance from the coil. Unlike DCES, which is difficult to deliver in a focal fashion since it travels through the entire brain, TMS only affects the 2 cm^3 volume of brain that lies beneath the coil (Wassermann 1998 ; Lisanby, Gutman et al. 2001; Wagner, Gangitano et al. 2004). This characteristic, which limits the reach of TMS, also affords it the ability to be directed at focal cortical regions, thus making it an ideal technique to use for the study of neural processes.

Two parameters that are frequently modified to optimize the delivery of TMS, include the intensity of stimulator output and pulse-frequency (i.e. Single Pulse vs. Repetitive TMS). Stimulation intensity refers to the overall magnitude of stimulator output. Greater stimulator intensity is associated with a greater disruption of neural activity and also a greater risk of seizures. Guidelines exist to reduce these risks, including the appropriate screening of subjects for seizure risk factors, titration of the individual motor threshold and its use for determining the intensity of stimulation, and by limiting TMS dosage (Wassermann 1998 ; Belmaker B 2003). Stimulator intensity is usually determined using one of three primary methods: as a percentage of each subjects' individual motor threshold (MT, see below for definition), as a percentage of each subjects' individual functional threshold for the task used in the study, or at a fixed percentage of stimulator output. For the current study, stimulator intensity was set at 100% of subjects' MT .

In addition to stimulator intensity, the frequency of pulses can also be modified to deliver TMS in either a single-pulse or a repetitive fashion. During single-pulse TMS, one pulse is delivered at a pre-specified time-point either before and/or after the presentation of a stimulus. Pulses do not follow a regular pattern, such as one pulse per second. Repetitive TMS (rTMS), on the other hand, refers to trains of TMS pulses being delivered during each trial, or repeated applications of TMS pulses at regular intervals. rTMS can be delivered in either a high or low frequency pattern. High frequency is operationally defined in the rTMS literature as trains of pulses exceeding 5Hz, or 5 pulses per second for a specific duration of time. Low frequency is operationally defined trains not exceeding 1Hz, or once per second. Based on research in the motor and visual systems, high-frequency rTMS was shown to result in excitatory physiologic changes while low fequency rTMS was shown to result in inhibitory effects. In the motor cortex, excitability is determined by measuring motor threshold (MT), or the lowest magnitude of stimulation required to invoke a twitch of the hand, either measured by visual observation of the hand or via the acquisition of motor evoked potentials (MEPs) of the hand muscles. Low-frequency rTMS (i.e. ≤1Hz) has been shown to decrease the excitability of the motor cortex, while high high-frequency rTMS (i.e. >5Hz) has been shown to increase motor cortex excitability, i.e. following trains of either low or high frequency rTMS to the primary motor areas, MT has been shown to either increase (the cortex becomes less responsive) or decrease (i.e. the cortex becomes more responsive), respectively (Maeda, Keenan et al. 2000; Boroojerdi, Meister et al. 2002; Gerwig, Kastrup et al. 2003; Robertson, Theoret et al. 2003). In the visual cortex, rTMS has been shown to modulate cortical activity in a similar fashion. Visual cortical excitability is measured via the Phosphene Threshold (PT), or the lowest magnitude of stimulation required to produce flashes of light perceivable by the subject. Various studies have demonstrated that low frequency rTMS (≤1Hz) significantly increases PT, a phenomena associated with a decrease in cortical excitability

When targeting areas other than the primary motor and visual cortices, it is assumed that high and low frequency rTMS modulate cortical excitability in a similar fashion and thus produce opposite effects on cortical function. Accordingly, it would follow that low frequency stimulation would decrease the excitability of the targeted cortex and thus lead to the disruption of function. Following this logic, high frequency rTMS could potentially enhance functionality of the targeted region. Alternatively, increasing the excitability of a particular cortical region could have the opposite effect: instead of enhancing functionality it could force the affected neurons into a hyperpolarized, inactive state.

Another source of variation among TMS studies is the timing with which pulses are delivered in relation to experimental stimuli. In particular, rTMS stimulation protocols consist of either *on-line* or *off-line* stimulation. On-line stimulation is when rTMS pulses are delivered in sync with the cognitive task; Off-line stimulation is when rTMS pulses are delivered *before* the subject completes the cognitive task. With on-line stimulation, it is possible to vary the delay between the onset of a pulse and the onset of the stimulus-presentation. On-line stimulation has been used to determine precisely the timing of specific cognitive events. For instance, Cracco et al. (1999) demonstrated that a TMS pulse delivered to an occipital target can suppress visual perception (letter recognition) when it is applied between 80 and 120msec after stimulus presentation, implying that only at these times was the occipital cortex involved in the task (Cracco, Cracco et al. 1999). In another study, Pascual-Leone and Walsh (2001) showed that the perception of a TMS-induced moving phosphene, which was induced via stimulation of motion area V5, can be suppressed by a second TMS pulse applied to primary visual cortex (V1) 10 to 40msec after the first pulse. These data suggest that V5-V1 feedback projections are necessary for the perception of motion (Pascual-Leone and Walsh 2001). This experiment highlights the utility of TMS to study cortical networks. The present study employs TMS for the study of the language network.

1.2.1 ***Early TMS studies of speech and language***

In most TMS studies, the effect of TMS on speech and language is determined by measuring the reaction-time (RT) and/or accuracy of participant's responses during different speech and language tasks (Pascual-Leone, Gates et al. 1991; Claus, Weis et al. 1993; Epstein, Lah et al. 1996; Epstein 1998; Wassermann 1998 ; Epstein, Meador et al. 1999; Wassermann, Blaxton et al. 1999). Early TMS studies of language localization focused on causing speech arrest via stimulation of frontally-located language areas (Pascual-Leone, Gates et al. 1991; Michelucci, Valzania et al. 1994). Many of these studies used round coils, which generate diffuse magnetic fields that led to the stimulation of the motor mouth areas, which are adjacent to frontally-located language regions. Stimulation of the motor mouth areas leads to an over-diagnosed bilateral language representation since disabling motor activity with either the dominant or non-dominant hemisphere leads to dysarthria (Pascual-Leone, Gates et al. 1991; Jennum, Friberg et al. 1994; Michelucci, Valzania et al. 1994).

More focal stimulation can be achieved by using a figure-eight coil. Epstein et al. (1996a) showed that speech arrest could be obtained using focal coils, but they concluded that the area of stimulation that produced speech arrest was always congruous with the area that yielded motor responses from the mouth muscle (Epstein, Lah et al. 1996). Speech arrest was never observed with stimulation given more anteriorly, at the expected site of Broca's area. Epstein et al. conclude that the location of speech arrest is congruous with the motor-speech area (Epstein, Meador et al. 1999). Later studies revealed that it was possible to affect speech production via TMS of Wernicke's area.

1.2.2 ***TMS of Wernicke's Area: The Facilitation Effect***

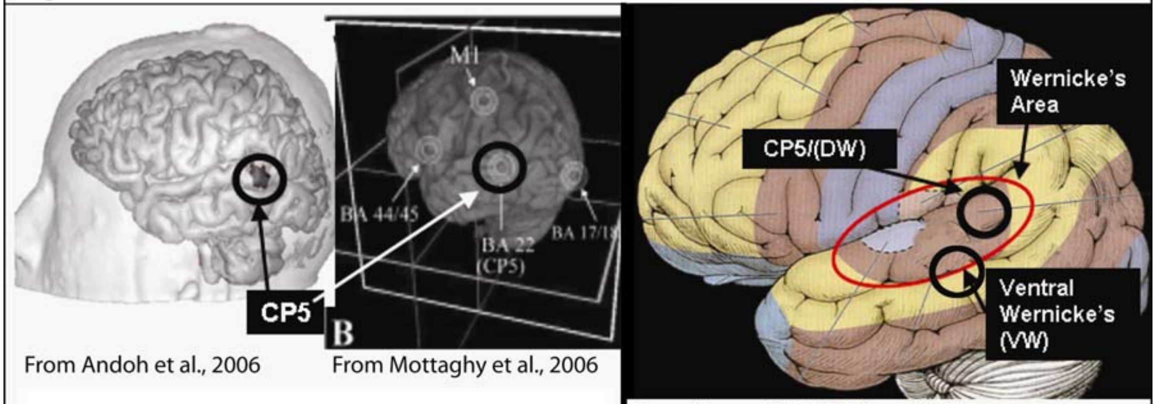
Wernicke's region has been the subject of many TMS studies. Most relevant to the current study, Topper et al. (1998) applied single-pulse TMS to Wernicke's area and left-sided motor cortex and assessed performance on picture naming. They serendipitously found that picture naming latency decreased after stimulation of Wernicke's area. Stimulating motor regions had no effect on naming latency. Moreover, the effect disappeared when the intensity of the stimulation was increased past 55% of the maximum stimulator output, a value at or slightly above the average subjects' motor threshold (see Methods section for a description of Motor Threshold in TMS) (Topper, Mottaghy et al. 1998). This finding was not expected, and so follow-up studies were conducted to further delineate the nature of this effect.

