

# **Pivotal disruption? Abnormal activity in motor control regions in stuttering**

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## **Introduction**

Stuttered speech can contain repetitions of sounds, or inability to initiate sounds and often occurs simultaneously with facial-motor disruption similar to tics seen in patients with movement disorders. People who stutter do not typically have other gross movement difficulties nor do they exhibit any sort of cognitive deficits. Components of the speech and motor systems are thus considered the most likely candidates for anomalous development in people who stutter. As there are no post-mortem studies to inform the debate on causes of stuttering, currently, the bulk of our knowledge about potential brain abnormalities comes from two sources: studies comparing structure and function in people who stutter and fluent controls. These studies typically use magnetic resonance imaging, or MRI, and when the same tool is used to look at changes in blood flow related to specific tasks it is called functional MRI or fMRI.

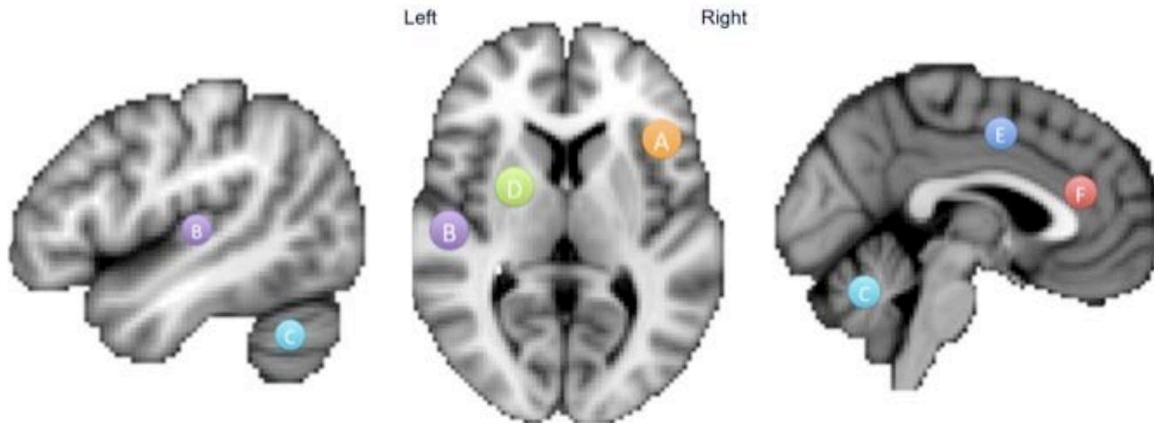
Structural imaging gives some evidence for disrupted grey matter development in the speech and motor systems in the form

of abnormal shape of the auditory cortex<sup>1</sup>, reduced thickness in speech-motor planning regions<sup>2</sup>, and increased volume in left basal ganglia<sup>3</sup>. Some groups have shown anomalous white matter development in portions of the corpus callosum<sup>4,5</sup>. A consistent finding across other diffusion studies show disrupted white matter underlying speech-motor planning regions<sup>6</sup> that also show disrupted function<sup>7</sup>; disrupted white matter in major speech and motor pathways including the major language pathways connecting the brain from front to back<sup>8-10</sup> and all three pairs of cerebellar peduncles that facilitate communication between parts of the brain and spinal cord, and integration of behaviours with different body parts<sup>10</sup>.

Functional imaging literature likewise supports disruption in the speech and motor systems in event-related and resting-state studies. A meta-analysis of overt speech in stuttering compared activation maps in people who stutter and in fluent controls in eight early neuroimaging studies<sup>11</sup>. The review concluded that all participants largely recruit the same brain regions during speech, though a diagnosis of stuttering was related to increased activation in lateral speech-motor regions and other components of the motor system including the supplementary motor area (SMA), cingulate cortex, and the vermis of cerebellum. The meta-analysis identified three “neural signatures” of stuttering 1) overactivation of the right frontal operculum, anterior insula, or both (Figure 1:A); 2) overactivation of the cerebellar vermis (Figure 1:C); and 3) an “absence” of activity in auditory cortex (Figure 1:B). Treatment studies combined with fMRI to evaluate outcome due to therapy also implicate the frontal operculum, which is resistant to interventions both during tasks and at rest<sup>2,12</sup>, whereas abnormal cerebellar activity appears to be related to treatment both during speech tasks and at rest.

