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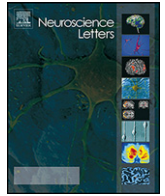
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Theta burst stimulation of dorsolateral prefrontal cortex modulates pathological language switching: A case report

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ABSTRACT

Although different lesion and neuroimaging studies had highlighted the importance of the dorsolateral prefrontal cortex (DLPFC) in language switching, the nature of this higher cortical disorder of communication and its neural correlates have not been clearly established. To further investigate the functional involvement of the DLPFC, we used transcranial magnetic stimulation (TMS) given as theta burst stimulation (TBS) in a bilingual patient showing pathologic language switching after an ischemic stroke involving the left frontal lobe. Inhibitory and excitatory TBS were applied to the left DLPFC, to the right DLPFC, or to an occipital cortical control site. A short-lasting interruption of the pathological language switching occurred after excitatory left DLPFC stimulation, while inhibitory left DLPFC TBS transiently increased the number of utterances produced in the unwanted second language. Effects were non-significant after right DLPFC and occipital TBS. Our findings suggest that left DLPFC is actively involved in language switching. TMS techniques may help in understanding the neural bases of bilingualism.

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Patients affected by pathological language switching alternate their languages across different utterances [1,23], whereas patients affected by pathological mixing intermingle different languages within a single utterance. While pathological mixing is mainly due to lesions in the parieto-temporal structures of the left hemisphere, the neural pathways involved in language switching have not yet been clearly described [9,15].

The process by which bilinguals are able to speak in an appropriate target language without interference from a non-target language has not been clearly defined so far. A separate brain region is thought to regulate this process and may allow multilingual subjects to switch easily from one language to another [26]. Lesions and functional neuroimaging studies suggest the prefrontal cortex, especially the dorsolateral prefrontal cortex (DLPFC) may be involved in this process [12,16,28], but other authors did not detect any evidence of increased activation or deactivation in brain regions associated with executive control (including the DLPFC) during language switching [27].

Transcranial magnetic stimulation (TMS) offers a spatial and temporal resolution rarely available in patient studies and complements the information available from functional neuroimaging techniques such as functional magnetic resonance imaging (fMRI), and positron emission tomography (PET). TMS has already become an important tool for studying language at both the cognitive and neural levels, and it is clear that further developments in TMS methodology are likely to result in even greater opportunities for language research.

A repetitive TMS (rTMS) protocol known as theta burst stimulation (TBS) requires less stimulation time and lower intensity to induce long lasting effects in the human cerebral cortex than other known rTMS protocols [18]. TBS differentially affects cortical circuits depending on the protocol used. Two main TBS modalities show opposite effects on cortical excitability: the intermittent TBS (iTBS) and continuous TBS (cTBS) generate excitatory and inhibitory effects, respectively. The aim of the present study was to evaluate the effects of facilitatory and inhibitory TBS on DLPFC in a bilingual patient showing pathological language switching after ischemic stroke affecting the left gyrus frontalis medius.

The patient is a 65-year-old right-handed man born in South Tyrol to German parents who first learned to speak Italian at the age of 6; he learned the second language (L2) to a high degree of proficiency. The patient sustained a thrombotic ischemic stroke involving cortical and subcortical areas of the left middle frontal

