Brain & Language 116 (2011) 125–135

Contents lists available at ScienceDirect

Brain & Language

journal homepage: www.elsevier.com/locate/b&l

Modulation of N400 in chronic non-fluent aphasia using low frequency Repetitive Transcranial Magnetic Stimulation (rTMS)

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A R T I C L E   I N F O

Article history:
Accepted 14 July 2010
Available online 3 August 2010

Keywords:
Repetitive Transcranial Magnetic Stimulation (rTMS)
Aphasia
Non-fluent aphasia
Event-related brain potentials (ERP)
Language rehabilitation

A B S T R A C T

Low frequency Repetitive Transcranial Magnetic Stimulation (rTMS) has previously been applied to language homologues in non-fluent populations of persons with aphasia yielding significant improvements in behavioral language function up to 43 months post stimulation. The present study aimed to investigate the electrophysiological correlates associated with the application of rTMS through measurement of the semantic based N400 Event-related brain potentials (ERP) component. Low frequency (1 Hz) rTMS was applied to the anterior portion of the homologue to Broca's area (pars triangularis), for 20 min per day for 10 days, using a stereotactic neuronavigational system. Twelve non-fluent persons with aphasia, 2–6 years post stroke were stimulated. Six participants were randomly assigned to receive real stimulation and six participants were randomly assigned to receive a blind sham control condition. ERP measures were recorded at baseline, 1 week and 2 months subsequent to stimulation. The findings demonstrate treatment related changes observed in the stimulation group when compared to the placebo control group at 2 months post stimulation indicating neuromodulation of N400 as a result of rTMS. No treatment related changes were identified in the stimulation group, when compared to the sham group from baseline to 1 week post stimulation. The electrophysiological results represent the capacity of rTMS to modulate neural language networks and measures of lexical-semantic function in participants with non-fluent aphasia and suggest that time may be an important factor in brain reorganization subsequent to rTMS.

1. Introduction

Low frequency Repetitive Transcranial Magnetic Stimulation (TMS) has recently been trialed experimentally to modulate and inhibit extraneous levels of right hemisphere (RH) activation in homologous language sites in participants with chronic non-fluent aphasia with favorable outcomes for behavioral language (Martin, Naeser, Ho, Doron, et al., 2009; Martin, Naeser, Ho, Treglia, et al., 2009; Naeser et al., 2004, 2005a, 2005b). fMRI studies accompanying rTMS applications have indicated that TMS has the capacity to decrease RH activations in some participants, with the translation of increased neural activation in left perilesional areas (Martin, Naeser, Ho, Doron, et al., 2009). Some studies have opted for time locked event-related brain potentials (ERP) recordings to provide important insight into sensory and cognitive processing associated with language tasks in normal controls and in aphasic participants (D'Arcy et al., 2003; Hagoort, Brown, & Swaab, 1996; Kojima & Kaga, 2003; Marchand, D'Arcy, & Connolly, 2002). rTMS applied to the aphasic brain informs theories of transcallosal disinhibition which may facilitate brain reorganization, promoting behavioral change (Thiel et al., 2006).

Current evidence suggests that in the healthy, undamaged brain, specialized neural areas (e.g. those specific to language function) inhibit regions ipsilateral, contralateral, or those in bilateral networks that do not participate in any specialized language function e.g. homologous sites (Netz, Ziemann, & Humberg, 1995). These mechanisms are termed collateral and transcallosal inhibition. Disruptions to these mechanisms may occur when a specialized neural area is damaged (e.g. by a stroke lesion), prompting

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doi:10.1016/j.bandl.2010.07.004

adaptive processes (plasticity) to facilitate functional reorganization. This results in a cessation of inhibitive processing, termed disinhibition (Thiel et al., 2006). Overall reorganization post stroke may draw on resources perilesional (collateral disinhibition) and contralateral (transcallosal disinhibition) to the damage (Witte et al., 1997). With respect to damage in left hemisphere (LH) language areas, transcallosal disinhibition may facilitate a functional shift in language processes from LH to the RH (homologue). In recent years, inhibitory (low frequency) rTMS has been applied to homologous language regions to modulate mechanisms of transcallosal disinhibition to promote functional reorganization to LH language regions.

An additional explanation to elucidate the effects of rTMS on the non-dominant hemisphere in chronic aphasia is offered by Hamilton et al. (2010) suggesting that language systems in the chronic aphasic brain exist in a stable yet maladaptive state and the application of rTMS may promote plastic changes and shift the language system to promote a more efficient state to support further language recovery (Devlin & Watkins, 2007). As clearly identified by Hamilton et al. (2010), this is the only existing theory that offers explanation of the continued improvements in language performance in the months post rTMS application as noted in previous investigations (Martin, Naeser, Ho, Doron, et al., 2009; Martin, Naeser, Ho, Treglia, et al., 2009; Naeser et al., 2005a) and may reflect additional improvements in connections within language networks responsible for language processing (Bi & Poo, 2001).

