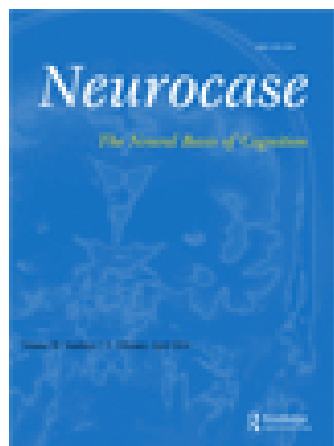


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Neural correlates of high frequency repetitive transcranial magnetic stimulation improvement in post-stroke non-fluent aphasia: A case study

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Damage to the left inferior frontal gyrus (IIFG) affects language and can cause aphasia in stroke. Following left hemisphere damage it has been suggested that the homologue area in the right hemisphere compensates for lost functions. An increasing number of studies have demonstrated that inhibitory 1-Hz repetitive transcranial magnetic stimulation (rTMS) targeting the right IFG can be useful for enhancing recovery in aphasic patients. In the present study we applied activating high frequency (10-Hz) rTMS, which increases cortical excitability, to the damaged IIFG daily for 3 weeks. Pre- and post-TMS EEG are performed, as well as language function assessments with the Aachen Aphasia Test Battery. Results demonstrate a decrease in rIFG activity post rTMS and normalization for the IIFG for beta3 frequency band. Also increased activity was in the right supplementary motor area for beta3 frequency band. In comparison to pre-TMS the aphasic patient improved on repetition tests, for naming and comprehension. After rTMS increased functional connectivity was shown in comparison to before between the IIFG and the rIFG for theta and beta3 frequency band. This case report suggests that 10 Hz rTMS of the IIFG can normalize activity in the IIFG and right IFG possibly mediated via altered functional connectivity.

Keywords: Aphasia; Stroke; TMS; Source localization.

More than 20% of patients with ischemic stroke experience aphasia, and 10–18% of the survivors develop persistent deficits (Wade, Hower, David, & Enderby, 1986). Patients' recovery is extremely variable, with complete restitution or persistent severe aphasia without spontaneous speech production (Winhuisen et al., 2005). Neuroimaging studies already have shown that damage in the left inferior frontal gyrus (IIFG) affects language and can cause aphasia in post-stroke patients (Crosson et al., 2007). Following left hemisphere damage it is hypothesized that the homologue area in the right hemisphere takes over lost functions (Crosson et al., 2007). Activation of the right inferior frontal gyrus

(rIFG) is essential for residual language function in patients experiencing aphasia after left hemispheric stroke (Peck et al., 2004). The rIFG may play a larger role in supporting recovery when there is greater damage to the left hemisphere language areas (i.e., IIFG) (Peck et al., 2004; Raboyeau et al., 2008).

Increased activation in the right hemisphere after left hemispheric stroke, as observed in some neuroimaging studies, might however relate to transcallosal disinhibition leading only to partial or incomplete recovery (Thiel et al., 2006). Thus, increased right hemispheric activation may be maladaptive leading to a “dead-end,” inefficient

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strategy for recovery, in non-fluent aphasia patients (Lefaucheur, 2006). For a better language recovery the left hemisphere may be more important, as patients with better recovery have been observed to have higher activation in the left hemisphere (Heiss & Thiel, 2006).

An increasing number of studies have demonstrated that low frequency (1 Hz) repetitive transcranial magnetic stimulation (rTMS) can be useful for enhancing recovery in aphasic patients (Lefaucheur, 2006; Martin et al., 2009). rTMS is a non-invasive tool provoking a strong impulse of magnetic field that induces an electrical current which can alter the neural activity at the applied area as well as functionally connected areas. This makes it possible to selectively and safely stimulate specific regions of the human brain. Typically, rTMS for aphasia is applied to the IFG in the undamaged hemisphere, at low frequency (1 Hz), which has an inhibitory effect of the stimulated area (Barwood et al., 2011; Hamilton et al., 2010; Kakuda, Abo, Uruma, Kaito, & Watanabe, 2010; Lefaucheur, 2006). The underlying rationale is that inhibiting the undamaged maladaptively compensating hemisphere permits reactivation of the homologue brain areas within the originally damaged hemisphere, promoting some functional recovery.

