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Lexical ambiguity resolution in Wernicke's area and its right homologue.

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Abstract

Introduction: There is an academic dispute regarding the role of the right hemisphere in language processing. TMS was used to test the hypothesis that Wernicke's area processes dominant meanings ("teller") whereas its right homologue processes subordinate meanings ("river") of ambiguous words ("bank"; Jung-Beeman, 2005).

Methods: Participants were asked to make a semantic decision on ambiguous words that were followed either by unrelated words or by words associated with their dominant or subordinate meanings. A 10Hz TMS train was applied on each trial over CP5 (left Wernicke), CP6 (right Wernicke) or Cz (vertex) scalp positions, and was synchronized with the word presentation.

Results: Accuracy and d' analysis revealed a TMS LOCATION by MEANING interaction. TMS over Wernicke's area resulted in more accurate responses and higher sensitivity to dominant meaning blocks compared to stimulating the right Wernicke's area and the vertex. In contrast, TMS over the right Wernicke's area resulted in more accurate responses and higher sensitivity to subordinate meaning blocks, compared to stimulating the left Wernicke's area and the vertex.

Conclusion: The left and right Wernicke's areas function as processors of dominant and subordinate meanings of ambiguous words, respectively. While previous research methods have yielded indecisive results, TMS proved to be a useful tool in demonstrating a causal role of the two brain regions in a double dissociation design with healthy subjects.

Key words: Wernicke's area, ambiguous, TMS, language, laterality

1. Introduction

More than a century ago, Broca (1865) and Wernicke (1874) argued that language is mainly a left hemisphere (LH) function. Their clinical findings showed that the left but not the right hemisphere lesions caused severe language impairments such as the inability to understand or generate speech. More recently it has been shown that damage to the Right Hemisphere (RH) in the homologue areas usually results in subtle language deficits such as impaired comprehension of jokes (Gardner et al., 1975) or metaphors (Winner and Gardner, 1977).

Numerous models have been put forward to account for hemispheric differences (Dien, 2008) with some overlap between theories. In the current study, we define hemispheric differences in semantic processing as characterized by a tendency of the LH to process stimuli analytically (Levy-Agresti and Sperry, 1968) when dealing with routine (Goldberg and Costa, 1981), frequent (Sergent, 1982) and salient meanings (Giora, 2007). By contrast, the RH processes in a Gestalt mode (Levy-Agresti and Sperry, 1968) and may perceive novel (Goldberg and Costa, 1981), infrequent (Sergent, 1982) and non-salient (Giora, 2007) aspects of language. Jung-Beeman (2005) suggested that in the RH, widespread groups of interconnected neurons are activated by lingual stimuli, whereas such stimuli activate a more restricted group of neurons in the LH. This restricted activation enables fine encoding in the LH which is appropriate when the precise, frequent meaning of a term is required. In a complementary fashion, the coarser processing in the RH may be useful when words are remotely associated (Giora, 2007). However the evidence to support the fine-coarse coding theory (Jung-Beeman, 2005) is correlational at best since it is drawn from the few existing fMRI studies.

As a test case to reveal potential hemispheric differences in semantic processing we studied ambiguous words that have a subordinate meaning in addition to their dominant, frequent meaning. Based on brain lesion observations (Gardner and Brownell, 1986) and divided visual field studies with healthy participants (Burgess and Simpson, 1988) it has been suggested that the RH has a special role in lexical ambiguity resolution. However, these research methods were unable to identify the specific region within the RH that participates in the process.

In contrast, today's imaging studies can contribute to finer localization of RH language centers. Rodd et al. (2005) contrasted auditory sentences containing ambiguous words (The *shell* was *fired* towards the *tank*) with matched sentences that did not contain ambiguous words. Although the study did not distinguish between subordinate and dominant meanings, the results showed that along with Broca's region and Wernicke's area (in the LH), the right homologue of Broca's region (the triangular and opercular parts of the right inferior frontal gyrus) were also activated by ambiguity. Since activation in the regions of interest was the dependent variable, it is impossible to determine whether the ambiguous stimuli caused RH activity which resulted in comprehension, or whether the ambiguous stimuli caused RH activity but comprehension was achieved independently by another neuronal mechanism. EEG studies have revealed that ambiguous word processing modulates the N400 ERP component under certain contextual conditions. Sitnikova et al. (2003) showed that the N400 component is more negative for an incongruent context of ambiguous words than a congruent context (see also Titone and Salisbury, 2004). This interaction was found for healthy subjects, and not patients with schizophrenia, a disease known to cause impaired processing of ambiguous words (Chapman et al., 1976). While these studies are informative as to the timing of neuronal processes, they cannot establish clear cut causal inferences regarding the role of the neuronal generator of the N400 component and the observed behavior, or shed light on the locus of the function.

