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Language improvements after TMS plus modified CILT: Pilot, open-protocol study with two, chronic nonfluent aphasia cases

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TMS; speech therapy; constraint-induced language therapy; aphasia; stroke rehabilitation

1. Introduction

1.1. Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) has been applied to promote poststroke recovery in the domains of 1) motor deficits (Fregni et al., 2006); 2) visuospatial neglect following right hemisphere (RH) stroke (Brighina et al., 2003; Koch et al., 2008); and 3) aphasia following left hemisphere (LH) stroke (Barwood et al., 2010; Hamilton et al., 2010; Martin et al., 2009a; Medina et al., 2012; Naeser et al., 2010a, 2005a, 2005b; Turkeltaub et al., 2012; Weiduschat et al., 2011). One principle supporting these improvements poststroke is that TMS may be used to modulate abnormal interhemispheric inhibition in chronic stroke, where increased excitability in parts of the undamaged hemisphere is present due to release of inhibition from the damaged hemisphere (Thiel et al., 2006).

Slow, 1Hz repetitive TMS (rTMS) may be used to suppress the hyper-excitability of parts of the undamaged hemisphere in patients who have suffered a stroke, in turn promoting better modulation of both hemispheres. In patients with aphasia due to stroke, better modulation has been observed to promote improved language behavior including naming and phrase length at 2 months or longer, following suppression of one specific, target area (1 cm square) in the RH, usually the R pars triangularis (PTr) (Barwood et al., 2010; Hamilton et al., 2010; Medina et al., 2012; Naeser et al., 2010a, 2005a, 2005b; Turkeltaub et al., 2012; Weiduschat et al., 2011).

Functional MRI scans during overt naming of pictures in a patient with chronic, nonfluent aphasia obtained pre- and post- a two-week series of TMS treatments to suppress the R PTr have shown improved naming to be associated with increased activation in parts of the LH, lasting up to 4 years post- TMS (Martin et al., 2009a). Weiduschat et al. (2011) used

activation positron emission tomography (PET) scans pre- and post- a two-week series of rTMS treatments (real rTMS to the R PTr versus control-real rTMS to the vertex of the head) plus 45 minutes of individualized speech therapy in a heterogeneous group of patients with subacute aphasia (<4 months poststroke onset). In that study, significant improvement in the overall Aachen Aphasia Test (AAT) score and in the subtest of naming was observed only in the real rTMS group where 1Hz rTMS was used to suppress the R PTr. There was no significant improvement in the overall AAT score or naming in the control rTMS group. In addition, those patients who received real rTMS to suppress the R PTr no longer retained an increased right-laterality index for increased activation for the inferior frontal gyrus/Broca's area (Weiduschat et al., 2011). These results suggest that rTMS to suppress RPTTr, combined with speech therapy can prevent retention of RH lateralization in patients with subacute aphasia; this may in turn, promote better recovery. A subsequent study by this group (with a larger number of patients) replicated these findings (Thiel et al., 2013). Cotelli et al. (2011) has applied high frequency rTMS to the L dorsolateral prefrontal cortex, followed immediately by 25 minutes of speech therapy (anomia treatment), where improved object naming was observed. Long-term TMS effects are believed to engage mechanisms of neural plasticity, thus likely rendering this technique especially suitable for improving poststroke behavior when combined with appropriate behavioral intervention (Rossi and Rossini, 2004; Talelli and Rothwell, 2006).

1.2. Constraint-induced language therapy

Constraint-induced language therapy (CILT) was originally based on a therapy developed to treat paralysis in patients who had suffered a stroke – e.g., constraint-induced movement therapy (CIMT) (Cherney et al., 2008; Hakkennes and Keating, 2005; Meinzer et al., 2007; Taub et al., 1999). CIMT can produce an increase in the amount and quality of movement of the affected limbs in patients with hemiparesis due to stroke, which carries over to a real-world environment (Taub et al., 1999). The principles applied during CIMT include: 1) restraining the unaffected limb with a sling, splint, or glove; 2) forcing the use of the affected limb; 3) intensive shaping and training of the affected limb through massed practice (6 hours or more per day for at least 2–3 weeks) (Taub et al., 1999). A fourth core component, the transfer package, has been designed to facilitate transfer of gains to real-world activities (Gauthier et al., 2008). Three hours versus six, of intensive therapy has been shown to improve use of the affected arm, along with parallel structural brain changes (increase in grey matter volume in hand and arm regions of the sensory and motor areas, anterior supplementary motor area, portions of the premotor area, and bilateral hippocampi) (Gauthier et al., 2008).

Based on the CIMT approach, constraint-induced principles have been applied to aphasia therapy, and these have been labeled as CILT or intensive language-action therapy (ILAT) (Difrancesco et al., 2012) including constraint-induced aphasia therapy (CIAT). These language therapies have applied the same basic, initial therapy components as CIMT, including 1) shaping (Taub, 2004; Taub et al., 1994), 2) massed (intensive) practice, and 3) forced use of verbal language only (Cherney et al., 2008). These constraint induced language treatment approaches have been reviewed (Berthier and Pulvermuller, 2011; Meinzer et al., 2012).

Naming was significantly improved following a series of 10 CILT treatments (Maher et al., 2006; Meinzer et al., 2005). CIAT has been associated with significant language improvement following 3–4 hours of treatment per day for 2 weeks, in patients with chronic aphasia (Pulvermuller et al., 2001). In an individual with chronic nonfluent aphasia, an increase in verb production was observed after a modified CIAT program was administered (Goral and Kempler, 2008). Intensive language therapies have been observed to have a lasting effect from 1 month (Maher et al., 2006) up to 6 months after therapy (Meinzer et al., 2005).

1.3. Functional imaging Pre-/Post- CILT

Functional imaging studies demonstrate changes in brain activity associated with CILT (Meinzer and Breitenstein, 2008) that suggest these therapies may also engage mechanisms of neural plasticity. After 2 weeks of CIAT, the naming performance of eleven patients with chronic aphasia significantly improved, and was correlated with increased activity in perilesional LH brain areas (Meinzer et al., 2008). Success following CIAT has also been correlated with a relative decrease of activation in RH areas, including the IFG/insular cortex (Richter et al., 2008). In 23 patients, using magnetoencephalography (MEG), Breier et al. (2009) identified three different patterns of behavioral and neurophysiologic responses to CILT: 1) Lost-Response in which any gains were lost 3 months post- treatment, and greater RH activation was present compared to the other response groups, at each MEG scanning session; 2) Responders who maintained significant gains at follow-up, and showed an increase in L temporal lobe activation after therapy, as well as a decrease in R frontal activation; and 3) Non-responders who did not improve after CILT and displayed greater L versus R parietal activation, with a decrease in L temporal activation after therapy (Breier et al., 2009).