Several studies have found that low frequency rTMS (≤ 1 Hz) decreases cortical excitability, while high frequency rTMS (> 1 Hz) increases cortical excitability (Chen et al., 1997; Wassermann, 1998; Wu, Sommer, Tergau, & Paulus, 2000). As low frequency rTMS for aphasia tries to inhibit the undamaged rIFG, as such permitting reactivation within the damaged IIFG, it can be hypothesized that high frequency TMS targeting the IIFG might induce a direct reactivation of the damaged area, promoting functional recovery. In the present study the authors apply high frequency (10 Hz) TMS to the IIFG on a daily basis (2000 pulses per day) for 3 weeks. Clinical pre- and post-treatment analysis is performed by the Aachener Aphasia Test Battery for evaluation of language function, and concomitant electrophysiological changes are evaluated by resting state source analyzed electroencephalography recordings.

CASE REPORT

A 55-year-old woman married, with two children, presents at the BRAI²N (Brain Research center Antwerp for Innovative & Interdisciplinary

Neuromodulation) clinic. She suffers from chronic non-fluent aphasia due to a stroke 39 months prior to consultation. Before her stroke she had an active professional life as a nurse in a geriatric facility. During adolescence she suffered from depression, for which she was successfully treated with psychotherapy and medication. After this episode medication was ceased and there were no further relapses. At the age of 51 she suffered an ischemic stroke in the left hemisphere, resulting in right hemiplegia and severe non-fluent transcortical motor aphasia. Figure 1 shows a MRI images (T2) with lesion at the left anterior temporal pole and the left inferior posterior frontal gyrus, but that the left anterior superior inferior frontal gyrus remains intact and brain tractography further shows that there is no disruption in the fasciculus arcuatus. Other cognitive dysfunctions such as deficits in memory and attention and apraxia were diagnosed. At this moment a depressive mood was observed. She participated in inpatient rehabilitation for 8 months, including cognitive therapy, aphasia therapy, and motor therapy. This period was followed by 16 months of aphasia therapy in an outpatient setting. Aphasia therapy was stopped at 24 months post onset. Motor therapy was continued on an outpatient basis persisting during the current treatment.

METHODS

Aachener Aphasia Test Battery

The Dutch version of the Aachener Aphasia Test (AAT) was used. The AAT is a standardized diagnostic language test battery that has been frequently used in aphasia studies (Graetz, De Bleser, & Willmes, 1990). The AAT comprises five subtests: (i) the token test (TT), (ii) repetition tests (RE), (iii) written language tests (WL), (iv) naming tests (NA), (v) and comprehension tests (CO). The AAT has high test-retest reliability (2-day interval: retest reliability $> .91$ for all subtests in persons with chronic aphasia (Graetz et al., 1990).

Repetitive transcranial magnetic stimulation

TMS is performed using a super rapid stimulator (Magstim Inc., Wales, UK) with a figure-eight coil. First the motor threshold was daily determined by placing the coil tangentially to the scalp and oriented so that the induced electrical currents would