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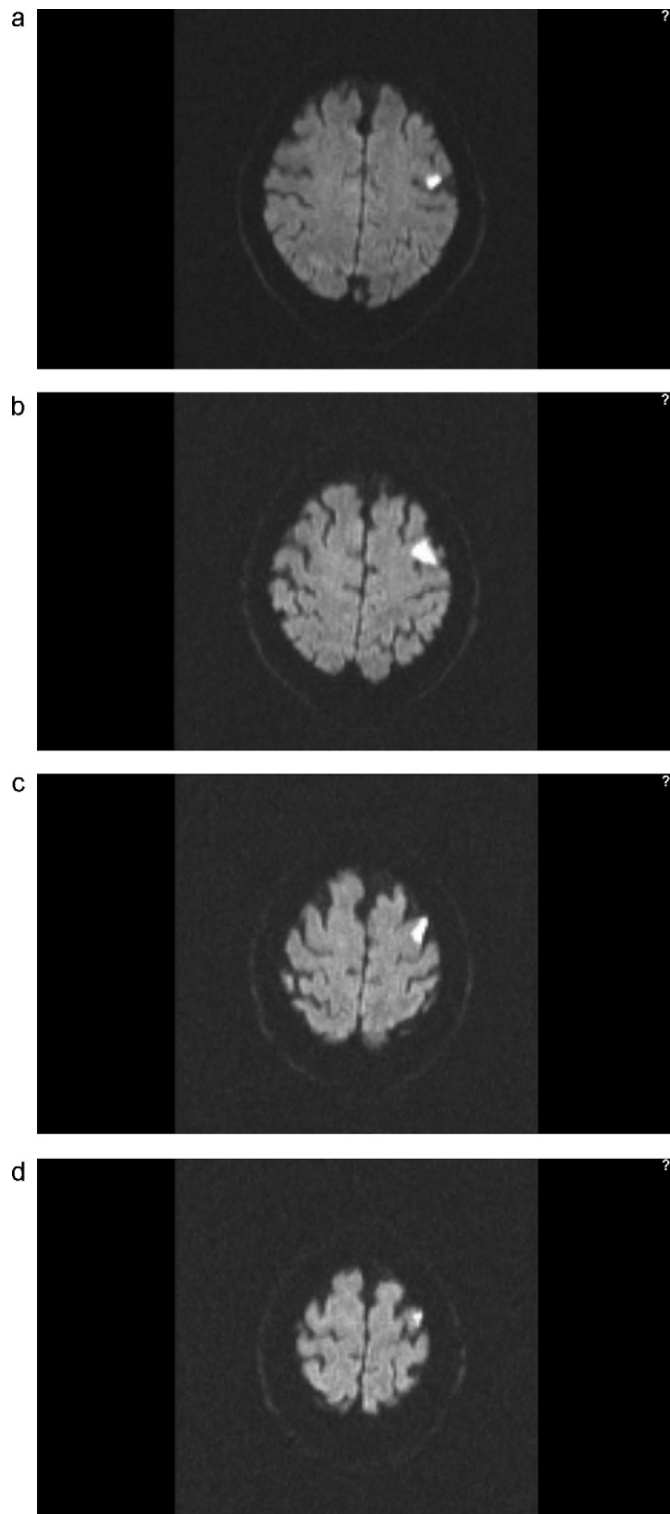


Fig. 1. (a–d) Diffusion-weighted magnetic resonance images showing abnormal hyperintense lesion in the left medial frontal gyrus, consistent with an acute ischemic event.

gyrus (Fig. 1a–d). After his stroke, the patient showed a compulsive tendency to alternate utterances in German and utterances in Italian, even if he was aware that he had to speak in only one language. The Italian and German speech of the patient was initially reported as appearing “slurred” but he was able to follow simple commands. The neurological examination was otherwise normal. With the exception of slurring, verbal production and comprehension

in both first language (L1) and L2 were preserved. Neuropsychological tests (Mini Mental State Examination, Rey’s Auditory Verbal Learning Test, Immediate visual memory, Raven’s colores matrices, Constructive praxis, Phonological verbal fluency) revealed that the patient did not present neither intellectual nor attentional or praxic disorders.

The baseline neurolinguistic assessment of the patient’s two languages was carried out on the first and second hospital days. The examiner first addressed the patient in Italian only. He was administered the short version of the Italian adaptation of the bilingual aphasia test (BAT) [24]. On the following day, the examiner addressed the patient in German only. He was administered the corresponding short version of the German adaptation of the BAT. At this time also German-Italian translation tests were administered. The neurolinguistic tests showed that the patient did not exhibit aphasic symptoms in any of the two languages tested, nor did he make translation errors in any of the two directions. However, the patient showed pathological switching, that is the compulsive tendency to alternate utterances in Italian and utterances in German. Even if he was aware that he had to speak in only one language, he switched to the other, and often apologised for it after doing so. Four weeks after onset of symptomatology, language pathological switching disappeared and the patient did not show any neurological abnormality except for a slight dysarthria. At follow-up examination eight weeks later, his language disturbance recovered completely.

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 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. Resting motor threshold (RMT) was defined as the minimum stimulus intensity that produced a liminal MEP (about 50 μ V in 50% of 10 trials) at rest. Active motor threshold (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. RTMS was delivered over the right DLPFC, the left DLPFC and the occipital cortex 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 DLPFC is a broad area; we used a site similar to that used by other research groups using TMS [8,19]. The coil was placed 5 cm anterior from the hand motor area on the left and right hemispheres and held parallel to the mid-sagittal line. The stimulation intensity was defined in relation to AMT; an intensity of 80% AMT was used. 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. We used the cTBS protocol in which 3 pulses of stimulation were given at 50 Hz, repeated every 200 ms for a total of 600 pulses.