Follow-up studies replicated the facilitation effect (Mottaghy, Hungs et al. 1999; Sparing, Mottaghy et al. 2001). In addition, similar to their previous results, using high-intensity stimulation (i.e. >55% of stimulator output) had no effect. Moreover, Wernicke's right-sided homologue was targeted and results indicate that stimulating Wernicke's homologue had no effect on picture naming latency. Finally, it was determined that in order for the facilitation effect to occur, the TMS pulse had to precede the onset of the stimulus (Sparing, Mottaghy et al. 2001). Using both single-pulse and rTMS produced the facilitation effect. When interpreting these results, the authors suggest that low frequency stimulation pre-activates the area stimulated and, in turn to those areas to which it is functionally connected. This pre-activation is thought to prime the language system for the upcoming stimulus (Mottaghy, Sparing et al. 2006).

1.2.3 ***TMS of Wernicke's Area: Where were they stimulating***

Wernicke's area is broadly defined as corresponding to Brodmann's area 22, which includes the posterior two-thirds of the superior temporal gyrus in the language-dominant hemisphere (Blumenfeld 2002). As mentioned previously, laboratory observations during presurgical fMRI speech and language mapping reveal at least two functional clusters within Brodmann's 22. In particular, one cluster is located on the inferior aspect of the superior temporal gyrus while the other is located on the anterior aspect of superior temporal gyrus. We termed these ventral Wernicke's area (VW) and dorsal Wernicke's area (DW), respectively (Figure 1). All aforementioned TMS studies of Wernicke's area used the CP5/6 sites from the 10-20 EEG system to locate Wernicke's area. This site is located near the angular gyrus, an area most consistent with dorsal Wernicke's area. A comparison of these two regions is shown below (Figure 1).

Figure 1: Location of dorsal and ventral Wernicke's areas



From Andoh et al., 2006

From Mottaghy et al., 2006

Previous TMS studies of Wernicke's area targeted the posterior aspect of the Superior Temporal Gyrus, an area consistent with the CP5 site in the 10-20 EEG system.

From Blumenfeld 2002 (modified)

The location of Wernicke's area is broadly defined in the literature. The red circle above is considered putative Wernicke's area. The black circles represent the observed locations of dorsal and ventral Wernicke's areas (DW and VW).

*1.3 **The present study***

The aims of the present study were threefold. First, we sought to validate our laboratory fMRI finding that discrete functional clusters exist within classic Wernicke's territory. Second, we sought to further differentiate the nature of the facilitation effect by targeting dorsal and ventral Wernicke's areas and their homologues with fMRI-guided TMS. Lastly, we sought to determine the efficacy of using fMRI-guided TMS for determining hemispheric language dominance prior to neurosurgery. In the discussion of the study, we extend the idea that DTI could be used to examine the underlying neural circuitry connecting different speech and language clusters.

Language-related activity was localized using visual picture naming, part of the Columbia University fMRI Center's presurgical language mapping battery (Ruge 1999; Hirsch, Ruge et al. 2000; Petrovich, Holodny et al. 2005). Each subject's fMRI map was co-registered to their structural MRI and imported into a frameless stereotactic neuronavigation device to allow for precise targeting during TMS. TMS targets included dorsal and ventral Wernicke's areas as well as their right-sided homologues. During the TMS experiment, subjects were instructed to say out loud the names of visually presented objects. Responses were recorded and analyzed to determine Reaction Time (RT) and Accuracy. Reaction time was compared across experimental conditions to characterize the nature of any TMS effects (see Methods for a more detailed description of study and analysis procedures).

2. Methods

The complete study consisted of two experimental sessions conducted on separate days: a fMRI language localizer and a single-pulse TMS experiment. Participants were paid for each day of participation, and had the option of completing both the fMRI and TMS parts of the study, or just the fMRI portion. The study was approved by the Institutional Review Boards of Queens College and Columbia University. All subjects were right-handed and without significant neurological history. Recruitment for the study was conducted by word-of-mouth.

2.1 ***fMRI Experiment***

2.1.1 ***Participants***

Thirty-six adults (20 female and 16 male; mean age=24.4 years, SD=5.3), many of whom were university students, gave consent according to Institutional Review Board (IRB) guidelines to participate in this paid study. All participants were right-handed and without significant neurological or psychiatric history. Thirty-one participants were native English speakers; five participants were native Spanish speakers. All participants generated object-names in their native language for the naming task. Screening forms were given before testing to assess handedness (Oldfield 1971) and to ensure that none of the participants had any contraindications to fMRI and/or TMS. All participants were informed that they were under no obligation to complete the experiment and could withdraw at any time. Participants were given the option to also participate in the TMS experiment.

2.1.2 ***The scanner***

Functional images were acquired on a 1.5 T Magnetic Resonance Scanner (General Electric Twin Speed) using echo planar imaging to obtain T2-weighted images with a gradient echo pulse sequence (TE (echo time), 60 ms; TR (repetition time), 2000ms; flip angle, 60^0). The in-plane resolution was 3.2 x 3.2 mm and slice thickness was 3.5 mm. For each run, 144 volumes were acquired, each containing twenty-seven contiguous brain slices. The duration of each run was 2 minutes and 24 seconds. Conventional T1-weighted high-resolution anatomical images (172 axial slices; FOV (field of view), 190mm; slice thickness, 1mm) were also acquired for each subject after the completion of the functional runs. All images were acquired parallel to a standard reference line that intersected the superior edge of the anterior commissure and the inferior edge of the posterior commissure in order to facilitate the co-registration process.

2.1.3 ***fMRI Design and Procedure***

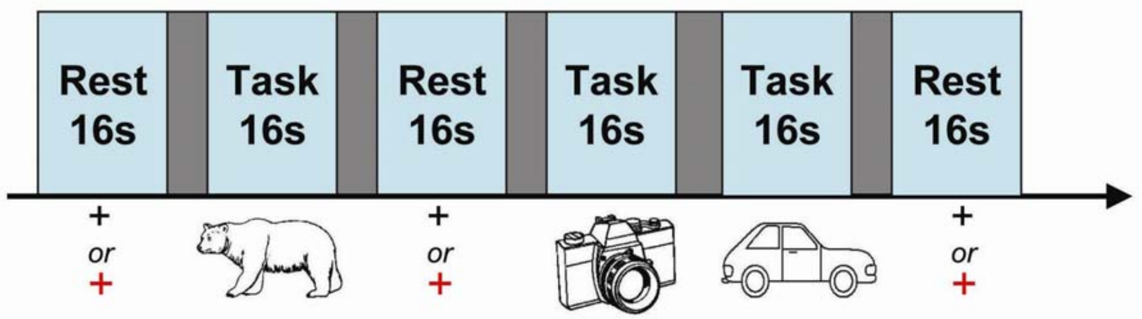
All participants received an fMRI scan while performing visual picture naming, one standard component of the clinical speech and language localization paradigm developed at the Columbia fMRI Research Center (Ruge 1999; Hirsch, Ruge et al. 2000; Hirsch J. 2001). The task was delivered in a block design fMRI paradigm with conditions alternating between activation and rest (see Figure 2). When analyzing the data, activity recorded during the activation block was compared to activity recorded during the rest (or control) block to produce the activation maps.

For the activation block of the Picture Naming task, participants were shown pictures of common objects from the Boston Naming Test (Busch, Frazier et al. 2005).

They were instructed to covertly name each picture and to use it in a sentence. Two participants were native-Spanish speakers and indicated that they felt more comfortable when using their native language. As a result, they were instructed to use their native language during the experiment. This decision is supported by past fMRI studies of bilingual participants indicating that the location of temporal lobe activation clusters does not change if participant's use their native or second language during picture naming (Kim, Relkin et al. 1997). During the rest block, participants were instructed to keep their eyes focused on a fixation cross located in the center of the screen. Experimental blocks were pseudorandomized to control for order effects. A different set of object pictures was used for the TMS experiment to avoid any priming effects.