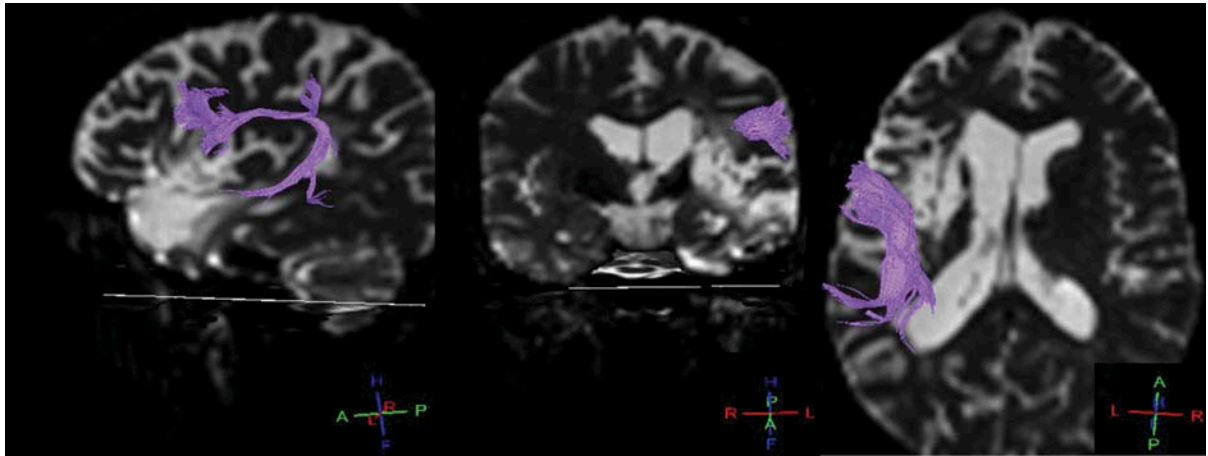


Figure 1. MRI images (T2) shows lesion at the left anterior temporal pole and the left inferior posterior frontal gyrus, but that the left anterior superior inferior frontal gyrus remains intact. Brain tractography further shows that there is no disruption in the fasciculus arcuatus. [To view this figure in color, please see the online version of this Journal.]

flow approximately perpendicular to the central sulcus, at 45° angle from the mid-sagittal line over the right hemisphere. EMG was used to diagnose the motor threshold exactly.

For the stimulation protocol the coil was placed overlying the IIFG using MRI guided neuronavigation. The target was opted as this we the area that was shown on source localized EEG. With the intensity of the stimulation set at 80% of motor threshold, using 10 Hz stimulation for 2000 pulses with an inter-train interval each 200 pulses. This stimulation protocol was repeated for 3 weeks, 5 days per week and in total 15 sessions.

EEG recording

EEG recordings were obtained in a fully lighted room with the patient sitting upright on a small but comfortable chair. The actual recording lasted approximately 5 min. The EEG was sampled with 19 electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, O2) in the standard 10–20 international placement, referenced to linked ears and impedances were checked to remain below 5 k Ω . Data were collected eyes-closed (sampling rate = 1024Hz, band passed 0.15–200 Hz). Data were resampled to 128 Hz, band-pass filtered (fast Fourier transform filter) to 2–44 Hz and subsequently transposed into Eureka! Software (Congedo, 2002), plotted and carefully inspected for manual artifact-rejection. All episodic artifacts including eye blinks, eye movements, teeth clenching, body movement, or ECG artifact were removed from the stream of the EEG. Average

Fourier cross-spectral matrices were computed for bands delta (1.5–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz), and gamma (30.5–45 Hz). EEG was recorded before and immediately after TMS treatment. To compare the patient with an aged matched control group, the normative database of the Brain Research Laboratories (BRL), New York University was used. None of these subjects had aphasia. Exclusion criteria for the BRL database were known psychiatric or neurological illness, psychiatric history drug/alcohol abuse in a participant or any relative, current psychotropic/CNS active medications, history of head injury (with loss of consciousness) or seizures, headache, physical disability.

Source localization

Standardized low-resolution brain electromagnetic tomography (sLORETA) was used to estimate the intracerebral electrical sources that generated the scalp-recorded activity in each of the eight frequency bands (Pascual-Marqui, 2002). sLORETA computes electric neuronal activity as current density (A/m²) without assuming a predefined number of active sources. The sLORETA solution space consists of 6239 voxels (voxel size: 5 × 5 × 5 mm) and is restricted to cortical gray matter and hippocampi, as defined by digitized MNI152 template (Fuchs, Kastner, Wagner, Hawes, & Ebersole, 2002). Scalp electrode coordinates on the MNI brain are derived from the international 10–20 system (Jurcak, Tsuzuki, & Dan, 2007).

Functional connectivity

Brain connectivity can refer to a pattern of anatomical links (“anatomical connectivity”), of statistical dependencies (“functional connectivity”) or of causal interactions (“effective connectivity”) between distinct units within a nervous system. Present research focuses on functional connectivity which captures deviations from statistical independence between distributed and often spatially remote neuronal units. Statistical dependence may be estimated by measuring correlation or covariance, spectral coherence or phase-locking. Functional connectivity is often calculated between all elements of a system, regardless of whether these elements are connected by direct structural links. Unlike structural connectivity, functional connectivity is highly time-dependent. Statistical patterns between neuronal elements fluctuate on multiple time scales, some as short as tens or hundreds of milliseconds. It should be noted that functional connectivity does not make any explicit reference to specific directional effects or to an underlying structural model.