Transcranial Magnetic Stimulation (TMS) has been used to locate language brain centers in simple tasks such as picture naming that do not normally call for RH involvement, similar to intraoperative methods which are used to prevent postoperative aphasia (Duffau et al., 2002; Eisner et al., 1996; Herholz et al., 1997; Ojemann, 1979; Ojemann et al., 1989; Rutten et al., 2002).

Two noninvasive TMS procedures have been used to assess the functionality of Wernicke's area.. In one case, high frequency (20Hz) stimulation decreased latency when applied during a naming task immediately before each trial (Mottaghy et al., 1999; Sparing et al., 2001). By contrast a 10-minute low frequency (1Hz) TMS train applied prior to the task (picture-name verification) resulted in inhibition (Drager et al., 2004; Flöel et al., 2000; Knecht et al., 2002). This suggests that Wernicke's region is enhanced by event-related high frequency TMS delivered during a behavioral experiment, and inhibited by offline low frequency TMS. Note that the TMS effect depends on location, task, intensity and frequency (Bestmann, 2008). Repetitive high frequency protocols may result in language inhibition if applied over different brain regions (e.g.,Stewart et al., 2001), and similarly, low frequency offline protocols may yield a facilitation of language processing (Drager et al., 2004).

Both of these TMS protocols can be used to explore the causal role of brain regions. If language function is indifferent to neuronal activity in any brain region, then neither excitation nor inhibition of neurons in that region should alter behavior. Inhibitory and excitatory TMS effects can be thought of as higher and lower thresholds for neuronal activity in the stimulated region; Neuronal input which normally causes neurons to fire will not suffice if the threshold was elevated by inhibitory TMS, whereas weak neuronal input may result in action potentials if the threshold was lowered by excitatory TMS. We chose an event-related design to explore the spatial and temporal characteristics of semantic processing. Following previous studies with similar protocols, we predicted facilitation following CP5/CP6 high frequency event-related stimulation.

We used a semantic decision task where participants were asked to decide whether an ambiguous word was related or not to a subsequent word. The following word could be related to the dominant or subordinate meaning of the ambiguous word or not related at all.

2. Methods

2.1. Participants

Six female and 5 male students with no history of neurological illness participated after giving their informed consent. All were right handed (scoring at least 90 on the Edinburgh Handedness inventory (Oldfield, 1971) and native Hebrew speakers. Their sight was normal or corrected to normal, and their age ranged from 20 to 36 years. They received an fee equivalent to $ 40 for participating in the two hour experiment.

2.2. Design

A factorial 2 × 3 × 2 design was applied, with BLOCK MEANING (dominant, subordinate), TMS LOCATION (left Wernicke, vertex, right Wernicke) and RELATEDNESS (related, unrelated) as within subject factors.

2.3. Visual stimuli

A list of 60 ambiguous Hebrew words, whose dominant and subordinate meanings had been validated in previous studies (Faust and Kahana, 2002; Peleg and Eviatar, 2008) was used. Each ambiguous word was presented once with a dominant association, once with a subordinate association and between 1 to 3 times with an unrelated word, a different one in each trial. The unequal number of repetitions aimed to prevent subjects from guessing the remaining number of positive responses for a given stimulus (e.g., reasoning such as "since 'bank' appeared twice with related associations next it will appear with an unrelated word"). The association words were taken from Peleg and Eviatar (2008) matched on latencies in a simple lexical decision task involving 36 subjects. The stimuli were matched on the basis of RT given the lack of frequency norms in Hebrew. The words were presented in the center of the screen in Courier New , 18 such that the average stimulus subtended 3.47°.

2.4. TMS procedure

TMS was applied in accordance with conventional safety regulations (Wassermann, 1998) using a Super-Rapid Magstim stimulator with about 2T maximum output, and a figure- 8 coil (outer diameter 70 mm). The procedures were approved by the Bar Ilan University Ethics committee. Subjects wore a Lycra hat and were requested to place their hands on their thighs with the palms facing up. For each subject the optimal scalp location for induction of visible contraction of finger muscles was identified for each hemisphere. A single-pulse TMS was then applied at decreasing intensities over these sites to determine the motor threshold for each hemisphere, defined as the minimal intensity required to induce 6 visible motor responses out of 12 (Baudewig et al., 2001; Rusconi et al., 2005; Stewart et al., 2001). CP5 and CP6 scalp positions were then marked on the Lycra hat according to the EEG 10-20 system to indicate the stimulation sites to be used during the semantic task. These positions were correlated with the left and right Wernicke's areas, respectively (Flöel et al., 2000; Sparing et al., 2001). TMS was applied at 100% of the motor threshold intensity for the same hemisphere.