Typical to many fMRI studies, naming in the scanner was performed covertly in order to reduce motion artifacts. While it is possible to have subjects vocalize their responses while in the scanner, this requires using an event-related design with built-in delays to exclude the acquisition of motion-related activity. This significantly increases scan-time and is not always practical for clinical applications (Eden, Joseph et al. 1999). To circumvent this issue, studies have been conducted to compare the centroids of activation that result from covert vs. overt object naming. While differences were found when comparing the location of certain frontally-located activation clusters (Petrovich, Holodny et al. 2005), temporally-located activation clusters were consistent across both covert and overt naming tasks (Schlosser, Luby et al. 1999). Since the present study focuses on temporally-located activation clusters, using a covert naming paradigm is empirically supported.

Figure 2: fMRI Task Design



The entire run consisted of alternating 16-second blocks of either ‘task’ or ‘rest’. Experimental blocks were pseudo-randomized to control for order effects. The entire run duration was two minutes and twenty-four seconds and was repeated twice for each participant. Pictures were selected from the Boston Naming Test stimulus collection.

Task Blocks:
During ‘task’ blocks, participants viewed object pictures and were instructed to name the picture and to use it in a sentence. They were told to press a button with their index finger when they were done with each item in order to advance the stimulus. This was done to reduce ‘off-task’ time within the activation block, which increases power .

Rest Blocks:
During ‘rest’ blocks, participants were instructed to fixate at the black plus-sign located at the center of the screen and to press a button with their index finger when the plus-sign turned from black to red. The item advanced when the button was pressed. A task is typically added to ‘rest’ blocks to maintain attention and fixation.

In between each 16-second ‘task’ or ‘rest’ block, an instruction screen notified participants whether the upcoming block would be a ‘task’ or ‘rest’ block (Gray bars in the above figure). These volumes were discarded during analysis.

For copyright reasons, pictures used in the figure above were not taken from the Boston Naming Test stimulus set.

2.1.4 ***fMRI Data Analysis***

All fMRI images were exported from the scanner at the fMRI Research Center to a nearby workstation where they were imported into Brain Voyager QX and subsequently reconstructed and aligned to correct for movement artifacts and to allow for direct comparisons using each participant’s common coordinate system. A two-dimensional

Gaussian filter was applied to enhance signal-to-noise characteristics, and voxel-by voxel intensities were compared during the stimulation and baseline epochs using the General Linear Model approach.

The General Linear Model (GLM) analysis, also known as Multiple Regression Analysis, is the standard statistical tool implemented in most fMRI statistical packages. In the context of analyzing brain imaging data, the GLM was first introduced by Friston et al. (Friston, Frith et al. 1990). More generally, The GLM is a statistical technique that forms the basis for many commonly used statistical procedures including but not limited to the t-test, analysis of variance (i.e. ANOVA), regression analysis, as well as various multivariate techniques (Gold, Christian et al. 1998; Bullmore, Fadili et al. 2003). In GLM analysis, a linear combination of several regressor variables (i.e. experimental or independent variables) is used to predict the variation of an observed variable (i.e. fMRI BOLD signal). In the context of the present study, the regressor variables refer to the various experimental conditions, naming and rest. The observed, or dependant variable, is the fMRI BOLD signal.

As a linear function, the GLM may be written as $Y=BX+E$ where Y is the dependent variable represented as a matrix with a series of measurements, X refers to an experimental and/or independent variable, B refers to an estimate of how X is related to Y (i.e the slope of the line), and E is a matrix containing errors or noise (Gold, Christian et al. 1998; Bullmore, Fadili et al. 2003). In fMRI analysis, the only dependent variable is the BOLD signal. When multiple conditions or regressor variables are being compared to one dependent variable, the analysis can be referred to as multiple linear regression or multiple regression. Specifically, in fMRI analysis, the dependent variable (Y) refers to a matrix of BOLD signals that were sampled at each voxel for all successive time-points within a given condition. As a univariate analysis, each voxel is considered independently of others. A matrix of values is generated for each condition at each voxel. All experimental conditions are defined by a user-defined stimulation protocol or design matrix that details all trials within a run.

In the present study, GLM was used to locate all of the voxels that were active during the ‘task’ block and *not* during the ‘rest’ block. Activation maps were co-registered to both standard space (i.e., Talairach space) and subject-space. Standard space was used to make group average maps of fMRI data. Subject-space was used to locate dorsal and ventral Wernicke’s areas and their homologues for use as targets during the TMS experiment.

2.2 ***TMS Experiment***

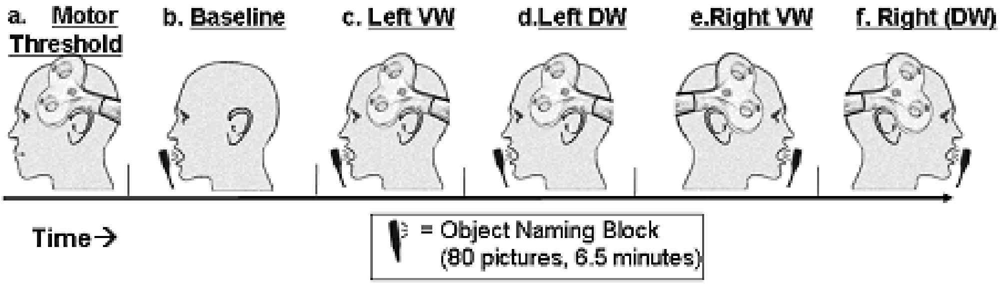
2.2.1 ***Participants***

Fourteen of the thirty-six fMRI participants volunteered to complete the TMS portion of the study. These participants returned to the fMRI center on a separate day to undergo TMS. All participants were informed that they were under no obligation to complete the experiment and could withdraw at any time. For the first six participants, left and right ventral Wernicke’s areas were targeted. For the remaining eight participants, left and right ventral Wernicke’s areas as well as left and right dorsal Wernicke’s areas were targeted. Two participants were native-Spanish speakers and indicated that they felt more comfortable naming in Spanish. These participants were instructed to generate object-names in their native language during the naming portion of the TMS study as they did in the fMRI part of the study.

2.2.2 ***TMS task design***

For each region targeted, participants were seated in a chair positioned in front of a 24” LCD monitor and completed a 6.5 minute block of overt visual picture naming during when they were instructed to name each picture as quickly as possible. Each participant’s motor threshold (MT) was determined prior to the experiment and was used to titrate the intensity of the TMS stimulator output. MT is the lowest magnitude of stimulation intensity required to invoke a twitch of the hand, either measured by visual observation of the hand or via the acquisition of motor evoked potentials (MEPs) of the hand muscles. For the current study, MT was measured using the ‘visual’ method. During TMS, the stimulator intensity was set to 100% of Motor Threshold, which is considered ‘low’ intensity (Mottaghy, Sparing et al. 2006). Pulses were delivered using a 70 mm figure-8 coil attached to a 1.5T Magstim 200 stimulator. Each language block included 80 unique pictures, 40 for each of two timing conditions (see Figure 3 for a depiction of the TMS protocol). All blocks were presented in a different random order across subjects to eliminate order effects. For similar reasons, stimuli were pseudo-randomized within each block.

Figure 3: TMS Protocol



a. *Threshold:* Each subjects' motor threshold (MT) was determined in order to titrate the intensity of TMS stimulation. TMS Pulses were delivered at 100% of each subjects' MT.

b. Baseline: Subjects underwent a baseline measurement during when they heard the click of the TMS stimulator but did not receive TMS.

c-f: Subjects received Single-Pulse TMS while naming object pictures. The stimulation sites included Left and Right Ventral Wernicke's Area (VW, 11 subjects) as well as left and right Dorsal Wernicke's Area (DW, 5 subjects).

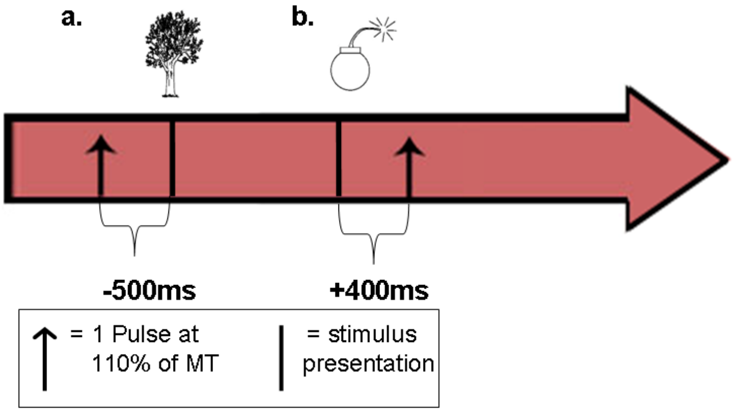
For all Single Pulse TMS conditions (b-f), the order of each block was counterbalanced across subjects to control for order effects. The timing of the pulses was varied with respect to stimulus onset (see figure 4).