Coherence and phase synchronization between time series corresponding to different spatial locations are usually interpreted as indicators of the “connectivity.” However, any measure of dependence is highly contaminated with an instantaneous, non-physiological contribution due to volume conduction (Pascual-Marqui, 2007a). Pascual-Marqui (2007b) introduced a new technique (i.e., Hermitian covariance matrices) that removes this confounding factor. As such this measure of dependence can be applied to any number of brain areas jointly, i.e., distributed cortical networks, whose activity can be estimated with sLORETA. Measures of linear dependence (coherence) between the multivariate time series are defined. The measures are expressed as the sum of lagged dependence and instantaneous dependence. The measures are non-negative, and take the value zero only when there is independence and are defined in the frequency domain: delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (13–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz), and gamma (30.5–45 Hz). Based on this principle lagged phase synchronization (=functional connectivity) was calculated. Regions of interest were the IIFG (BA44/45) and rIFG (BA44/45).

Region of interest analysis

The log-transformed electrical current density was averaged across all voxels belonging to the region of interest. Regions of interest were respectively the IIFG (BA44/45) and rIFG (BA44/45). Region of interest analysis were computed for the different frequency bands separately. The difference scores were normalized over the frequency band for respectively the IIFG and rIFG pre- and post-treatment. A lateralization index was calculated for each frequency band

$$\text{Lateralization index} = \frac{(\text{IIFG} - \text{rIFG})}{(\text{IIFG} + \text{rIFG})}$$

where IIFG and rIFG are the log-transformed electric current density. This method is similar to Weisz et al. (2007).

RESULTS

Family report

The patient’s husband reports that family and friends noticed that the patient spoke more fluently, made longer sentences and used a larger vocabulary.

Achener Aphasia Test Battery

In comparison to pre-TMS treatment the aphasic patient had an improvement for the repetition tests from percentile 79 to 98, for the naming tests from percentile 33 to 65 and comprehension from percentile 57 to 61 after the TMS treatment. However, the patient also showed a decrease in written language test from percentile 65 to 52 and a small decrease in the token test from percentile 69 to 67 after the rTMS treatment.

Four months after treatment we still see an improvement on the repetition (percentile 96) and naming test (percentile 61). For comprehension a small reduction (percentile 59) was found in comparison to directly after the TMS treatment, but still a small improvement in comparison to pre-treatment (see Table 1).

Source localization

A comparison between the aphasic patient versus an age-matched control group in the pre-treatment

TABLE 1
Pre- and post-treatment results for the Aachen Aphasia Test

	Pre-TMS		Post-TMS		Follow-up	
	Raw scores	Percentile	Raw scores	Percentile	Raw scores	Percentile
Spontaneous language	2/4/4/4/4/4	–	3/4/5/4/4/4	–	4/5/5/4/4/4	–
Token test (TT)	21	69	22	67	23	65
Repetition (RE)						
RE-1	30/30		30/30		30/30	
RE-2	30/30		30/30		30/30	
RE-3	27/30		30/30		30/30	
RE-4	23/30		29/30		30/30	
RE-5	23/30		29/30		30/30	
Total	133/150	79	148/150	98	146/150	96
Written language						
WL-1	30/30		30/30		29/30	
WL-2	14/30		13/30		13/30	
WL-3	22/30		9/30		20/30	
Total	66/90	65	52/90	52	62/90	61
Naming						
NA-1	15/30		22/30		25/30	
NA-2	20/30		23/30		24/30	
NA-3	5/30		21/30		22/30	
NA-4	13/30		23/30		22/30	
Total	53/120	33	89/120	65	93/120	70
Comprehension						
CO-1	21/30		21/30		21/30	
CO-2	27/30		27/30		27/30	
CO-3	23/30		24/30		23/30	
CO-4	17/30		18/30		18/30	
Total	88/120	57	90/120	61	89/30	59

condition revealed a significantly decreased beta3 activity in the left inferior frontal gyrus and left temporopolar area that might be related to the stroke lesion and increased beta3 activity in the rIFG and right temporopolar area for the aphasic patient in comparison to the norm (see Figure 2). A similar analysis for the post treatment status revealed a decreased activity in rIFG and increased activity in the right supplementary motor area and cuneus for beta3 frequency band for the aphasic patient in comparison to the BRL norms (see Figure 2).

In addition the patient demonstrated decreased alpha activity in the motor cortex in comparison to the BRL norms. This might be related to the right-sided hemiparesis (see Figure 3). No significant results were obtained for the delta, theta, beta1, beta2, gamma frequency bands.

