Statistical Analysis Plan

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

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Data Analysis

Behavioral Data. Treatment effect sizes for treated and untreated items were calculated separately for each sound target using the Busk and Serlin (1992) d_2 statistic. This effect size is derived by calculating the difference between the average performance from the comparison design phases (e.g., M_{A1} and M_{A2}) and dividing this difference by the pooled standard deviation of the two phases:

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

where M_{A1} was based on the final five probe trials during the baseline phase prior to treatment, and M_{A2} was based on the final three probe trials at the end of the treatment phase (consistent with prior SPT studies; Wambaugh et al. 2013). For participants who were trained on more than one target sound, the d_2 value represents the average d_2 across targets (Beeson & Robey, 2006). Based on previous SPT research (Bailey et al., 2015), the cut-off value for what was considered a large effect size for treated items was d = 9.6, d = 7.0 for a medium effect size, and d = 5.2 for a small effect size. The cut-off values for untreated items were d = 6.7 for large effect size, d = 3.8 for medium effect size, and d = 2.2 for small effect size.

MRI Data. To relate treatment effect size to lesion site, participants' normalized lesions were first visualized in MRIcron and overlaid on the automated anatomical labeling (AAL) atlas, which is based on 116 parcellations of the brain (Tzourio-Mazoyer et al., 2002). We focused on 4 regions of interest (ROIs) that have been previously implicated in AOS, SPGI, Broca's area, SMG, and pre-central gyrus. The percentage of each AAL region affected by an individual's lesion was then calculated in MRIcron. Participants' behavioral data (effect size) and individual anatomical lesion data were analyzed using a Partial Least Square (PLS) regression: Effect size was related to the lesion variables in a leave-one-out manner.

For the white matter analysis, T1 anatomical images were processed using FreeSurfer 5.3, which includes intensity normalization, segmentation, inflation of surfaces to spheres, and spherical registration of spherical surfaces to a standard template (Dale et al., 1999; Fischl et al., 1999). FreeSurfer provides neuroanatomical parcellation of the cortex, defined by Desikan-Killiany (Desikan et al., 2006). It was necessary to virtually implant 20mm of the medial-most portion of the right hemisphere onto the

left hemisphere in order to fill in holes created by the large lesions in the left hemisphere that prevented the Free Surfer program from completing processing. This virtual implant into the left hemisphere using FreeSurfer has negligible effects on cortical thickness measurements and Desikan parcellations in the right hemisphere (Solodkin et al, 2010). FreeSurfer also provides labels of the segmented subcortical structures, some of which are termination zones of white matter structures investigated in the current study (Abe et al., 2010; Fischl et al., 2002; Fischl et al., 2004).

We wanted to limit the number of possible comparisons for analysis. Therefore, the analyses were confined to a subset of Desikan-Killiany regions previously implicated in imaging studies of speech and language treatment: Broca's area homologue in ventrolateral prefrontal cortex, precentral cortex, insular cortex, inferior parietal cortex, superior temporal sulcus, and middle and superior temporal cortices. Thickness measurements were computed by FreeSurfer and then averaged over the chosen Desikan parcels. Thickness measurements have been shown to be stable across scanning sessions (Han et al 2006), and particularly reliable in Desikan parcels within an individual (Wang et al 2010).

The mean images from realigned B_0 and diffusion-weighted images (DWIs) were coregistered to individuals' anatomical images after distortions were corrected using field maps (Jezzard & Balaban, 1995; Jones & Cercignani, 2010). The mean images from realigned B_0 and DWIs were co-registered and resampled to a high-resolution anatomical image space using the entropy-based algorithm in SPM8 (www.fil.ion.ucl.ac.uk/spm/). Mean images were used to increase the stability of the coregistration (Rohlfing et al., 2005).The individual B_0 and DWIs were then re-aligned and resampled to their respective mean images. FA was computed using the standard formula from the eigenvalues of the tensor (Basser & Pierpaoli, 1996; Pajevic & Basser, 2003) and was averaged in selected fiber tracts.

Average FA was calculated for white matter tracts in the right hemisphere based on probabilistic atlases (Mori et al., 2008; Oishi et al., 2008). The skull-stripped brain volume from each participant's T1 image was normalized to MNI305 template space (Evans et al., 1993) using FreeSurfer, and each normalized brain image was then coregistered to the ICBM template containing the probabilistic tract atlases (Mazziotta et al., 2001). Then the FA data, coregistered to the T1 image, were sampled in ICBM space using a tract threshold of 25% probability and then averaged. The analyses focused on four white matter tracts previously implicated in speech-language recovery/treatment: the inferior longitudinal fasciculus

(ILF), the inferior frontal occipital fasciculus (IFOF), the superior longitudinal fasciculus (SLF, fronto-temporal component), and the uncinate fasciculus (UF).

The percent change in FA values and cortical thickness from pre- to post-SPT was calculated as:

$$Diff(A,B) = \frac{A-B}{(A+B)/2} \times 100\%$$

where A is the post-MRI value and B is the pre-MRI value. We report both descriptive statistics and correlation coefficients relating treatment effect size to FA and cortical thickness changes.