Introduction
• Speech production network characterized by neuroimaging is based largely on small N studies or meta-analyses of such studies
• Picture may therefore be incomplete due to false negatives arising from relatively low power
• Here we describe efforts to understand the brain regions involved in speech using a mega-analysis approach
• This approach (i) increases statistical power; (ii) can result in a more heterogeneous and representative sample; and (iii) provides a means to better characterize the sources of variability across subjects and studies (Cox et al., 2000; Van Horn, 2004)
• Functional imaging data pooled across 10 fMRI studies of speech production (See Table 1 for list of study designs)
• Results used to determine functional ROIs for speech processes

Methods
Functional Analyses
Common pipeline: 1-level analysis of realigned functional images (no normalization or spatial smoothing) using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8). Speech-Baseline contrasts (all experiments) and Perturbed Speech-Non-perturbed Speech contrasts (three experiments) estimated for each subject

Inter-experiment equalization: 1-level contrast volumes normalized by experiment-specific scaling factor: standard deviation of Speech-Baseline contrast across entire brain, averaged across all subjects within each experiment.

Surface-based analyses: Cortical surfaces extracted from T1 volumes for each subject using FreeSurfer (https://surfer.nmr.mgh.harvard.edu; Dale et al., 1999; Fischl et al., 1999). Contrast values at the pial surface extracted after functional-anatomical coregistration and entered into vertex-level 2-level analyses. Perturbed Speech-Non-perturbed Speech contrast values spatially smoothed (approx. 8 mm FWHM kernel) prior to 2nd-level analyses.

2nd-level analyses controlled for false positives using vertex-level corrected p < 0.01 threshold, and a cluster-level whole-brain FWE-corrected p < 0.05 threshold. Preprocessing with 6 mm spatial smoothing kernel on the cortical surface resulted in approximately 15 distinct regions in each hemisphere. Only ROIs with significant average functional Speech-Baseline (FDR-corrected p < 0.05) were retained.

Between-subjects variability clustering: Neighboring vertices/ROIs sequentially grouped based on the similarity of their patterns of functional responses (minimization of within-ROI variability in Speech-Baseline contrast values across all subjects; Seghier et al., 2009). Resulting hierarchical tree trimmed to contain 100 ROIs per hemisphere. The average functional responses (minimization of within-ROI variability in Speech-Baseline contrast across entire brain, averaged across all subjects within each experiment).

Between-subjects variability clustering: Neighboring vertices/ROIs sequentially grouped based on the similarity of their patterns of functional responses (minimization of within-ROI variability in Speech-Baseline contrast values across all subjects; Seghier et al., 2009). Resulting hierarchical tree trimmed to contain 100 ROIs per hemisphere. The average functional responses within these ROIs accounted for 74% of the overall variability in responses across all vertices in the cortical surface. Only ROIs with significant average functional Speech-Baseline (FDR-corrected p < 0.05) retained.

Summary
• Pooled analysis reveals distinct peaks within the Speech Production network, characterized by Average Activity Clustering. In particular:
  - medial prefrontal/singular cortex, insular/superior cortex
  - Between-Subjects Variability Clustering identified additional functionally distinct anterior-posterior bands in the core sensorimotor regions that subserve speech production
• Pooled analysis of Perturbed/Non-perturbed contrast revealed greater lateral frontal-right hemisphere activity with distinct peaks in premotor cortex, inferior frontal gyrus, and anterior insula
• First step in building a functional-anatomical atlas for speech production

Future Directions
• Integrate subcortical analysis
• Incorporate remaining studies (29 additional datasets) add more??
• Investigate functional and structural connectivity between functionally derived ROIs - currently have ~90 DTI datasets
• Quantify functional-anatomical relationships
• Explore task, behavior, and demographic effects and compare to variability-based clustering to identify functional-anatomical relationships
• e.g. pMFg activity greater in women than in men during speech

Table 1: Studies in Analysis Pool

<table>
<thead>
<tr>
<th>Task</th>
<th>Structural Acquisition</th>
<th>Functional Acquisition</th>
<th>Production in PWS</th>
<th>Speech Rate, Clarity, and Expression</th>
<th>ROIs</th>
<th>Sequence Learning</th>
<th>Sequence Learning in PWS</th>
<th>Production in PWS</th>
<th>Speech Rate, Clarity, and Expression</th>
<th>pMFg activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>15 Blocks / Run</td>
<td>3 Volumes / Trial</td>
<td>32 axial slices</td>
<td>32 Channel Coil</td>
<td>32 Channel Coil</td>
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<tr>
<td>Equipment</td>
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<td>9T Siemens Trio</td>
<td>9T Siemens Trio</td>
<td>9T Siemens Trio</td>
<td>9T Siemens Trio</td>
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</tr>
<tr>
<td>Structural Acquisition</td>
<td>17% visual/17% verbal</td>
<td>17% visual/17% verbal</td>
<td>17% visual/17% verbal</td>
<td>17% visual/17% verbal</td>
<td>17% visual/17% verbal</td>
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<td></td>
</tr>
<tr>
<td>Functional Acquisition</td>
<td>1% visual/1% verbal</td>
<td>1% visual/1% verbal</td>
<td>1% visual/1% verbal</td>
<td>1% visual/1% verbal</td>
<td>1% visual/1% verbal</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Production in PWS</td>
<td>120 visual/120 verbal</td>
<td>120 visual/120 verbal</td>
<td>120 visual/120 verbal</td>
<td>120 visual/120 verbal</td>
<td>120 visual/120 verbal</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Speech Rate, Clarity, and Expression</td>
<td>10% gap</td>
<td>10% gap</td>
<td>10% gap</td>
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</table>

Table 2: ROIs of Interest

<table>
<thead>
<tr>
<th>ROI-Level Cluster Activity</th>
<th>Activation Mass</th>
<th>pMFg Activity</th>
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<tbody>
<tr>
<td>Left</td>
<td>p5f 1375 -0.96</td>
<td>0.031</td>
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<tr>
<td>Right</td>
<td>df0 2148 &lt;0.01</td>
<td>0.025</td>
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</table>

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References