Brain & Language 127 (2013) 510–519

Contents lists available at ScienceDirect

Brain & Language

journal homepage: www.elsevier.com/locate/b&l

Regional brain activity change predicts responsiveness to treatment for stuttering in adults

Roger J. Ingham [a,*], Yuedong Wang [b], Janis C. Ingham [a], Anne K. Bothe [d], Scott T. Grafton [c]

[a] Department of Speech and Hearing Sciences, University of California, Santa Barbara, USA
[b] Department of Statistics and Applied Probability, University of California, Santa Barbara, USA
[c] Department of Psychological and Brain Sciences, University of California, Santa Barbara, USA
[d] Department of Communication Sciences and Special Education, University of Georgia, USA

ARTICLE INFO

Article history:
Accepted 14 October 2013
Available online 5 November 2013

Keywords:
Stuttering
Treatment
Oral reading
Monologue
PET

ABSTRACT

Developmental stuttering is known to be associated with aberrant brain activity, but there is no evidence that this knowledge has benefited stuttering treatment. This study investigated whether brain activity could predict progress during stuttering treatment for 21 dextral adults who stutter (AWS). They received one of two treatment programs that included periodic H_2 ^{15}O PET scanning (during oral reading, monologue, and eyes-closed rest conditions). All participants successfully completed an initial treatment phase and then entered a phase designed to transfer treatment gains; 9/21 failed to complete this latter phase. The 12 pass and 9 fail participants were similar on speech and neural system variables before treatment, and similar in speech performance after the initial phase of their treatment. At the end of the initial treatment phase, however, decreased activation within a single region, L. putamen, in all 3 scanning conditions was highly predictive of successful treatment progress.

1. Introduction

Brain imaging studies conducted since the mid-1990s have consistently shown that AWS, of both genders, show aberrant patterns of neural activity during speech and even during rest when compared with normally fluent controls (Bloodstein & Ratner, 2008; Ingham, Cykowski, Ingham, & Fox, 2008; Ingham, Grafton, Bothe, & Ingham, 2012). A meta-analysis of positron emission tomography (PET) and fMRI studies of mainly dextral AWS and normally fluent controls incorporated many of these studies (Brown, Ingham, Ingham, Laird, & Fox, 2005). This meta-analysis showed that there were common activations in speech-motor brain areas for both groups, but in the AWS group there were (1) over-activations in these areas, (2) anomalous right-dominant lateralization in these areas, (3) additional areas of activation (motor and nonmotor) not seen in the controls, and (4) an absence of auditory association area activations bilaterally. However, more recent PET and fMRI studies on similar groups, while identifying aberrant activity in various brain areas for AWS, have shown decreasing agreement in regard to the particular areas that are aberrant (Ingham et al., 2012). Additional anomalous brain-related findings have appeared in recent diffusion tensor imaging (DTI) studies that have identified white matter (WM) abnormalities in adults and children who stutter (Chang, Erickson, Ambrose, Hasegawa-Johnson, & Ludlow, 2008; Chang, Horwitz, Ostuni, Reynolds, & Ludlow, 2011; Cykowski, Fox, Ingham, Ingham, & Robin, 2010; Sommer, Koch, Paulus, Weiller, & Büchel, 2002; Watkins, Smith, Davis, & Howell, 2008), especially within left superior longitudinal fasciculus (Chang et al., 2011; Cykowski et al., 2010).

The effects of stuttering treatments on putative abnormalities of brain activity in AWS have been the object of a number of brain mapping studies. An early study (Boberg, Yeudall, Schopflocher, & Bo-Lassen, 1983) used EEG to investigate hemispheric activations before and after an intensive prolonged speech based treatment program. Signs of a shift towards more left hemisphere activation during single-word production by a group of dextral AWS ($N = 11$) were reported. Cerebral blood-flow (CBF) treatment studies of AWS began with a 2001 H_2 ^{15}O PET study (De Nil, Kroll, & Houle, 2001) that reported sustained reductions in stuttering frequency resulting from a well-established behaviorally-based treatment [Precision Fluency Shaping (PFS) (Webster, 1974)] with AWS ($N = 13$). Only activations in cerebellum were examined. The treatment

Abbreviations: AUC, area under the curve; AWS, adults who stutter; CONT, controls; E, establishment; FDR, false discovery rate; FG, fail group; MONO, monologue; MPI, modifying phonation intervals; NAT, speech naturalness; PG, pass group; %SS, percent syllables stuttered; PS, prolonged speech; PT, pretreatment; READ, oral reading; REST, eyes closed rest; ROC, receiver operating characteristics; SFSPM, stutter-free syllables spoken per minute; T, transfer; TRPI, target range phonated interval.

* Corresponding author. Address: Department of Speech and Hearing Sciences, University of California, Santa Barbara, CA 93108, USA. Fax: +1 805 893 4431.
E-mail address: rjingham@speech.ucsb.edu (R.J. Ingham).

0093-934X/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.bandl.2013.10.007

resulted in reduced excessive cerebellar activations during speaking tasks when compared with normally fluent controls. Subsequent studies have involved whole brain analyses of the effects of stuttering treatment. One of these (De Nil, Kroll, Lafaille, & Houle, 2003) also used H_2 ^{15}O PET to test for rCBF changes before and after a PFS program with 13 dextral male AWS and 10 normally fluent controls. They were scanned during a single-word task that was spoken overtly and covertly before treatment and at a 12-month posttreatment follow-up. Prior to treatment there were bilateral activations in superior temporal gyrus (L > R), the pre- and post-central gyrus (L > R), insula (L > R) and cerebellum (R > L). In the right-hemisphere, activations occurred in the medial frontal gyrus, anterior cingulate and putamen – activation patterns that also differed from previous findings (see Brown et al., 2005). Improved fluency was sustained at a 1-year follow-up and activation was observed bilaterally in motor execution areas, including insula (L > R), pre-central (R > L) and post-central gyrus (L > R), and right cerebellum. Some previously unobserved activation occurred in superior temporal gyrus (R > L) and L. cingulate gyrus.