1.4. Rationale

The present study examined the effect of TMS plus a modified CILT (mCILT) in two patients with chronic, nonfluent aphasia. Motivation for our design was based on other stroke studies where improved behavior was associated with a combination of treatment modalities – e.g., pharmacological intervention plus speech therapy (Berthier et al., 2009; Kessler et al., 2000); TMS or transcranial direct current stimulation (tDCS) plus physical therapy (Bolognini et al., 2009; Hesse et al., 2007); TMS plus speech therapy (Cotelli et al., 2011; Weiduschat et al., 2011); and tDCS plus concurrent speech therapy (Baker et al., 2010; Floel et al., 2011; Vines et al., 2011).

Our rationale for including TMS plus mCILT is as follows: 1) Studies have shown that rTMS alone improves naming at 2 months or more after the last treatment (Naeser et al., 2005a, 2005b; Hamilton et al., 2010); and 2) Studies have shown that CILT also improves naming at 1 month or more after the last treatment (Maher et al., 2006; Meinzer et al., 2005). Imaging studies with each of these therapies have shown changes in activation after treatment. These changes suggest that each therapy engages mechanisms of neural plasticity (Meinzer and Breitenstein, 2008; Martin, 2009a; Weiduschat et al., 2011). Thus, our hypothesis was that the combination of TMS plus mCILT would optimize improvements

induced by each treatment modality, resulting in further language recovery in chronic stroke patients.

2. Methods

2.1. Participants

Two patients with chronic, nonfluent aphasia who had completed our initial TMS protocol (Naeser et al., 2005b), without concurrent speech therapy, entered into this TMS+mCILT study. This is the first study to examine the effects of TMS alone, and later, TMS plus CILT in the same chronic stroke patients. Thus, the criteria for entry into this study were as follows: 1) the patient must have shown significant improvement in naming after the first series of TMS treatments alone; and 2) the patient must still be able to name at least 3 pictures on the Boston Naming Test (BNT) (Kaplan et al., 2001). Demographics and clinical characteristics for each participant are included in Table 1; the language data are provided in Table 2. Institutional Review Board approval, signed informed consent, and HIPAA consent were obtained. In the current study, neither patient received any additional speech therapy (besides mCILT) during the 2-week treatment protocol, or throughout the follow-up testing.

2.1.1. Patient 1 (P1)

P1, Summary of Previous TMS Participation: At age 43 he had suffered an embolic L MCA stroke that resulted in slight Rhemiparesis and mild-moderate nonfluent aphasia; intravenous tissue plasminogen activator had been administered. He had no visual field defect or hearing problem. Previous medical history was remarkable for obstructive sleep apnea. At 12.5 months poststroke onset, he began medical treatment for the obstructive sleep apnea, using continuous positive airway pressure (CPAP) treatment at night. After 5 months of CPAP, he was more alert, and there was associated language improvement (Naeser et al., 2010a). The patient used CPAP throughout all the TMS studies. His structural magnetic resonance imaging (MRI) scan is shown in Fig. 1A. He had subcortical, capsular-putaminal lesion, plus cortical lesion in the more anterior portion of L superior temporal gyrus. Parts of the subcortical, white matter lesion are compatible with nonfluent speech. Lesion spared most of the white matter, anterolateral to the left frontal horn, medial subcallosal fasciculus (vertical arrow), but lesion was present in the periventricular white matter adjacent to the body of lateral ventricle (horizontal arrow); this combination of white matter lesion is compatible with recovery of some speech (Naeser et al., 1989).

At 2 years 2 months poststroke, P1 received TMS alone (Naeser et al., 2010a); 8 months after starting CPAP. A baseline was established at that time. At 3 and 6 months after the initial series of TMS treatments, he showed significant improvement (>2 SD) on the BNT, and additional aspects of speech production including Number of Narrative Words and Mean Length of Utterance (MLU). See Table 3.

At 2 years 7 months after the initial series of TMS treatments, P1 entered the current TMS +mCILT protocol. At entry into the TMS+mCILT program, his BNT naming score was within the confidence interval (± 2 SD) of his BNT scores at 6 months post- TMS alone (the latest testing time post- TMS alone). His total number of narrative words for the cookie theft picture description was also within the confidence interval of his number of narrative words

at 3 months post-TMS alone. (Propositional speech had not been tested at 6 months post-TMS alone.) Thus, the significant gains in naming and propositional speech that P1 had made during TMS alone appeared to remain stable in the intervening 2 years, 7 months before entry into this TMS+mCILT program (Table 3). Patient 1 did not receive individual speech therapy after the initial TMS series.

2.1.2. Patient 2 (P2)

P2, Summary of Previous TMS Participation: At age 51, she had suffered a LH intracerebral hemorrhage that required surgical intervention and resulted in severe nonfluent aphasia and R hemiplegia. She wore a hearing aid and had no visual field defect. Her structural MRI scan is shown in Fig. 1B. She had primarily subcortical white matter lesion. No lesion was present in Broca's or Wernicke's cortical areas. White matter lesion included the medial subcallosal fasciculus (vertical arrow), and the periventricular white matter (horizontal arrow). This extensive white matter lesion combination is compatible with severe nonfluent speech (Naeser et al., 1989).

At 6.5 years poststroke, P2 received TMS alone (Naeser et al., 2005a). At 2 months, and at 4 years 3 months after the initial series of TMS treatments, she showed improvement on the BNT, but no change in Phrase Length, which remained 0–1 word. See Table 4. P2 had received some speech therapy for a few months, starting at 1 year after the initial TMS alone, treatment series. At that time, she continued to show improvement in language skills, especially in auditory comprehension, and in the voluntary use of words and phrases appropriate to her environment (Naeser et al., 2005a).

At 5 years 10 months after the initial series of TMS, P2 entered the current TMS+mCILT protocol. At entry into the TMS+mCILT program, her mean BNT naming score (11.67) was within the confidence interval of her previous score (10, at 4 years 3 months post that initial TMS treatment series). Her number of narrative words on the cookie theft picture description had improved from 0–1 word at 4 years 3 months post- the initial series of TMS treatments, to a mean of 4.33, at Baseline testing for TMS+mCILT. The gains that had been made after the initial TMS treatment series (and following the speech therapy intervention at 1 year post- TMS), were stable on the BNT or improved on number of narrative words, at the time of entry into the TMS+mCILT program (Table 4).

