Plastic changes following imitation-based speech and language therapy for aphasia: a high-density sleep EEG study

Sarasso, S; Määttä, S; Ferrarelli, F; Poryazova, R; Tononi, G; Small, S L

Abstract: BACKGROUND OBJECTIVE: measurement of plastic brain changes induced by a novel rehabilitative approach is a key requirement for validating its biological rationale linking the potential therapeutic gains to the changes in brain physiology. Objective. Based on an emerging notion linking cortical plastic changes to EEG sleep slow-wave activity (SWA) regulation, we aimed to assess the acute plastic changes induced by an imitation-based speech therapy in individuals with aphasia by comparing sleep SWA changes before and after therapy. METHODS: A total of 13 left-hemispheric stroke patients underwent language assessment with the Western Aphasia Battery (WAB) before and after 2 consecutive high-density (hd) EEG sleep recordings interleaved by a daytime session of imitation-based speech therapy (Intensive Mouth Imitation and Talking for Aphasia Therapeutic Effects [IMITATE]). This protocol is thought to stimulate bilateral connections between the inferior parietal lobule and the ventral premotor areas. RESULTS: A single exposure to IMITATE resulted in increases in local EEG SWA during subsequent sleep over the same regions predicted by the therapeutic rationale, particularly over the right hemisphere (unaffected by the lesion). Furthermore, changes in SWA over the left-precentral areas predicted changes in WAB repetition scores in our group, supporting the role of perilesional areas in predicting positive functional responses. CONCLUSIONS: Our results suggest that SWA changes occurring in brain areas activated during imitation-based aphasia therapy may reflect the acute plastic changes induced by this intervention. Further testing will be needed to evaluate SWA as a non-invasive assessment of changes induced by the therapy and as a predictor of positive long-term clinical outcome.

DOI: https://doi.org/10.1177/1545968313498651

Posted at the Zurich Open Repository and Archive, University of Zurich
ZORA URL: https://doi.org/10.5167/uzh-89042
Accepted Version

Originally published at:
Sarasso, S; Määttä, S; Ferrarelli, F; Poryazova, R; Tononi, G; Small, S L (2014). Plastic changes following imitation-based speech and language therapy for aphasia: a high-density sleep EEG study. Neurorehabilitation and Neural Repair, 28(2):129-138.
DOI: https://doi.org/10.1177/1545968313498651
Sleep electrophysiology in aphasia treatment

Plastic changes following imitation-based speech and language therapy for aphasia: A high density (hd) sleep EEG study

Simone Sarasso, PhD1,2, Sara Maatta, MD, PhD3, Fabio Ferrarelli, MD, PhD1, Rositsa Poryazova, MD4, Giulio Tononi, MD, PhD1, Steven L. Small, MD, PhD5,6

1Department of Psychiatry, University of Wisconsin-Madison, Madison, Wisconsin, USA
2Department of Biomedical and Clinical Sciences “Luigi Sacco”, University of Milan, Milan, Italy
3Department of Clinical Neurophysiology, Kuopio University Hospital, University of Eastern Finland, Kuopio, Finland
4Department of Neurology, University Hospital Zurich, Switzerland
5Department of Neurology, The University of Chicago, Chicago, Illinois, USA
6Department of Neurology, University of California, Irvine, Irvine, California, USA

Corresponding author:
Dr. Simone Sarasso, PhD. Department of Biomedical and Clinical Sciences “Luigi Sacco”, University of Milan, Milan, Italy. Via G.B. Grassi, 74. 20157 Milan, Italy.
Phone: +39.02.503.19885; Fax: +39.02.503.19886;
email address: simone.sarasso@unimi.it

Word Count: 4182
Figures: 4
Tables: 3
Abstract

Background: Objective measurement of plastic brain changes induced by a novel rehabilitative approach is a key requirement for validating its biological rationale linking the potential therapeutic gains to the changes in brain physiology.

Objective: Based on an emerging notion linking cortical plastic changes to EEG sleep slow wave activity (SWA) regulation, we aimed to assess the acute plastic changes induced by an imitation-based speech therapy in individuals with aphasia by comparing sleep SWA changes before and after therapy.

Methods: Thirteen left-hemispheric stroke patients underwent language assessment with the Western Aphasia Battery (WAB) before and after two consecutive high density (hd)-EEG sleep recordings interleaved by a daytime session of imitation-based speech therapy (IMITATE). This protocol is thought to stimulate bilateral connections between the inferior parietal lobule and the ventral premotor areas.