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Figure 1. Regions in which we predict differences between CON and AWS based on the “neural signatures” of stuttering (A=Frontal Operculum, B=Auditory Cortex, C=Cerebellar Vermis) and components expected to be taxed by the spontaneous speech component of our tasks (D=Basal Ganglia, E=pre-Supplementary Motor Area, F=Anterior Cingulate Cortex).



Though notably not a conclusion in the meta-analysis, abnormal basal ganglia activity is likely in stuttering, particularly as other core motor system components including cerebellum and supplementary motor area (SMA) are consistently overactive across studies. It is unlikely that overactivity in core components of the motor network would occur independent of any disruption to the hub that excites and inhibits activity of those other components. Empirical support for basal ganglia dysfunction in stuttering can be found in: treatment success of dopamine blockers (for review see<sup>13</sup>); early imaging studies of increased dopamine uptake in the basal ganglia components<sup>14</sup>; increased activity within individuals subsequent to treatment<sup>12</sup> or compared to fluent controls during speech-related fMRI<sup>7</sup>; altered connectivity at rest<sup>2,15,16</sup>; correlations between activity and stuttering severity or constellations of symptom<sup>17,18</sup>. There is strong theoretical evidence for central involvement of the motor control system in stuttering, still, there is a lack of continuity across functional imaging studies implicating specific basal ganglia structures or the direction of abnormalities relative to controls.

The primary aim of this study is to explore the influence of stuttering on overt speech-related brain activity. We use two tasks to elicit overt speech: 1) Sentence Reading and 2) Picture Description. We selected these conditions because traditionally stuttering is only elicited through more complex, longer utterances<sup>11</sup>. Additionally, the conditions should be well matched for speech production generally, as they place similar demands on the articulatory system. We expect recruitment of additional regions in the picture description task, which has a spontaneous speech component involving planning of both speech content and motor movement, across groups, resulting in increased activation in the components of the speech-motor planning system. This system includes regions identified as neural signatures of abnormal activity in stuttering and is likely dysfunctional in stuttering. The contrasts of interest include each condition relative to baseline and the picture description condition relative to sentence reading.

Empirical support for basal ganglia dysfunction in stuttering is ample: treatment success of dopamine blockers (for review see<sup>13</sup>); early imaging studies of increased dopamine uptake in the basal ganglia components (Wu et al., 1997); increased activity within individuals subsequent to treatment<sup>12</sup> or compared to fluent controls during speech-related fMRI<sup>7</sup>; altered connectivity at rest<sup>2,15,16</sup>; correlations between activity and stuttering severity or constellations of symptom<sup>17,18</sup>. There is strong theoretical evidence for central involvement of the motor control system in stuttering, still, there is a lack of continuity across functional imaging studies implicating specific basal ganglia structures or the direction of functional abnormalities (over vs. underactivity) relative to controls.

The primary aim of this study is to explore the influence of stuttering on overt speech-related brain activity. We use two tasks

to elicit overt speech: 1) sentence reading and 2) picture description. We selected these conditions because traditionally stuttering is only elicited through more complex, longer utterances<sup>11</sup>. Additionally, the conditions should be well matched for speech production generally, as they place similar demands on the articulatory system. Previous studies have used sentence reading (e.g.<sup>7</sup> and described differences in brain activity in several regions including some of those identified as neural signatures. We expected recruitment of additional regions in the picture description task, which has a spontaneous speech component involving planning of both speech content and articulatory movement, which we predicted would result in further increased activation in the components of the speech-motor planning system. Furthermore, we significantly increased the amount of speech produced in the scanner from that obtained in previous studies that was mostly fluent. By effectively doubling the amount of speech and including the picture description condition, we hoped to be able to capture utterances that were both fluent and dysfluent and compare the related patterns of activity (see next chapter). The contrasts of interest include each condition relative to baseline and the picture description condition relative to sentence reading. Within AWS we examine the effect of sex, handedness, and severity on activity in regions showing differences between groups.