2.2. Treatment methods

2.2.1. Transcranial magnetic stimulation procedure—The TMS portion of this TMS+mCILT protocol is based on our initial published TMS treatment procedure (Naeser et al., 2005b). Based on each patient's participation in the previous TMS study (without speech therapy), the R PTR was suppressed with 1Hz rTMS (Naeser et al., 2005a, 2010a). This area is marked on the right lateral MRI view for each case in Fig. 1A and B.

The same TMS equipment that was used in the previous TMS study (without speech therapy), was used in this current study. On each of the ten days of treatment, 1Hz rTMS was applied for 20 min. using an air-cooled, figure 8-shaped TMS coil (each wing was 7 cm in diameter) (Fig. 1C). The rTMS pulses were delivered at 90% of resting motor threshold

for the L first dorsal interosseus muscle, with a Super-Rapid High Frequency MagStim Magnetic Stimulator (Magstim, UK). Positioning of the TMS coil on the scalp was guided using the patient's own structural MRI scan in combination with the neuronavigation system, Brainsight (Rogue Industries, Montreal). Patients stayed overnight at the Beth Israel Deaconess Medical Center, General Clinical Research Center for the length of the treatment series.

2.2.2. Modified constraint-induced language therapy procedure

Pre-Testing of Color Pictures: Prior to any TMS+mCILT treatment, naming ability was tested on a set of up to 500 color pictures of nouns (potential pictures for use during mCILT) (Language Builder, 2004; Stark, 1998). Before any testing, in order to be sure the patient understood the intended target name, the patient was initially shown each picture card and the tester said aloud the expected name. During the testing sessions, each color picture was presented for 10 sec. on a laptop (Apple iBook). The size of each picture was controlled to be 3.5×4.8 inches, with a thin black border on a white background.

The color pictures were presented sequentially by frequency of occurrence, from high frequency-of occurrence words to low frequency-of-occurrence words, based on the frequency of nouns from The Corpus of Contemporary American English (<http://www.americancorpus.org>) (Davies, 2008). Testing continued until the pictures became too difficult to name and 10 pictures were missed in a row. On these color pictures, P1 did not miss 10 pictures in a row until a maximum of 360 pictures had been presented. P2 did not miss 10 pictures in a row until a maximum of 250 pictures had been presented. Each patient was then tested two more times on his/her maximum set of pictures (for P1, 360 picture-set; for P2, 250 picture-set), for a total of three testing times. The patients were not trained on the color pictures at this time, nor did they receive any feedback.

Based on the patient's responses for each picture at the 3 testing times, the maximum set of pictures (for later use during mCILT therapy) were divided as follows: 1) "always-named" (3/3 correct); 2) "sometimes-named" (1/3 or 2/3 correct); and 3) "never-named" (0/3 correct).

Administration of mCILT: One hour of mCILT was administered immediately following each 20-min TMS session. After a 1-hour break for lunch, 2 more hours of mCILT were administered, for a total of 3 hours each day of massed, intensive practice.

The patient participated with a Speech-Language Pathologist (SLP), instead of with another patient or group of patients. One patient was treated at a time with mCILT. The patient was constrained to verbally respond with a spoken name for a stimulus picture (no gestures, writing or sound effects were permitted). An opaque screen was placed on a table between the SLP and the patient, who were seated across from each other. The screen had a large opening at the bottom for passing the cards back and forth between the SLP and the patient (Fig. 2, arrow). There was eye contact above the screen. Two clinicians were involved in the mCILT session. If the patient started to gesture, the second clinician, who had a view of the patient's hands, reminded the patient that no gesturing was permitted and asked the patient to "sit on his/her left hand" during that response in order to prevent gesturing. The patient

was then able to use his left hand to turn over the next card or pass the card through the barrier.

Level of Difficulty (Frequency of Occurrence) within and across mCILT sessions Pictures were sorted by frequency of occurrence, such that higher frequency-of-occurrence pictures were presented for naming on day 1, and the lower frequency-of-occurrence pictures, on day 10. The pictures gradually increased in difficulty both throughout each day, and across days 1–10 over the two-week mCILT treatment series. Although different from the traditional CILT approach by Pulvermuller et al. (2001), increasing the level of difficulty of the task was similar to other constraint-induced therapy programs (Breier et al., 2009; Goral and Kempler, 2008; Maher et al., 2006) where behavioral shaping or scaling was used.

During each mCILT session, 2 of the 6 pictures in a set were from the category of “always-named” at entry; 2 of the 6 pictures, “sometimes-named”; and 2 of the 6 pictures, “never-named”. The “always-named” pictures were included in order to reduce frustration for the patient. P2, the severe nonfluent patient did not have enough “always-named” pictures at entry, to present during all 10 days of therapy. Therefore, during days 5–10, the color pictures presented to P2 consisted only of those pictures “sometimes-named”, or “nevernamed”. P2 responded well to therapy even on these more difficult pictures.

First and Second hours of mCILT: Therapy took the form of a card game during hours 1 and 2 of mCILT. This card game was modeled after the dual-card task of Maher et al., 2006. One set of 6 different, color picture cards was used at a time, per game. The same set of 6 color pictures was played for three games. Each day, three sets of 6 pictures each, were presented (18 different pictures). Picture cards to be named aloud were turned over one at a time by the patient, for each set of 6 pictures. The pictures were individualized to each patient, from his/her maximum set of color pictures from the pre- testing of color pictures.

Third hour of mCILT: The patient and SLP participated in a different card game during hour 3. The 18 pictures previously trained during hours 1 and 2 were used. The therapist had a board with 9 different pictures. The patient had a board with the other 9 pictures. The therapist passed through the screen one picture card to name. If the patient named the picture correctly, the patient could place a chip over that picture on either his/her board or the therapist’s board. Play continued until both boards were completed and all 18 pictures had been named once. This constituted one round. In the next round, the therapist and patient then switched boards. There were three rounds per day, with the same 18 pictures. Therefore, over the course of one day, each color picture was presented to the patient 6 times.

Scoring: Similar to other therapy techniques such as ‘cueing hierarchy’ treatment for anomia (Fridriksson, 2010, 2006, 2007), the SLP provided the following structure and sequential cueing after each card was turned over, or presented for naming: 1) The patient was encouraged to name the picture; 2) If named incorrectly, the patient was encouraged to name the picture again; 3) If not named, the SLP gave a phonological cue for the initial phoneme; 4) If still not named, the SLP gave a sentence for completion (from a prepared set of sentences where the target was the last word); 5) If still not named, the SLP had the

patient repeat the correct name. A patient completed a set of pictures if he/she had at least one successful response without cueing for each of the 6 pictures.