Results: A single exposure to IMITATE resulted in increases in local EEG SWA during subsequent sleep over the same regions predicted by the therapeutic rationale, particularly over the right hemisphere (unaffected by the lesion). Further, changes in SWA over the left precentral areas predicted changes in WAB repetition scores in our group, supporting the role of perilesional areas in predicting positive functional responses.

Conclusions: Our results suggest that SWA changes occurring in brain areas activated during imitation-based aphasia therapy may reflect the acute plastic changes induced by this intervention. Further testing will be needed in order to evaluate SWA as a
non-invasive assessment of changes induced by the therapy and as a predictor of positive long-term clinical outcome.
Introduction

About a third of patients suffering from ischemic stroke have speech and language problems at the onset, and more than half of these have persistent aphasia, accompanied by its marked physical and social consequences\textsuperscript{1,2}.

Depending on individual factors (e.g., the extent of neural tissue spared by the lesion in functional networks involved in speech and language production and comprehension), aphasic patients may undergo some degree of spontaneous recovery, which can be fostered by rehabilitative therapy\textsuperscript{3}.

Classically, behavioral treatment of non-fluent aphasia has focused on speech production, therefore relying on an intrinsically impaired domain in these patients. This approach has often yielded minimal clinical benefits\textsuperscript{4}. More recently, neuroimaging studies have revealed that the same brain areas implicated in impaired speech production are also involved in speech perception and observation\textsuperscript{5}, thus paving the road for a conceptually new approach to non-fluent aphasia rehabilitation.

Along these lines, a new computer-based therapy, the Intensive Mouth Imitation and Talking for Aphasia Therapeutic Effects (IMITATE) has been recently proposed\textsuperscript{6}. IMITATE is an intensive protocol based on action observation and imitation, which are thought to activate the brain circuits underlying action execution in the observer, even without explicit motor output\textsuperscript{7,8}. Imitation has historically played an important role in many treatments for aphasia\textsuperscript{9}, with the rationale that sensory input complements other available information for the benefit of oral speech mechanisms. Interestingly, speech imitation is associated with bilateral connections between the inferior parietal lobule and the ventral premotor areas\textsuperscript{10}. Therefore, facilitating the complex interaction between
these brain areas may contribute to the cortical synaptic plastic changes underlying functional recovery in aphasia\textsuperscript{11}.

The ability to measure objectively such plastic changes in individuals undergoing rehabilitative protocols is a key requirement for validating the neurobiological basis of the therapeutic rationale as well as for linking the potential behavioral gains to the changes in brain physiology.

Increasing evidence in healthy humans and animals suggests that sleep slow wave activity (SWA) plays an important role in regulating synaptic plasticity and reorganization\textsuperscript{12–15}. Specifically, while wakefulness favors synaptic potentiation, sleep SWA may promote synaptic depression to obtain a general rescaling of synaptic strength, therefore serving a homeostatic function\textsuperscript{16}.

An intriguing implication of the link between sleep SWA and synaptic strength is that, as synaptic efficacy is strengthened more during the day in a specific cortical area, subsequent sleep SWA should be locally increased in that area as compared to the rest of the cortex\textsuperscript{12}. This effect relies on the notion that stronger synapses lead to stronger cortico-cortical connections and, in turn, in increased synchronization among populations of neurons\textsuperscript{17}. Increased synchronization is then reflected in slow waves of larger amplitude at the EEG level\textsuperscript{16}.

More generally, sleep offers important advantages for investigating potential electrophysiological markers of therapeutic efficacy in neurological patients. In fact, sleep recordings minimize waking-related confounding factors, including fluctuation in attention and reduced cognitive ability\textsuperscript{18}. 
In this study we assessed the local plastic changes induced by IMITATE in individuals with aphasia using sleep SWA as an electrophysiological marker. By comparing high density (hd)-EEG sleep recordings before and after IMITATE we aimed at non-invasively locating the cortical areas involved in the reorganization induced by the IMITATE protocol, thus directly testing the neurophysiological principles underlying this specific rehabilitative approach.