The control group consisted of eight healthy bilingual (German–Italian) subjects.

To evaluate the specificity of the TBS effect, the patient and the normal controls were given cTBS and iTBS to the right DLPFC, the left DLPFC and an occipital cortical control site (sham stimulation) on separate days. The order of the rTMS treatment was randomly assigned.

In each of the six experimental sessions the short version of the Italian and German adaptation of the BAT were again administered at baseline (T_0), during the 20 min following the TBS (T_1) and 60 min after TBS (T_2), with an inter-session interval of at least 12 h. The mean outcome measures were the percentage of appropriate,

Table 1
Upper panel: percentages of appropriate, switched and mixed utterances produced by the patient. Lower panel: mean values and standard errors (in brackets) of the percentage of appropriate, switched and mixed utterances produced by the eight control subjects.

		Site Language Time	Left DLPFC						Right DLPFC					
			L1			L2			L1			L2		
			T0	T1	T2	T0	T1	T2	T0	T1	T2	T0	T1	T2
Patient	iTBS	Appropriate	58	93	65	56	90	62	58	62	60	58	59	58
		Switching	39	4	30	40	6	31	39	34	37	39	37	38
		Mixing	3	3	5	4	4	7	3	2	2	3	4	4
	cTBS	Appropriate	58	40	48	57	42	50	58	60	57	58	58	59
		Switching	40	57	47	39	56	43	40	38	41	39	40	39
		Mixing	2	3	5	3	2	7	2	2	2	3	2	2
Controls	iTBS	Appropriate	98.8 (0.37)	98.3 (0.42)	98.8 (0.24)	98.3 (0.33)	98.2 (0.59)	96.6 (3.57)	98.6 (0.40)	99.0 (0.52)	98.5 (0.33)	98.0 (0.55)	97.8 (0.39)	97.8 (0.24)
		Switching	0.83 (0.25)	1.23 (0.35)	0.79 (0.16)	0.94 (0.19)	1.06 (0.34)	1.4 (0.34)	0.85 (0.28)	0.61 (0.19)	0.95 (0.21)	1.08 (0.32)	1.34 (0.29)	1.4 (0.18)
		Mixing	0.38 (0.14)	0.54 (0.13)	0.41 (0.11)	0.75 (0.14)	0.7 (0.27)	0.78 (0.23)	0.55 (0.19)	0.39 (0.22)	0.55 (0.14)	0.84 (0.19)	0.96 (0.26)	0.78 (0.19)
	cTBS	Appropriate	98.4 (0.26)	98.6 (0.24)	97.2 (3.79)	97.9 (0.42)	98.1 (0.27)	96.9 (3.46)	98.5 (0.34)	98.6 (0.23)	98.6 (0.45)	98.1 (0.55)	98.0 (0.36)	97.6 (0.29)
		Switching	1.04 (0.18)	0.88 (0.18)	0.85 (0.19)	1.13 (0.22)	0.99 (0.17)	1.18 (0.36)	0.89 (0.23)	0.83 (0.13)	0.85 (0.34)	1.08 (0.25)	1.2 (0.24)	1.41 (0.25)
		Mixing	0.61 (0.11)	0.52 (0.12)	0.75 (0.21)	0.96 (0.22)	0.9 (0.15)	0.73 (0.23)	0.61 (0.12)	0.63 (0.12)	0.56 (0.14)	0.85 (0.32)	0.8 (0.14)	1.01 (0.08)
		Site Language Time	Occipital											
L1			L2											
T0	T1		T2	T0	T1	T2								
Patient	iTBS	Appropriate	57	58	58	58	59	57						
		Switching	39	40	39	40	38	40						
		Mixing	4	2	3	2	3	3						
	cTBS	Appropriate	58	56	60	57	58	59						
		Switching	40	38	37	38	40	38						
		Mixing	2	6	3	5	2	3						
Controls	iTBS	Appropriate	97.8 (0.43)	98.3 (0.33)	98.6 (0.40)	98.0 (0.36)	98.1 (0.54)	97.9 (0.53)						
		Switching	1.39 (0.22)	1.05 (0.14)	0.9 (0.31)	1.18 (0.29)	1.09 (0.35)	1.29 (0.27)						
		Mixing	0.83 (0.24)	0.65 (0.21)	0.5 (0.14)	0.95 (0.28)	0.89 (0.27)	0.81 (0.29)						
	cTBS	Appropriate	98.6 (0.34)	97.2 (3.79)	98.5 (0.32)	97.9 (0.42)	98.3 (0.29)	98.1 (0.56)						
		Switching	0.83 (0.22)	1.01 (0.25)	0.98 (0.28)	1.11 (0.23)	0.9 (0.18)	1 (0.31)						
		Mixing	0.59 (0.15)	0.59 (0.16)	0.44 (0.18)	0.98 (0.2)	0.8 (0.12)	0.86 (0.29)						

