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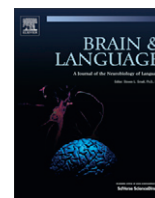
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Short Communication

Transient beneficial effects of excitatory theta burst stimulation in a patient with phonological agraphia after left supramarginal gyrus infarction

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ABSTRACT

We report a patient showing isolated phonological agraphia after an ischemic stroke involving the left supramarginal gyrus (SMG). In this patient, we investigated the effects of focal repetitive transcranial magnetic stimulation (rTMS) given as theta burst stimulation (TBS) over the left SMG, corresponding to the Brodmann area (BA) 40. The patient and ten control subjects performed a dictatorial words and nonwords writing task before, and 5 and 30 min after they received excitatory intermittent TBS (iTBS) over the left BA 40, the right hemisphere homologous to BA 40, the Wernicke's area, or the primary visual cortex.

iTBS over the left SMG lead to a brief facilitation of phonological non-words writing to dictation. This case study report illustrates that rTMS is able to influence, among other language functions, the phonological loading processes during the written language production in stroke patients.

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1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) seems to be particularly effective in promoting cortical plasticity in stroke (Lefaucheur, 2006; Talelli & Rothwell, 2006; Ziemann, 2005). A novel protocol of rTMS named theta burst stimulation (TBS) (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005) has several advantages in stroke patients because it employs low intensities, has a robust and long-lasting effect both in normal subjects (Di Lazzaro et al., 2005; Huang et al., 2005) and in chronic stroke patients (Di Lazzaro et al., 2006; Talelli, Greenwood, & Rothwell, 2007). Different patterns of delivery of TBS (continuous versus intermittent) produce opposite effects on synaptic efficiency of the stimulated cortex. The paradigm named intermittent TBS (iTBS) produces a consistent LTP-like effect, causing a prolonged increase of motor cortex excitability (Cooke & Bliss, 2006; Huang et al., 2005). If brain plasticity can be enhanced by these procedures then there are important implications for the development of therapeutical strategies based on TMS techniques in patients with acute stroke.

Phonological agraphia is a spelling disorder characterized by the inability to write nonwords (NW) to dictation, while the ability

to write words to dictation and to orally repeat words and NW is intact (Shallice, 1981). Phonological processing, short-term memory, and sequencing of phonemes have been reported to engage the left inferior parietal region, more precisely the Brodmann area (BA) 40 (Gelfand & Bookheimer, 2003; Jacquemot, Pallier, LeBihan, Dehaene, & Dupoux, 2003; Paulesu, Frith, & Frackowiak, 1993). The anterior-inferior part of the left supramarginal gyrus (SMG) has been pointed to as the lesion site underlying phonological agraphia (Roeltgen, Sevush, & Heilman, 1983).

We recently encountered a patient with pure phonological agraphia after infarction in the left SMG. This study aimed to evaluate in this patient the facilitatory effects of iTBS on a dictatorial writing task.

2. Results

The patient and ten control subjects performed a dictatorial writing task before, 5 min and 30 min after they were given excitatory intermittent TBS (iTBS) over the left BA 40, the right hemisphere homologous to BA 40, the Wernicke's area, or the primary visual cortex.

The 58-year-old right-handed man presented with speech disturbances. He complained of difficulties in finding appropriate words, even if these difficulties were not so severe as to cause problems in usual conversation. On hospital admission he was

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alert, with intact orientation. Language function examination revealed an impairment of repetition, while verbal fluency in spontaneous speech was preserved, except for occasional interruptions due to word-finding difficulties. Paraphasias were not observed. His spontaneous and dictatorial writing of words and short sentences showed no error in spelling. His auditory and reading comprehension was intact, even with long and complex sentences. The language deficit was thus compatible with conduction aphasia. No abnormality was found in tests of other cognitive functions, such as praxis, left–right orientation, calculation, finger naming, and spatial attention. The neurological examination was otherwise normal, including examination of the cranial nerves, motor and sensory functions, and reflexes.