High levels of activation in language homologues have been identified in persons with aphasia post stroke using a variety of language tasks associated with functional neuroimaging techniques (Musso et al., 1999; Saur et al., 2006; Thompson, 2000) and ERP studies (Cobianchi & Giaquinto, 2000). The role of RH recruitment in the aphasic brain post stroke remains ill-defined and is widely accepted to be a compensatory mechanism for restitution of neural language function. Despite this, recruitment of LH sites spared by the lesion is most likely to provide the key to optimal aphasia recovery into the chronic phase of impairment (Heiss & Thiel, 2006; Karbe, Kessler, Herholz, Fink, & Heiss, 1998; Rosen et al., 2000). Exploiting its inhibitory effects, low frequency rTMS has been applied to the homologue to Broca's area in LH lesioned participants with chronic non-fluent aphasia. Significant improvements in semantic based picture naming performance have been reported post stimulation (Martin, Naeser, Ho, Doron, et al., 2009; Naeser et al., 2005a). Low frequency rTMS is postulated to inhibit overactivation in language homologues facilitating reorganization of bilateral language networks to favor left perilesional sites (Naeser et al., 2005a).

1.1. Measuring the effects of rTMS on neural language networks

Low frequency (1 Hz) rTMS has an inhibitory effect on neural activity and has been applied to the contralateral Broca's homologue, specifically Brodmann area 45, to counteract overactivation in this region. Previous investigations have demonstrated the short-term and long-term potential of rTMS to successfully modulate picture naming performance in chronic non-fluent aphasia (Martin, Naeser, Ho, Doron, et al., 2009; Naeser et al., 2005a). Additionally the incorporation of a placebo (sham) form of stimulation has been used to provide a comparison of behavioral language effects against real stimulation. To date, the neural correlates for the modulation of language in response to rTMS are ill-defined. The key question remains, can rTMS really facilitate an interhemispheric shift of language processes in persons with chronic aphasia from the RH to left perilesional regions? Further, can ERP measures targeting lexical-semantic processes in aphasia provide an accurate and sensitive indication of neurophysiological changes induced by TMS? Indeed, Hansenne, Laloyaux, Mardaga, and Ansseau (2004) have indicated the inhibitory effects of low frequency (1 Hz) rTMS administered for 15 min to the LH in normal controls can cause increased latency of P300 ERP component. Despite these significant findings, no previous investigations have sought to characterize the effect of low frequency rTMS on semantic based ERP components in the aphasic brain to inform theories of brain reorganization. Shifts in cortical activation patterns measured by fMRI post rTMS are reported with increases in left IFG cortical activations, and decreases in RH activations accompanying behavioral language improvements in aphasia (Martin, Naeser, Ho, Doron, et al., 2009). fMRI and PET techniques are commonly used to inform neural activation patterns across specific brain regions in response to a particular task or paradigm. These techniques provide spatial accuracy relating to neural language responses however, these notably lack aspects of temporal acuity seen in ERP recordings (Laganaro, Morand, Schwitter, Zimmermann, & Schnider, 2008; Lau, Phillips, & Poeppel, 2008). ERPs provide specific and beneficial information regarding language processing in the aphasic brain.

1.2. Event-related brain potentials informing language reorganization in aphasia

Event-related brain potentials (ERPs) have been increasingly used to investigate specific brain functions involved in language comprehension and production (Caplan, 1994; Friederici, 1995; Friederici, Hahne, & Mecklinger, 1996; Kutas & van Petten, 1994) across a myriad of language based paradigms. The electrophysiological changes associated with language recovery in aphasia have been also been documented using a variety of experimental paradigms (Cohen et al., 2001; Dobel et al., 2002; Laganaro et al., 2009; Meinzer et al., 2004; Nolfe, Cobianchi, Mossuto-Agatiello, & Giaquinto, 2006) overall demonstrating the remediation of some deviant neural patterns over time. Time locked ERPs are widely accepted as a sensitive measure of changes in language processing in participants with organic language deficits (Angrilli, Elbert, Cusumano, Stegagno, & Rockstroh, 2003; Dobel et al., 2001, 2002; Friederici, von Cramon, & Kotz, 1999; Marchand, D'Arcy, & Connolly, 2002). For instance, mean amplitude and latency of ERP components are reported to be reduced and ERP topography deviated in participants with aphasia when compared to normal controls (Papanicolaou, Moore, Levin, & Eisenberg, 1987; Reuter, Schönle, & Kurthen, 1994; Swaab, Brown, & Hagoort, 1997). Although the multitude of ERP investigations on the aphasic brain are beneficial to provide insight into neural correlates associated within impaired language processing, the wide array of paradigm designs and variances in multi modal stimuli presentation impede the interpretation of many ERP responses and what they represent in terms of recovery mechanisms.

Characterizing ERP measures in persons with aphasia has been constructive in understanding the anatomical substrates of compensatory brain responses in the presence of a lesion. Szelies, Mielke, Kessler, and Heiss (2002) provided evidence to show that preservation of LH is important for compensation, and attributed abnormal EEG responses within and outside speech areas to compensation and recovery in post stroke aphasia. Similar compensatory neural responses in aphasia have been reported in fMRI studies (Heiss et al., 1997; Karbe et al., 1998) exhibiting activations in language homologues and left perilesional sites. Additionally, ERP measures have been utilized to measure neurophysiological changes and reorganization associated with behavioral therapy interventions. Pulvermuller, Hauk, Zohsel, Neininger, and Mohr (2005) measured the electrophysiological changes associated with a protocol of constraint induced language therapy on 10 participants with chronic aphasia indicating stronger ERP amplitudes