2.5. Apparatus and Procedure

Participants came to the lab twice, with a one- week interval between sessions. In each session, one hemisphere was stimulated twice, once in a dominant meaning block and once in a subordinate meaning block, where each block contained 40 trials. The second hemisphere was stimulated in the second session, in the same MEANING order. A control block was run in the middle of each session with half a block in the first meaning condition and the second half in the second meaning condition, while stimulating the vertex. Meaning order, location order and stimuli lists were counterbalanced across subjects.

The task was practiced in a 24 trial- session during the first session, with the same meaning order used throughout the experiment, with visual feedback for responses but without TMS. Six TMS trials followed for practice. The stimulus display was controlled by E-prime 1.1 software (Psychology Software Tools, Inc., PA, US). Each trial started with a fixation cross presented for 700msec, followed by an ambiguous word presented for 750msec, a 50msec blank screen, a 500msec fixation cross and presentations of an associated or an unrelated word for 190msec. A 500msec TMS train was applied at the onset of the association word. Responses where recorded for 1810msec following the second word offset during which a blank screen was displayed, followed by a 500msec gray screen presented as preparation for the next trial sequence (see Figure 1).

(Insert Figure 1 about here)

3. Results

Repeated measure ANOVAs were run separately for correct RT and accuracy, with BLOCK MEANING (dominant, subordinate), RELATEDNESS (related, unrelated) and TMS site (CP5, Cz, CP6) as within subject factors.

3.1 Accuracy

The main effect for BLOCK MEANING was significant with a higher accuracy rate for dominant (.92) compared to subordinate meaning blocks (.87; F(1,10=6.48, p=0.029). More importantly, the BLOCK MEANING by TMS LOCATION interaction was significant (F(2,20)=10.993 , p<.001). Planned comparisons revealed that LH stimulation increased accuracy rates in dominant meaning blocks compared to the other two locations (t(10)=3.92, p=.0029), whereas stimulating the RH increased sensitivity in subordinate meaning blocks compared to the other two locations (t(10)=2.81, p=.018); see Fig. 2A. No further effects were significant (p>.12).

3.2 Signal detection analysis

D' was calculated for the 3 TMS LOCATIONS × 2 MEANINGS for each subject. The MEANING × TMS LOCATION interaction was significant ($F(2,16)=8.01$, $p = .0039$) with no further significant results ($p>.16$). Planned comparisons revealed that LH stimulation increased sensitivity in dominant meaning blocks compared to the other two locations ($t(8)=2.81$, $p = .011$), whereas stimulating the RH increased sensitivity in subordinate meaning blocks compared to the other two locations ($t(8)=1.86$, $p = .049$); see Fig. 2B).

(Insert Figure 2 about here)

3.3 RT

The main effect for MEANING was significant ($F(1,10)=6.10$, $p=.033$) with faster responses for dominant (854msec) compared to subordinate meaning trials (926msec). The main effect for RELATEDNESS was also significant ($F(1,10) = 24.4$, $p< .001$). No further effects were significant. There was a trend toward a RELATEDNESS by MEANING interaction ($F(1,10)=3.30$, $p=.099$) with a greater advantage of dominant over subordinate blocks for related (85msec) than for unrelated trials (55msec). All the other main effects and interactions yielded p values over .4.

4. Discussion

The aim of the current study was to explore the involvement of the right homologue of Wernicke's area in the processing of subordinate meanings of ambiguous words. It has been claimed that the left and right hemispheres focus on processing the dominant and subordinate meanings of ambiguous words, respectively, however a causal relationship between the hemispheres and meaning types could not be established with certainty. We used TMS to demonstrate causal links between cortical areas and cognitive functions. Since we used a high frequency event related protocol which in previous studies of CP5 scalp position resulted in facilitation of behavior, we expected performance to be facilitated while stimulating the expert hemisphere for the same meaning condition. As predicted, responses in the experimental blocks that contained dominant meanings were more accurate when TMS was applied over Wernicke's area, as compared to stimulating the right homologue of the same area or the vertex. The opposite pattern emerged for subordinate meaning blocks, with more accurate responses when stimulating the right homologue of Wernicke's area compared to the other two locations. The interaction of BLOCK MEANING and TMS LOCATION was significant over and above the RELATEDNESS conditions; i.e., for related as well as for unrelated trials. This pattern of results implies that when subordinate meanings of ambiguous words are expected (which is a consequence of the block design), the RH is not only involved in deciding that a word pair is semantically associated but also in negating such an association when it is absent. This finding is intriguing since little is known about negation processes in the brain. It has been suggested that in the processing of complex language functions such as irony, which can be seen as a form of negation (Giora, 1995), the right hemisphere plays a role (Gardner and Brownell, 1986; Giora et al., 2000).