Magnetic resonance imaging showed T_2 prolongation and restricted diffusion consistent with subacute stroke in the left SMG (Fig. 1A and B).

On the third hospital day a further assessment of language function was performed with the Italian version of the Western Aphasia Battery (WAB) (Kertesz, 1982). Spontaneous speech, auditory comprehension, and naming remained intact. The patient's oral repetition was significantly improved, the repetition of single words or shorter sentences was normal, while he had difficulties only in repeating sentences composed of 5 or more words. The WAB Aphasia Quotient was 98.4.

On the same day, more detailed tests of repetition in auditory and written forms were administered to evaluate his performance in repetition more thoroughly. First, the patient was asked to orally repeat 15 HFW, 15 LFW, and 15 NW immediately after each item was spoken to him. The word lists were matched for written word frequency, rated familiarity, imageability, and for number of letter and syllables. The syllable length of the words and NW ranged from 1 to 4. The patient repeated all words and NW correctly. Second, he was asked to write the words and NW as soon as he heard them. He correctly wrote, at the first examination, all 15 HFW words, 14 LFW, and 6 NW. These tests revealed a selective impairment of writing NW to dictation, compatible with phonological agraphia. The patient wrote NW syllables that were similar but different from what was spoken to him; he wrote words correctly, and made errors only in dictatorial writing, but not in oral repetition.

Ten age-matched control subjects of his education level have been examined and performed on the same dictatorial words and NW writing task.

The scores of the repetition tests of written high-frequency words (HFW), low-frequency words (LFW) and NW for the patient and the control group of 10 subjects are shown in Table 1. The

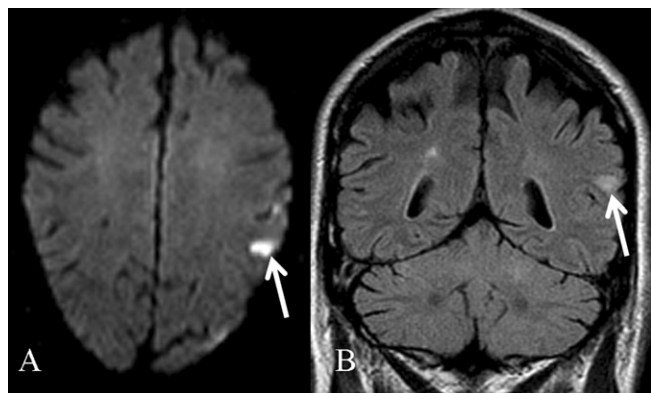


Fig. 1. (A and B): Magnetic resonance imaging showing restricted diffusion (A) and T_2 prolongation (B) consistent with subacute stroke in the left supramarginal gyrus (arrows).

prediction lower bound (1) was 0.968 against an observed value of $\pi_0 = 1$ for the patient in the HFW repetition test, 0.916 against $\pi_0 = 0.933$ in the LFW repetition test and 0.873 against $\pi_0 = 0.383$ in the NW repetition test. Therefore, we concluded that the patient showed statistically lower performances only in the NW repetition task. The results for all the NW repetition tests are illustrated in the Fig. 2.

Estimation of model (2) showed that only the effect of ID was statistically significant ($\chi^2 = 287.743$, $df = 1$, $p < 0.001$) with $\beta_{ID}^D < 0$, in accordance with an overall lower performance of the patient in the NW tests when compared to the control group. Collapsing: (i) SITE = 2 and SITE = 3 with SITE = 4 (i.e. $\beta_2^{SITE} = \beta_3^{SITE} = 0$) and (ii) TIME = 2 with TIME = 0 (i.e. $\beta_2^{TIME} = 0$) was supported by the data as shown by $\chi^2 = 0.5469$, $df = 3$, $p = 0.909$. Note that (i) corresponds to the similar performances in NW repetition tasks after iTBS on right BA 40, Wernicke's area and visual cortex, while (ii) reflects the disappearance of the iTBS effect at TIME = 2.