We made the following predictions regarding the differences between groups:

- Across conditions we expect overactivity in right inferior frontal cortex, underactivity in auditory cortex, and overactivity in the cerebellum in Adults who stutter (AWS) relative to the control group (CON), consistent with the

reported “neural signatures” of stuttering (Figure 1; A, B, C, respectively).

- We predict that the contrast between conditions (Picture description > sentence reading) will be greater in AWS than in CON in primary speech-motor planning regions (pre-SMA and medial prefrontal cortex; Figure 1: E, F, respectively) and in regions supplying internal cuing about speech initiation to the medial frontal cortex (i.e. striato-pallidal-thalamic outputs of the basal ganglia: Figure 1: D).

## **Methods**

### *Participants*

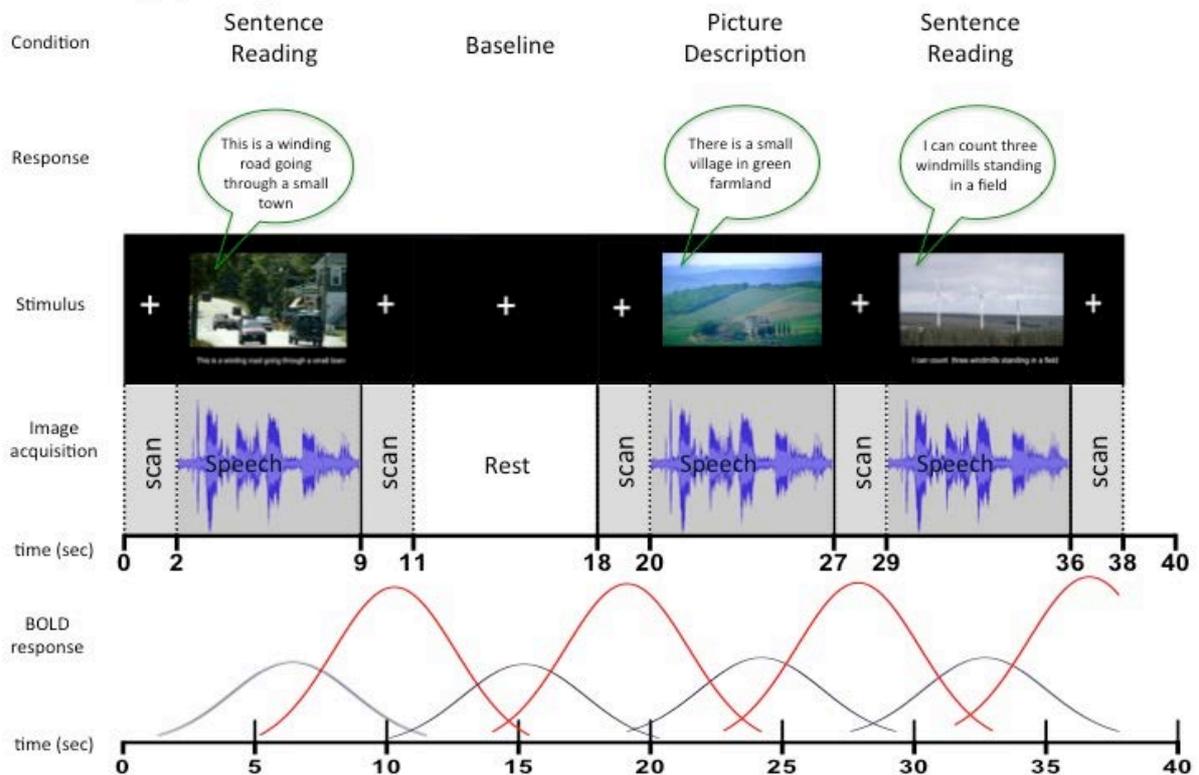
Seventeen adults who stutter (AWS: 13M:4F; aged 19–54 years; 3 left-handers) and 17 age- and sex-matched fluent controls (CON: 13M:4F; aged 19–53 years; 3 left-handers) were scanned using functional MRI. No controls had a history or diagnosis of learning or speech disorders. All participants gave informed consent to their participation in the research in a protocol approved by University of Reading’s ethics committee. Stuttering ranged in severity from very mild to severe, as assessed by a speech therapist using the Stuttering Severity Instrument-3<sup>19</sup>. The data from some of the sample (CON) were used in a previous report, but further data have been added (AWS). Stuttering ranged in severity from very mild to severe, as assessed by a speech therapist (DW) using the Stuttering Severity Instrument-3<sup>19</sup>.