Another variant of PFS was employed in two German studies. In the first (Neumann et al., 2005) 9 AWS were scanned using event-related fMRI while reading aloud short sentences (3-s) before and after 12 weeks of treatment. Although little stuttering was recorded on the same task during a pretreatment scanning session, in the posttreatment scans during the same speaking tasks there was more activation in the frontal speech production regions (including L. anterior insula and rolandic operculum) and the temporal areas, particularly on the left. Significantly, the former occurred directly above a previously identified area of WM abnormality (Sommer et al., 2002). In the second study (Kell et al., 2009) event-related fMRI (supplemented by DTI) was also used to assess 13 male AWS before and after 3 weeks of treatment. They were compared with 13 male adults described as Recovered Stutterers (RS) because recovery was reported to have occurred either without assistance or 4–38 years after an unsuccessful treatment. It has been hypothesized that by employing a RS group it might be possible to identify the extent or type of neural change that is optimal for maximum recovery from stuttering (see Kell et al., 2009). The most prominent and surprising finding was that only one region, L. BA 12/47, distinguished between recovery and persistent stuttering; the RS group had stronger activations in L. BA 12/47, along with fewer left inferior frontal structural anomalies. At issue though is whether strong activations in L. BA 12/47 constitute a necessary condition for recovery. Unfortunately, the generality of findings to RS populations might be limited because there was a definite level of stuttering in this study's RS participants, complicating claims with respect to their brain activation data and their status as RSs.

There is, however, a broader limitation on the generality of brain imaging findings on AWS. It is important to recognize that the neural activation findings from all of the abovementioned studies have been based on group data. The variability among the findings from brain imaging studies with AWS (Ingham et al., 2012) strongly suggests that imaging studies on individual AWS may have little in common with findings from group studies. This was illustrated in a recent fMRI study (Wymbs, Ingham, Ingham, Paolini, & Grafton, 2013) with 4 AWS who were scanned while producing stuttered and nonstuttered words. The regions that differentiated between stuttered and fluent utterances for each participant were shown to be activated with high consistency across occasions when the task was repeated at least 3 weeks later. However, the differentiating regions identified for each individual showed very little in common across the 4 participants. Consequently, this finding presents a potential challenge for studies, including the present one, that aim to identify neural markers among participants in treatment studies involving groups of AWS. Such markers should, ideally, predict all AWS who succeed in treatment and who do not succeed.

The aim of the present study was to determine if it was possible to identify neural system changes that will predict AWS who succeed and AWS who fail to generalize their treatment gains. For this purpose participants were selected from an intensive stuttering treatment study that involved two different treatment programs, the effects of which were evaluated for behavioral and neurologic change at important stages of treatment. Participants within both treatment programs who failed or succeeded in advancing through their program were compared for behavioral and neural changes that might differentiate among all participants in both groups. The inconclusive brain imaging findings on stuttering and the increasing evidence of individual differences in stuttering-related neural regions necessitated testing the null hypothesis: that there would be no common neural system changes that would differentiate those AWS who succeed from those who fail to progress through treatment.

2. Method

2.1. Participants

Twenty-two AWS (17 males; age range 20–64 years; mean = 35.9 years; median 35 years) and 8 adults who do not stutter or controls (CONT) (6 males; age range 20–64 years; mean 37.8 years; median 32 years) participated in this study which was conducted at the Research Imaging Institute, University of Texas Health Science Center, San Antonio. All were healthy adult volunteers, including 17 AWS who were identified from treatment waiting lists and via advertisements in San Antonio, Austin, and Houston and five who were from UC Santa Barbara's treatment waiting list. All AWS self-reported stuttering since early childhood and displayed chronic stuttering as confirmed by the principal investigator and a certified speech-language pathologist using standard clinical assessments. All participants in both groups were right-handed [>+80 on the Edinburgh Handedness Inventory (Oldfield, 1971)]; displayed no signs of any neurologic disorder (other than stuttering-related regional differences); reported no other current speech, language, cognitive, or behavioral disorder; and passed a hearing screening.

All AWS had experienced various therapies, but no participant reported receiving treatment for stuttering during the preceding 3 years. All produced at least three percent syllables stuttered (%SS) during each of three 3-min within-clinic speaking tasks (oral reading, monologue, and a telephone conversation). All CONT participants met the same selection criteria, except that they were required to produce 0%SS during each of the three speaking tasks and not report either the presence or a history of stuttering.

2.2. Treatment procedures

The AWS were enrolled in a larger study that was designed to investigate the short- and long-term effects of two stuttering treatment programs: Modifying Phonation Intervals (MPI) (Ingham & Student, 2013; Ingham et al., 2001) and a previously described and evaluated prolonged speech (PS) program (Ingham, 1987; Onslow, Costa, Andrews, Harrison, & Packman, 1996). Both programs followed the same 5-phase format: *Pretreatment* (PT), *Establishment* (E), *Transfer* (T), *Maintenance*, and *Follow-up*. Repeated within- and beyond-clinic audio or audio-visual recordings were obtained during each phase, plus a PET scanning session (see below) occurred at the end of each phase. With the exception of the *Pretreatment* and *Follow-up* phases, each phase incorporated a schedule of speaking tasks that was partially managed by the

participant (Ingham & Andrews, 1973). (This study did not consider *Maintenance* and *Follow-up* data.)