**Methods**

*Patients*

Seventeen right-handed individuals with previous left hemisphere ischemic stroke and resulting aphasia were recruited to participate in the study. Inclusion criteria were assessed by a preliminary screening as follows: 1) history of a single, chronic (> 9 months), CT or MRI documented ischemic stroke of the left hemisphere; 2) medical and neurological stability; 3) native speaker of English. All patients meeting these criteria underwent a language assessment with the Western Aphasia Battery. Those with an Aphasia Quotient (AQ) between 20 and 95 were invited to participate in the sleep study. Two candidates were excluded at this stage (both had AQ scores > than 95, indicating a very modest speech impairment). Each of the remaining 15 participants underwent two sleep recordings, one at baseline and another following a session of imitation-based aphasia therapy with IMITATE. Two patients were excluded from the study during this portion of the study, one who dropped out after the first sleep recording (very poor sleep quality, probably due to the novel experimental setting) and the other due to technical
reasons during the second sleep recording (computer hard drive failure during data acquisition). Results are thus presented for a sample that includes the remaining thirteen patients (8 male; mean age 52 ± 10.9; mean age at stroke 46 ± 10.6). See Table 1 for details. The Institutional Review Board of the Division of Biological Sciences of The University of Chicago approved all experimental procedures. All participants provided written informed consent prior to any behavioral testing or sleep studies.

Language assessment

Language and cognitive assessments were conducted prior to the first night of sleep and repeated following the second night of sleep. Speech-language testing comprised administration of 3 standardized measures including the Apraxia Battery for Adults-2 (subtests 1, 2A, 2B, 5), the Boston Naming Test, and the Western Aphasia Battery (Part 1; Aphasia Quotient). For a full description of the speech assessment scores before and after IMITATE see Table 2.

Structural Magnetic Resonance Imaging (MRI) assessment

To obtain precise indication of overall lesion extent at the time of the recordings, patients underwent structural MRI assessment. Three patients were excluded due to contraindications to MRI (one patient had a pacemaker and two others felt discomfort during the scan session and had to be withdrawn). MRI scans were acquired at the Center for Advanced MRI at Northwestern University using a Siemens 3T Trio scanner. Image acquisition consisted of a single T1-weighted high resolution, three-dimensional whole brain anatomical scan, using a magnetization-prepared rapid gradient echo [MPRAGE] sequence (1 mm isotropic resolution).
IMITATE therapy

IMITATE is an intensive physiologically-based therapy, which uses over 3,000 unique video clips of words and phrases spoken by six different standard American English speakers. During the therapy session, participants viewed videos of six different talkers uttering the identical word or phrase, followed by a 20 second period during which they were asked to produce the same word or phrase as many times as they could. The therapy uses only ecologically valid stimuli, i.e., English words and sentences spoken by a visible speaker using normal prosody). For a detailed description of IMITATE features, please see 6. For this study, we used a modified version of the IMITATE rehabilitation protocol, that compressed the six-week, ninety minute per day protocol to a 3.5 hour intensive single session occurring between the two nights of sleep. Patients enrolled in the research were naive to the IMITATE protocol before the study procedures, but several were subsequently enrolled in the six-week study.

Study procedures

All sleep EEG recordings were performed in the General Clinical Research Center (GCRC) of The University of Chicago. Following initial behavioral testing, participants donned EEG electrode caps, and were instructed to go to bed at their usual bedtime. After eight hours in bed, the baseline night recording was stopped and the EEG sensor cap was removed. After the baseline sleep period, participants spent the morning in their room at the GCRC, and were allowed to carry out their normal daytime activities. In the afternoon (around 2 PM), patients performed a 3 hour long IMITATE session divided into six blocks of one half hour each. After dinner (around 8PM) they performed another half-hour block of IMITATE. Once rehabilitative procedures were terminated, they again
donned the EEG sensor cap and were allowed to go to bed. Lights were turned off at the same time as on the baseline night, and post-treatment sleep EEG data were acquired for eight hours.

Sleep EEG acquisition

Whole night, EEG sleep recordings were acquired with a 256-sensor, high-density (hd) (EGI Inc., Eugene, OR) EEG system on two consecutive nights. This procedure allows for a within-subject comparison of the sleep EEG topographies with adequate spatial resolution, thus allowing for the detection of local changes in EEG power. During both recording nights, sleep EEG signals were sampled at 500 Hz, acquired referenced to Cz electrode and online filtered DC-200Hz using NetStation software (EGI Inc., Eugene, OR). Impedance were kept below 50 KOhm at the beginning of each recording for all EEG derivations.