### *Data acquisition*

Functional MRI data were obtained at the University of Reading using a 3-T Siemens Trio scanner with a 12-channel head

coil. Whole-head T2\*-weighted echo-planar images (TE=30ms) were acquired every 9s with a silent delay of 7s (i.e. sparse sampling) and comprised 2-s acquisition of 32 4-mm axial slices (in-plane resolution 3 mm x 3 mm). A '+' appeared in the middle of the screen during the 2-s acquisition period (Figure 2).

**Figure 2. Tasks design and scanner acquisition method. Two conditions: Read (Sentence Reading) and Speech (Picture Description) were used to assess speech-related brain activity. Sparse sampling catches the final part of the stimulus-locked activity by exciting just after the task event.**



During the 7-s silent delay between measurements, subjects saw a stimulus via scanner-compatible goggles that was either a picture with a descriptive sentence below it, a picture with no text, or a '+' in the middle of the screen. Subjects were instructed to read the sentences aloud (Sentence Reading condition) or to overtly describe the pictures (Picture Description condition) and were explicitly told to stop speaking when the crosshair appeared so that there would be no speech-related movement of the head during data collection. Prior to the scan the task was explained to subjects who were allowed to practice outside the scanner. For

each of the conditions and the baseline condition, 40 volumes of data were acquired for a total of 120 volumes (18 min); the order of conditions was fixed and pseudorandom. Two runs were acquired in each subject, yielding 80 volumes of each condition (Sentence Reading, Picture Description, and Baseline).

### *Speech analysis*

Speech was recorded using an MRI-compatible microphone. These recordings were later checked for task compliance. Most subjects produced a total of 160 task-related utterances in the scanner. In a single AWS, who was not excluded from the analysis, 37% of trials were not confirmed due to equipment malfunction, but all remaining trials were clearly compliant. Sentences were marked as normal or dysfluent.

### *Image analysis: Whole-brain*

The functional images were analysed using the FMRIB Software Library (FSL; <http://www.fmrib.ox.ac.uk/fsl><sup>20</sup>). In addition to the standard motion correction; which adds six head-motion parameters as covariates at the first level for each subject, volumes that were motion outliers were included as separate regressors in the model. Excessive motion (i.e. > 4mm) was observed during the end of a single scan session in one AWS and the volumes following the movement were removed from the time series (i.e. the run was truncated). The remaining data analysed normally. Each dataset was unwarped using a fieldmap and PRELUDE and FUGUE software running in FSL<sup>20</sup>, spatially smoothed with an 8 mm full-width at half maximum smoothing kernel. A temporal high-pass filter with a cutoff of 150 seconds was used to remove low-frequency fluctuations in the signal. Two further regressors were used in the first-level analysis to remove

residual image artefacts. The mean time-courses from a 4 mm radius sphere within cerebrospinal fluid of the anterior lateral ventricle (standard space coordinates 2, 10, 8) and white matter in the dorsal posterior frontal lobe (-26, -22, 28) were extracted from preprocessed data<sup>21</sup>. Images were registered using boundary-based registration<sup>22</sup> to the individual subject's T1-weighted structural image (1 mm<sup>3</sup> voxels; GRAPPA sequence TR = 20.2 ms, TE = 2.9 ms, flip angle = 9<sup>0</sup>), which in turn was registered using FNIRT (FMRIB's nonlinear registration tool) to the MNI-152 template.