Establishment for the MPI program was focused on teaching the speaker to reduce the frequency of short phonated intervals (periods of voicing/vocal fold vibration) that were produced within a range of short durations (labeled Target Range PIs or TRPIs). The training was identical to a previously described procedure (Ingham et al., 2001, p. 1223) and is reproduced below:

> The aim of the Establishment phase was to instate stutter-free, natural-sounding speech within the clinic by reducing by at least 50% the frequency of TRPIs. Participants were taught to meet self-rated and clinician-verified speech performance criteria on a series of speaking tasks. The performance-contingent format of this phase (and subsequent phases) has been previously outlined (see Ingham, 1999). Briefly, participants spoke in 1-, 2-, and 3-min trials and were required to achieve a cumulative sequence of 3 successful trials with TRPI feedback (via response-contingent auditory signals and counts in the boxes) and then a sequence of 3 consecutive trials without TRPI feedback. This procedure was followed across a hierarchy of speaking tasks: reading alone, reading with another person present, speaking in monologue alone, speaking in monologue with another person present, conversing with another person present, and conversing on the telephone. Each set of tasks was completed only when a sequence of three 3-min trials was completed successfully *without* TRPI feedback. If the allowable TRPI count was exceeded, the program would automatically fail the speaker and return to an earlier step to be repeated. At the end of each trial, participants scored themselves as having stuttered or not stuttered and rated their naturalness on the 9-point speech-naturalness scale. To progress, each trial had to be self-judged as stutter free and natural (1–3 rating). In addition, successful completion of the sixth and final step in sections where a listener (clinician) was present required the clinician to agree that the trial was stutter free and natural sounding.

For the PS program all of the *Establishment* speaking tasks and sequences were identical to those used for the MPI program's *Establishment* phase. However, a *Pre-Establishment* phase was provided to train the participant to use a speech pattern provided by audio-recorded models. The recordings introduce the required degree of prolonged speech via four "speech rate patterns," with audio models provided for each speech rate pattern. Those patterns modeled speech produced at 40, 70, 100, and 130 syllables per minute (SPM). A performance-contingent hierarchy of tasks involving reading aloud and in concert with the audio model was followed by self- and clinician-judged 1–2 min solo speaking tasks; these were used to gradually shape the participant's speech pattern towards stutter-free and natural sounding speech. Details of this part of the program are provided in a manual (Ingham, Moglia, Kilgo, & Felino, 2007) along with the recordings (all are available from the first author on request). Participants then entered and endeavored to complete the *Establishment* phase described above for the MPI program, but were not provided with TRPI feedback.

Successful completion of *Establishment* meant that the participants achieved the target behaviors (zero stuttering and natural-sounding speech) within the clinic setting. Participants in both treatments then entered an identical *Transfer* phase described for the MPI (Ingham et al., 2001, p. 1234) program as follows:

> The aim of this phase was to shift within-clinic treatment gains to beyond-clinic speaking conditions. In this phase, each participant's individualized beyond-clinic (assessment [speaking] tasks) was integrated into the treatment. The hierarchy arrangement that applied in Establishment was also fundamental to Transfer. Participants were required to complete a sequence of three stutter-free and natural-sounding recordings. . .of Task 1, followed by Task 2, and then (on to Task 6). No more than one attempt could be made on a given day. The third recording in each sequence also had to be judged by the clinician as meeting the performance criteria.

Successful completion of *Transfer* meant that the participant had achieved the target behavior, natural-sounding fluent speech, in selected and wide-ranging beyond-clinic settings.

Because of the performance-contingent nature of both treatment programs the duration of each phase varied considerably across participants. The *Pretreatment* (baseline) phase required a minimum of 8 weeks of periodic speech assessments. The average duration of *Establishment* was 8 weeks, for *Transfer* 27 weeks, and for *Maintenance* 64 weeks. *Follow-up* occurred 12 months later. It is relevant to this particular study to note that both treatment programs relied upon the participant learning to change and control phonation during speech production (see Section 4). For purposes of the present study the focus was on speech production and imaging data gathered periodically from *Pretreatment* through *Transfer*. This made it possible for the participants to be classified into those who were successful in completing *Transfer* (Pass Group or PG) and those who were not successful (Fail Group or FG) (see Section 3).

Each AWS and CONT participant completed a set of 6 PET scans acquired during 3 different conditions on specified occasions. For AWS those occasions were at the end of PT and at the end of each phase of the treatment program. For the CONT participants these assessments occurred on two occasions (see below). Each scanning session included six pairs of randomly ordered scanning conditions: oral reading (READ), monologue (MONO) and eyes-closed rest (REST). During READ participants read passages from a book (Abbey, 1975) that were presented on a video monitor suspended above the participant – approximately 14 in. from the eyes. During MONO participants spoke on a self-selected topic. During READ and MONO scans each participant spoke for 60 s from the onset of the 90 s scan; they were then instructed to close their eyes. Prior to each REST condition participants were instructed to think of a pleasant countryside scene. Speech and imaging data obtained during the first 60 s were used in the data analysis. A 10-min inter-scan interval was employed – sufficient for isotope decay (five half-lives). Parallel within-clinic audio-visual and beyond-clinic audio recordings were obtained in conjunction with the scans – all obtained before the participant continued treatment. The within-clinic tasks were a 3-min oral reading (using self-selected text); a 3-min monologue, again on a self-selected topic, and a 3-min telephone conversation with a friend. The beyond-clinic tasks were conversation with a peer, telephone conversation with a business, and a self-selected task that the participant identified as a personally problematic speaking task that the participant could use to gauge treatment efficacy.