On days 9 and 10, P1 (the mild-moderate patient), had successfully named at least once, without cueing all 360 color pictures presented to him; thus, therapy was focused on sentence production. He was asked to verbalize a new and unique sentence based on the picture shown to him. All mCILT sessions were audio and videotaped for later reviewing and scoring.

2.3. Design

We utilized a multiple baseline, case study design where each patient served as his/her own control. Significant improvement post- treatment was defined as >2 SD above mean Baseline scores, across three separate test administrations, for any given test or subtest.

2.4. Outcome measures

The primary outcome measures included the BNT (Kaplan et al., 2001), the BDAE Picture Naming, and elicited propositional speech for the cookie theft picture description (Goodglass et al., 2001). Although not primary outcome measures, the Repetition subtests, and all four of the Auditory Comprehension subtests from an earlier version of the BDAE (Goodglass and Kaplan, 1983) were also administered. Each test was administered three times during separate testing sessions at entry in order to establish a Baseline mean and SD; and once, at 1–2 months post- TMS+mCILT. P1 was tested again at 16 months post- TMS+mCILT, and P2 was tested again at 6 months post- TMS+mCILT.

Elicited propositional speech (cookie theft picture) was analyzed using Quantitative Production Analysis (QPA) to determine changes in the grammatical structure, and lexical content of propositional speech samples (Berndt et al., 2000; Rochon et al., 2000; Saffran et al., 1989). Data were collected for the following aspects of speech production: longest uninterrupted phrase length, total number of narrative words, total number of nouns, number of different nouns, total number of verbs, number of different verbs, and mean length of utterance. Patients were allowed a maximum of 2 minutes to describe the cookie theft picture.

2.5. Secondary analyses

During each treatment session, accuracy (percent correct) for color pictures named correctly within each category (“always-named” at entry; “sometimes named”; and “never-named”) was recorded for each patient. Secondary analyses were performed for accuracy within each of these three separate categories, as well as the total, for each patient, for each day.

3. Results

3.1. Results for P1

3.1.1. P1, outcome measures—At 2 months post- TMS+mCILT, P1 (patient with mild-moderate nonfluent aphasia) showed significant improvement (>2 SD compared to Baseline) on the BNT, and on the BDAE subtest, Tools/Implements (Fig. 3A, B and Table 2). At 16

months post-TMS+mCILT, his score on the BNT was 16, which continued to be higher (but not significantly so) compared to Baseline (mean of 14.3; SD, 1.15); and his score on the BDAE subtest, Tools/Implements returned to Baseline.

On the BDAE cookie theft picture description, his pre- TMS+mCILT Baseline mean for longest uninterrupted phrase length was 10.67 (SD, 4.16), and at 2 months post- TMS+mCILT it remained 10. However, there were some quantitative and qualitative differences in his utterances. P1 had a significant increase in the total number of narrative words produced, from a pre- TMS+mCILT Baseline mean of 46 (SD, 5.57), to a 2 month post-TMS+mCILT total of 59 (Fig. 4A and Table 2). He also had a significant increase in number of different nouns produced from a pre- TMS+mCILT Baseline mean of 7.67 (SD, 1.15), to a 2 month post- TMS+mCILT total of 12 (Fig. 4B and Table 5A). P1 showed no significant increase in the number of different verbs produced post- TMS+mCILT (Table 5A). At 16 months post- TMS+mCILT he showed no lasting change in his utterances, including number of narrative words, or number of different nouns produced.

3.1.2. P1, secondary analyses—The total percent of color pictures named correctly each day during treatment (Fig. 5) remained relatively flat across days 1–8 (range, 85–94%, without cueing) despite the increasing level of difficulty (lower frequency of occurrence words). The percent of color pictures named within each of the three categories (“always-named” at entry; “sometimes-named”; and “never-named”), for days 1–8, are shown in Fig. 5.

Table 6A lists the color pictures “never-named” at entry, but successfully named (without cueing) each day (1–8). The number after each word reflects the number of times P1 successfully named that picture, immediately after turning over the card. This ranges from 1, to a maximum of 6 for any given day. On day 1, for P1, seven words previously “never-named” at entry, were now each named correctly, immediately after turning over the card (6×), without any cueing or training, including the first time that picture was shown (e.g., table, team, foot, plate, shirt, chain, bottle).

For P1, performance on naming was also examined by level of difficulty (frequency of occurrence) during mCILT, and this was compared to performance on naming by level of difficulty (frequency of occurrence) at entry. The following steps were taken in order to make this comparison: 1) The maximum set of 360 pictures for P1 was divided into deciles by frequency of occurrence; 2) The patient’s performance at entry for each decile was calculated, and this is plotted in Fig. 6A (circles). This line shows that the percent of color pictures named at entry, by decile, was negatively correlated with increasing level of difficulty (lower frequency-of-occurrence words), by decile ($r = -0.850$, $p = 0.002$); 3) The patient’s performance during mCILT for each decile was calculated, and this is also plotted in Fig. 6A (triangles). This line shows that the percent of color pictures named correctly, by decile, during mCILT was also negatively correlated with increasing level of difficulty (lower frequency-of-occurrence words), by decile ($r = -0.731$, $p = 0.016$); 4) The difference between the percent of color pictures named correctly during mCILT, by decile, and the percent of color pictures named correctly at entry, by decile (overall, from highest frequency-of-occurrence to lowest) was calculated. See Fig. 6B. For P1, these differences in

naming performance during mCILT (by decile), versus at entry (by decile), increased as the level of difficulty increased (slope = 3.72, $r = 0.721$, $p = 0.019$). This shows that relative to entry naming performance, during each day of TMS+mCILT, naming performance continued to improve, despite increasing level of difficulty (lower frequency-of-occurrence) presented for naming (Fig. 6B).

3.2. Results for P2

3.2.1. P2, outcome measures—P2 (patient with severe nonfluent aphasia) showed significant improvement (>2 SD) on the BDAE subtests for Action Naming, and Tools/ Implements, at 1 and 6 months post- TMS+mCILT (Fig. 7A, B and Table 2); and Single Word Repetition at 6 months post- TMS+mCILT (Fig. 7C and Table 2).