In addition to the standard motion correction; which adds six head-motion parameters as covariates at the first level for each subject, volumes that were motion outliers were included as separate regressors in the model. Excessive motion (i.e. > 4mm) was observed towards the end of a single scan session in one AWS and one CON, and these volumes (< 15% of total trials) were removed from the time series (i.e. the run was truncated). The remaining data were analysed normally. Each dataset was unwarped using a fieldmap and PRELUDE and FUGUE software running in FSL and spatially smoothed with an 8-mm full-width at half maximum smoothing kernel. A temporal high-pass filter with a cutoff of 150 seconds was used to remove low-frequency fluctuations in the signal. Two further regressors were used in the first-level analysis to remove residual image artefacts. These regressors were the mean time-courses from a 4-mm radius sphere within cerebrospinal fluid of the anterior lateral ventricle (standard space coordinates 2, 10, 8) and white matter in the dorsal posterior frontal lobe (-26, -22, 28), which were extracted from preprocessed data<sup>21</sup>. Images were registered using boundary-based registration<sup>22</sup> to the individual subject's T1-weighted structural image (1 mm<sup>3</sup> voxels; GRAPPA sequence TR = 20.2 ms, TE = 2.9 ms, flip angle = 9<sup>0</sup>), which in turn was registered using FNIRT (FMRIB's

nonlinear registration tool) to the MNI-152 template.

For individual subjects, statistical maps were generated to show patterns of activation during each condition relative to baseline and between the Picture Description and the Sentence Reading conditions. Contrast masking was used at the first level to examine differences between conditions only in regions where positive activation ( $Z > 0$ ) occurs in response to the stimuli in each condition separately. The data for the two runs in each subject were combined using a fixed-effects analysis. Group averages and contrasts between groups were analysed using FMRIB's Local Analysis of Mixed Effects stage 1<sup>23</sup>. Masking was used for the group comparisons to show only regions in which both groups had positive activity ( $Z > 0$ ) for each contrast of interest overall. Because AWS and CON were well-matched on age, sex, and handedness, we did not model these variables for inclusion in whole-brain group comparisons.

## **Results**

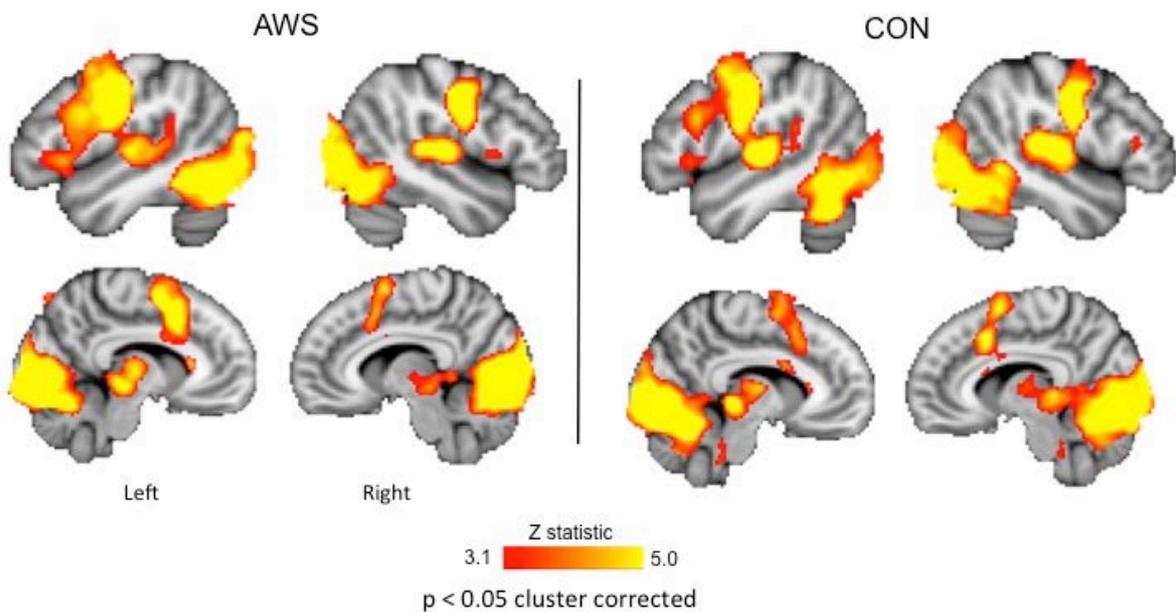
We predicted the picture description condition would place additional demands on linguistic and motor planning and self-initiated speech processes that could be disrupted in AWS. We expected the conditions to be otherwise well matched for articulatory efforts and overt speech execution. AWS stuttered in the scanner, on average 20 times out of 160 utterances. CON showed some dysfluencies, but many fewer (2 of 160). Stuttering frequency was equivalent across conditions. Results reported in this chapter contain all speech events.