Eight normally fluent, age-matched male speakers served as controls (CONT). (Difficulties were experienced in recruiting CONT participants who were willing to complete their PET and non-PET speech performance assessments on two occasions, especially with the second having to be at a specified time.) For each CONT, these two occasions were separated by the same amount of time as their "yoked" AWS's PT and T phase assessments. That time differed for the 8 AWS and accordingly for the 8 yoked CONT participants; the time ranged from 17 to 43 weeks.

2.3. Image acquisition

PET data were obtained using an ECAT HR + imaging system. This high-resolution PET system has 32 rings with 576 BGO detectors each. The system includes the scanner, an integrated workstation, and a 3-D advanced computation system. This scanner

provides images in 63 planes and has a 15.5 cm axial field of view. The transaxial resolution in 3-D mode is 4.1 FWHM mm at the center. True sensitivity is 850,000 cps/μCi/cc. Because the ECAT HR + imaging system has improved sensitivity relative to the previous PET system employed at the University of Texas Health Sciences Center at San Antonio (Scanditronix 4096 scanner providing images in 15 planes) it is possible to scan with significantly reduced tracer dosage levels. Thus, instead of a customary 70 mCi $H_2\ ^{15}O$ per injection, a 40–50 mCi per injection is sufficient. This made it possible to obtain with safety 14 (50 mCi/injection) to 18 (40 mCi/injection) scans per participant per year. In other words, for purposes of this experiment sessions involving six scans (2 rest and 4 task scans) were able to be repeated 3-times within a year.

An anatomical MRI obtained prior to the first scan session was used to optimize spatial normalization of PET images. MRI was acquired on a 1.9-Tesla Elscint Prestige scanner using high-resolution 3D gradient-recalled acquisitions in the steady state (GRASS) sequence: repetition time = 33 ms.

2.4. Image analysis

PET images were reconstructed into 60 slices, each 2 mm thick with an image matrix size of 60 × 128 × 128 mm, using a 5-mm Hann filter, resulting in images with a spatial resolution of approximately 7 mm at FWHM and value normalized to a whole-brain mean of 1000. For each subject, PET images were registered to each other and coregistered to the same participant's MRI scan. These aligned data were then spatially normalized to the Montreal Neurologic Institute (MNI) 152 subject atlas in SPM8 using the default method. Spatially normalized PET images were smoothed with a Gaussian 12 mm filter. All scans were rescaled to a global CBF value of 50 ml/min/100 g tissue, calculated within a whole brain mask consisting of all voxels with activity at least 5 ml/min/100 g. Talairach coordinates (Talairach & Tournoux, 1988) were derived from MNI coordinates by using the Talairach Client (Lancaster et al., 1997, 2000). Cerebellar locations and labels were derived using the MRI atlas of the human cerebellum (Schmahmann et al., 1999).

A region of interest analysis approach was adopted. A set of 46 neural regions was selected for analyses based on our previous studies comparing AWS and CONT speakers (Brown et al., 2005; Ingham et al., 2012); they are itemized in Appendix A. More specifically, the peak voxel within each region in a previous study (Ingham et al. (2012) significantly activated by AWS and CONT during oral reading and monologue conditions was tabulated ($N = 23$) by an automatic detection algorithm. There was no observer selection for potential bias. Homologous voxels in the opposite hemisphere were also included. This resulted in 46 voxels that were the center of a spherical region of interest in the current analysis. For each site, a 1 cm diameter volume of relative CBF was extracted for each scan, and participant. The mean regional relative CBF over all the voxels in the ROI were averaged together, and data from duplicate scans of the same task were then averaged.

2.5. Speech data

Audio-visual recordings were obtained from each scanning and within-clinic trial and were assessed for stuttering frequency (%SS), speech rate [stutter-free syllables per minute (SFSPM)], and speech naturalness (NAT), a 1–9 scale (Martin, Haroldson, & Triden, 1984). These are considered the minimal behavioral measures necessary for stuttering treatment outcome evaluation (Costello & Ingham, 1984). These measures were obtained by two independent and trained judges for each recording and according to the definitions and methods available in a standard and freely available audiovisual stuttering judgment training program (Ingham, Bakker, Ingham, Kilgo, & Moglia, 1999). Reliability (replicability) of experimental data was assured by using as the data for all analyses the mean of the two independent judges' ratings. In addition, all recordings for which the two judges' data differed by more than 10% were identified and re-rated before the experimental data were finalized.

2.6. Brain region activity change analyses

All computations were carried out in R (version 2.15.1), a language-environment for statistical computing and graphics (www.r-project.org). For identification of differential activation in brain regions, mean % change in rCBF measures, from PT to the end of E, was computed and a Student's *t*-test for the difference in % of change between groups PG and FG was calculated (see Section 3.1). Differentially activated regions were identified at 10% False Discovery Rate (FDR) using the Benjamini–Hochberg multiple testing correction (Benjamini & Hochberg, 1995). To identify brain regions that contributed significantly to success at the completion of T a logistic regression model was applied to the mean % change in rCBF using all 46 brain regions as potential covariates. Important regions were selected by the Lasso (least absolute shrinkage and selection operator) method (Friedman, Hastie, & Tibshirani, 2008). An exhaustive search for a logistic regression model was also conducted to locate the best subset of brain regions. Both methods revealed the same results. R libraries glmnet, bestglm and glm were used to fit Lasso logistic regression, to select the best subset for logistic regression and to fit logistic regression models.

3. Results

3.1. Participant distribution

Table 1 shows the number of participants in this study and how they were distributed at each of the three treatment evaluation phases that provided data for the present study. The AWS participants received the Modified Phonation Interval (MPI) (Ingham 1987) ($N = 12$) or Prolonged Speech (PS) ($N = 9$) treatment program.