During each block, the timing of the pulse was varied such that it was delivered either 500ms prior to the onset of the stimulus or 400ms after the onset of each stimulus (see Figure 4). The two timing conditions were randomly interleaved within each block. For each subject, a baseline block was included to serve as an experimental control. The baseline block was identical to the other blocks except that the TMS coil was not applied to the scalp. Accordingly, no stimulation was being applied to the brain but participants could hear the click of the stimulator at 500ms prior or 400ms post stimulus onset.

The 80 unique pictures per block were selected from a pool of 480 object pictures included in the International Picture Project database (Bates, D'Amico et al. 2003; Szekely, D'Amico et al. 2003). The International Picture Project database is a set of object pictures that were

Figure 4: TMS Timing Conditions

- Pulses were delivered at either 500ms before (a) or at 400ms following stimulus onset (b). Each block contained a set of 80 unique pictures, 40 for each timing condition.



cross-culturally normed across different measures of familiarity. Only those pictures with a familiarity rating of .75 or higher were used, which means that 7.5 out of 10 people included in the normative sample could accurately name each picture.

2.2.3 ***Selection of TMS targets***

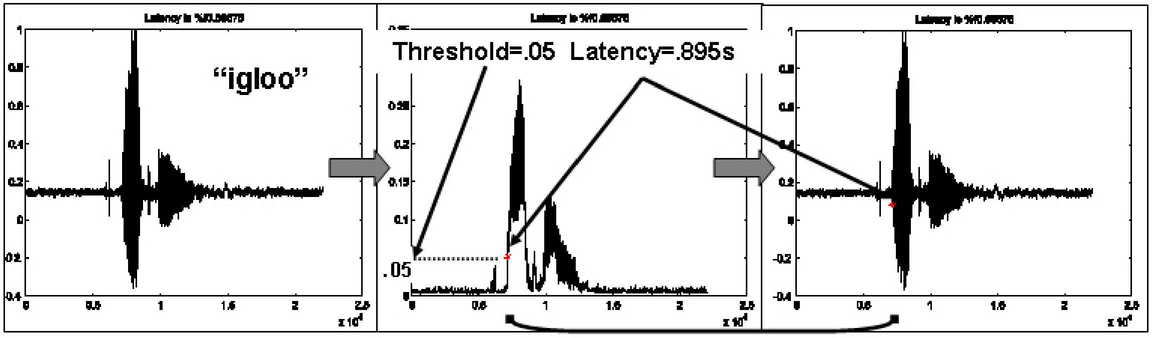
Activation patterns produced during the fMRI experiment were used to determine the targets of TMS stimulation. For six of the fourteen subjects, only ventral Wernicke's area was targeted bilaterally. Preliminary analyses revealed the surprise finding that the facilitation effect was present following both left and right-sided stimulation. We subsequently went back to the literature and realized that previous TMS studies were targeting the dorsal Wernicke's site. As a result, we modified the TMS acquisition to include stimulation of bilateral dorsal and ventral Wernicke's areas. For the remaining 8 subjects, functional clusters consistent with the locations of bilateral dorsal and ventral Wernicke's area were used to select TMS targets. Since the radius of TMS spread using a 70mm figure-eight coil is approximately 2cm^3 (Barker 1999), we measured the distance surrounding each activation cluster to ensure that there was a distance of at least 2cm between the ventral and dorsal ROI. The distance between dorsal and ventral Wernicke's areas was >2.5 cm in all TMS subjects. Recent studies indicate that using fMRI to locate TMS allows for a millimeter level of precision (Sparing, Buelte et al. 2008), well within the minimal distance allowed between dorsal and ventral Wernicke's area. Activation maps were imported into Brainsight, a frameless stereotactic neuronavigation device used to precisely locate brain regions within each subject (Brainsight Frameless, Rogue Research, Montreal, QC, Canada).

2.2.4 ***Data Acquisition and Analysis***

During the TMS blocks, participants responded by saying out-loud the name of each picture. Unlike the fMRI naming task, participants were not asked to use the words in a sentence as this would have disproportionately increased the total run duration. Each response was recorded by a microphone placed near the subject's mouth. Responses were discarded if the subject failed to name the item correctly (see a complete description of this process below). To determine reaction time, each sound wave was transformed to its root mean square, which accounts for both amplitude and frequency. To account for the level of background noise at the time of the experiment and the volume of the participant's voice, an arbitrary threshold was set to reliably indicate the beginning of the response. All waveforms were individually checked with a human eye to eliminate false-positive determinations of response onset caused by external noise (see Figure 5).

Figure 5: Determination of Reaction Time

To determine reaction time, the 2-second response window is recorded and the sound wave is plotted (a). Subsequently, the root mean square of the sound wave (b) is plotted and an arbitrary threshold is selected that reliably detects the beginning of the subject's response. All waveforms are visually checked with a human eye to ensure that there are no false positive determinations of response onset.



To determine accuracy, three different categories of exclusions were defined: (1) semantically incorrect responses, (2) responses with multiple onset due to verbal searching and (3) extremely delayed responses. Semantically incorrect responses occurred when a participant did not recognize a given picture, or when the picture was misperceived. Verbal searching, also known as the 'tip of the tongue' phenomenon (Brown and McNeill 1966), is observed as pauses filled with interjections (such as 'uh', 'uh', 'uh'), self-commenting phrases and/or prolonged empty pauses. Since TMS could induce semantic errors or be responsible for response delays, the number of exclusions was calculated and compared between experimental conditions. Extreme delay was defined as a naming latency that exceeded the individual's average naming latency by more than 2 standard deviations.

3. Results

*3.1 **fMRI Results***

All 36 fMRI participants (20 females) showed significant activation of the left inferior frontal and superior temporal gyri (i.e., Broca's and Wernicke's areas) as expected (see Figure 8). In addition, all participants demonstrated activation clusters in the parietal and medial frontal regions, areas known to be part of the language network activated by visual picture naming (Hirsch J. 2001).

For the left hemisphere, all participants (100%) displayed an activation cluster that extended from the ventral aspect of the superior temporal gyrus to the superior aspect of the middle temporal gyrus. We termed this area ventral Wernicke's area. All but three participants (92%) displayed activation on the dorsal aspect of the superior temporal gyrus in an area just anterior to the angular gyrus (see Table 1 below). We termed this dorsal Wernicke's area.

For the right hemisphere, thirty-five of thirty-six participants (97%) had a cluster of activity in ventral Wernicke's homologue. Only eight participants (22%) demonstrated a completely bilateral representation, meaning they had clearly distinguishable clusters of activity in both the ventral and dorsal homologues of Wernicke's area (see Table 1 below). These results are consistent with modern theories of language organization that propose a left-sided dominant, bilateral, distributed language network (Hickok and Poeppel 2007).