### *Picture description compared to baseline*

Both groups activated the expected network of areas involved in overt speech production, namely bilateral posterior

superior temporal cortex, sensorimotor cortex at about the level of the face representation, SMA and preSMA, and left lateralized posterior IFG. Extensive medial and lateral occipital cortex activity was seen in occipital cortex due to the presentation of the picture stimulus for description (Figure 3).

**Figure 3. Speech-related activity during picture description in adults who stutter, and controls. The expected network of auditory cortex in both hemispheres, motor cortex, pre-supplementary motor area, basal ganglia, and frontal speech-motor regions were observed.**



Examination of these group averages shows the AWS and CON to be strikingly similar in terms of the speech networks activated. The AWS show more extensive activation of the left IFG, lateral and medial premotor cortex relative to CON, with decreases occurring in both hemispheres while generating spontaneous speech for picture description.

Direct contrasts between the groups revealed that these cortical regions on the lateral and medial surface were significantly more active in AWS compared to CON but only at an uncorrected threshold of  $p < 0.01$  and extent  $> 30$  voxels (see Table 1, Figure 4). Additionally, at the same statistical threshold, the head of the caudate nucleus and putamen in the left hemisphere were more active in AWS compared to controls (see Table 1). Furthermore,

AWS had significantly less activity than CON in the right IFG, superior temporal gyrus/sulcus, left posterior STG (including auditory cortex), and left posterior lobe of the cerebellum (Table 1, Fig 4).

**Table 1: Regions where there were differences between groups in activity during Picture Description vs. baseline.**

Brain Region	voxels	Z statistic	X	Y	Z
<i>AWS &gt; CON</i>					
Left caudate (head)	34	2.99	-18	16	10
Left putamen	42	2.6	-20	10	-4
Left preSMA	341	3.65	-10	6	48
Left cingulate gyrus		3.33	-12	6	38
Left inferior frontal junction pars opercularis	78	2.81	-52	2	18
Left lingual gyrus	36	3.38	-28	-58	-2
Right dorso lateral occipital cortex	137	3.1	28	-68	22
Left ventrolateral occipital cortex	53	3.1	-52	-70	-20
Right occipital pole	88	3.54	42	-94	0
<i>CON &gt; AWS</i>					
Right inferior frontal gyrus pars triangularis	30	2.75	52	32	8
Right superior temporal gyrus	61	3.02	64	0	-4
Left auditory cortex Heschl's Gyrus	88	2.93	-56	-12	2
Left superior temporal gyrus (ant)		2.61	-58	-10	-8
Left posterior lobe of the cerebellum	133	2.99	-46	-52	-30

*Location of the highest peak in a cluster is given: voxelwise,  $p < .01$ , uncorrected with  $> 30$  voxel extent. Selected sub-peaks within the large clusters are also described. There were no areas where  $AWS > CON$  for Sentence reading. The number of voxels in a cluster is listed along with the peak height and coordinates of the peak location in MNI-152 standard space.*

### *Sentence Reading compared to baseline*

Both groups activated the expected network of areas

involved in overt speech production, namely bilateral posterior superior temporal cortex, sensorimotor cortex at about the level of the face representation, SMA and preSMA, and left lateralized posterior IFG. Extensive medial and lateral occipital cortex activity was seen due to the presentation of the picture stimulus for description, as was the case in picture description. Examination of these group averages shows the AWS and CON to be strikingly similar in terms of the reading networks activated. The AWS show relatively less activation of the left IFG, lateral and medial premotor cortex relative to the controls.

Direct contrasts between the groups revealed that these cortical regions on the lateral and medial surface were more active in AWS compared to CON but only at an uncorrected threshold of  $p < 0.01$  and extent  $> 30$  voxels (see Table 2, Figure 4). AWS showed relatively less activation for the sentence reading compared to CON occurring bilaterally in several speech regions including auditory and superior temporal cortex, bilaterally and in inferior frontal cortex and superior temporal cortex.