PET scanning sessions for the AWS occurred immediately before treatment, at *Pretreatment* (PT), upon completion of the *Establishment* phase (E), the goal of which was to establish stutter-free, natural sounding speech in the treatment clinic), and upon completion of the *Transfer* phase (T), the goal of which was to carry over stutter-free, natural sounding speech to speaking situations in the natural environment). Table 1 shows that 22 AWS were allocated to a treatment program (MPI or PS); 21/22 AWS completed the *Establishment* phase of their assigned treatment program and 12/21 AWS completed the *Transfer* phase (one PS participant failed to complete *Establishment* and thus was not included in this study). The 9 AWS who failed to complete *Transfer* included 4 in the MPI

Table 1
The total number of adults who stutter (AWS) and control (CONT) group participants who received PET scans and within- and beyond-clinic assessments at the end of each treatment phase in the study. The phases were PT (*Pretreatment*), E (*Establishment*) and T (*Transfer*). Twelve AWS participants were enrolled in the MPI program and 10 in the PS program. The 8 CONT participants were only scanned twice, corresponding to the PT and T phases.

	Participants		
	AWS		CONT
	(MPI)	(PS)	
PT	12	10	8
E	12	9	
T	8	4	8

program and 5 in the PS program. Hereafter, the 12 who completed *Transfer* are labeled PG (Pass Group), and the 9 who failed to complete *Transfer* are labeled FG (Fail Group). The failure to complete the *Transfer* phase by FG participants can be mainly attributed to the repeated failure to pass one particular step (different across participants) within the *Transfer* phase, making them unable to advance to program completion. However, two MPI participants were compelled to leave the program for reasons not obviously related to the program (imprisonment and domestic violence), although their progress during *Transfer* was the slowest of all participants.

The seven participants who failed to complete the *Transfer* phase were, with the exception of the two above-mentioned MPI participants were reassigned to the alternative treatment program. In other words, the two MPI participants in FG were then treated in the PS program and the five PS participants in FG were treated in the MPI program. Their data were not included in the final evaluations of either treatment program.

3.2. Speech performance data

Table 2 shows the mean speech performance sores for the PG, FG and CONT groups during PET scanning sessions at PT, E, and T. There were two scans of oral readings of a text passage (READ), two of a self-generated monologue (MONO) and two eyes-closed rest (REST); scores are the averages across both scans. In order to test for neural system differentiation, comparisons were made between participants who succeeded in completing *Transfer* (PG) and those who did not (FG). It should be noted that in order to complete *Establishment* all AWS participants were required to achieve target levels of speech performance in their treatment sessions across a range of speaking tasks including oral readings, monologues and telephone conversations. Those target levels were 0.0% syllables stuttered (%SS) and speech naturalness ratings of 3 or less (1–9 scale). However, as Table 2 shows PG and FG performance mean scores during the four scanning tasks did not quite meet the fluency target level, despite being obtained within 24 h after each participant completed *Establishment*. All tests for performance differences used *t*-tests with a significance level of $\alpha = .01$.

Table 2 also shows that before treatment (P) the PG and FG were not significantly different on any of the measures from both tasks (see *p*-values in PG column). At E, however, PG spoke at a significantly faster stutter-free syllable per minute (SFSPM) rate than FG during both scanning tasks. At T, the PG and CONT groups' speech performance measures were mostly not significantly different; the exception was during MONO where PG was still significantly less fluent than the CONT group (1.0%SS vs 0.0%SS, $p = .003$).

Because FG showed relatively more stuttering and poorer speech naturalness than PG during the scanning session at the completion of E, this could be a plausible reason why they failed to complete T successfully, i.e., their fluency skills were not sufficiently well established. However, closer inspection of the speech performance scores of FG during the E session shows that their higher mean scores were not significantly different from the PG scores, except for the SFSPM measures, as mentioned above (see Table 2). More importantly, the %SS, SFSPM and NAT differences on the READ task were essentially due only to 2/9 FG participants, and for MONO to 3/9 FG participants (2 participants were common to the 2/9 and 3/9 participants). The %SS, SFSPM and NAT scores by the other FG participants were completely within the range of the PG scores (see Table 3). This is an important factor to take into account when considering the results of this study. In other words, if the subsequent failure of the FG participants to proceed successfully through T was simply due to their poorer speech performance at the end of E then this could not be the case for 6/9 of the FG participants. Analyses were repeated with these three FG participants removed and as Table 3 shows, the groups were not significantly different at E.

One other important consideration was whether READ and MONO speech performance measures derived during scanning conditions were similar to READ and MONO speech performance measures obtained outside of the scanner. That was possible to evaluate because the within-clinic and scanning speech performance data were obtained on the same day. The *t*-test result for that comparison found *p*-values that were not significantly different for any speech performance measure, ranging from 0.056 for FG's READ SFSPM scores at E to 0.974 for PG's READ SFSPM scores

Table 2
READ and MONO means plus standard deviations for %SS, SFSPM and NAT scores during PET scan trials for groups PG, FG and CONT. Note that PG completed PET scans at the end of the *Pretreatment* (PT), *Establishment* (E), and *Transfer* (T) phases, while FG only completed scans at the end of the PT and E phases. The CONT group completed scans at the end of PT and at the end of T. The *p-values* in the columns of PG are for comparison between PG and FG, *p-values* in the column of FG are for the comparison between FG and CONT, and *p-values* in the column of CONT are for the comparison between PG and CONT.