On the cookie theft picture description, at 1 month post- TMS+mCILT, P2 showed a significant increase in the total number of narrative words (Fig. 8A), number of different nouns (Fig. 8B), and different verbs (Table 2). At 6 months post- TMS+mCILT, the number of different nouns remained significant. Examples of her nouns and verbs produced during elicited propositional speech are provided in Table 5B.

3.2.2. P2, secondary analyses—The total percent of color pictures named correctly each day during treatment (Fig. 9) ranged from 52–72% (without cueing), despite the increasing level of difficulty (lower frequency of occurrence words). The percent of color pictures named within each of the three categories (“always-named” at entry; “sometimes-named”; and “never-named”), for days 2–10 are shown in Fig. 9. (The data for day 1 were incomplete.)

Table 6B lists the color pictures “never-named” at entry, but successfully named (without cueing) each day (days 2–10). The number after each word listed reflects the number of times P2 successfully named that picture, immediately after turning over the card. This ranges from 1×, to a maximum of 6×. On day 3, for P2, two words previously “never-named” at entry, were now named correctly immediately after turning over the card, without any cueing or training (6×), including the first time that picture was shown (e.g., baseball, boat).

For P2, performance on naming was also examined by level of difficulty (frequency of occurrence) during mCILT, and this was compared to performance on naming by level of difficulty (frequency of occurrence) at entry. The following steps were taken in order to make this comparison: 1) The maximum set of 250 pictures for P2 was divided into deciles by frequency of occurrence; 2) The patient’s performance at entry for each decile was calculated, and this is plotted in Fig. 10A (circles). This line shows that the percent of color pictures named at entry, by decile, was negatively correlated with increasing level of difficulty (lower frequency-of-occurrence words), by decile ($r = -0.73$, $p = 0.026$); 3) The patient’s performance during mCILT for each decile was calculated, and is plotted in Fig. 10A (triangles). Note, data for the first decile are not plotted because naming data for this decile during mCILT were incomplete (day 1). This line shows that the percent of color pictures named correctly, by decile, during mCILT was flat and not significantly correlated with increasing level of difficulty (lower frequency-of-occurrence), by decile ($r = 0.007$,

n.s.); 4) The difference between the percent of color pictures named correctly during mCILT, by decile, and the percent of color pictures named correctly at entry, by decile (overall, from highest frequency-of-occurrence to lowest) was calculated. See Fig. 10B. For P2, these differences in naming performance during mCILT (by decile), versus at entry (by decile) increased as the level of difficulty increased (slope = 4.61, $r = 0.71$, $p = 0.034$). This shows that relative to entry naming performance, during each day of TMS+mCILT, naming performance continued to improve, despite increasing level of difficulty (lower frequency-of-occurrence) presented for naming.

4. Discussion

This study showed that it was feasible to apply rTMS and immediately follow this with three hours of mCILT. Results showed a significant improvement in naming pictures of objects or actions, and in propositional speech (total number of narrative words and different nouns) at 1–2 months post- TMS+mCILT for each patient. While this study was not designed to specifically compare the effect of TMS alone versus TMS+mCILT, each patient did show significantly higher scores on naming pictures of objects (including tools/implements) or actions, and in total number of narrative words at 1–2 months post- TMS+mCILT, than had been previously observed post- the initial series of TMS treatments (Tables 3 and 4). It is unknown if the significant improvements in naming pictures, and elicited propositional speech were associated with the second series of TMS, or this first series of mCILT, or a combination of both.

For P1 (mild-moderate nonfluent aphasia), at 2 months post- TMS+mCILT, there was significant improvement on the BNT, the BDAE subtest Tools/Implements, and in measures of propositional speech (total number of narrative words and different nouns). At 16 months post- TMS+mCILT, the significant gains that had been present at 2 months post- TMS +mCILT no longer remained.

For P2 (severe nonfluent aphasia), there was significant improvement on the BDAE naming subtests for Tools/Implements, and Actions, at 1 and 6 months post- TMS+mCILT. At 1 month post- TMS+mCILT, propositional speech (total number of narrative words and different nouns and different verbs). At 6 months post- TMS+mCILT the significant improvement on number of different nouns remained; there was new improvement in Single Word Repetition where she repeated 7 of the 10 words, whereas at Baseline she had repeated only 3 of the words.

Although verb production was not specifically targeted during this mCILT therapy for P2, a significant increase in the number of different verbs produced during the cookie theft picture description was observed at the 1-month testing (3 verbs versus mean of 0.67 at Baseline). She also showed a significant improvement in naming Actions on the BDAE subtest at 1 and 6 months post- TMS+mCILT where 6 and 7 Action pictures were named versus a mean of 4.33 at Baseline. Improvement in naming pictures of Actions was not previously observed in this patient following the initial TMS treatment series alone (Table 4). Verb production in narrative words for the cookie theft picture description, however, returned to zero at 6 months after the last TMS+mCILT treatment.

Both patients stayed overnight at the Beth Israel Deaconess Medical Center, General Clinical Research Center for the 10 days of treatment. Despite the intensive aspects of mCILT, both patients cooperated fully. There were no adverse events and all treatment hours were completed. Although the color pictures became increasingly difficult (lower frequency-of-occurrence) at each successive day, the total percent of color pictures named correctly each day (without cueing) remained greater than at entry (Figs. 6A and 10A). Furthermore, both patients began to name pictures that were previously “never-named.” On day 1, for example, P1 named (without cueing), seven previously “never-named” pictures. The ability to name these previously “never-named” pictures on day 1 could be attributed to the TMS portion of the treatment that day. However, on subsequent days, in addition to TMS, the cumulative impact of massed practice for naming additional pictures throughout the day (mCILT) could have contributed. This is unknown.

4.1. Possible mechanisms for TMS

The underlying mechanisms supporting improvements in naming and narrative speech following TMS suppression of the R PTr are not fully known. Neuroplasticity provides the ability to adapt to change; however, evidence suggests that this adaptation is not always successful (Pascual-Leone et al., 2005). Thus, patients with chronic aphasia may operate in stable, but maladaptive states (Belin et al., 1996; Hamilton et al., 2010; Rosen et al., 2000).

The observation of improved language behavior in patients with aphasia following rTMS to suppress the R PTr has been reported in several studies (Barwood et al., 2010; Hamilton et al., 2010; Martin et al., 2009a; Naeser et al., 2005a, 2005b, 2010a; Weiduschat et al., 2011). These TMS studies have suggested that following unilateral stroke, an imbalance in interhemispheric inhibition develops (Thiel et al., 2006). Repetitive TMS modulates neural activity, thus promoting changes and potential reorganization within the language networks resulting in improved behavior (Devlin and Watkins, 2007). Slow, 1Hz rTMS may be used to suppress the disinhibition within the R frontal region in patients who have suffered a LH stroke including L frontal areas, promoting better modulation in parts of each hemisphere, resulting in improved brain function and behavior. Neither participant in this study was able to participate in 3T functional MRI (due to medical reasons) that could have provided information regarding neural network changes after TMS alone, or following TMS+mCILT.