Sleep EEG Spectral Analysis

Sleep stages were offline visually scored in 20-second epochs (American Academy of Sleep Medicine standard criteria\textsuperscript{19}). NREM sleep episodes were defined according to standard criteria\textsuperscript{20,21} applied on the C3A2 and C4A1 derivations as well as to right and left electrooculographic (EOG), and electromiographic (EMG) signals derived from bipolar re-referencing of EEG derivations located over frontal and neck regions, respectively. After removing electrodes located on the neck/face as well as those with impedances >150 KOhms at the end of the recording, signals from all the remaining derivations (175-185) were processed using custom Matlab routines. Signals were first first-order high-pass filtered (Kaiser type FIR, 0.1 Hz), downsampled to 128 Hz using the Matlab function \textit{resample}, then average referenced and filtered (0.5 to 40Hz; 2-way least-
squares FIR bandpass filter) using the `eegfilt` function of the EEGLab Matlab toolbox \(^{22}\). Spectral density analysis (Welch’s averaged modified periodogram with a Hamming window, averages of five 4-second epochs) with a 0.25 Hz bin resolution was performed. NREM sleep epochs exceeding a threshold based on the mean power values in the 0.75 to 4.5 Hz and 20 to 30 Hz frequency bands in at least one channel were excluded from the analysis. For each EEG electrode SWA was calculated as the average spectral density between 1 and 4.5 Hz in artifact-free 20 second NREM epochs. In order to investigate topographical changes before and after IMITATE, SWA values for each electrode were then normalized by the mean value across all derivations for the two nights separately. For the topographical display of SWA, we used the `topoplot` function of the EEGLab Matlab toolbox \(^{22}\).

**Statistics**

Statistical nonparametric mapping (SnPM \(^{23}\)) was used to assess topographical changes in hd-EEG SWA analysis induced by IMITATE. This method takes advantage of the actual data distribution and accounts for multiple comparisons testing in hd-EEG recordings. For sleep parameters, we used two-tailed paired t-tests with significance set at \(p < 0.05\).

**Results**

As shown in Figure 1, most patients (8 out of 10) had lesions located over left precentral regions (inferior frontal gyrus, pars opercularis and insula) and over left postcentral regions (inferior parietal lobule), while fewer patients had lesions involving a
broad range of cortical regions of the left hemisphere. Group average aphasia severity assessed by the Western Aphasia Battery (WAB) Aphasia Quotient (AQ) was 77.85 \pm 3.51 (minimum: 56.8; maximum: 95; n=13). Table 1 summarizes the clinical features of our participant group.

**Speech assessment before and after IMITATE**

We collected a post-treatment language assessment on most of our patients (n=11). As expected for a single exposure to the therapeutic regimen, the overall AQ (as well as WAB subscores), the Apraxia Battery for Adults-2 subtests and the Boston Naming Test did not show any significant change after IMITATE (see Table 2).

**Sleep parameters before and after IMITATE**

After IMITATE, sleep parameters were substantially unchanged as compared to those observed during baseline sleep (see Table 3). Altogether, these observations confirm that patients slept in a comparable manner during both nights in the GCRC, also suggesting that their baseline sleep was not affected by a “first-night effect”, sometimes found without a proper adaptation night.

**IMITATE effects on NREM Sleep EEG**

Average slow-wave activity (SWA) was calculated for each NREM sleep episode for both baseline and post-treatment nights. Figure 2A shows the average SWA during the initial 30 minutes of the first NREM sleep episode for both nights. This part of the night is characterized by the highest SWA and has been previously employed to demonstrate plasticity-related SWA changes \(^{12,24}\). Here we found that IMITATE produced a significant local increase in SWA at a cluster of electrodes located across the right central
sulcus (Figure 2B; p < 0.05; SnPM, supra-threshold cluster analysis) over a region overlapping motor, premotor, superior temporal and parietal cortical areas. This local increase (14 ± 4% compared to baseline) was not confined to the beginning of the night but was also present during the entire first, second, and third NREM sleep episodes (Figure 3; p < 0.05), consistent with previous findings from our group 25. Finally, we tested whether such local effects were specific for the SWA range. To do so, we subdivided the broadband (1 to 30 Hz) spectral density calculated over the significant cluster into standard frequency ranges (SWA: 1-4.5Hz; Theta: 5-8Hz; Alpha: 8-12Hz; Sigma: 12-16Hz; Beta: 16-30Hz) during the first 30 minutes of the first NREM sleep episode. In addition to the above-mentioned SWA effect, a paired t-test showed increased Beta activity (p < 0.05, data not shown).