Conditions	Measures		PG			FG			CONT		
			PT	E	T	PT	E	T	PT	E	T
READ	%SS	Mean	8.8	1.3	0.9	10.6	3.7		0.0		0.0
		SD	7.2	1.7	1.9	11.2	5.3		0.0		0.0
		p-Value (t)	0.551	0.091		0.001			0.000		0.112
	SFSPM	Mean	186	209	225	175	168		244		248
		SD	66.0	40.6	47.9	67.8	39.8		38.7		36.9
		p-Value (t)	0.614	0.004		0.002			0.001		0.104
	NAT	Mean	5.4	2.9	2.7	6.0	4.0		2.1		2.5
		SD	1.8	0.9	1.2	2.3	2.0		0.7		1.0
		p-Value (t)	0.369	0.048		0.000			0.000		0.653
MONO	%SS	Mean	7.1	1.1	1.0	10.8	4.2		0.0		0.0
		SD	5.9	1.5	1.5	9.3	5.3		0.0		0.0
		p-Value (t)	0.151	0.035		0.000			0.000		0.003
	SFSPM	Mean	175	195	199	183	153		204		225
		SD	50.9	47.3	41.1	58.0	37.5		31.4		43.8
		p-Value (t)	0.670	0.004		0.206			0.036		0.068
	NAT	Mean	4.8	2.9	2.9	6.1	3.8		2.0		2.5
		SD	1.9	0.9	0.8	2.0	1.6		0.8		0.9
		p-Value (t)	0.049	0.084		0.000			0.000		0.134

Table 3
Comparison between PG and FG (minus 3 participants) during E scan session. With one exception, there was no significant difference between the groups on any of the speech performance measures during both speaking tasks (READ and MONO) at E. The FG's mean %SS score at E in MONO was significantly less than the PG's mean at E. However, the direction of this difference counters suggestions that the PG group progressed to T only because they achieved superior fluency during the E phase.

Conditions	Measures	PG mean (sd)	FG mean (sd)	*p*-Value	Cohen's *d* score
READ	%SS	1.3 (1.7)	.3 (.4)	0.017	0.052
	SFSPM	209 (40.6)	183 (41.9)	0.129	0.315
	NAT	2.9 (.9)	3.0 (1.3)	0.757	0.091
MONO	%SS	1.1 (1.5)	1.7 (2.8)	0.494	0.280
	SFSPM	195 (47.3)	165 (41.2)	0.099	0.678
	NAT	2.9 (.9)	3.0 (.9)	0.874	0.111

at T. In other words, the data gathered during scanning appear to have excellent external validity.

3.3. Brain imaging data analyses

The rCBF measures were obtained from 46 different locations throughout the brain (see Appendix A). During scanning sessions CBF data were collected at each of those regions for all PG and FG participants, as well as for the eight controls. Two different analyses were used to locate brain regions that would differentiate between the PG and FG participants at the end of E by comparison with their neural region activations at PT. The first was to try to locate neural regions for PG and FG that showed significant changes from PT to E across the 3 scanning conditions (ORAL, MONO, and REST). The second was to use logistic regression models to identify neural regions that contributed significantly to success at the end of T.

The first analysis derived the percentage of rCBF change from PT to E for each region under each scanning condition and for each participant. The hypothesis that there was no difference in percent of change between FG and PG was tested using *t*-tests. An FDR test was used to control for multiple comparisons. At 10% FDR, L. claustrum showed a significant CBF change for all three conditions, READ, MONO, and REST; R. Lobule VI showed a significant % CBF change for READ, but no other regional % CBF change was significant at 10% FDR. The mean % CBF changes (plus *p-values*) in L. claustrum (−28, −6, 18) are shown in Table 4. The % CBF change in this region was directionally different across groups; there was a decrease in activation for PG and an increase for FG with significant differences and very large (>1.0) effect sizes (Cohen, 1988). It is also important to note that the differences in the PG's and FG's L. claustrum activation levels were not present before treatment; that is, at PT. The PG and FG local maxima voxel mean CBF scores per task were respectively 404.6 vs 399.5 (READ), 415.6 vs 408.3 (MONO), and 399.3 vs 390.2 (REST). A *t* test of differences between these pairs of mean scores showed that none was significant.

For the second analysis, Lasso logistic regression was used with PG and FG as a binary response and with all 46 neural regions as covariates. For all three scanning conditions the Lasso method selected a single region: L. claustrum. The effect of percent of change in the region L. claustrum is significant for all three conditions with *p*-values 0.0218, 0.0222 and 0.0267 for READ, MONO, and REST, respectively. Based on the final logistic regression models, every 1% decrease in CBF in the region L. claustrum increases the odds of a participant being in the PG by 1.35, 1.24 and 1.23 for READ, MONO, and REST, respectively. Therefore, the logistic regression model with percent of change in the region L. claustrum provided a highly accurate classification of individual participants. Fig. 1 shows the receiver operating characteristic (ROC) curves for READ, MONO, and REST, where predictive probabilities were calculated using the logistic regression model and leave-one-out cross validation. Area under the curve (AUC) scores are 0.8611, 0.8426 and 0.8426 for READ, MONO, and REST respectively. With cut-off values selected by maximizing the Youden index (sensitivity + specificity − 1) for the predictive probabilities, logistic regression was able to classify 18 out 21 participants correctly.

An additional factor that impacts interpretation of the findings concerns the cluster of voxels related to the maximally activated voxel in L. claustrum. The image analysis found a cluster of 58 significantly activated voxels in PT that were essentially connected to the voxel located at −28, −6, 18. The image of that cluster (see Fig. 2) shows that it mainly overlaps L. putamen. For that reason it is more accurate to identify L. putamen, rather than L. claustrum, as the region that was most functionally related to the differentiation between PG and FG.

Finally, there were strong indications that in PG, L. claustrum (putamen) showed changes in level of activation by the end of T that were, ultimately, not significantly different from the levels produced by the CONT group (see Table 5). The combined mean activation level of L. claustrum (putamen) across READ, MONO, and REST was significantly larger in PG than CONT at PT, and then showed a significant reduction from PT to E. There was a slight, albeit significant, increase from E to T, but to a level that was not in excess of the CONT group's level.