The addition of mCILT immediately after rTMS may have taken advantage of newly reset networks from rTMS, and enhanced these language connections further. This combined treatment may have promoted additional improvement not seen with TMS alone, and perhaps even some generalization - i.e., P2 improved in verb production, although verbs were not specifically trained with her during mCILT.

P1, mild-moderate aphasia, successfully named all pictures at least once without cueing and therefore in the last two days of treatment, he was asked to create sentences using the picture shown on the card. This increase in level of task difficulty is consistent with the notion of behavioral shaping. It is unknown how this increase in task difficulty impacted his naming or propositional speech.

The optimum 1 cm square cortical area to treat with rTMS is important to consider for each patient. In this study, the RH rTMS target site that had been previously determined as each patient's "Best Response" area for rTMS treatment alone, was used (Naeser et al., 2005a, 2010a). However, it is possible that this target site was no longer the "optimum" target site, due to neural changes, including changes in functional connectivity that may have occurred after the initial TMS series. This is unknown, however, both patients showed significant improvements with this same rTMS target stimulation site. Some improvements in language have also been reported after rTMS to other brain regions (Cotelli et al., 2011; Jung et al., 2010; Kakuda et al., 2010).

4.2. Future studies

It was not possible to separate out the relative contribution of a second series of TMS treatments from the addition of the mCILT treatments to the language improvements observed in the two aphasia patients presented in this report. A larger, controlled clinical trial is needed to assess this. Also, further studies are needed to determine if an additional TMS treatment series alone, and/or a language therapy series alone may be necessary to sustain the new language improvements long-term. P2 improved in the Action naming subtest of the BDAE and in number of different verbs in elicited propositional speech post-TMS+mCILT. CILT programs should be expanded to include targeted verb production (Goral and Kempler, 2008). Factors such as lesion site and aphasia severity are also important to consider in better understanding potential for recovery (Naeser and Palumbo, 1994). Additionally, a fourth core component (a transfer package adapted for aphasia) should be added. This transfer package would be similar to the fourth core component of CIMT, which facilitates transfer of gains made to real-world situations. Thus, carryover of improved functional communication after TMS+mCILT should be documented, including language use, during activities of daily living.

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Fig. 1.

A) and B): T1-weighted structural MRI scans, with axial, and L and R reconstructed lateral views for each patient. White triangle on the R lateral view marks the area of cortex (R PTr) where 1 Hz rTMS was used to suppress that cortical area, in each case. C) Application of rTMS with the figure 8-shaped, hand-held rTMS coil, using the neuronavigation system, Brainsight (Rogue Industries, Montreal).

Fig. 2.
mCILT treatment session setup. An opaque screen was placed on the table between the clinician and the patient. There was eye contact only above the screen. There was a window to pass the card back and forth (arrow). The patient was expected to name the picture on the card. No gestures, writing or sound effects were permitted.

Fig. 3.

Performance on language outcome measures pre- and post- TMS+mCILT (black bars) for P1 (mild-moderate nonfluent aphasia) on A) BNT, and B) BDAE subtest, Tools/Implements. Previous scores are also shown when intervention was TMS alone (gray bars). * $\geq +2$ SD above Baseline for each treatment intervention series (TMS alone, or TMS +mCILT). See also Table 3.

Fig. 4.

Elements of propositional speech (cookie theft) pre-and post -TMS+mCILT (black bars) for P1 (mild-moderate nonfluent aphasia) for A) total number of narrative words, and B) number of different nouns. Previous scores are also shown when intervention was TMS alone (gray bars). *= ± 2 SD above Baseline.

Fig. 5.

P1 (mild-moderate nonfluent aphasia), total percent of pictures named correctly (without cueing) during each mCILT treatment day; “Always-named” at entry; “Sometimes-named”; and “never-named”. Note, P1 continued to correctly name pictures never named at entry, even for the lower frequency-of-occurrence words. By days 9 and 10, P1 had successfully named his maximum set of 360 color pictures at least once without cueing. mCILT therapy then focused on sentence production.

Fig. 6.

P1 (mild-moderate nonfluent aphasia), A) performance on naming by level of difficulty (frequency of occurrence) by decile, during mCILT (triangles). Performance on naming by level of difficulty (frequency of occurrence) by decile, at entry (circles). B) The black diamonds show the *difference* between percent of color pictures named correctly *during mCILT intervention by decile*, and the percent of color pictures named correctly *at entry by decile* (slope = 3.72, $r = 0.721$, $p = 0.019$). Thus, the *differences* in naming performance during mCILT (by decile), and at entry (by decile), *increased* as the level of difficulty increased. This suggests a beneficial effect of the TMS+mCILT intervention in naming performance across the deciles, despite the increasing level of difficulty.

Fig. 7.

Performance on language outcome measures pre- and post- TMS+mCILT (black bars) for P2 (severe nonfluent aphasia) on BDAE subtests: A) Action naming; B) Tools/Implements; and C) Single Word Repetition. Previous scores are also shown when intervention was TMS alone (gray bars). * $\geq +2$ SD above Baseline. See also Table 4.

Fig. 8.

Elements of propositional speech (cookie theft) pre-and post -TMS+mCILT (black bars) for P2 (severe nonfluent aphasia) for A) total number of narrative words, and B) number of different nouns. *= ± 2 SD above Baseline. Her phrase length, pre-and post -TMS alone, was only 0-1 word (not plotted here).

Fig. 9.

P2 (severe nonfluent aphasia), total percent of pictures that were named correctly (without cueing) during each mCILT treatment day; “always-named” at entry; “sometimes-named”; and “never-named”. Data were incomplete for day 1. Note, P2 continued to correctly name pictures never named at entry, even for the lowest frequency-of-occurrence words. No color pictures in the “always-named” category from entry testing were available for presentation during days 5–10.

Fig. 10.