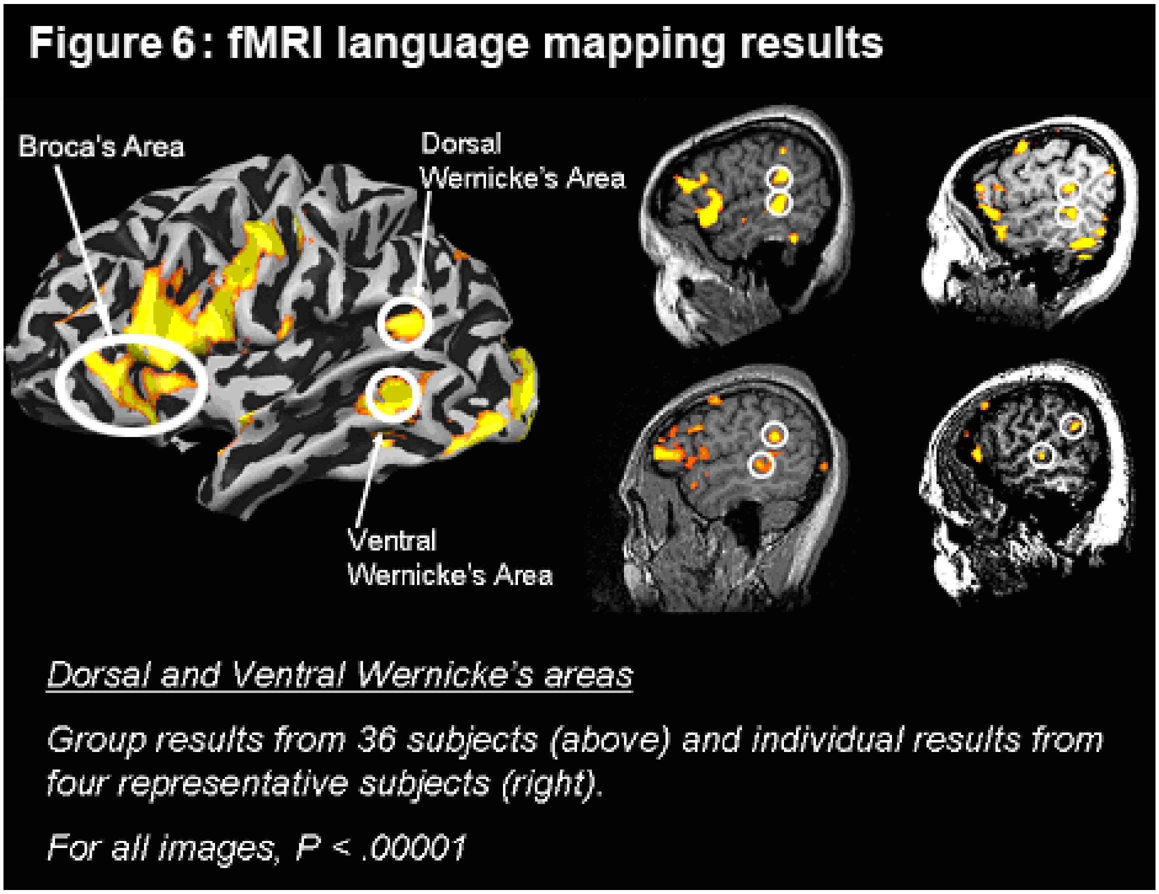


Figure 6: fMRI language mapping results

Dorsal and Ventral Wernicke's areas

Group results from 36 subjects (above) and individual results from four representative subjects (right).

For all images, $P < .00001$

Table 1: **Presence of dorsal and ventral Wernicke's area and their homologue's for the 36 fMRI participants during Picture Naming** (20 females, 16 males; Mean age: 24±5.3).
For each participant, the x,y,and z Talairach coordinates are listed below. The coordinates refer to the centroids of each activation cluster. The size of each cluster (i.e., number of active voxels) is reported in parentheses. N/A indicates that no activation was present.

	Sex	**Age**	**Left VW**	**Left DW**	**Right VW**	**Right DW**
1	**F**	**51**	-56,-36,1 (389)	N/A	50,-26,2 (1109)	N/A
2	**F**	**27**	-61,-25,-1 (109)	-61,-44,21 (1480)	59,-19,2 (134)	N/A
3	**F**	**23**	-52,-42,-8 (3362)	-59,-45,15 (827)	61,-28,1 (1022)	N/A
4	**F**	**22**	-55,-38,4 (3423)	-50,-40,21 (2977)	44,-26,1 (1917)	N/A
5	**F**	**24**	-51,-34,-4 (1844)	-57,-40,12 (1654)	52,-32,2 (1664)	N/A
6	**F**	**25**	-45,-46,2 (1536)	-52,-46,19 (1045)	60,-35,4 (418)	N/A
7	**F**	**24**	-47,-35,0 (3535)	-47,-34,16 (2241)	56,-26,1 (1347)	N/A
8	**F**	**20**	-51,-35,0 (2991)	-57,-39,14 (1150)	58,-33,2 (81)	59,-31,17 (596)
9	**F**	**20**	-60,-32,3 (2437)	-60,-46,25 (2096)	53,-26,0 (2207)	N/A
10	**F**	**20**	-54,-32,0 (2122)	-54,-41,27 (375)	56,-25,7 (533)	N/A
11	**F**	**22**	-52,-40,2 (619)	-57,-42,20 (242)	61,-43,4 (159)	63,-40,23(69)
12	**F**	**22**	-60,-31,0 (1623)	-58,-51,20 (1281)	53,-32,1 (1220)	53,-41,14 (1709)
13	**F**	**26**	-61,-36,6 (5581)	N/A	63,-30,5 (2014)	N/A
14	**F**	**26**	-59,-38,5 (235)	-56,-41,15 (696)	56,-27,1 (538)	N/A
15	**F**	**22**	-57,-32,4 (3635)	-57,-50,21 (842)	55,-23,1 (725)	N/A
16	**F**	**26**	-56,-41,1 (1019)	-52,-42,17 (395)	47,-42,4 (578)	N/A
17	**F**	**26**	-50,-42,0 (4061)	-60,-43,18 (2610)	46,-35,5 (3439)	N/A
18	**F**	**28**	-50,-28,1 (1013)	-50,-47,22 (1288)	44,-28,0 (2097)	57,-40,19 (620)
19	**F**	**24**	-57,-30,0 (2465)	-52,-29,34 (1003)	N/A	N/A
20	**F**	**28**	-56,-40,2 (3560)	-56,-37,19 (1282)	53,-31,5 (1098)	N/A
21	**M**	**24**	-60,-32,6 (2705)	-59,-34,19 (2213)	58,-33,10 (2827)	N/A
22	**M**	**20**	-62,-31,4 (1115)	-57,-48,34 (572)	49,-35,8 (1014)	N/A
23	**M**	**21**	-54,-34,0 (397)	-56,-52,10 (880)	64,-35,1 (941)	56,-50,8 (1187)
24	**M**	**21**	-58,-36,1 (2269)	-54,-44,23 (719)	48,-37,11 (621)	N/A
25	**M**	**28**	-53,-32,-6 (4158)	-61,-35,14 (3157)	58,-27,4 (1527)	N/A
26	**M**	**24**	-58,-28,-4 (765)	-53,-40,13 (293)	50,-19,-2 (569)	N/A
27	**M**	**22**	-60,-30,8 (1790)	N/A	43,-33,7 (1089)	N/A
28	**M**	**27**	-59,-49,4 (821)	-55,-44,17 (126)	N/A	54,-25,20 (99)
29	**M**	**24**	-63,-30,0 (2203)	-60,-41,18 (555)	48,-27,4 (257)	N/A
30	**M**	**23**	-50,-40,1 (833)	-58,-44,10 (1103)	-48,-39,0 (1519)	55,-44,13(313)
31	**M**	**29**	-64,-40,7 (2574)	-53,-46,18 (811)	-46,-40,8 (1068)	54,-50,15(94)
32	**M**	**22**	-58,-34,1 (2397)	-58,-43,21 (295)	48,-33,0 (1507)	N/A
33	**M**	**23**	-42,-35,5 (1782)	-51,-42,26 (1190)	46,-23,4 (506)	50,-40,25(120)
34	**M**	**21**	-58,-25,4 (2107)	-58,-39,22 (1023)	48,-20,0 (578)	N/A
35	**M**	**21**	-57,-32,1 (3654)	-52,-39,19 (1831)	46,-28,1 (1345)	N/A
36	**M**	**21**	-62,-30,1 (477)	-62,-38,14 (1434)	48,-24,-3 (152)	N/A

*3.2 **TMS Results***

Fourteen of the thirty-six fMRI subjects participated in the TMS study. For six of the fourteen subjects, only left and right ventral Wernicke's areas were targeted (see Figure 9). For the remaining eight subjects, left and right dorsal Wernicke's areas were targeted in addition to left and right ventral Wernicke's areas (see Figure 10). For all subjects, accuracy was unaffected across all conditions. This was expected since only high-frequency pictures were used for the picture naming task. In addition, past TMS studies of Wernicke's area that employed picture naming as the dependent variable did not demonstrate any change in accuracy (Topper, Mottaghy et al. 1998; Mottaghy, Hungs et al. 1999; Sparing, Mottaghy et al. 2001; Mottaghy, Sparing et al. 2006). Instead, reaction time (RT) was the relevant dependent variable. Similar to previous TMS studies, results did not reach significant levels until group averages were obtained and compared.

