CORTEX 48 (2012) 1179–1186

Available online at www.sciencedirect.com

SciVerse ScienceDirect

Journal homepage: www.elsevier.com/locate/cortex

Research report

The right hemisphere is not unitary in its role in aphasia recovery

Peter E. Turkeltaub [a,b,*], H. Branch Coslett [a], Amy L. Thomas [a], Olufunsho Faseyitan [a], Jennifer Benson [a], Catherine Norise [a] and Roy H. Hamilton [a]

[a] Laboratory for Cognition and Neural Stimulation, Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA

[b] Department of Neurology, Georgetown University, Washington, DC, USA

ARTICLE INFO

Article history:
Received 24 March 2011
Reviewed 6 May 2011
Revised 19 May 2011
Accepted 10 June 2011
Action editor Roberto Cubelli
Published online 30 June 2011

Keywords:
Aphasia
Transcranial magnetic stimulation
Plasticity
Neuromodulation
Interhemispheric inhibition

ABSTRACT

Neurologists and aphasiologists have debated for over a century whether right hemisphere recruitment facilitates or impedes recovery from aphasia. Here we present a well-characterized patient with sequential left and right hemisphere strokes whose case substantially informs this debate. A 72-year-old woman with chronic nonfluent aphasia was enrolled in a trial of transcranial magnetic stimulation (TMS). She underwent 10 daily sessions of inhibitory TMS to the right pars triangularis. Brain activity was measured during picture naming using functional magnetic resonance imaging (fMRI) prior to TMS exposure and before and after TMS on the first day of treatment. Language and cognition were tested behaviorally three times prior to treatment, and at 2 and 6 months afterward. Inhibitory TMS to the right pars triangularis induced immediate improvement in naming, which was sustained 2 months later. fMRI confirmed a local reduction in activity at the TMS target, without expected increased activity in corresponding left hemisphere areas. Three months after TMS, the patient suffered a right hemisphere ischemic stroke, resulting in worsening of aphasia without other clinical deficits. Behavioral testing 3 months later confirmed that language function was impacted more than other cognitive domains. The paradoxical effects of inhibitory TMS and the stroke to the right hemisphere demonstrate that even within a single patient, involvement of some right hemisphere areas may support recovery, while others interfere. The behavioral evidence confirms that compensatory reorganization occurred within the right hemisphere after the original stroke. No support is found for interhemispheric inhibition, the theoretical framework on which most therapeutic brain stimulation protocols for aphasia are based.

1. Introduction

In 1877, Barlow described a boy who developed aphasia after a stroke involving Broca's area, recovered significantly, but then worsened after a symmetric stroke in the right hemisphere (RH) (Barlow, 1877). This case was taken as evidence that the RH can reorganize in order to assume functions of the left hemisphere (LH) in aphasia, and launched a debate regarding the role of the

* *Corresponding author*. Georgetown University, Neurology Department, 4000 Reservoir Road, Building D Suite 207, Washington, DC 20057, USA.

E-mail address: turkeltp@georgetown.edu (P.E. Turkeltaub).

0010-9452/$ – see front matter

http://dx.doi.org/10.1016/j.cortex.2011.06.010

RH in aphasia recovery that continues today. Only a few similar cases have followed (Basso et al., 1989), and the validity of the original case has recently been subject to debate (Hellal and Lorch, 2007). Behavioral studies demonstrating a left visual field or left ear advantage for verbal stimuli, Wada studies demonstrating worsening with right carotid injection, and cases of language recovery after left hemispherectomy supported RH involvement in aphasia recovery [see Basso et al. (1989) for review]. However, as research tools have become more precise, the role of the RH has become less clear. Some functional imaging studies have supported compensatory RH recruitment (Blasi et al., 2002; Leff et al., 2002; Musso et al., 1999; Ohyama et al., 1996; Saur et al., 2006), although the RH is thought to be computationally less efficient in its language processing than native LH areas (Heiss et al., 1999, 2003; Winhuisen et al., 2005). Others have concluded that RH activity is "ineffective" (Postman-Caucheteux et al., 2010; Richter et al., 2008) or is associated with nonlinguistic processes like executive control that are called upon nonspecifically when processing load is high (van Oers et al., 2010).