Local SWA changes and speech performance

We then tested whether SWA changes were associated with changes in speech and language performance as measured with the WAB. Among the WAB subscales, the Repetition subscale was the only showing a trend towards a significant improvement after the imitation-based therapy (from 75.5 to 79.3; two-tailed t-test p = 0.06, uncorrected). We therefore performed a planned correlation (Pearson's correlation) between the change in WAB Repetition subtest score and the change in SWA during the first 30 minutes of the first NREM sleep episode across all the EEG derivations. Results are illustrated in Figure 4. A cluster of significant (p < 0.05) positive correlations was found over the left hemisphere involving central as well frontal derivations.
Discussion

In the present study we employed whole-night sleep hd-EEG recordings to investigate the effects of a single intensive exposure to speech-language therapy on brain plasticity. We focused on an imitation-based computer-assisted rehabilitative protocol for aphasia treatment aimed at brain remodeling in the parietal-frontal motor pathway known to be important in action observation and imitation. During NREM sleep following the IMITATE protocol -practiced for 3.5 hours during a single day- we found a local increase in EEG SWA in a group of individuals with ischemic stroke and accompanying aphasia.

This local increase in SWA was found over a set of cortical areas shown to be particularly active during both speech observation and imitation in healthy individuals (e.g., 5,10,26). Results derived from activation networks based on structural equation modeling (SEM) of fMRI series during observation and imitation of syllables showed that bilateral connections between the inferior parietal lobule and premotor ventral areas are involved in both observation and imitation, pointing to the notion that observation and imitation of speech engage a frontal-parietal network with significant homologies to the “mirror neuron” circuit in macaque 11.

It is well established that sleep slow waves can be regulated at a local level based on prior waking activity 27–31. Many recent studies, however, have also shown that changes in NREM SWA reflect the occurrence of changes in synaptic strength in local networks, consistent with the idea that neuronal plasticity and sleep need are linked 16,32. In humans, a 5 Hz potentiation protocol using repetitive transcranial magnetic stimulation (rTMS) results in local potentiation of cortical responses, consistent with synaptic strengthening followed by a local increase in sleep SWA 33,34. Similarly, paired-associative stimulation...
(PAS) protocols involving induction of either cortical potentiation or depression results in local NREM SWA increases and decreases, respectively \(^{35}\). Finally, in both humans and rats, learning a motor task increases NREM SWA specifically in the trained cortical area \(^{12,36}\). Thus, it is likely that the increase in sleep SWA over the right hemisphere observed in the present study may underlie a change in synaptic strength in those cortical circuits engaged by the IMITATE protocol during the day.

It is worth reporting that NREM sleep EEG spectral features \(^{37}\) and topographies \(^{38}\) have been previously shown to be very stable within individuals across different nights even after massive global behavioral and pharmacological manipulations such as total sleep deprivation \(^{39}\) and the administration of GABAergic agents \(^{40}\). This sleep EEG power “fingerprint” may reflect individual peculiarities of brain functional anatomy, which are known to be determined by genetic factors. It is therefore likely that the local topographical SWA changes found here are reflective of genuine effects induced by the behavioral intervention occurring between the two nights (see similar effects reported in \(^{24}\)).

These changes were found during the course of the entire night (Figure 3). As previously discussed in \(^{25}\), plastic events occurring closer to sleep time may have a larger influence on NREM EEG at the beginning of sleep, during the first sleep cycle. By contrast, plastic events occurring at an earlier time during the day may be more detectable at a later time in sleep NREM EEG power. In line with this study, our IMITATE protocol was carried out during the afternoon up until few hours before the patients' bedtime, thereby inducing SWA changes throughout the night.
In addition, following therapy, high frequency EEG activity in the beta range was found to be increased over the same area that showed SWA effects. This result is in line with a previous report showing that human sleep slow waves tend to modulate spindle as well as beta EEG activity. Thus, increased synchronization leading to larger slow waves (as reflected by increased SWA) may be also associated with more synchronous beta frequency modulation and, in turn, to increased beta activity.

This is the first study in which the link between local sleep SWA and plasticity is investigated in a population presenting cortical brain lesions. Although observation and imitation of speech is known to involve both hemispheres in healthy individuals (e.g.\textsuperscript{10}), here, the relative heterogeneity of cortical lesion over the left hemisphere (Figure 1) characterizing our patients' group may explain why the observed changes induced by IMITATE (Figure 2) were most consistently found over the right, healthy hemisphere.

