**Study Protocol**

**Study Title:** Brain Biomarkers of Response to Treatment for Apraxia of Speech

**NCT#:** 02046941

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**Study Protocol**

**Behavioral Protocol**

Performance on the pre-testing measures was used to identify candidate target sounds for the SPT protocol for each individual. Up to 3 target sounds were identified for each participant, as in previous studies with SPT (see Bailey et al., 2015). The targets sounds were single consonants or clusters tested at the word level (see Table 1). Lists of 16-20 words with the target sounds were generated and administered to participants during subsequent pre-treatment sessions. For every target sound, two lists of 8-10 words each were generated in order to have a trained and untrained item list. The trained list(s) were those items that were trained/treated using SPT during the treatment phase. For the probe trials, participants were asked to simply repeat each word in the list spoken by the SLP. At least 5 baseline probe trials were conducted prior to treatment, and performance had to fall between 50-100% errors for each target to be included in the treatment phase. This criterion ensured a sufficiently low baseline to minimize ceiling effects in the behavioral data during treatment. Also, performance on the final three probe trials prior to treatment had to fall within 15% of each other, in order to establish a stable baseline; otherwise, the baseline phase was extended until this criterion was met (see Fisher et al., 2003).

Following the pre-treatment (baseline) phase, the treatment phase consisted of the SPT protocol delivered to participants in 1-hour sessions, 3 days a week, for a total of 16 sessions over 5.5 weeks. The SPT protocol was the same as that developed and extensively studied by Wambaugh and colleagues (see Wambaugh & Nessler, 2004). Table 2 shows the SPT hierarchy, which involves verbal repetition, imitation, and articulatory placement cueing. The same list(s) of 8-10 trained items developed during the baseline phase were trained using this hierarchy throughout the 5.5 week period.

*SPT Treatment Hierarchy*

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| **Step 1:** SLP produces target word in carrier phrase, "I say" and requests a repetition of the word in the phrase. If correct, SLP provides feedback concerning accuracy, requests 5 additional productions, and the next item is presented. If incorrect, SLP provides feedback concerning accuracy, and the next step in the hierarchy is attempted. |
| **Step 2:** SLP shows the target word in printed form and underlines the sound(s) produced incorrectly. SLP indicates problem sounds, produces the target word (no carrier phrase), and requests a repetition. If correct, SLP provides feedback concerning accuracy, requests 5 additional productions, and the next item is presented. If incorrect, SLP provides feedback concerning accuracy, and the next step in the hierarchy is attempted. |

**Step 3:** SLP says, "Watch me, listen to me, say it with me" and produces the target word simultaneously with the participant. This procedure is attempted up to three times in the hope of eliciting a correct production. If correct, SLP provides feedback concerning accuracy, SLP requests 5 additional productions, and the next item is presented. If incorrect, SLP provides feedback concerning accuracy, and the next step in the hierarchy is attempted.

**Step 4:** SLP provides articulatory placement cues appropriate to the sound production errors and repeats the procedures in Step 3. If correct, SLP provides feedback concerning accuracy, requests 5 additional productions, and the next item is presented. If incorrect, SLP provides feedback concerning accuracy, and the next item is presented.

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Improvement in response to the SPT protocol was measured by performance (percent correct) on the probe trials during the treatment phase. The probe trials were administered prior to the start of every other SPT session. Following the treatment phase, participants underwent post-testing with the same standard speech and language measures used during pre-treatment.

*Behavioral Data Analysis.* The primary behavioral outcome measure in the current study was SPT effect size on trained items ($d_2$ index; Busk & Serlin, 1992). This $d_2$ index reflects the difference in probe trial performance during pre-treatment versus the end of treatment:

$$d_2 = \frac{M_{A2} - M_{A1}}{SD_{pooled}}$$

where $M_{A1}$ is the mean percent correct on the last five probe trials during the baseline phase prior to treatment, $M_{A2}$ is the mean percent correct on the last three trials at the end of the treatment phase, and $SD_{pooled}$ is the pooled standard deviation of the two phases. Effect size ($d_2$) calculation reflects both magnitude of change and variability (Bloom, Fischer, & Orme, 2003; Cohen, 1988). When there was more than one target sound, the average effect size was used in the analyses relating treatment effects to plasticity changes (Beeson & Robey, 2006).