We argue here that the facilitative TMS effects we found suggest a causal role for the right and left Wernicke's areas in processing subordinate and dominant meanings of ambiguous words, respectively. When conceptualizing TMS effects as adding neuronal noise, an alternative interpretation might be that the TMS actually inhibited the stimulated areas. Their inhibition decreased inhibitions these areas might have over other areas (in a dis-inhibition mechanism), where these distant areas are involved in processing lexical ambiguity rather then the areas that were directly stimulated. However such interpretation is not supported by previous studies of Topper et al. (1998), where they found facilitation for picture naming while stimulating left Wernicke's area, which cannot be explained by inhibitory processes.

TMS applied to a single area can have either a positive or a negative effect depending on the rate of stimulation (Walsh and Rushworth, 1999). Causality, however, is always assumed when a significant TMS effect occurs (whether facilitative or inhibitory) as there is brain imaging evidence showing that TMS coincides with a critical epoch of cortical processing. Paus et al. (1997), for example, found an increase in cortical synaptic activity as indexed by increased regional cerebral blood flow (rCBF) in the cortex below the point of magnetic stimulation that had a facilitative effect on performance. In accordance, Silvanto and Muggleton (2008) suggested that TMS effect is increasing excitability of neurons rather then adding neuronal noise.

In terms of signal detection theory (Egan, 1975), stimulating the expert hemisphere (the LH in dominant blocks and the RH in subordinate blocks) increased sensitivity (d') to associations between words because both miss errors (related trials) and false alarm errors (unrelated trials) were reduced compared to the findings when stimulating the non-expert hemisphere and the vertex (Fig 2B.). The predicted double dissociation was found: TMS over Wernicke's area resulted in a more accurate detection of dominant meaning associations, whereas stimulating Wernicke's right homologue resulted in a more accurate detection of subordinate meaning associations.

It could be argued that the TMS over the RH location actually reduced RH activity but still increased accuracy for subordinate meanings by an increased activation of LH language. If so, RH stimulation should also facilitate dominant meaning processing in the LH, but in fact RH TMS yielded the lowest accuracy rates for dominant meaning blocks. If this trend, which was not significant in the current study, is found to be significant in future studies, this would imply that the right Wernicke's area is not only involved in processing subordinate meanings but also in suppressing dominant meanings in the left Wernicke's area.

The current study contributes to functional brain mapping by revealing, for the first time, the important role the right Wernicke's area plays in processing subordinate meanings of ambiguous words, and hence lends weight to Jung-Beeman's theory (Jung-Beeman, 2005). Rodd et al. (2005) did not specify this region as responsive to ambiguity in their fMRI study, but this could be due to the use of a different task and stimuli which involved sentential context where no distinction was made between dominant and subordinate meanings. It may also be that both right Broca (Rodd et al., 2005) and Wernicke's right homologues (the current work) participate in ambiguity processing but the fMRI only measured the input to the right Broca's region and not the source of the signal (Logothetis et al., 2001) that may have come from the right Wernicke's area (Matsumoto et al., 2004). A study combining TMS with EEG, or TMS with fMRI may shed light on this question of connectivity (Bestmann, 2008).

The current study only answers the "when" question to a limited extent. Accuracy was improved while five magnetic pulses were given at time 0, 100, 200, 300 and 400msec from target onset, showing that the activity of the left or right Wernicke's area (depending on the expected meaning) is important for the task during this time interval, which is congruent with previous EEG results (Sitnikova et al., 2003; Titone and Salisbury, 2004). In order to provide better time resolution in future experiments a single pulse design at various points in time could be used (Skarratt and Lavidor, 2006).