Recently, a regional increase in SWA was found to be associated with behavioral improvement in performance on a previously learned task\textsuperscript{12}, thus strictly linking synaptic downscaling during sleep with behavioral gains\textsuperscript{16}.

Here we observed a correlation between the SWA changes and the improvement in WAB Repetition subscale scores after IMITATE in a cluster of electrodes located over the left hemisphere and overlapping with the areas predicted by the therapeutic rationale.

These preliminary observations, although limited by the single exposure to speech therapy and by the small sample size, seem to suggest that the effects of IMITATE over perilesional left-hemispheric regions might be predictive of functional outcome.

Supporting this view, previous preliminary work based on fMRI data from a single aphasic patient reported long term reorganization of a left hemispheric functional
network towards the normative model\textsuperscript{10} after the administration of the full six week IMITATE therapy\textsuperscript{42}. This is consistent with recent\textsuperscript{43} and earlier imaging studies\textsuperscript{44} of aphasia recovery.

Any intense behavioral manipulation involving experience-dependent plasticity exerts its effect over widespread areas of the cortex involved in the task execution. Our data are in line with previous human and animal models of stroke recovery revealing functional and structural neural plasticity occurring both in perilesional areas and in brain regions distant from the lesion site\textsuperscript{45–48}, and further imply a dynamic process for aphasia recovery. The observed changes in SWA after IMITATE over the right hemisphere (here not predictive of functional outcome) may thus reflect functional reorganization induced by the therapy possibly related to the specific task execution \textit{per se} rather than linked to speech function recovery.

Although the role of the left versus the right hemisphere in facilitating recovery from aphasia has been a highly debated issue in clinical research\textsuperscript{49}, it is becoming increasingly accepted that perilesional left hemisphere activity in aphasia post-stroke predicts the best language outcomes. Of course, such activity – and the concomitant outcome – largely depends on the left hemispheric lesion extent. Usually, patients with small lesions of the left hemisphere tend to recruit left perilesional areas with variable involvement of right-hemispheric structures\textsuperscript{44,50,51}. Conversely, in patients with relatively large lesions in the left hemisphere, the only path to recovery may be through the recruitment of homologous language and speech-motor regions in the right hemisphere\textsuperscript{50–54}.

Thus, in order to shed light on which path to recovery IMITATE protocol is more actively stimulating, future studies should apply the standard six week IMITATE
protocol on patients affected by small left hemispheric lesions versus patients with lesions involving large portions of the left hemisphere. In addition, in order to test the reliability of the changes in sleep SWA in predicting positive long-term clinical outcomes, patients' sleep as well as speech assessment should be reassessed both after the first exposure to IMITATE and at the end of the full therapeutic regimen therefore also excluding potential learning effects due to repeated exposure to the WAB items.

In order to test for the specificity of the observed local changes, in future studies, it would also be important to compare the effects on sleep SWA following IMITATE with those obtained by applying other intensive speech therapeutic interventions not specifically targeting the imitation domain.

Altogether, these findings suggest that plastic changes occurring in areas activated during the execution of IMITATE, possibly reflecting the effectiveness of such intervention, therefore providing evidence for the neurobiological rationale of the therapy. Furthermore, these results support the notion that sleep hd-EEG, and the topographical analysis of SWA, is well suited to investigating local brain plastic changes underpinning functional recovery in neurological populations, allowing for a non-invasive and repeatable assessment of such changes.

Acknowledgements

The work described here has been supported by the National Institute of Deafness and other Communication Disorders of the National Institutes of Health of the United States of America under grant R01-DC-0007488 (Dr. Small) and by the James S. McDonnell
Foundation grant to the Brain Network Recovery Group and The Virtual Brain project (Drs. Small and Tononi) as well as by the support of “Dote ricerca”: FSE, Regione Lombardia (Dr. Sarasso). The aphasia testing described here was performed by speech-language pathologists in the laboratory of Dr. Leora Cherney at the Rehabilitation Institute of Chicago, including Edie Babbitt, Robert Rosalind Hurwitz, and Jaime Lee. In addition, both Blythe Buchholz and Rob Fowler provided critical technical support at The University of Chicago, and Susan Duncan helped significantly at the University of California, Irvine. The support of our funding agencies and these supporting personnel is gratefully acknowledged.