## MRI Protocol

Our MRI imaging protocol is consistent with the imaging parameters described in the NIH CDEs for MRI Trauma Protocol for 3T-Tier 1. Brain imaging data was acquired on a new Siemens Magnetom Verio open-bore 3T MRI scanner with 12-channel parallel imaging capabilities. With its wide and short bore, this scanner has been designed to optimize patient comfort. We acquired high-resolution structural scans using a 3D T1w MPRAGE (magnetization-prepared rapid gradient echo) protocol with 1 $mm^3$ isotropic resolution (TR/TE/TI = 2400 / 3.16 / 1000 ms, flip angle = 8°; FOV = 256 mm; imaging matrix = 256 x 256;

acquisition time = 4.5 minutes). Two T1w images were acquired and averaged to improve the contrast-to-noise ratio. FLAIR and fast spin echo T2-weighted images were also acquired with the default Siemens pulse sequences for the visual assessment of brain lesions.

High angular resolution diffusion imaging (HARDI) data were acquired with a high diffusion weighting (b factor = 2000 s/mm$^2$) and 64 gradient (40 mT/m) encoding vectors, uniformly distributed on a sphere. These parameters maximize diffusion sensitivity and angular contrast while attaining clinically feasible acquisition times (Jones et al., 2002). Parallel imaging (iPAT, Siemens) with GRAPPA (generalized auto-calibrating partially parallel acquisition) was employed to reduce echo train length and echo time (TE) in the DW-MRI measurements, and to reduce the susceptibility-induced EPI geometric distortions and to improve the signal-to-noise ratio (SNR). 8 non-diffusion weighted (B0, b = 0 s/mm$^2$) images were also acquired, one before each group of 8 diffusion weighted images. Other HARDI acquisition parameters are: Twice-refocused spin-echo (TRSE) echo-planar imaging (EPI); 2 mm$^3$ isotropic voxel resolution; TR/TE = 15,500/93 ms; Bandwidth = 1817 Hz; 65 axial slices in the inter-commissural plane (interleaved, no gap) for whole-cerebral coverage; Flip angle = 90°; Field of view (FOV) = 240 cm; Imaging matrix = 120 x 120; GRAPPA acceleration factor = 2; 6/8 phase partial Fourier (PPF) sampling. The bipolar (twice-refocused) diffusion gradients implemented on Siemens VB17 are designed to minimize eddy current effects. In order to minimize the effects of brain pulsations, cardiac gating were applied to trigger image acquisition at the beginning of the R-R cardiac cycle. Total acquisition time was 19-20 minutes. A field map was also acquired with the same slice prescription as the HARDI images for off-line EPI geometric distortion correction.

Fiber pathways were traced using the streamline tractography technique (Wakana, et al., 2007; Wedeen, et al., 2008). Whole-brain tractography approach was used to trace fibers from seed points in all white matter voxels using the Fiber Assignment by Continuous Tracking (FACT) algorithm (Mori, et al., 1999) implemented in TrackVis. For DTI data, FACT find the best matching fiber trajectory that is consistent with the orientations of voxel-wise principle diffusion direction vectors identified from the diffusion tensor. Multiple diffusion direction vectors are possible at each voxel, depending on the orientation distributions determined by the high-angular resolution measurements (Schmahmann, et al., 2007; Wedeen, et al., 2005, 2008). This allows crossing-fibers to be resolved and fibers to be traced towards their cortical origins and terminations. Stopping criteria for fiber tracing were an angle threshold of 45° and FA threshold of 0.15. While FA thresholds of 0.2 or higher are more commonly used (Mori et al., 2001), FA values are

lower in stroke patients (Ciccarelli, Catani, Johansen-Berg, Clark, & Thompson, 2008), so that a lower threshold is more appropriate. White matter segmentations obtained from T1 anatomical images was used to mask out regions where tractography might provide erroneous results. Fibers shorter than 50 mm and longer than 200 mm were also excluded to reduce false positives (i.e., artifactual/spurious fibers).