An ANOVA was performed with 4 factors: subject, side (i.e. left or right), timing (i.e. -500ms or +400ms) and location (i.e. Dorsal Wernicke's area, Ventral Wernicke's area). Significant main effects were found for *subject* and *timing*, and for the interactions of *side* and *timing* and for *timing* and *location* (See Tables 2 and 3). In order to measure the magnitude of the effect at each location, the averages obtained for each condition were compared with those obtained during the baseline conditions. Significance was determined using a student's t-test ($p < .05$). For the +400ms timing conditions, no significant effect was observed. For the -500ms timing conditions, significant differences were found such that RT was significantly reduced when ventral Wernicke's area and its right-sided homologue were targeted (see Figures 9 and 10). Our result at ventral

Wernicke's area is a new finding. When dorsal Wernicke's area was targeted (see Figure 10), RT was significantly reduced compared to the baseline condition when left dorsal Wernicke's area was targeted. Targeting right dorsal Wernicke's area had no effect. This finding is a replication of previous TMS studies that targeted the CP5 site (Topper, Mottaghy et al. 1998; Mottaghy, Hungs et al. 1999; Sparing, Mottaghy et al. 2001; Mottaghy, Sparing et al. 2006).

To quantify the magnitude of significant RT differences, the average naming latency for a particular condition was compared to the average naming latency during the baseline condition. Accordingly, the magnitude of the facilitation effect was determined to be 68ms, 53ms and 47ms for left ventral Wernicke's, left dorsal Wernicke's and right ventral Wernicke's, respectively. These values are comparable to previous studies in which the magnitude of the facilitation effect was found to range between approximately 50ms and 60ms (Topper, Mottaghy et al. 1998).

Figure 7: Group TMS results, Ventral Wernicke's Only (n=6)

For each location targeted average RT for the -500ms and +400ms trials was compared to the average RT during the baseline (click-only) blocks. Error bars represent standard error. The magnitude of the facilitation effect is displayed atop significant bars.

(Significance (**) was determined using a student's t-test with $P < 0.05$)

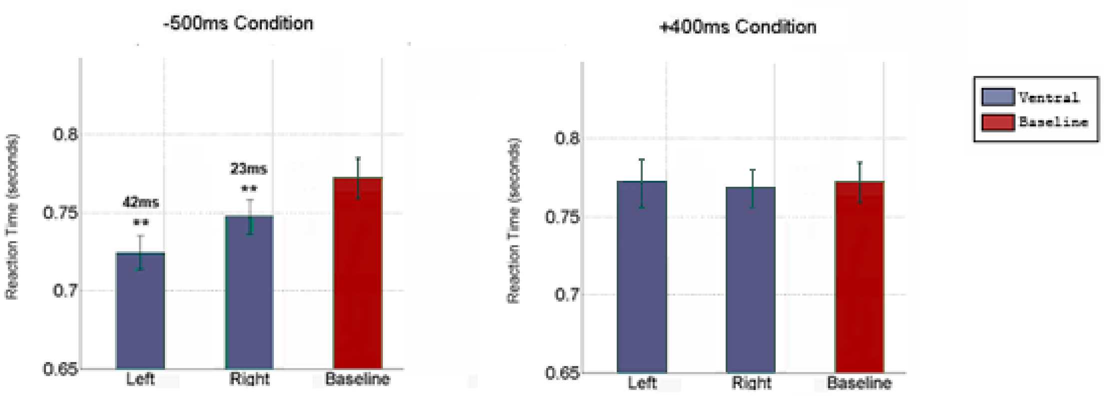
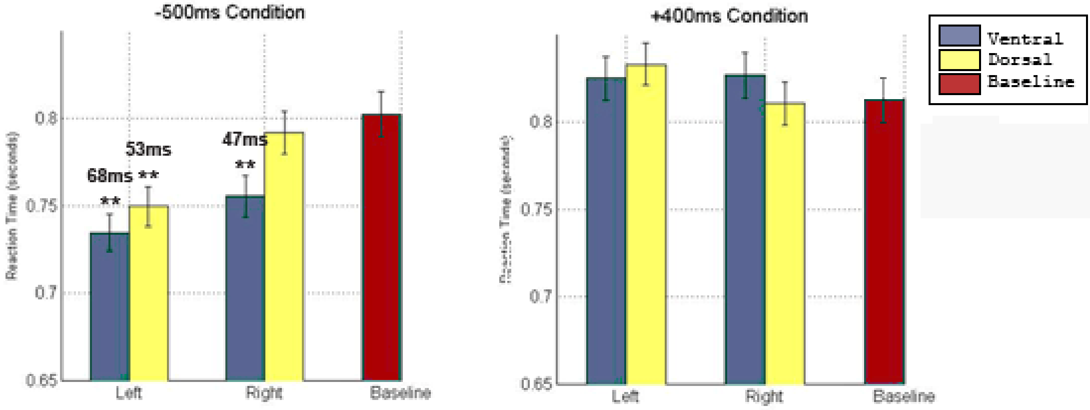


Figure 8: Group TMS results, Dorsal and Ventral Wernicke's (n=8)

For each location targeted average RT for the -500ms and +400ms trials was compared to the average RT during the baseline (click-only) blocks. Error bars represent standard error. The magnitude of the facilitation effect is displayed atop significant bars.

(Significance (**) was determined using a student's t-test with $P < 0.05$)



It is important to note that study participants had a variety of fMRI activation profiles. In particular, five participants demonstrated the most common profile (dorsal and ventral in the left, ventral only on the right; see Table 1), two participants demonstrated a completely bilateral fMRI profile (dorsal and ventral Wernicke's area on both sides; see Table 1), and one subject had activity in bilateral ventral Wernicke's area only (see Table 1). The number of participants in each group was not balanced, and so a proper comparison of fMRI activation profile and TMS results was not performed.

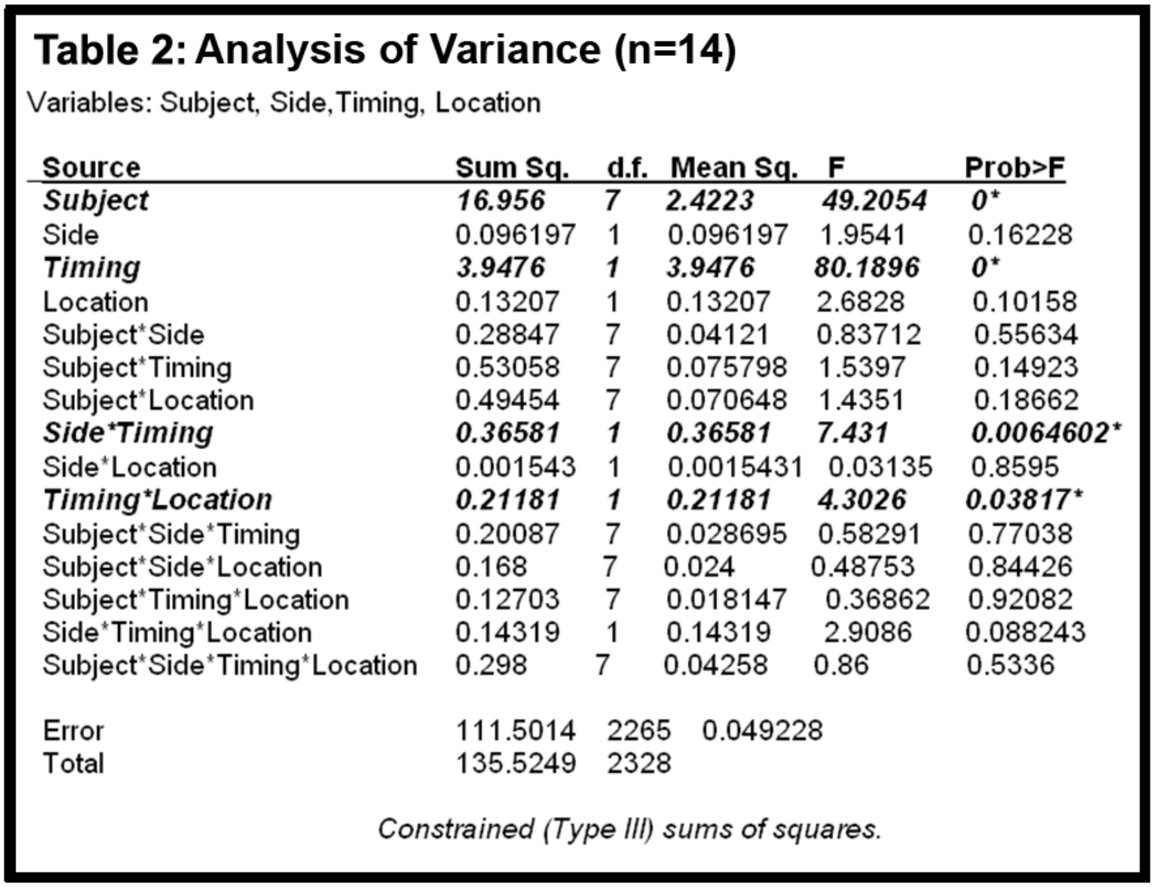


Table 2: Analysis of Variance (n=14)