The model with SITE as indicator of left BA 40 and TIME as indicator of T_1 showed a significant and positive coefficient for the interaction between SITE and ID ($\chi^2 = 4.5667$, $df = 1$, $p = 0.0326$), confirming that iTBS on left BA 40 increases the patient's performance in the NW repetition test. The increase was clearly due to the test score at TIME = 1 (Fig. 2), as shown by the significant and positive three-way interaction among SITE, ID and TIME ($\chi^2 = 4.9929$, $df = 1$, $p = 0.02545$). A similar conclusion can be drawn by evaluating the Pearson residuals of model (2), i.e. the difference between the score and the predicted number of successes divided by the binomial standard deviation (Agresti, 2002). The score of the patient at TIME T_1 and SITE left BA 40 had a statistically high residual (2.566), indicating that model (2) fitted this observation poorly. Therefore, we concluded that iTBS on left BA 40 determined a significant improvement at T_1 of the patient's performance in the NW repetition test, but failed to affect his performance at T_2 and at all sample times when applied on right BA 40, Wernicke's area and visual cortex (see Table 1). The patient was re-tested and similar results in the NW repetition test were obtained in the second experimental session (see Table 1). Therefore, the temporal order of the task presentation did not alter the conclusions drawn above.

3. Discussion

Aphasic disturbances can result from stroke affecting these cortical regions (of the dominant hemisphere) that are involved in language processing. The cortical reorganization which is associated with language recovery after stroke is partly unknown. Late recovery from aphasia after a focal lesion can also be attributed to a partial lesion effect, with recovery of perilesional tissue to support impaired language functions. Indeed, it has been demonstrated that even limited salvage of peri-infarct tissue with acute stroke treatments will have an important impact on the rehabilitation of language and other cognitive functions (Warburton, Price, Swinburn, and Wise, 1999). Perilesional activation and reactivation of the affected regions of the left hemisphere were correlated with the efficacy of language rehabilitative therapy (Léger et al., 2002). Since TBS is a non-invasive way of producing potent changes in cortical excitability, and experimental studies suggest that brain hyperexcitability may positively influence recovery by facilitating activity-dependent plastic change (Hagemann, Redecker, Neumann-Haefelin, Freund, & Witte, 1998), it is reasonable that this approach might demonstrate useful in promoting also language recovery.

For neurolinguistic correlates, the left anterior–inferior SMG has been suggested as the anatomical substrate for phonological agraphia (Roeltgen et al., 1983). However, the lesion localization in previous described patients is quite variable; phonological

Table 1
Performances in the tests of repetition in written forms. Bold type indicates abnormal values (significant differences from control subjects). Italic type indicates observations with high Pearson residuals in the estimation of model (2).

	Site	Left BA 40									Right BA 40								
		HFWD			LFW			NW			HFWD			LFW			NW		
		T ₀	T ₁	T ₂	T ₀	T ₁	T ₂	T ₀	T ₁	T ₂	T ₀	T ₁	T ₂	T ₀	T ₁	T ₂	T ₀	T ₁	T ₂
Controls	Mean	14.9	14.8	14.9	14.5	14.6	14.6	14.1	14.0	14.0	14.9	14.9	14.8	14.4	14.4	14.6	14.2	14.1	14.0
	s.d.	0.32	0.42	0.32	0.53	0.52	0.52	0.57	0.47	0.82	0.32	0.32	0.42	0.52	0.52	0.52	0.42	0.57	0.47
Patient	Test	15	15	15	14	14	14	6	12	7	15	15	15	14	14	14	6	6	6
	Re-test	15	15	15	14	14	14	8	13	8	15	15	15	14	13	14	8	6	8
		Wernicke's area									Visual cortex								
Controls	Mean	14.9	14.8	14.8	14.6	14.5	14.7	14.2	14.3	14.3	14.9	14.9	14.8	14.7	14.7	14.7	14.2	14.4	14.3
	s.d.	0.32	0.42	0.42	0.52	0.53	0.48	0.42	0.48	0.48	0.32	0.32	0.42	0.48	0.48	0.48	0.63	0.52	0.48
Patient	Test	15	15	15	14	14	14	5	6	6	15	15	15	14	14	14	6	6	6
	Re-test	15	15	15	14	14	14	7	8	8	15	15	15	14	14	14	8	8	8