Table 4
Mean % change in rCBF measures from Pretreatment (PT) to the end of the Establishment (E) (plus SDs) for groups PG and FG. Both groups displayed significant changes (with large Cohen's *d* scores) within L. claustrum (−28, −6, 18) during READ, MONO, and REST. For PG all changes were towards a decrease in activation, while for FG the changes were towards an increase in activation.

Condition	PG mean (sd) L. claustrum	FG mean (sd) L. claustrum	*p*-Value	Cohen's *d* score
READ	−5.61 (5.28)	5.05 (9.00)	0.003	1.493
MONO	−5.25 (10.05)	6.66 (8.70)	0.012	1.270
REST	−5.65 (9.18)	7.38 (10.33)	0.007	1.336

4. Discussion

The present study was designed to determine if it was possible to identify neural system changes that will predict AWS who succeed and AWS who fail to transfer stuttering treatment gains. This study is, in fact, the first reported attempt to isolate a neural region(s) that could functionally influence progress during a stuttering treatment. A decrease in activity in L. putamen was discovered to be such a factor. The most impressive finding was that the L. putamen changes were essentially consistent in two very different speaking tasks and during a non-speaking task, eyes-closed rest. The positive outcome of this attempt, while promising, at this point must be related to a particular form of stuttering treatment for adults. In fact, each of the AWS participants in this study received one of two different, but related types of treatment within a very strictly organized format. This means that the differences between these therapies may be functionally relatively small. Since prolonged speech was first identified (Goldiamond, 1965) as a derivative of oral reading during delayed auditory feedback it has

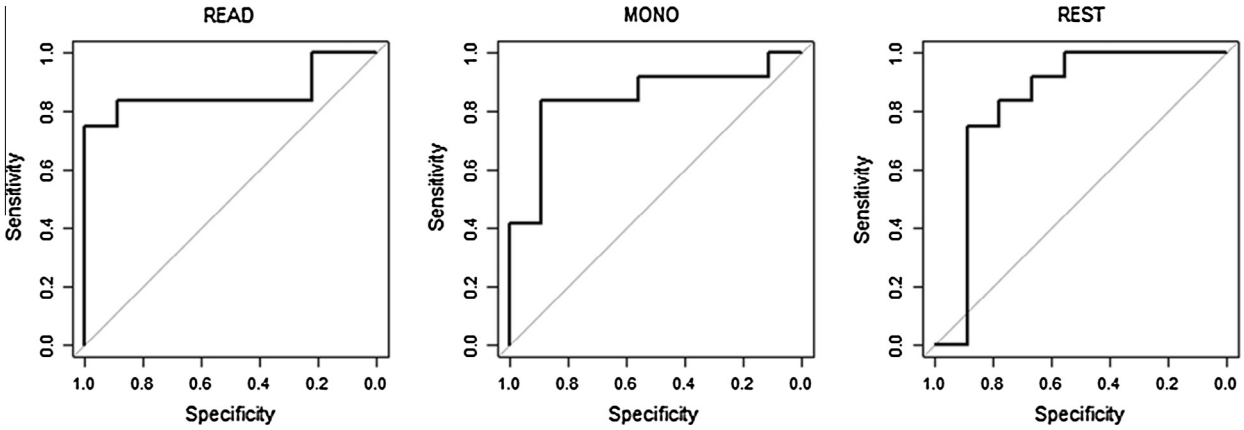

Fig. 1. The receiver operating characteristic (ROC) curves for READ, MONO, and REST. Predictive probabilities were calculated using leave-one-out cross validation based on the logistic regression model with percent of change from PT to E in the region L. claustrum as the predictor.

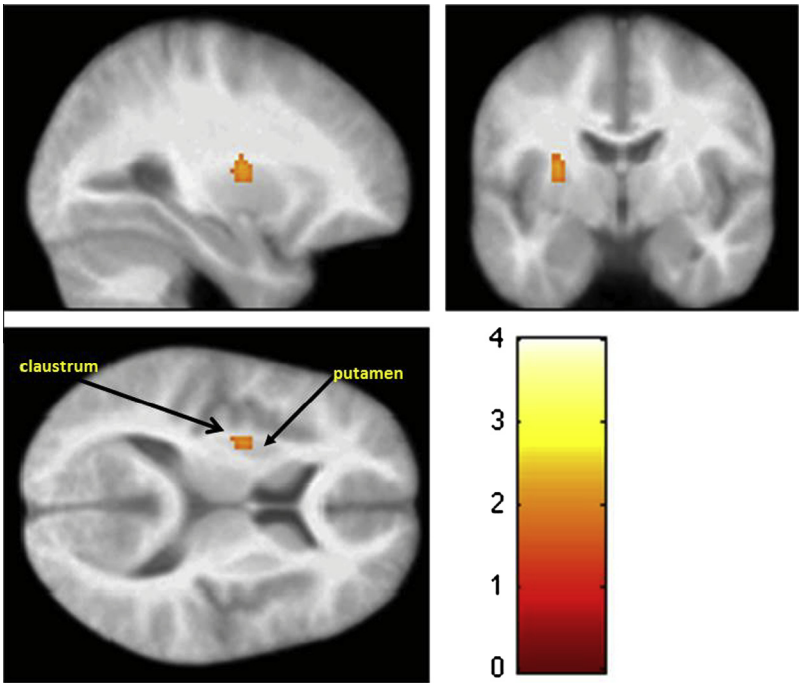

Fig. 2. The cluster of voxels associated with L. claustrum as reported in the original study by Ingham et al. (2012, p. 14). As the 3 image figures show, the cluster of 58 voxels actually spread mainly into L. putamen. Similarly, the region of interest centered on this cluster mainly overlaps with the putamen. For that reason L. putamen is recognized in this study as having greater functionality than L. claustrum.

become, in one form or another, a staple part of stuttering treatment for AWS (Bloodstein & Ratner, 2008; Bothe, Davidow, Bramlett, & Ingham, 2006; Ingham, 1984). It was also the foundation of one of the treatment programs (PS) in this study. The definitive features of this speech pattern have almost defied definition (Ingham, 1984; Prins & Ingham, 2009); however, audio-recorded models of the speech pattern have been used for some time as a means for instating this fluency-inducing speech pattern (Ingham & Andrews, 1973; Onslow et al., 1996). The second treatment program, MPI (Ingham et al., 2001), focuses on reducing the frequency of short phonation intervals, or PIs. In short, both treatment programs rely on modifying a participant's customary manner of using phonation during speech.