Variables: Subject, Side,Timing, Location

Source	Sum Sq.	d.f.	Mean Sq.	F	Prob>F
Subject	***16.956***	***7***	***2.4223***	***49.2054***	***0****
Side	0.096197	1	0.096197	1.9541	0.16228
Timing	***3.9476***	***1***	***3.9476***	***80.1896***	***0****
Location	0.13207	1	0.13207	2.6828	0.10158
Subject*Side	0.28847	7	0.04121	0.83712	0.55634
Subject*Timing	0.53058	7	0.075798	1.5397	0.14923
Subject*Location	0.49454	7	0.070648	1.4351	0.18662
Side*Timing	***0.36581***	***1***	***0.36581***	***7.431***	***0.0064602****
Side*Location	0.001543	1	0.0015431	0.03135	0.8595
Timing*Location	***0.21181***	***1***	***0.21181***	***4.3026***	***0.03817****
Subject*Side*Timing	0.20087	7	0.028695	0.58291	0.77038
Subject*Side*Location	0.168	7	0.024	0.48753	0.84426
Subject*Timing*Location	0.12703	7	0.018147	0.36862	0.92082
Side*Timing*Location	0.14319	1	0.14319	2.9086	0.088243
Subject*Side*Timing*Location	0.298	7	0.04258	0.86	0.5336
Error	111.5014	2265	0.049228		
Total	135.5249	2328			

Constrained (Type III) sums of squares.

4. Discussion

The aims of the present study were threefold. First, we sought to validate our laboratory fMRI finding that discrete functional clusters exist within classic Wernicke's territory. Second, we sought to further delineate the nature of the facilitation effect by targeting dorsal and ventral Wernicke's areas and their homologues with fMRI-guided TMS. Lastly, we sought to determine the efficacy of using fMRI-guided TMS for clinical purposes, such as for mapping and confirming essential language areas in neurosurgical candidates.

Our fMRI speech and language mapping results add to the growing position that there are observable subdivisions within classically-defined Wernicke's area. In most subjects, ventral Wernicke's area was observed bilaterally while dorsal Wernicke's area was only active on the left side (see Table 1). Our group TMS results are consistent with our fMRI results in that picture naming latency was decreased (i.e., naming was facilitated) when TMS was applied to both left and right-sided ventral Wernicke's area as well as left-sided dorsal Wernicke's area (see Figures 9 and 10). This result is consistent with previous studies that used only the dorsal site as a target (Mottaghy, Sparing et al. 2006) and provides new evidence that stimulating the ventral site also produces the facilitation effect.

As mentioned previously, the suspected mechanism of action for this effect is that TMS leads to a preactivation of the region stimulated and/or the areas to which the region is connected. This theory is based on the fact that the facilitation effect disappears when high intensity stimulation, known to have a debilitating effect (Pascual-Leone, Gates et al. 1991), is used. Assuming this theory to be true, producing a facilitation effect does not necessarily mean that the targeted area is *directly* involved in the task at hand. Instead, this area could be connected to a different region or group of regions that are involved in the task. Recent theories (see below) of cortical speech and language organization provide a nice model in which to frame these results.

4.1 ***Relation to modern theories of the neural organization of speech and language***

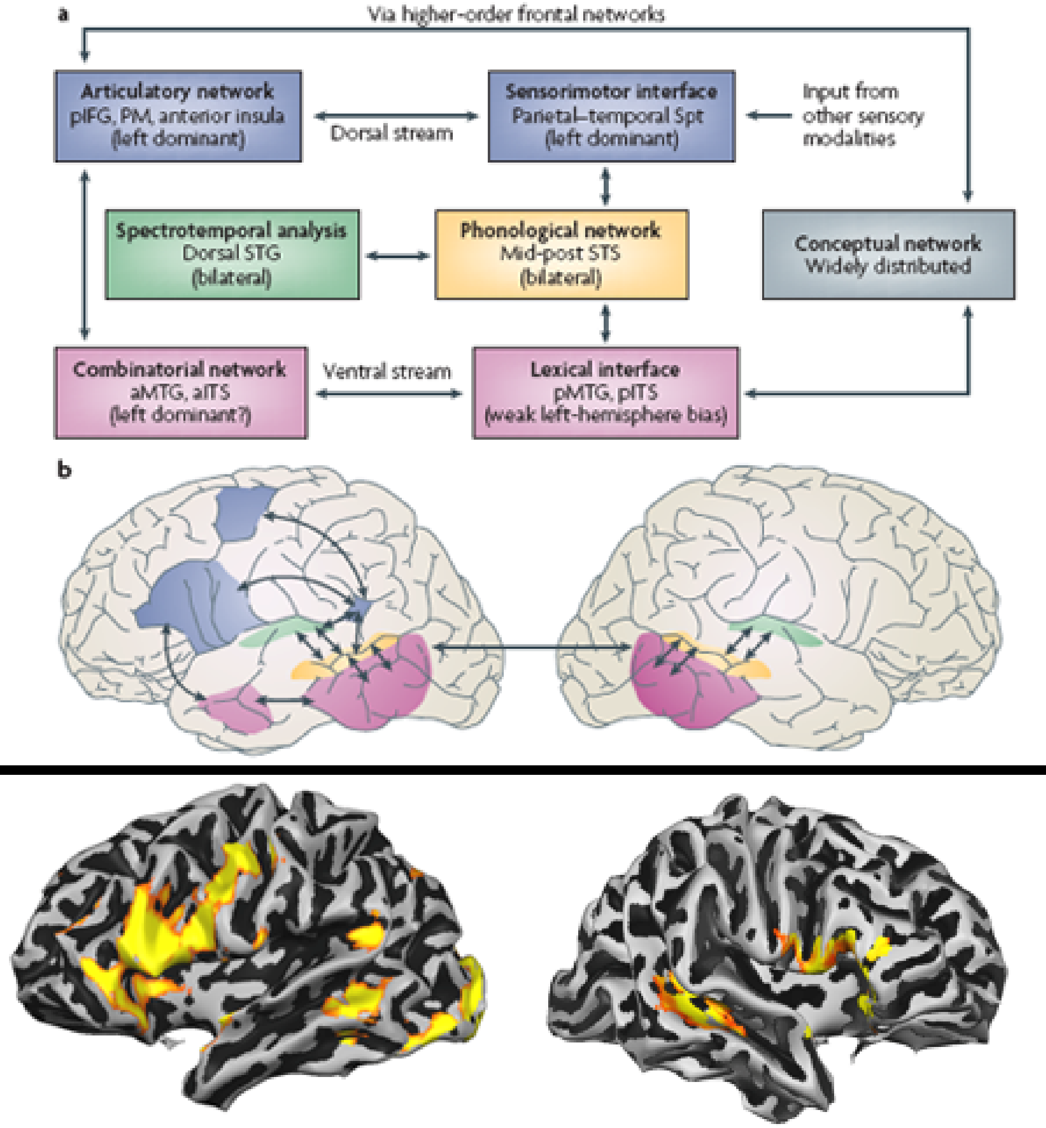
One recent model of auditory processing that encapsulates the bilateral, widespread nature of the language system supported by functional neuroimaging is the dual-stream model (Hickok and Poeppel 2004; Poeppel and Hickok 2004; Hickok and Poeppel 2007). According to the dual-stream model, auditory processing is organized into two streams, similar to the visual system. In the visual system, the dorsal and ventral visual streams comprise the “where” and “what” pathways, respectively (Ishai, Ungerleider et al. 2000). The ‘where’ pathway, which extends from early visual areas up toward various occipito-parietal areas, is involved in determining the spatial relationship between an object and its environment, such as when tracking moving objects. The ‘what’ pathway travels ventrally from the early visual areas into occipito-temporal regions located adjacent to Wernicke’s territory and is thought to be involved in attaching semantic knowledge to visual information (Ungerleider and Mishkin 1982; 2000).

In the dual-stream model of auditory processing, speech comprehension is divided into speech perception and speech recognition. Speech perception refers to sub-lexical processing, such as syllable discrimination, or the acknowledgement that a certain auditory stimulus is intelligible speech. For instance, while we may not understand a foreign language, we are almost always able to determine that we are listening to some form of verbal communication. Speech recognition, on the other hand, requires lexical access, or retrieving from memory either the meaning of a word.