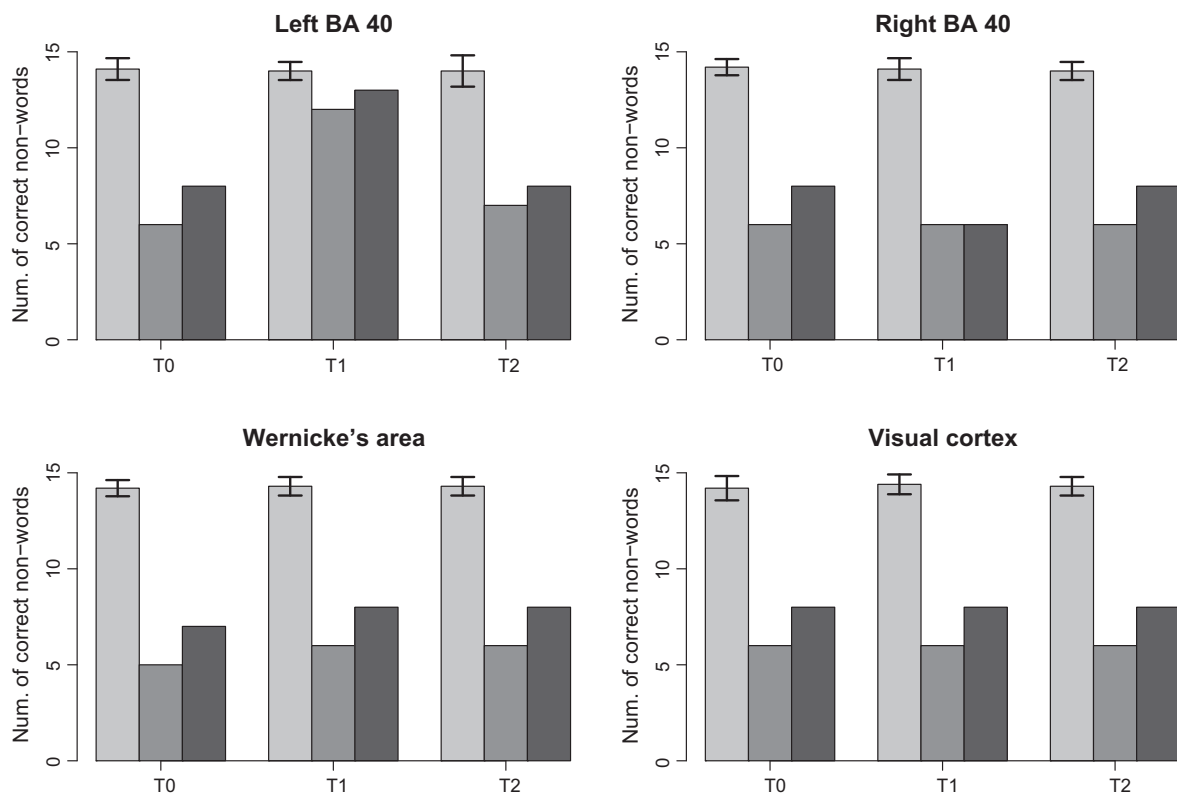


Fig. 2. Graphic showing the number of non-words (NW) correctly written by the controls (mean \pm s.d., light gray), and by the patient in the first dictational writing test (gray) and in the second dictational writing test (dark gray). Legend: T₀ = at baseline; T₁ = 5 min after intermittent theta burst stimulation (iTBS); T₂ = 30 min after iTBS.