Functional connectivity

For theta and beta3 increased significant lagged phase synchronization (=functional connectivity)

was found between the IIFG and rIFG post-treatment in comparison to pre-treatment (see Figure 2). No significant functional connectivity changes were found for the delta, alpha, beta1, beta2, gamma frequency bands.

Lateralization index

For the lateralization index theta and beta3 frequency band differences are noted. For theta a clear increase in the IIFG and/or decrease in the rIFG after TMS treatment is noted in comparison to pre-TMS, although in the pre-TMS treatment condition IIFG was higher than the rIFG (see Figure 4). More beta3 activity in the rIFG in comparison to the IIFG is noted pre-TMS, while post-TMS treatment the opposite was revealed.

DISCUSSION

This study reports results for high frequency rTMS (10 Hz) to modulate the IIFG in a chronic non-fluent post-stroke aphasia patient. We hypothesized

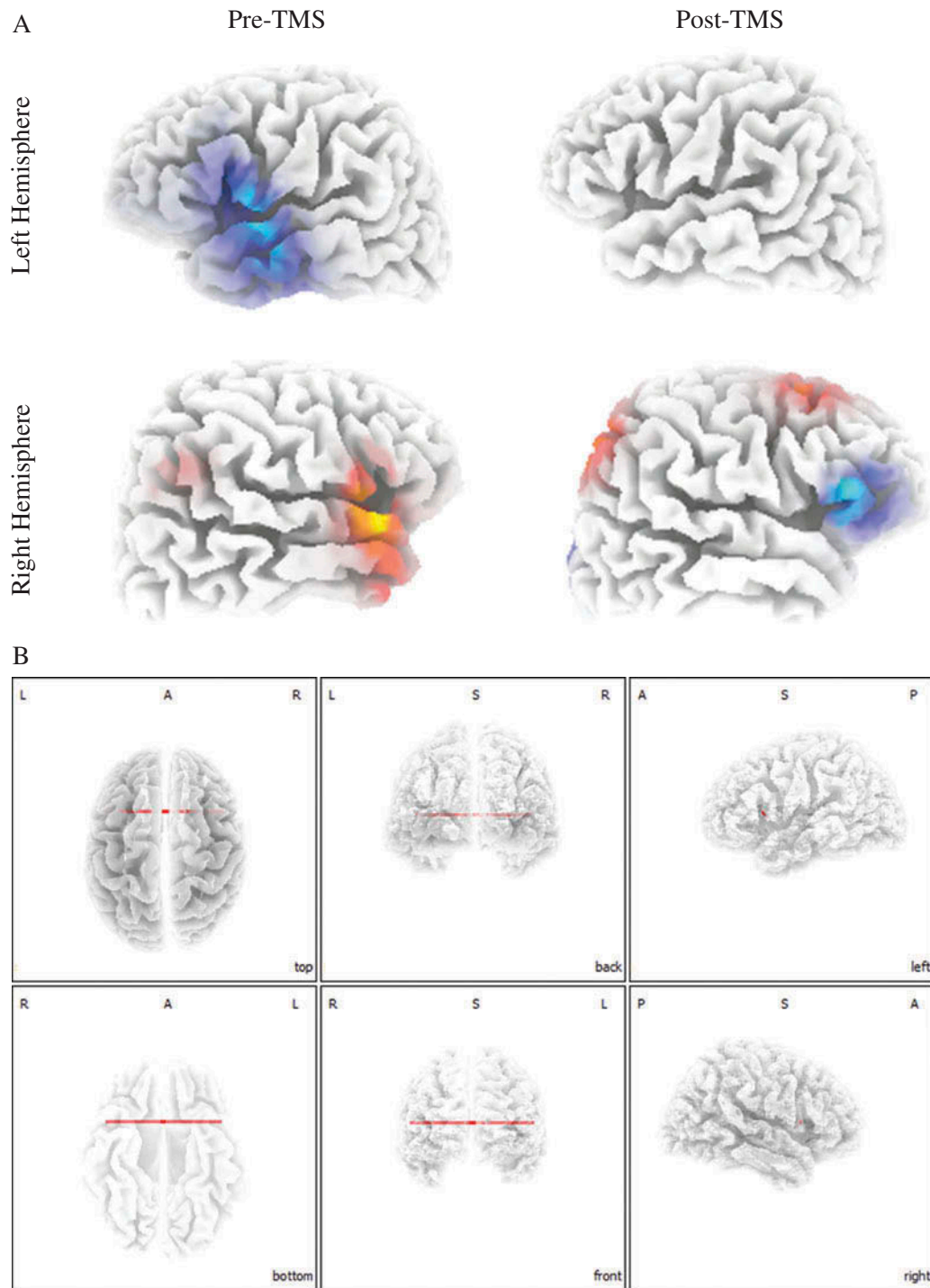


Figure 2. (A) Results for sLORETA analysis indicated significant decreased synchronized in the left inferior frontal gyrus and left superior temporal gyrus and increased synchronized activity in the rIFG and right temporopolar area for beta3 frequency band pre-TMS for patient in comparison to the BRL norms, and decreased synchronized activity in rIFG and increased synchronized activity in the right supplementary motor area and cuneus for beta3 frequency band post-TMS for patient in comparison to the BRL norms. (B) A significant increased synchronized functional connectivity for the theta and beta3 frequency band post-treatment in comparison to pre-treatment. [To view this figure in color, please see the online version of this Journal.]

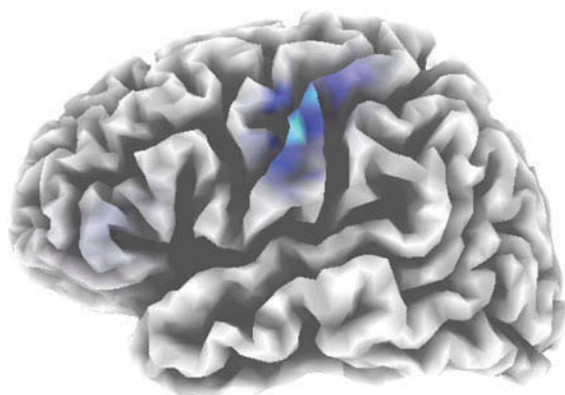


Figure 3. Results for sLORETA analysis indicated significant decreased alpha activity in the motor cortex in comparison to the BRL norms. [To view this figure in color, please see the online version of this Journal.]