P2 (severe nonfluent aphasia), A) performance on naming by level of difficulty (frequency of occurrence) by decile, during mCILT (triangles). Performance on naming by level of difficulty (frequency of occurrence) by decile, at entry (circles). B) The black diamonds show the *difference* between percent of color pictures named correctly *during intervention by decile*, and the percent of color pictures named correctly *at entry by decile* (slope = 4.61, $r = 0.71$, $p = 0.034$). Thus, the *differences* in naming performance during mCILT (by decile), and at entry (by decile), *increased* as the level of difficulty increased. This suggests a beneficial effect of the TMS+mCILT intervention in naming performance across the deciles, despite the increasing level of difficulty.

Table 1

Clinical characteristics for two patients with nonfluent aphasia

	Age at time of entry into TMS +mCILT (Yrs)	Years Post-CVA at time of entry into TMS +mCILT	Time interval between last TMS alone treatment and entry into TMS+mCILT	Gender	Education	CVA	Hemiparesis	Aphasia Type	Native English	Handedness	Other
P1	47	4 Yr. 7 Mo.	2 yr. 5 Mo.	M	2 Yr. Junior College	L MCA, embolic; tPA administered	R slight; some finger flexion/spasticity	mild-moderate nonfluent	Native English; Fluent Spanish	Right	Obstructive Sleep Apnea; nightly CPAP
P2	63	12 Yr. 3 Mo.	5 Yr. 10 Mo.	F	4 Yr. College	L ICH, with neurosurgery	R hemiplegia	severe nonfluent	Native English	Right	

Table 2

Language data for two patients with nonfluent aphasia treated with TMS+mCILT

	P1, Patient with mild-moderate Nonfluent Aphasia		P2, Patient with severe Nonfluent Aphasia	
Time poststroke at entry into TMS+mCILT	4 Yr. 7 Mo.		12 Yr. 3 Mo.	
Time interval between last TMS alone Tx. and entry into TMS+mCILT	2 Yr. 5 Mo.		5 Yr. 10 Mo.	
	Baseline (3×) Pre-TMS+mCILT	2 Mo. Post-TMS+mCILT	Baseline (3×) Pre-TMS+mCILT	1 Mo. Post-TMS+mCILT
<i>Boston Naming Test</i>	16 Mo. Post-TMS+mCILT	16 Mo. Post-TMS+mCILT	1 Mo. Post-TMS+mCILT	6 Mo. Post-TMS+mCILT
First 20 pictures (max = 20)	14.33 (1.15)	17*	16	16
<i>Boston Diagnostic Aphasia Exam</i>			11.67 (2.89)	12
<i>Naming Subtests</i>				
Tools/ Implements (max = 12)	5.67 (0.58)	8*	5	3*
Actions (max = 12)	3.00 (0.58)	3	3	6*
Animals (max = 12)	9.33 (0.58)	10	9	4
<i>Picture Description (Cookie Theft)</i>				
Narrative Words	46.00 (5.57)	59*	31	8*
Different Nouns	7.67 (1.15)	12*	8	5*
Different Verbs	8.00 (1.00)	6*	8	3*
Total Verbs	12.00 (1.00)	12	7	3*
Mean Length of Utterance (MLU)	6.30 (1.90)	7.4	7.8	1
<i>Repetition</i>				

* Score changed at least 2 standard deviations from Baseline. DNT = Did not test.

Table 3
Comparison of language results for TMS alone, and Pre- TMS+mCILT testing for P1, mild-moderate nonfluent aphasia

	TMS Alone				Comparisons: TMS Alone, and TMS+mCILT				
	Baseline (3x) Pre-TMS alone	+2 SD	-2 SD	3 Mo. Post-TMS alone	6 Mo. Post-TMS alone	Baseline (3x) Pre-TMS+mCILT	+2 SD	-2 SD	Was testing at 6 Mo. Post-TMS alone, within 2 SD of Baseline, Pre-TMS+mCILT? [†]
Time Poststroke Onset	1 Yr. 5 Mo.	2 Yr. 5 Mo.	2 Yr. 9 Mo.	4 Yr. 7 Mo.	4 Yr. 11 Mo.	6 Yr. 1 Mo.			
<i>Boston Naming Test</i>									
First 20 pictures (max = 20)	8.67 (1.41)	11.4	5.85	12* 13*	14.33 (1.15)	16.63	12.03	Y	16
<i>Boston Diagnostic Aphasia Exam</i>									
<i>Naming Subtests</i>									
Tools/Implements (max = 12)	5.67 (1.89)	9.45	1.89	5 2	5.67 (0.58)	6.83	4.51	N, -2SD	5
Actions (max = 12)	3.33 (1.71)	6.75	0	4 5	3.00 (0.58)	4.16	1.84	N, +2SD	3
Animals (max = 12)	8.00 (2.06)	12.1	3.88	7 7	9.33 (0.58)	10.49	8.17	N, -2SD	9
<i>Picture Description (Cookie Theft)</i>									
Mean Length of Utterance (MLU)	2.9 (0.74)	4.38	1.42	6.9* DNT	6.30 (1.9)	10.10	2.50	-	7.8
Narrative Words	21.75 (9.64)	41.0	2.11	48* DNT	46.00 (5.57)	57.14	34.86	-	31
<i>Repetition</i>									
Single Words (max = 10)	8.67 (0.5)	9.67	7.67	8 8	8.70 (0.58)	9.86	7.54	Y	9
<i>Auditory Comprehension (v. 1983)</i>									
Word Discrimination (max = 72)	66.33 (5.50)	77.3	55.33	67 65.50	67.67 (3.18)	74.03	61.31	Y	69

	TMS Alone				Comparisons: TMS Alone, and TMS+mCILT							
	Baseline (3x) Pre- TMS alone	+2 SD	-2 SD	3 Mo. Post- TMS alone	6 Mo. Post- TMS alone	Baseline (3x)	Pre-TMS+mCILT	+2 SD	-2 SD	Was testing at 6 Mo. Post-TMS alone, within 2 SD of Baseline, Pre-TMS Pre-TMS +mCILT? †	2 Mo. Post-TMS+mCILT	16 Mo. Post-TMS+mCILT
Commands (max = 15)	10.67 (1.89)	14.4	6.89	11	13.00	10.67 (1.53)		13.73	7.61	Y	11	DNT
Complex Ideational Material (max = 12)	6.00 (1.50)	9.00	3.00	6	5	3.67 (1.53)		6.73	0.61	Y	6	DNT

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* Score increased at least 2 SD from Baseline (3×), for each treatment intervention series (TMS alone or TMS+mCILT).

[†]Time Interval between last testing Post- TMS alone and entry into TMS+mCILT = 1 Yr. 10 Mo. DNT = Did not test.