agraphia has been reported following a large right frontal infarction, superior temporal and anterior parietal destruction (Bolla-Wilson, Speedie, & Robinson, 1985), an extensive left perisylvian infarction (Shallice, 1981), a left insula and basal ganglia infarction (Kim & Na, 2000), a focal left anterior insulo-opercular infarction (Marien, Pickut, Engelborghs, Martin, & De Deyn, 2001) and a superior temporal gyrus infarction (Kim, Chu, Lee, Kim, & Park, 2002). Alexander and colleagues suggested (1992) that phonological agraphia could be produced by lesions in a wide range of perisylvian cortical regions.

Furthermore, there is considerable variability in the clinical manifestations (Iribarren, Jarema, & Lecours, 2001; Roeltgen et al., 1983; Shallice, 1981). Some patients showed additional difficulties in oral repetition of NW (Roeltgen et al., 1983), while others had serious problems in writing real words and NW to dictation

(Kim & Na, 2000; Marien et al., 2001; Roeltgen et al., 1983). One patient (Bud & Kertesz, 1982) showed significantly higher performance in writing words than NW to dictation, but oral naming was extremely poor. Our patient showed no impairment in phonological input processing and phonological output processing, as evidenced by normal performance on oral repetition of NW; the deficit was limited to phonological writing to dictation.

The TMS effects in the present case, in which a selective lesion of left SMG was associated with phonological agraphia with little or no impairment in other aspects of the linguistic functions, substantiate the view that this area plays an important role in phonological linkage of auditory input with orthographic output, as needed for writing NW to dictation.

The most salient finding of this study was that iTBS of the left SMG, corresponding to left BA 40, has an impact on the phonolog-

ical agraphia which results in an improved ability to write NW to dictation.

Focal magnetic stimulation when delivered over left BA 40 may be able to facilitate the phonological route involved in writing process (since NW have no lexical or semantic representation). It has been suggested, (Roeltgen et al., 1983) that this phonological route is mediated by a segmentation process, in which syllable sequences of words or NW are broken down into phonemes, and the phoneme-to-grapheme conversion, in which the segmented phonemes are translated into graphemes. The selective loss of either of these two processes or both may lead to phonological agraphia. RTMS techniques may be thus able to reverse the selective impairment in associating input phonological representations with output orthographic representations.

Our findings are in agreement with previous studies (Huang et al., 2005) reporting that TBS effect remained significant within 5–10 min after stimulation. After 30 min a facilitation of phonological writing to dictation was no longer detectable. Since the fact that we did not confirm the site of stimulation by the use of other methods such as MRI, there still remains the possibility that the observed effect might be explained by an inadvertent activation of other cortical areas such as the superior temporal cortex or the sensory cortex. But the facilitative effect appeared to be specific for stimulation of the left SMG, because we did not find any changes after stimulation the right-hemisphere homologous to the BA 40, the Wernicke's area, or of the primary visual cortex.

According with the interhemispheric competition model, the right hemisphere homologous to the BA 40 may be overactivated, revealing maladaptive plasticity or the breakdown of inter-hemispheric control within the neural network for this language task. We found a slight, but statistically not significant, worsening of the repetition performance at the second examination. The application of iTBS on the right BA 40 might further enhance the relative hyperactivity of this region, however after a single session the functional effect seems to be irrelevant.

Even if stereotaxic placement of the coil provides best accuracy, using the 10–20 system for TMS positioning is an easily applicable in its practical use at low cost and may reach desired cortex regions on a larger scale level (Herwig, Satrapi, & Schönfeldt-Lecuona, 2003). When targeting TP3 (a not standard electrode position midway between the left temporal and left parietal electrode sites) mainly the SMG and the angular gyrus (corresponding to BAs 40 and 39 respectively), were reached. In one study (Koessler et al., 2009), the CP5 electrode site corresponded to SMG; however, according to the literature, this site correlates best with the location of Wernicke's area (among others Fiori et al., 2011; Fuggetta, Rizzo, Pobric, Lavidor, & Walsh, 2009; Harpaz, Levkovitz, & Lavidor, 2009; Homan, Herman, & Purdy, 1987; Jennum, Friberg, Fuglsang-Frederiksen, & Dam, 1994).