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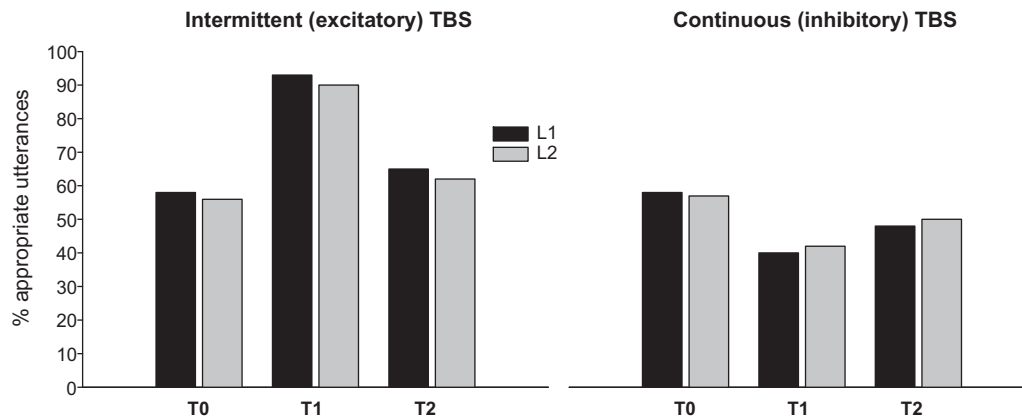


Fig. 2. Intermittent and continuous theta burst stimulation (TBS) over the left dorsolateral prefrontal cortex. Percentage of utterances in the appropriate language and of utterances in the unwanted language (switching) when the patient is requested to speak in the first language (L1) and in the second language (L2) baseline (T0), during the 20 min after TBS (T1) and 60 min after TBS (T2).

switched and mixed utterances produced when the patient (or the control subject) was requested to speak in each language.

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 [29], and approved by the Ethics Committee.

In order to assess the effects of TBS on the verbal behaviour, we used a linear mixed effect model [21] that accounts for dependence across repeated measurements at the individual level. We used the logit of the percentages of appropriate utterances in a given language as response variable (denoted by y). For each stimulation site (left DLPFC, right DLPFC or occipital) we considered 6 observations according to the TBS modality (iTBS or cTBS) and to the time of BAT administration (T0, T1, or T2). The value of y_{ti} for a given observation indexed by t on the i th individual can be written as follows:

$$y_{ti} = \beta_0 + \beta_1 T1_{ti} + \beta_2 T2_{ti} + \beta_3 Site1_{ti} + \beta_4 Site2_{ti} + \beta_5 TBS_{ti} + u_{0i} + \varepsilon_{ti} \quad (1)$$

In model (1) we include two indicator variables for time of linguistic examination, $T1_{ti}$ and $T2_{ti}$, and two indicator variables for the stimulation site, $Site1_{ti}$ and $Site2_{ti}$, which represent the left DLPFC and the right DLPFC, respectively. TBS_{ti} is an indicator variable that indicates the iTBS treatment. We assume that fixed effects associated with T0, Site = occipital and TBS = iTBS are set to zero (reference levels). The u_{0i} term represents the random intercept associated with individual i , and the residuals ε_{ti} associated with all the observations of individual i are assumed to be independent and identically distributed with normal distribution. Estimation was performed on the group of 8 control subjects, hence prediction intervals were performed in order to check if the patient showed any significant difference in the response to TBS.

At T0 when requested to speak in L1 the patient produced 58% of the utterances in that language, 39% in the unwanted L2 and 3% of mixed utterances; when requested to speak in L2, the patient produced 56% of utterances in L2, 40% of utterances in L1 and 4% of mixed utterances.

Percentage of appropriate, switched and mixed utterances produced when the patient and the eight control subjects were requested to speak in each language are shown in Table 1.