References


### Table 1. Study Participants

Demographic and clinical data on the 13 participants who completed the study.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (y)</th>
<th>Age at Stroke (y)</th>
<th>Psychoactive Medication</th>
<th>Aphasia Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>50</td>
<td>48</td>
<td>N/A</td>
<td>Broca's</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>64</td>
<td>51</td>
<td>N/A</td>
<td>Wernicke's</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>58</td>
<td>56</td>
<td>N/A</td>
<td>Anomic</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>59</td>
<td>55</td>
<td>N/A</td>
<td>Anomic</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>52</td>
<td>42</td>
<td>Phenytoin</td>
<td>Broca's</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>46</td>
<td>43</td>
<td>Levitracetam</td>
<td>Broca's</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>74</td>
<td>71</td>
<td>Levitracetam</td>
<td>Conduction</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>45</td>
<td>40</td>
<td>Oxacarbazepine, Phenytoin</td>
<td>Broca's</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>31</td>
<td>30</td>
<td>Oxacarbazepine, Methylphenidate, Escitalopram, Donepezil</td>
<td>Anomic</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>50</td>
<td>44</td>
<td>N/A</td>
<td>Anomic</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>56</td>
<td>46</td>
<td>N/A</td>
<td>Anomic</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>53</td>
<td>43</td>
<td>N/A</td>
<td>Anomic</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>44</td>
<td>43</td>
<td>Gabapentin, Escitalopram</td>
<td>Broca's</td>
</tr>
<tr>
<td>Test</td>
<td>before IMITATE</td>
<td>after IMITATE</td>
<td>t-statistic</td>
<td>p-value*</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>----------------</td>
<td>---------------</td>
<td>-------------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td><strong>Western Aphasia Battery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous Speech (AQ)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information Content</td>
<td>8.64 (0.28)</td>
<td>8.36 (0.20)</td>
<td>-1.39</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Fluency</td>
<td>6.45 (0.59)</td>
<td>6.55 (0.64)</td>
<td>1.00</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Comprehension (AQ)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes-Yes Questions</td>
<td>55.91 (1.47)</td>
<td>56.73 (0.94)</td>
<td>0.81</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Auditory Word Recognition</td>
<td>55.73 (1.43)</td>
<td>55.45 (1.63)</td>
<td>-0.36</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Sequential Commands</td>
<td>58.18 (3.53)</td>
<td>56.45 (4.66)</td>
<td>-0.59</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Repetition (AQ)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repetition</td>
<td>75.55 (4.49)</td>
<td>79.36 (4.40)</td>
<td>2.08</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Naming (AQ)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Object Naming</td>
<td>51.27 (3.09)</td>
<td>51.18 (3.39)</td>
<td>-0.10</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Word Fluency</td>
<td>9.00 (1.37)</td>
<td>9.55 (1.38)</td>
<td>0.73</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Sentence Completion</td>
<td>8.55 (0.62)</td>
<td>9.09 (0.39)</td>
<td>1.03</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Responsive Speech</td>
<td>7.91 (0.98)</td>
<td>8.73 (0.73)</td>
<td>1.57</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>Aphasia Quotient (AQ)</td>
<td>77.62 (3.38)</td>
<td>78.26 (3.36)</td>
<td>1.23</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td><strong>Boston Naming Test</strong></td>
<td>34.54 (4.55)</td>
<td>38.63 (4.95)</td>
<td>2.66</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td><strong>Apraxia Battery for Adults</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Diadochokinetic rate</td>
<td>21.90 (2.99)</td>
<td>27.91 (8.27)</td>
<td>0.95</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>2A. Increasing word length 1</td>
<td>4 (1.15)</td>
<td>3.62 (1.05)</td>
<td>-0.64</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>2B. Increasing word length 2</td>
<td>4.85 (0.82)</td>
<td>4.14 (0.67)</td>
<td>-0.43</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>5. Repeated Trials</td>
<td>21.09 (2.32)</td>
<td>22.72 (2.11)</td>
<td>1.38</td>
<td>ns</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Speech assessment before and after IMITATE.