Table 4

Comparison of language results for TMS alone, and Pre- TMS+mCILT testing for P2, patient with severe nonfluent aphasia

	TMS Alone				Comparisons: TMS Alone, and TMS+mCILT				
	Baseline (1×) Pre-TMS alone	2 Mo. Post-TMS alone	4 Yr. 3 Mo. Post-TMS alone	Baseline (3×) Pre-TMS+mCILT	+2 SD	-2 SD	Was last testing at 4 Yr. 3 Mo. Post-TMS alone, within 2 SD of Baseline, Pre-TMS+mCILT [†]	1 Mo. Post-TMS+mCILT	6 Mo. Post-TMS+mCILT
Time Poststroke Onset	6 Yr. 4 Mo.	6 Yr. 7 Mo.	10 Yr. 8 Mo.	12 Yr. 3 Mo.				12 Yr. 5 Mo.	12 Yr. 10 Mo.
<i>Boston Naming Test</i>									
First 20 pictures (max = 20)	4	7	10	11.67 (2.89)	17.45	5.89	Y	16	12
<i>Boston Diagnostic Aphasia Exam</i>									
<i>Naming Subtests</i>									
Tools/Implements (max = 12)	2	3	2	1.67 (0.58)	2.83	0.51	Y	3*	4*
Actions (max = 12)	3	4	3	4.33 (0.58)	5.49	3.17	N, -2SD	6*	7*
Animals (max = 12)	0	1	2	4.67 (1.15)	6.97	2.37	N, -2SD	4	4
<i>Picture Description Cookie Theft</i>									
Narrative Words	1	1	1	4.33 (1.15)	6.63	2.03	N, -2SD	8*	6
<i>Repetition</i>									
Single Words (max = 10)	4	4	4	3.00 (2.00)	7.00	0	Y	3	7*
<i>Auditory Comprehension (v. 1983)</i>									
Word Discrimination (max = 72)	53	54	49.50	48.83 (4.07)	56.97	40.69	Y	47	55
Commands (max = 15)	3	6	6	6.00 (1.73)	9.46	2.54	Y	3	4
Complex Ideational Material (max = 12)	2	2	4	2.00 (1.00)	4.00	0	Y	2	1

* Score increased at least 2 SD from Baseline (3×), for treatment intervention series (TMS+mCILT).

[†] Time Interval between last testing Post- TMS alone and entry into TMS+mCILT = 1 Yr. 6 Mo.

Table 5

Elicited propositional speech examples- BDAE, cookie theft picture, for P1 and P2

	Pre- TMS+mCILT Baseline (3 testing sessions)	2 Months Post- TMS+mCILT (1 testing session)	16 Months Post- TMS+mCILT (1 testing session)
A) P1, Patient with mild-moderate Nonfluent Aphasia			
Number of Different Nouns	Range: 7–9 boy, stool, cookie jars, cookies, water, dishes, sink, floor, mother	Total: 12 * boys, bench, cookies, jar, hand, sister, bed, mother, water, cabinets, dishes, sink	Total: 8 mother, plates, sink, water, kid, cookie jars, girls, cookies
Number of Different Verbs	Range: 7–9 getting, is (3×), selling, was (3×), getting, started, fell, flowing, washing	Total: 7 were, was, going, has, cooking, falling, is	Total: 7 is, was (2×), watching, overflowed, went, fell, going
	Pre-TMS+mCILT Baseline (3 testing sessions)	1 Month Post- TMS+mCILT (1 testing session)	6 Months Post- TMS+mCILT (1 testing session)
B) P2, Patient with severe Nonfluent Aphasia			
Number of Different Nouns	Range: 3–4 picture, water, cookie, man, boy, towel	Total: 5 * cookie, boy, water, man, dishes	Total: 5 * cookie, boy, water, benches, dishes
Number of Different Verbs	Range: 0–1 falling	Total: 3 * working, walking, falling	Total: 0 None uttered

* Score changed at least 2 SD from Baseline.

Table 6

List of color pictures, 'never-named' at entry, but successfully named at least once during TMS+mCILT (without cueing), for P1 and P2

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9*	Day 10*
A) P1, Patient with mild-moderate Nonfluent Aphasia (max = 6× per picture presentation)									
table × 6	refrigerator × 6	rainbow × 6	maid × 6	necklace × 6	typewriter × 6	caterpillar × 6	eggplant × 6		
team × 6	rabbit × 6	rug × 6	turtle × 6	noodles × 6	gem × 5	chick × 6	police car × 6		
foot × 6	doll × 6	triangle × 6	sunglasses × 6	peanuts × 6	waterfall × 5	easel × 5	pickles × 6		
plate × 6	oval × 6	orange × 6	knot × 5	olives × 6	cherries × 4	grapefruit × 5	faucet × 5		
shirt × 6	curtains × 6	well × 5	scarf × 5	ruler × 6	raisins × 4	rectangle × 4	saxophone × 5		
chain × 6	shorts × 5	jeep × 3	hose × 4	strawberries × 6	hurdle × 2	headphones × 4	sweatshirt × 4		
bottle × 6	hook × 5	cereal × 3	robe × 1	napkin × 6	safe × 2	leash × 4	calculator × 3		
blocks × 5	helmet × 5	chess × 3		bubbles × 5		rooster × 3	cooler × 2		
pepper × 5	goat × 5	butterfly × 3		mug × 5		remote control × 2	chimes × 2		
blocks × 5	fountain × 5	tissues × 2		briefcase × 5		beads × 1			
bowl × 5	bow × 3	ribbon × 1		blender × 5					
ring × 4				magnet × 4					
piano × 3				plug × 4					
grill × 3				coffee table × 3					
shell × 2				lighthouse × 2					
				mixer × 2					
				bracelet × 1					
				beetle × 1					
B) P2, Patient with severe Nonfluent Aphasia (max = 6× per picture presentation)									
	road × 4	baseball × 6	circle × 3	jacket × 6	dirt × 6	rocks × 5	couch × 5	van × 3	crown × 6
	window × 3	boat × 6	cheese × 2	cat × 5	deer × 5	soup × 3	watch × 5	gym × 2	gloves × 6
	girl × 3	foot × 5	basketball × 1	juice × 4	knee × 4	cigarette × 2	jeans × 5	tunnel × 1	medal × 2
Incomplete Data	glass × 1	beach × 4		train × 4	stairs × 4	muscle × 2	wing × 4	shell × 1	leaf × 1
		square × 3		chain × 2	mail × 2				
					vegetables × 1				

* All pictures were successfully named at least once, without cueing, thus treatment focused on sentence production.