On the other hand, the range of mismatch for targets identified by MRI compared to the 10–20 system is about 2 mm in the three spatial dimensions *x*, *y* and *z* (Herwig et al., 2003). Therefore, given the patient's very circumscribed lesion, it is plausible that the actual lesion site was not directly stimulated. However, it is reasonable to hypothesise that behavioral improvement was mediated by facilitation of activity in spared perilesional brain regions rather than in the infarcted tissue of the lesion itself.

Moreover, it should be considered that iTBS may need modification to produce maximal effects when applied to non-motor areas of cortex (Franca, Koch, Mochizuki, Huang, & Rothwell, 2006).

Despite these limitations, this preliminary case report study provides further evidence that it is possible to improve performance on a language task by means of external stimulations applied to the damaged brain. This finding highlights the potential value of TBS for non-invasively investigating language function in humans. TBS is able to influence many language functions, includ-

ing phonological processes in this condition reflecting a disconnection within the phonological writing system. Thus, TMS techniques may also contribute to a better understanding the neurolinguistic mechanisms for writing.

However, there is currently no evidence that these intriguing task-specific improvements are persistent or have any impact on real-life communication abilities. Anyway, our results point to a preservation of cortical tissue capable of supporting the phonological route of writing. iTBS could thus be applied to the perilesional cortex as a sort of "recovery stress test" evaluating its potential to support lost functions. Further studies are needed in order to establish whether TBS-induced changes can produce functionally relevant clinical changes and whether these changes can be enhanced and transformed into longer lasting and clinically relevant changes by means of repeated TBS sessions and by combining TBS with rehabilitation.

4. Methods

4.1. Magnetic stimulation

Magnetic stimulation was performed using a high-power Magstim 200 magnetic stimulator (The Magstim Company Ltd, Whitland, UK). A figure-of-eight coil with external loop diameters of 9 cm was held over the motor cortex at the optimum scalp position to elicit motor evoked potentials (MEPs) in the contralateral first dorsal interosseous (FDI) muscle. The induced current flowed in a posteroanterior direction.

We first evaluated bilaterally threshold of MEPs, which reflect the excitability of motor cortex, and the latency of MEPs, that reflects the conduction along the corticospinal tract. RTMS was delivered by using a high frequency magnetic stimulator (Magstim Rapid, the Magstim Company Ltd., Whitland, UK) connected to a standard Magstim figure-of-eight coil. The coil was positioned tangentially to the skull, with the handle parallel to the sagittal axis and pointing occipitally. For the stimulation of the left SMG the coil was centered over TP3 of the International 10–20 System (Herwig et al., 2003). When targeting TP3, mainly the SMG and the angular gyrus (corresponding to BAs 40 and 39 respectively), were reached. According to the literature, the BA 40 correlates best with the location of left SMG (Herwig et al., 2003).

To evaluate the specificity of the TBS effect, the patient and the normal controls were given iTBS, on separate days, over the left BA 40, the right hemisphere homologous to BA 40, the Wernicke's area, or the primary visual cortex. The homologous area of the right hemisphere was stimulated over TP4. For the stimulation of Wernicke's area, the coil was centered over CP5 of the International 10–20 System (Homan et al., 1987; Jennum et al., 1994). The primary visual cortex was stimulated at the occiput (Amassian et al., 1989).