Another hypothesis is that the RH is aberrantly recruited after a LH stroke due to a release of left-to-right transcallosal inhibition. Over-activity in RH areas then putatively inhibits recovery of LH perilesional cortex, limiting recovery from aphasia. This "theory of interhemispheric inhibition" has motivated several studies attempting to use inhibitory RH transcranial magnetic stimulation (TMS) as a treatment to improve aphasia (Barwood et al., 2011; Naeser et al., 2005). Responses to local inhibition of the RH using TMS have varied between patients (Winhuisen et al., 2007), and between stimulation targets (Hamilton et al., 2010), but the most consistent effect of RH TMS has been sustained improvement in speech production after inhibition of the right pars triangularis (Barwood et al., 2011; Hamilton et al., 2010; Martin et al., 2009b; Naeser et al., 2005). This beneficial effect of inhibitory RH TMS on aphasia recovery has been taken as evidence that RH recruitment is detrimental to recovery.

Variation between patients in the role of the RH in aphasia recovery may explain some of the inconsistencies in the literature, but it is equally plausible that different areas within the RH play competing roles in aphasia recovery even within a single patient. Reorganization after LH injury may result in compensatory recruitment of some RH areas, while others interfere with recovery. Here we present a patient whose aphasia improved after TMS-induced inhibition of the right pars triangularis, but then worsened after a distant RH stroke. Specific patterns in performance demonstrate unequivocally that the initial LH stroke induced compensatory reorganization within RH networks supporting language. The dissociation between the effects of TMS and the RH stroke provides clear evidence that different areas of the RH can have opposing effects on aphasia recovery in a single patient, and raises questions regarding the proposed mechanism of therapeutic TMS.

2. Methods

2.1. *Clinical trial and neuropsychology methods*

The patient was enrolled in a randomized subject-blinded sham-controlled partial crossover trial of TMS for chronic nonfluent aphasia (clinicaltrials.gov ID: NCT00608582). Procedures were approved by the University of Pennsylvania IRB. Written informed consent was obtained from the subject. The trial protocol has been described in detail previously (Martin et al., 2009b). The subject underwent three sessions of neuropsychological testing to establish a stable baseline measurement of language and cognitive function prior to TMS exposure. This battery included the first 30 items of the Boston Naming Test (BNT), selected subtests of the Boston Diagnostic Aphasia Examination (BDAE), and the Cognitive Linguistic Quick Test (CLQT). CLQT composite scores were calculated excluding the symbol cancelation subtest due to a difference in the method of administration between sessions. The same neuropsychological battery was repeated two and six months after TMS treatment to assess the long-term effects of TMS. To facilitate comparison across tests, raw neuropsychological scores at follow-up sessions were *Z*-transformed based on the mean and standard deviation (SD) of the three baseline assessments [i.e., (Follow-up score − Mean of baseline scores)/(SD of baseline scores)]. Significance of *Z*-scores was tested at a Bonferroni corrected 2-tailed alpha of .05.

2.2. *TMS methods*

To identify a TMS target for treatment, 1 Hz repetitive TMS (rTMS) was applied at 90% resting motor threshold (rMT) for 10 min to each of 6 candidate RH targets in separate sessions. The rMT was determined as the intensity that induced visible contractions of the left first dorsal interosseous muscle on 5 out of 10 pulses delivered to the right motor hand area. Candidate sites were selected based on gyral anatomy on the patient's T1-weighted magnetic resonance imaging (MRI) scan to include the three major divisions of the inferior frontal gyrus (pars opercularis, pars triangularis, and pars orbitalis) and the motor cortex mouth area, maintaining relatively equal distances along the brain surface between targets. A picture-naming task was given before and after stimulation at each session to assess for TMS-induced improvement. Items were presented on a computer monitor for 3 sec with an additional 7-sec response period. Item lists were matched for frequency and consisted of 20 repeated pictures tested at every session and 20 items only presented once across all sessions (40 items total per list, 400 sec total task duration per administration). After all candidate sites were tested, the treatment target was selected as the site with the largest percent increase in naming accuracy from pre- to post-TMS. Ten daily 20-min treatment sessions of 1 Hz TMS were then administered at 90% rMT to this therapeutic target over two weeks.

2.3. *fMRI methods*

Block-designed fMRI was performed comparing overt picture naming to pattern viewing [3 runs using the paradigm described by Martin et al. (2005)]. Scans were acquired on a 3 T Siemens Trio scanner; T1-weighted (160 slice, time to repeat (TR) = 1620, time to echo (TE) = 3.87 msec, field of view (FOV) = 192 × 256, 1 × 1 × 1 mm voxels) and echoplanar images (31 slices, TR = 3000, TE = 35 msec, FOV = 64 × 64 mm, 3.75 × 3.75 × 4 mm voxels) were acquired. In the task condition, pictures from the Snodgrass and