that in chronic non-fluent aphasia, after “activating” treatment of the IIFG, source localized EEG would show a shift in activation from the rIFG to the IIFG concomitant with a clinical response on the AAT. Our results indeed confirm that after left-sided high frequency rTMS a decrease was shown in the rIFG and normalization (in comparison to the norm) for the IIFG for beta3 frequency band. Also increased activity was found for the beta3 frequency in the right supplementary motor area and cuneus. Post-rTMS the patient demonstrated an improvement for the repetition tests, for the naming and comprehension tests directly after TMS treatment as well as 4 months after stimulation. It was further

revealed that after rTMS an increased functional connectivity was obtained between the IIFG and the rIFG for theta and beta3 frequency band.

Using transcranial direct current stimulation, activating left frontal cortex with anodal stimulation has been shown to improve a naming task in aphasia (Baker, Rorden, & Fridriksson, 2010; Monti et al., 2008). Our results confirm these findings by modulating the IIFG with high frequency rTMS, which is known to increase cortical excitability.

Recovery from stroke has been attributed to neural plasticity occurring in both perilesional and contralateral hemisphere (Schlaug & Renga, 2008). Increased activation in the contralateral hemisphere after stroke may however be maladaptive leading to an inefficient strategy for recovery (Lefaucheur, 2006; Price & Crinion, 2005). This also applies for aphasia, which suggests that when there is a lesion of the Broca area (i.e., IIFG), the rIFG might compensate, but that compensation might be suboptimal. It is also known that applying low frequency rTMS, which is known to decrease cortical excitability, on the rIFG can modulate aphasia. In this patient, an increased activity in the rIFG together with a decreased activity in the IIFG in resting state activity was observed, associated with the non-fluent aphasia. After applying high frequency rTMS on the IIFG, normalization was found of activity in the IIFG as well as a decrease of beta activity in the rIFG in comparison to a control group. In addition there was