The stimulation intensity was defined in relation to AMT (measured using the biphasic stimulator); an intensity of 80% AMT was used. AMT was defined as the minimum stimulus intensity that produced a liminal MEP (about 200 μ V in 50% of 10 trials) during isometric contraction of the tested muscle (Rothwell et al., 1999). We used the iTBS protocol in which 10 bursts of high-frequency stimulation (3 pulses at 50 Hz) were applied at 5 Hz every 10 s for a total of 600 pulses.

For each stimulation site the above mentioned dictational writing test was administered at baseline (T_0), 5 min after iTBS (T_1), and 30 min after iTBS (T_2). The same list of words, with their order of presentation varied systematically, was used. The mean outcome measures were the number of words and NW correctly written. The sequence of stimulation was: Wernicke's area, left BA 40, visual cortex, right BA 40.

The patient was re-tested 4 weeks later. The order of task execution was different from the first examination, to confirm that the results are not due to the order of presentation.

In this second experimental session the temporal order of the iTBS application was: visual cortex, right BA 40, left BA 40, Wernicke's area.

The patient and the healthy subjects provided informed consent before participation in the study, which was performed according to the recently updated safety and application guidelines (Rossi, Hallett, Rossini, Pascual-Leone, & The Safety of TMS Consensus Group, 2009), and approved by the Ethics Committee.

4.2. Statistical analysis

In order to assess whether the performances of the patient in the repetition tests in written forms were statistically lower than those of the control group, we derived prediction lower bound for the probability π_0 of writing words/NW correctly at time T_0 based on the 10 controls, then we checked if the corresponding values of the patient were smaller than the prediction lower bound. If this was the case, we drew the conclusion that the patient has significantly abnormal lower prediction and he cannot be assimilated to a healthy subject. For each repetition test (HFW, LHW and NW) we considered four observations at T_0 , each one consisting of the outcome in 15 Bernoulli trials with probability of success π_0 . The prediction lower bound of level $1-\alpha$ based on the assumption of independence among the 10 controls' outcomes is given by

$$\bar{\pi}_0 - z_\alpha(\bar{\pi}_0(1 - \bar{\pi}_0)(1/n + 1/m))^{1/2} \quad (1)$$

where z_α is the $100(1 - \alpha)$ percentile of the standard normal distribution, while π_0 is the overall relative frequency of correct words at time T_0 for the 10 controls, hence based on $n = 10 \times 4 \times 15$ trials. This was compared with the relative frequency for the patient, hence based on $m = 4 \times 15$ trials. The prediction level was set to 0.99. Successively, in order to study the effect of TBS stimulation on the performance in the NW test, we used logistic regression. For Y the binary response for each of the 15 NW in a single test, we studied the effect of the predictors SITE (factor with levels "left BA 40" ($i = 1$), "right BA 40" ($i = 2$), "Wernicke's area" ($i = 3$) and "visual cortex" ($i = 4$)) and TIME (factor with levels " T_0 " ($j = 0$), " T_1 " ($j = 1$) and " T_2 " ($j = 2$)) controlling for the group (indicator ID for the patient's observations). Let $\pi_{ijk} = P(Y = 1 | \text{SITE} = i, \text{TIME} = j, \text{ID} = k)$. The starting model had main effects only:

$$\begin{aligned} \text{logit}(\pi_{ijk}) &= \alpha + \beta_i^{\text{SITE}} + \beta_j^{\text{TIME}} + \beta_k^{\text{ID}}, \quad i = 1, 2, 3, 4, \quad j \\ &= 0, 1, 2, \quad k = 0, 1 \end{aligned} \quad (2)$$

where the fixed effects associated with TIME = 0, SITE = 4 and ID = 0 were set to zero (reference levels). Then, we performed model selection by either collapsing two or more levels of a predictor, or by introducing interaction terms among the three predictors. The relative goodness of a model was assessed via the residual deviance: the reduction in deviances between two models that can be nested was tested against the χ^2 -distribution with degree of freedom (df) equal to the change in the number of estimated parameters (Agresti, 2002).

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