Since the meaning was manipulated between blocks, it is possible that participants noticed when set-shifting from responses to dominant meanings to a search for subordinate meaning was necessary. This shift from automatic, LH processing to global, RH processing can be seen as a top-down influence since the expectation of a certain stimulus leads to a different semantic interpretation of words. Since the frontal lobes are necessary for set-shifting (Konishi et al., 1998; Pantelis et al., 1999) the shift from LH to RH processing may take place in the frontal lobes. The finding that schizophrenia is characterized by deficits in frontal lobe functioning (Andreasen et al., 1992), together with impairments in set-shifting (Gold et al., 1997) and in subordinate meaning processing (Chapman et al., 1976), strengthens this hypothesis.

Individual differences in language lateralization were ignored in this study, but it may be worthwhile to check in future TMS studies whether individuals who have a RH dominance for language, as determined by fMRI or fTCD (Flöel et al., 2000), use their left Wernicke's area to process non-salient meanings. The paradigm can also be applied to explore abnormal brain asymmetry in schizophrenia. If the reported deficit in ambiguity processing of schizophrenic patients (Chapman et al., 1976) is a consequence of the inability to use the RH (Mitchell and Crow, 2005), stimulating the right, but not left Wernicke's area may temporarily restore the patients' subordinate meaning processing to normal. Further studies are needed to assess the precise effect of stimulation on brain activity. TMS interleaved with fMRI can reveal whether stimulation results in callosal inhibition, or possibly in intra-hemispheric facilitation of other language regions.

In summary, functional mapping was carried out by using a method that allowed for an inference of causality in healthy brains. The effect of stimulating the left and right Wernicke's areas was symmetric in nature. TMS induced neuronal activity in the left and right Wernicke's areas, which resulted in increased accuracy for dominant and subordinate meaning blocks, respectively. Further experiments should explore connectivity with other regions, better time resolution and possible medical applications.

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Figure 1.

An illustration of the timeline in a typical trial presenting a related trial in a subordinate meaning block. Each trial started with a fixation cross presented for 700msec, followed by an ambiguous word presented for 750msec (PEN in this example), a 50msec blank screen, a 500msec fixation cross and an associated or an unrelated word presented for 190msec (FARMER). A 500msec TMS train of 10Hz was applied with the onset of the association word. Responses where registered during 1810msec following the second word offset while a blank screen was displayed, followed by a 500msec gray screen presented as a pre-cursor for the initiation of the next trial sequence.

Figure 2.

Accuracy rates (A) and sensitivity (B) as a function of TMS LOCATION and BLOCK MEANING. Accuracy and d' were selectively modified by the magnetic stimulation. In dominant meaning blocks, Accuracy rates and d' were higher when the coil was placed over Wernicke's region compared to the other two locations, whereas in subordinate meaning blocks, Accuracy and d' were higher when the coil was placed over the right homologue of Wernicke's region compared to the other two locations. *p<0.05, **p<0.01. Error bars delineate standard errors, RT values in msec are detailed in the bottom of Fig 2A.

Figure
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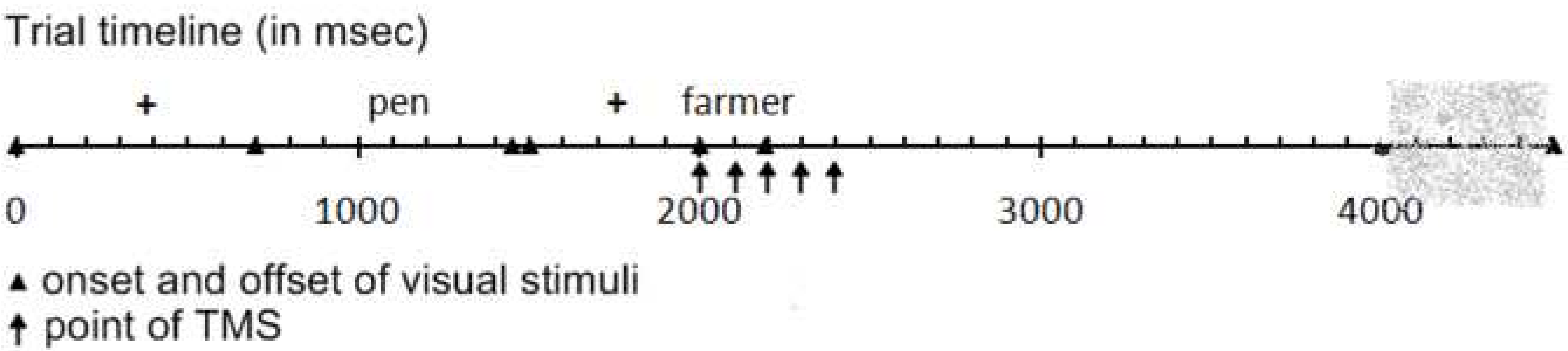

Figure
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