**Table 2: Regions where there were differences between groups in activity during Sentence Reading vs. baseline.**

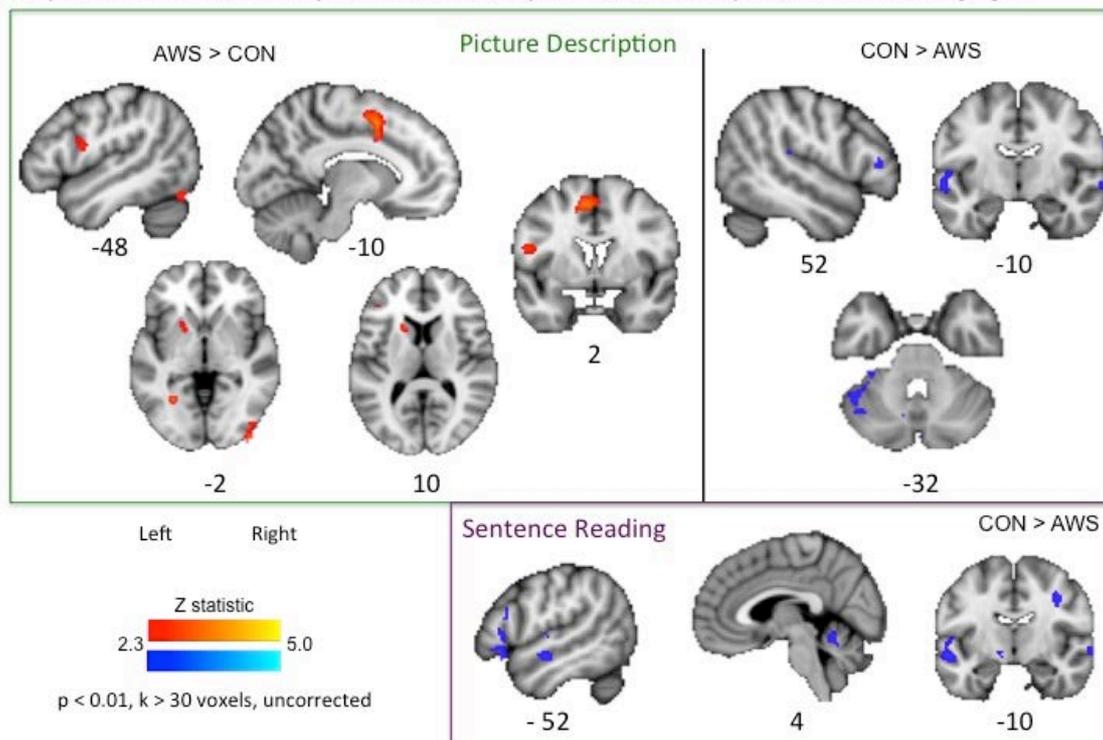
Brain Region	voxels	Z statistic	X	Y	Z
<i>CON &gt; AWS</i>					
Left frontal pole pars orbitalis	105	3.5	-46	26	-10
Right inferior frontal gyrus pars triangularis	33	3.01	54	34	8
Right inferior frontal gyrus pars opercularis	64	3.66	44	20	20
Left inferior frontal gyrus pars opercularis	216	3.03	-44	20	22
Left inferior frontal gyrus pars triangularis		2.74	-58	20	4
Right motor cortex	64	3.14	36	-8	40
Left superior temporal gyrus	251	3.02	-56	-10	-10
Left auditory cortex		2.8	-56	-12	2

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Heschl's Gyrus					
Left temporal pole		2.73	-64	4	-6
Right insular cortex	76	3.04	40	-24	20
Right parietal operculum		2.72	46	-26	20
Right anterior vermis	69	2.6	6	-52	-18
Right posterior lobe of the cerebellum	45	3.13	16	-86	-26
Left ventrolateral occipital cortex	38	2.68	-34	-86	8
Right dorsolateral occipital cortex	56	3.41	40	-88	20

Location of the highest peak in a cluster is given: *voxelwise,  $p < .01$ , uncorrected with  $> 30$  voxel extent*. The number of voxels in a cluster is listed along with the peak height and coordinates of the peak location in MNI-152 standard space. Selected sub-peaks within the large clusters are also described. There were no areas where AWS  $>$  CON for Sentence reading.