In the dual-stream of auditory processing (Figure 13, top panel), the dorsal stream includes a region of the angular gyrus as well as frontally-located motor and language-related regions. This pathway is said to mediate sound to action, or the auditory-motor component of language, and is left-side dominant. The dorsal stream is conceptualized as a multimodal sensorimotor interface that brings semantic information received from different sensory modalities into the articulatory network, a necessary component of speech. We suspect that dorsal Wernicke’s area is part of the unilateral dorsal stream (Figure 13, bottom panel).

Figure 9: Comparison of the Dual-Stream model of auditory speech processing and fMRI picture naming

(reprinted from Hickok and Poeppel 2007)



Group picture naming results, current study ($p < .00001$)

The ventral stream, on the other hand, includes areas of the superior temporal gyrus known to be involved in the processing of speech and non-speech sounds (Binder, Frost et al. 1996; Rauschecker 1998; Binder, Frost et al. 2000; Wise, Scott et al. 2001;

Price, Thierry et al. 2005; Zaehle, Jancke et al. 2007). This area is the site of the phonological network, a bilateral region involved in providing sub-lexical access. We suspect that bilateral ventral Wernicke's area is part of the ventral stream (Figure 13, bottom panel).

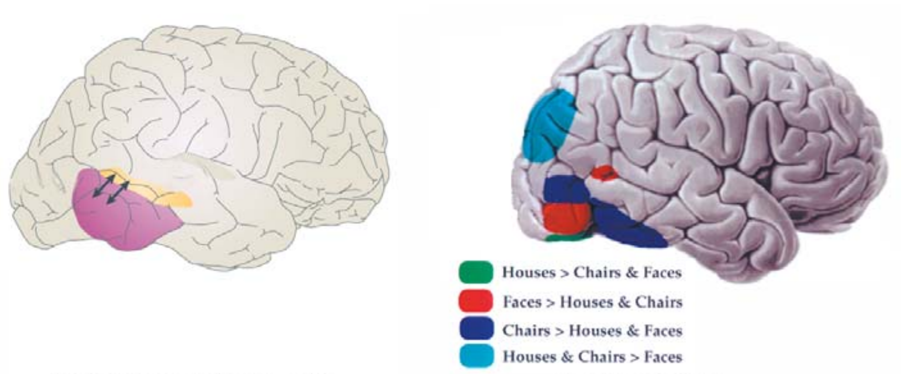
More evidence for the dual-stream model can be derived from studying lexical agraphia, or the inability and/or the loss of the ability to spell (Henry, Beeson et al. 2007). In particular, cognitive and academic testing of brain-damaged and learning disabled individuals has led to evidence suggesting distinct neural substrates for two distinct 'spelling' routes, a lexical and a sub-lexical route. One can either spell a word by accessing from memory the correct spelling (lexical route), or they can sound the word out using the phonological rules of the English language (sub-lexical, or phonological route). Since the English language contains a significant amount of irregular words, or those words which do not 'play by the rules', using the phonological route alone will result in a disproportionate amount of spelling errors when spelling irregular words (i.e. the word 'tomb' spelled phonetically would be toomb). Relying on the lexical route will lead to a disproportionate amount of spelling errors for all words that are unfamiliar, including pronounceable nonwords, such as 'flib'.

Accordingly, the lexical route is memory based while the sub-lexical route is rule-based. More specifically, the lexical route is involved with the spelling of known words, or those words which are already in one's lexicon. The sub-lexical route, on the other hand, relies on one's knowledge of the phoneme-grapheme relationship of the English language. With regards to the neural substrates of the two proposed routes, the lexical route has been associated with the the left posterior inferior temporal cortex, which is located just inferior to ventral Wernicke's area. This area is represented in 'pink' in Figure 11 , and has been shown to be bilateral with a weak left-sided bias (Rapcsak and Beeson 2004). The sub-lexical, or phonological route is associated with the posterior middle temporal gyrus. This region, which is thought to be completely bilateral is represented in yellow region in Figure 11.

4.1.2 ***A need for multimodal imaging studies***

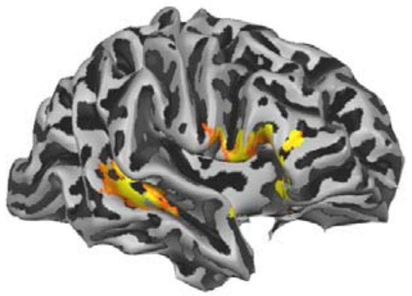
Though the anatomy of the dual-stream model is similar to the anatomy of our results, the modality of investigation is entirely different. The duel-stream model is a model of auditory processing. In the present study, word labels were attached to visual, not auditory stimuli. Nonetheless, we suspect that the middle temporal areas that are active in these studies are the same areas implicated in the lexical interface and/or phonological network of linguistic processing. While many imaging studies have demonstrated activity in middle temporal regions for visual object and face processing (Ishai, Ungerleider et al. 2000; Haxby, Gobbini et al. 2001; Mechelli, Price et al. 2004) (see Figure 14), these studies are mostly focused on the perception of visual form, not lexical access to visually presented stimuli. As a result, their experiments are designed to detect differences between the processing of different categories of objects, and their analyses become restricted to inferior occipito-temporal regions. Future studies are needed to examine the extent to which the ventral stream of auditory processing overlaps with the ventral stream of visual object processing. One question of interest that remains to be studies directly, are the regions that are involved in providing lexical access to auditory stimuli the same regions responsible for providing lexical access to visual stimuli?

Figure 10: Ventral Wernicke's area activation compared across different studies. A comparison of right-sided regions associated with the recognition of auditory (left, top panel) and visual stimuli (right, top panel) and with visual picture naming (bottom panel). Evidence exists implicating analogous areas on the left side for both auditory and visual processing.



Auditory recognition results
From Hickok and Poeppel (2007)

Passive viewing
From Ishai, Ungerleider et al. (2000)



Covert Object Naming
Results from current study.

4.2 ***Potential clinical applications***

We propose using the observed pattern of language-related activity as a way of determining hemispheric language dominance. According to this method, the identifying characteristic of the language-dominant hemisphere is the presence of dorsal and ventral Wernicke's areas with the absence of dorsal Wernicke's area in the contralateral hemisphere, which was the case for 90% of subjects. As highlighted in the present study, one potential way to confirm the presence of dorsal and ventral Wernicke's areas is to use fMRI with TMS and/or DTI.

The present study fell short of clinical applicability since in order to demonstrate a significant TMS facilitation effect, group results were needed. While this is acceptable when answering basic research questions, it is not sufficient for clinical applications which require individual results to be significant. One way to increase the power of the present study would be to increase the effectiveness of TMS by modifying the stimulation parameters, perhaps by using repetitive TMS (rTMS). rTMS utilizes repeated application of TMS pulses at regular intervals which acts to amplify the net effect of TMS (Maeda, Keenan et al. 2000).

Another way to improve the current paradigm for future studies is to increase the power of the dependent variable (i.e., naming task RT). Increasing the power of the dependent variable could be accomplished by using 'overlearned' instead of 'unique' stimuli. During the TMS portion of the current study, the stimulus set was comprised of unique pictures (i.e., participants did not receive a duplicate image) since previous studies that used overlearned stimulus sets had already failed to produce significant within-subject results. Moreover, using unique stimuli seemed appropriate for a clinical application since you may not always have the opportunity to train a patient to perform a task. One major downfall of using unique stimuli is that response variability increases, which increases the minimum number of stimuli required to show a desired effect. Accordingly, the present study used 600 unique pictures for each participant, (80 pictures for each experimental run). Past studies that used overlearned stimuli repeated blocks of the same 20 pictures throughout the entire experiment (Topper, Mottaghy et al. 1998). Since the magnitude of the observed facilitation effect in the present study was nearly identical that of past studies, the extra time and effort was not justified.

4.1.2 ***Incorporating Diffusion Tensor Imaging (DTI)***

Diffusion Tensor Imaging (DTI) is an MRI imaging sequence that makes it possible to measure and trace the brains white matter pathways. Analyzing white-matter anatomy in relation to the location of fMRI activation clusters is one way to examine the extent to which white-matter structure is related to fMRI/TMS results. Perhaps the facilitation effect occurs only when there is a cross-callosal connection at ventral Wernicke’s area, Broca’s area or both? Future fMRI and/or TMS studies could use DTI to better characterize and interpret their results. In particular, these studies should be designed to test for correlations between fMRI activity profile, DTI fiber pattern and TMS results.

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