Estimation of model (1) on the control group showed that, in each language, the 99% prediction interval for the percentage of appropriate utterances at time T0 did not cover the corresponding values observed in the patient, confirming that the patient cannot be assimilated to a healthy subject. Estimation of model (1)

also showed that β_1, \dots, β_5 were not significantly different than zero (p -values for likelihood ratio test larger than 0.05 for both L1 and L2), which confirms that TBS failed to modify verbal behaviour on healthy subject. Finally, 99% prediction intervals based on estimation of model (1) led to conclude that (i) iTBS over the left DLPFC determined a significant increase at T1 and a non-significant increase at T2 in the percentage of appropriate utterances when the patient was requested to speak in each language (Fig. 2, left panel); (ii) cTBS over the left DLPFC determines a significant decrease at T1 and a non-significant decrease at T2 in the percentage of appropriate utterances when the patient was requested to speak in each language (Fig. 2, right panel); (iii) both iTBS and cTBS over the right DLPFC and the occipital cortex produce non-significant effects on the percentage of appropriate utterances produced in each language.

No side effects were observed in the patient and in the controls.

TMS is increasingly more often used in cognitive neuroscience to test brain-behaviour relation, through its capacity to disrupt task-related neuronal activity ("virtual lesion"). These virtual lesion studies offer not only the ability to explore causal relations between brain regions and language functions absent in functional neuroimaging, but also spatial and temporal precision not available in patient studies [6]. When rTMS is given as TBS, LTP- or LTD-like changes can be induced. Although little is known about whether the deliberation of cTBS and iTBS over non-motor regions causes the same modulatory effects, the results of this study confirm that stimulation frequency of TMS may play a crucial role in the modulation of language processing.

The most salient finding of the present study is that TBS, by modulating left prefrontal function, affects language switching in a bilingual subject. Moreover, pathological switching has never been reported following a lesion selectively involving the middle frontal gyrus.

Facilitatory iTBS applied to the left prefrontal cortex transiently reversed language switching while inhibitory cTBS further increased the number of utterances produced in the unwanted L2. The effects appeared during the 20 min after the stimulation.

We provide further evidence in a bilingual brain damaged subject for the important role played by the left frontal and prefrontal structures in switching between the languages.

Interestingly, TBS did not produce any effect in the normal subjects. One might speculate that TBS trains have a different influence on the cortical network whether it is healthy and balanced or damaged and imbalanced. It is known, that the state of cortical excitability before and during rTMS has a strong impact on after effects of stimulation [30]. The DLPFC that is abnormally hypoactive

because of disruption of the anterior loop of language planning, that comprises the cortico-subcortical circuit between the prefrontal cortex and basal ganglia in the dominant hemisphere [11], may be more susceptible to the TBS effects.

A central issue in understanding the cognitive control in language switching is whether the decision to speak in one language rather than in another in bilinguals is regulated by a specific cognitive system peculiar to bilingual subjects or by a general system responsible for switching between various behavioural patterns. Bilingual individuals must have effective neural mechanisms to prevent interference or competition between the two languages, especially considering that L1 and L2 may have overlapping neuro-anatomical bases. The switching from a given behaviour to another or from one language to another may all be regulated by the same general neural mechanism [25] which may be functionally separate and independent of the linguistic or translational system [10].

We demonstrated that DLPFC participates actively in the process of language switching in a bilingual individual. Our findings are consistent with the literature indicating that switching between languages involves increased general executive processing and that alternating between languages leads to activation in brain structures (especially the DLPFC) which play a role in executive control and articulatory and motor planning. Bilinguals recruit a set of neural areas that are involved in executive function and motor processing, articulation and phonological retrieval in conditions which involve language switching. DLPFC serves to attenuate interference that results from having to actively enhance and suppress two languages in alternation. Previous studies have documented the importance of DLPFC in tasks which require the use of context in order to overcome the preponderant response [2,22]. The findings of our study also seem to be in good agreement with the evidence of DLPFC involvement in other cognitive switching tasks [7,20] and executive control in general [3,13,31]. Language switching involves competition between language task schemas which are responsible for the enhancement of the correct language and suppression of the incorrect language [14], and involves lexical selection of words in the target language and may involve inhibition of the non-target language [4,5]. Verhoef et al. [32] recently demonstrated that inhibition, even if not necessary, can modulate the efficiency of language switching. Interestingly, two bilingual patients have been reported in whom language switching was apparently triggered by high frequency rTMS applied to the left DLPFC [17].

Despite the limitations imposed by a single case study, these preliminary findings highlight the potential value of rTMS for non-invasively investigating language function in humans and support the role of the left DLPFC in language switching in bilinguals. TMS studies may lead to a more advanced understanding of language organisation in the multilingual brain.

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