Figure 4. Group activation differences during tasks conditions in adults who stutter compared to controls. AWS show increased activity relative to CON only in the picture description condition, which has an additional spontaneous speech component. This increased activity in AWS is localized to pre-SMA, left frontal operculum, and the basal ganglia.



*Picture Description versus Sentence Reading*

Both groups showed the expected increase in motor-planning regions during the picture description condition relative to the sentence reading condition.

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Major components of the classic motor-planning network showed a more pronounced change between conditions in AWS relative to CON at the uncorrected threshold: as would be expected given the patterns seen in each condition relative to silent baseline. The network included extensive portions of the inferior frontal cortex including frontal operculum, ventral premotor cortex, pre SMA, and subcortical grey matter localized in the head of the caudate nucleus and extending into putamen and thalamus on the left (Table 3).

**Table 3: Regions where there were differences between groups in activity during Picture Description vs. Sentence Reading vs. baseline.**

Brain Region	voxels	Z statistic	X	Y	Z
<i>AWS &gt; CON</i>					
Left inferior frontal gyrus	2779	4.09	-44	36	4
pars triangularis		3.95	-42	32	6
pars opercularis		3.86	-48	10	18
ventral premotor cortex		3.83	-44	12	34
superior frontal gyrus		3.76	-24	14	56
preSMA		3.25	-4	4	52
Left caudate	297	3.35	-12	12	8
Putamen		2.5	-20	0	6
Thalamus		2.5	-12	-6	4
Left supramarginal gyrus	53	2.96	-32	-42	38
Right temporal occipital fusiform cortex	510	3.42	28	-54	-16
lingual gyrus		3.35	22	-40	-10
parahippocampal gyrus		3.03	30	-40	-12
Left temporal occipital fusiform cortex	671	4.21	-28	-58	-8
Lingual gyrus		3.09	-20	-42	-12
parahippocampal gyrus		3.21	-30	-40	-12
Precuneus	655	3.44	8	-70	54
Left occipital	230	3.46	-54	-78	12
Left occipital	37	2.71	-8	-64	72
Right occipital	292	3.64	44	-84	-4
Right occipital	33	2.74	46	-68	6
Right occipital pole	226	3.16	12	-96	8
Right occipital pole	62	2.9	34	-94	16
<i>CON &gt; AWS</i>	20	3.69	-38	-20	-18
Left anterior lobe of the cerebellum	37	2.67	-32	-50	-32

*Location of the highest peak in a cluster is given: voxelwise,  $p < .01$ , uncorrected with  $> 30$  voxel extent. The number of voxels in a cluster is listed along with the peak height and coordinates of the peak location in MNI-152 standard space. Selected sub-peaks within the large clusters are also described. There were no areas where AWS  $>$  CON for Sentence reading.*

## **Discussion**

Our primary finding was of largely similar overt speech networks in adults who stutter relative to fluent controls.

We did not observe, even at lowered thresholds any clear evidence of altered cerebral dominance in stuttering. In fact, in the auditory cortex, we observed the predicted reduced activity in stuttering, bilaterally, consistent with the conclusions of the seminal meta-analysis<sup>11</sup>. We observed some support for theories of altered speech-motor and motor planning activity in stuttering through subtle group differences in the components of the associated networks, which were only observable at lowered thresholds. Our findings also lend support theories of basal ganglia involvement in stuttering. These structures are important for feedback processing and in particular are critical for motor learning and showed task-specific over-recruitment in AWS for internal generation of speech content relative to reading.

As the chance of our finding false positive results is quite high, we will not over speculate regarding the importance of qualitative group differences at length. The degree to which this altered activity is maladaptive, compensatory, or some combination of the two is likewise beyond the scope of this paper. However, we replicated some previous reports of functional abnormalities in the speech and motor system in stuttering. It is unclear which differences reflect general traits of the disorder and which are

related to the dysfluent state, an area begging for further exploration.

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### **AFFILIATIONS AND FUNDING:**

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