Reported values refer to the mean (± SEM) with n=11.* = Bonferroni correction for multiple comparisons applied (corrected p=0.003).
<table>
<thead>
<tr>
<th>Variable</th>
<th>BSL</th>
<th>Post-IMITATE</th>
<th>t-test</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST (min)</td>
<td>407.9 (20.3)</td>
<td>407.6 (14.02)</td>
<td>-0.01</td>
<td>ns</td>
</tr>
<tr>
<td>N1 (% of TST)</td>
<td>12.6 (2.12)</td>
<td>9.3 (1.04)</td>
<td>-2.11</td>
<td>ns</td>
</tr>
<tr>
<td>N2 (% of TST)</td>
<td>43.7 (2.23)</td>
<td>38.7 (3.10)</td>
<td>-2.09</td>
<td>ns</td>
</tr>
<tr>
<td>N3 (% of TST)</td>
<td>25.0 (1.90)</td>
<td>28.4 (2.54)</td>
<td>1.90</td>
<td>ns</td>
</tr>
<tr>
<td>REM sleep (% of TST)</td>
<td>18.4 (1.90)</td>
<td>23.5 (1.75)</td>
<td>2.40</td>
<td>ns</td>
</tr>
<tr>
<td>SE (%)</td>
<td>86.3 (3.09)</td>
<td>91.1 (1.84)</td>
<td>1.68</td>
<td>ns</td>
</tr>
<tr>
<td>SOL (min)</td>
<td>22.1 (4.14)</td>
<td>29.5 (10.7)</td>
<td>0.94</td>
<td>ns</td>
</tr>
<tr>
<td>WASO (min)</td>
<td>63.2 (14.50)</td>
<td>39.3 (8.39)</td>
<td>-1.97</td>
<td>ns</td>
</tr>
<tr>
<td>REML (min)</td>
<td>128.9 (25.83)</td>
<td>85.7 (19.66)</td>
<td>-2.10</td>
<td>ns</td>
</tr>
</tbody>
</table>

Table 3. Sleep Parameters before and after IMITATE.

Reported values refer to the mean (± SEM) with n=13. SEM, standard error of the mean. BSL, baseline; TST, total sleep time; N1-3, NREM stages 1,2,3; SE, Sleep Efficiency; SOL, Sleep Onset Latency (first occurrence of N2); WASO, Waking After Sleep Onset; REML, REM Latency (first occurrence of REM from SOL). * = Bonferroni correction for multiple comparisons applied (corrected p=0.005).
Ten out of the thirteen participants who completed the study (see the MRI methods section for details on the exclusion of three patients) had high-resolution T1-weighted volumetric (MP-RAGE) MRI scans, and their brain lesions were manually delimited in the volume. The volumes were converted into surface rendering using Freesurfer and lesion overlaps were computed. Note on the Figure that all the patients had injury to the ventral premotor cortex of the left hemisphere, an important link in the parietal-frontal action comprehension and imitation circuit.
Figure 2. IMITATE effects on sleep SWA.

A. Topographic distribution of absolute SWA during the first 30 minutes of the first NREM sleep episode before (Baseline) and after IMITATE therapy (Post-IMITATE). Values (mean of 13 subjects) were plotted at the corresponding position on the planar projection of the scalp surface and interpolated (biharmonic spline) between electrodes.

B. Topographic distribution of t-values from paired t-tests contrasting SWA power changes Post-IMITATE relative to Baseline during the first 30 minutes of the first NREM episode. Dots represent channels showing a significant increase in spectral power after IMITATE (p < 0.05; two-tailed paired t-test); In addition, black dots represent channels with significant differences following statistical non-parametric mapping (SnPM, supra-threshold cluster analysis).
The percentage change (mean ± SEM) in average SWA calculated on the first 30 minutes of the first NREM episode (NREM1 30 min) and on the three NREM episodes (NREM 1-2-3) of the night after IMITATE as compared to the baseline night. We selected the electrode within the significant cluster represented in Figure 2 (black dots) yielding the highest t-value at the SnPM supra-threshold cluster analysis (channel 195; t-value: 3.07). SWA was significantly increased across all intervals (p< 0.05, Hotelling's $T^2$ test) as indicated by the asterisks.
Figure 4. Correlation between IMITATE effects on speech and local sleep SWA.

A. Topographic distribution of p-values from Pearson’s correlation (n=11) between changes in WAB Repetition subscale scores and changes in SWA Post-IMITATE relative to Baseline during the first 30 minutes of the first NREM sleep episode. Dots represent derivations with significant correlations (p < 0.05). B. Scatterplot (r=0.67; p=0.02) for a representative channel within the significant cluster (colored in white in A).