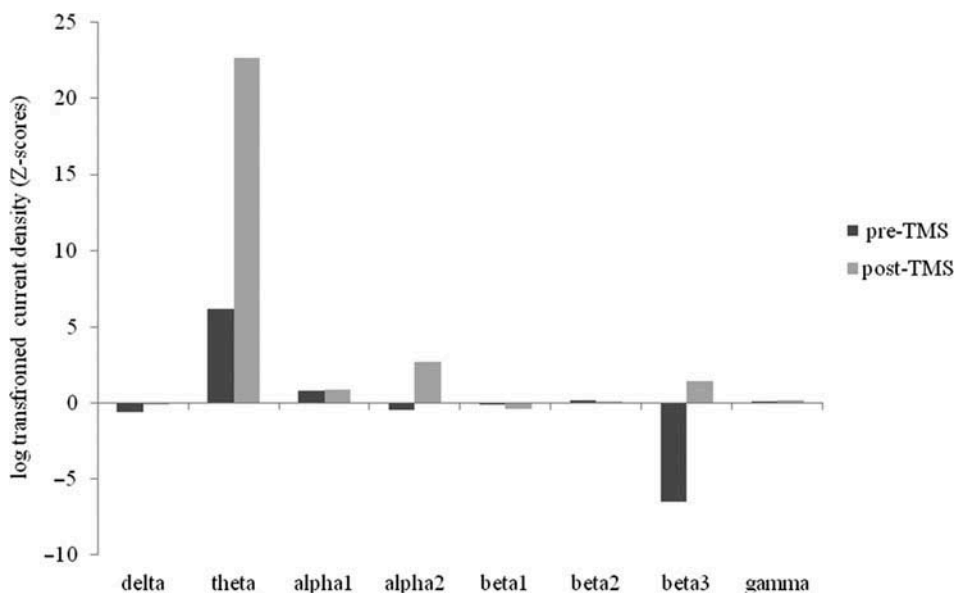


Figure 4. The lateralization index of inferior frontal gyrus for the different frequency bands pre- and post-TMS.

an increased functional connectivity between the left and right IFG, suggesting a better communication between both areas. As such, our results are in alignment with the hypothesis that a focal lesion disrupts the balance of interhemispheric inhibition and high frequency rTMS can normalize this disbalance.

We also found decreased beta activity in the left temporopolar area and increased beta activity in the right temporopolar area in the pre-treatment phase. Previous research already demonstrated that the left temporopolar area is important for word comprehension and a relationship between semantic deficits and left temporopolar atrophy has been shown (Butler, Brambati, Miller, & Gorno-Tempini, 2009; Sapolsky et al., 2010). It has further been shown in patients with left temporal damage that right superior temporal cortex activity correlates with response accuracy when subjects respond to simple and repetitive auditory instructions (Musso et al., 1999) or perform semantic decisions on auditory words (Sharp, Scott, & Wise, 2004). However, right temporopolar area activation does not necessarily reflect a laterality shift as the right hemisphere is also engaged by neurologically intact subjects in semantic decisions on auditory words (Sharp et al., 2004; Zahn et al., 2004).

PET-scan studies have demonstrated that rTMS not only modulates the directly stimulated cortical area, but that it has an effect on remote areas functionally connected to the stimulated area (Kimbrell et al., 2002). In this study it was shown that rTMS also increased activity in the Supplementary Motor Area (SMA). SMA is an area known to be involved in language: subjects who speak aloud show more activation in this area (Petersen, Fox, Posner, Mintun, & Raichle, 1988). The SMA might be part of the articulatory loop which includes a subvocal rehearsal system and a phonological store (Baddely, 1986; Paulesu, Frith, & Frackowiak, 1993). In aphasia patients activation of the SMA strongly correlates with improvement in language functioning (Saur et al., 2006). As such, the improvement on the AAT might not only be due to a normalization of IIFG and a decrease of the rIFG but also due to activation of the SMA.

Although these findings are promising further research needs to include a placebo-arm. However in our case the patient remained stably improved after TMS treatment, precluding a proper placebo arm. As the patient did not demonstrate any improvement anymore the last 2 years before starting the TMS treatment, even though she followed

speech therapy for 24 months following her stroke, it suggests the improvement is due to the TMS. Further research may use a delay start design, in which a group first receives a sham session followed by real TMS session, while another group immediately starts with the real TMS sessions.

In summary, this case study provides further evidence suggesting that IIFG and SMA are important for aphasia recovery and that high frequency rTMS can potentially promote further recovery even in long standing non-fluent aphasia.

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