The decision to combine the MPI- and PS-treated participants was partly based on the need to use as many participants as possible to offset the small sample size for the logistic regression analysis. However, it also made it possible to identify a critical neural region that was common to both treatment programs, rather than seek program-dependent regions. And, of course, such regions would carry even more external validity if they reappeared in a replication study that employed different treatments that produced similar outcomes. It is impressive, therefore, that the present study was able to locate a principal neural region [L. claustrum (putamen) −28, −6, 18] that differentiated between continuing treatment success and failure at a relatively early stage of treatment for 85.7% of participants – and was essentially independent of their speech performance – given that all participants had met stringent fluency, speech rate and speech naturalness criteria at the end of the *Establishment* phase of their treatment. In that respect it is also noteworthy that the L. claustrum (putamen) finding not only applied to the scanning conditions where speech was produced (READ and MONO), but also to the scanning condition that did not include speech (REST).

In one respect the findings draw attention to two regions of the brain: putamen and claustrum. The role of claustrum in processes related to speech is unclear. Different reviews of the function of

Table 5
The mean and standard deviations of CBF volume measures at the local maxima voxel for L. claustrum (L. putamen) for the CONT and PG groups when ORA, MON and ECR values are combined. Group PG received PET scans at the PT, E and T sessions; the CONT group received scans at the PT and T sessions. The CONT and PG groups' scores were significantly different at PT, but not at T. PG's scores showed a significant increase from E to T.

		Combined scan conditions	
		PG	CONT
PT	M	406.5	370.9
	SDs	45.2	40.4
E	M	376.7	
	SDs	52.6	
T	M	408.5	390.6
	SDs	49.2	29.9
CONT vs PG			
PT			p = 0.004
T			p = 0.093
PG E vs T			p = 0.010

claustrum have noted that it seems to be implicated in speech production. An extensive review (Weiller, Bormann, Saur, Musso, & Rijntjes, 2011) of claustrum's somewhat ignored significance concluded that along with anterior insula it may be implicated in an important way in the dichotomy of dorsal routes between Wernicke's and Broca's areas. Nonetheless, not a great deal has been learned about claustrum's function since Crick and Koch (2005) concluded that it is "enigmatic." L. claustrum, however, may be less immediately important to the findings of this study because closer examination revealed that most of the cluster of activated voxels attached to the site were actually located in L. putamen – a region that may be heavily implicated in treatments that emphasize altering phonation.

The role of putamen in speech production has been relatively well described in two extensive reviews (Price, 2010, 2012). The first concluded that "the initiation and execution of speech [involves] left putamen, pre-SMA, SMA, and motor cortex; and for suppressing unintended [speech] responses in the anterior cingulate and bilateral head of caudate nuclei" (Price, 2010, p. 62). Of more relevance, however, was a later conclusion that "putamen and caudate were more activated for slower (more controlled) speech production" (Price, 2012, p. 832). This would be expected within the AWS group while they learned to produce a new and stutter-free speech pattern during *Establishment*. These conclusions about putamen's role also drew upon the findings of a series of fMRI studies on the hemodynamics of speech motor control (Riecker, Ackermann, Wildgruber, Dogil, & Grodd, 2000; Riecker, Brendel, Ziegler, Erb, & Ackermann, 2008; Riecker, Kassubek, Groschel, Grodd, & Ackermann, 2006; Riecker et al., 2005). Perhaps the most relevant is one that investigated the effect on specific neural regions of normal speakers repeating a short phonated utterance at different rates (Riecker et al., 2006). Systematically increased rates were associated with a systematic decrease in putamen activation. Indeed, it was reported that overall "computation of rate-to-response functions of the BOLD signal revealed a negative linear relationship between syllable frequency and response magnitude within the striatum whereas cortical areas and cerebellar hemispheres exhibited an opposite activation pattern" (Riecker et al., 2006, p. 46). Putamen has also been integral to the role in stuttering that Alm (2004, 2007) theorizes is played by excessive basal ganglia activity. Excessive putamen activation would be consistent with impairment to the cortico-striatal-thalamic circuit which, in turn, could disrupt fine-grained speech movements by AWS – even during rest conditions if they happen to include covert preparation for speech (also see below re the role of "set" during REST).

Civier, Bullock, Max, and Guenther (2013) recently published a "neurocomputational" speech production model of stuttering that might also appear to have relevance to the present findings. Their GODIVA model of stuttering relies on the presence of disruptions to a syllable-sequencing circuit. This particular circuit, which involves basal ganglia, thalamus and L. ventral premotor cortex, is disrupted because of WM and dopaminergic abnormalities. In particular, it implicates dopaminergic projections to the putamen. Our results reveal a central role in the putamen as well, although we cannot distinguish dopamine specific disturbances.

If a decrease in putamen activation is necessary for successful treatment progress, then this would seem to suggest a need for procedures or treatment methods that will reduce putamen activation. At this time not enough research has been devoted to the investigation of such methods. However, the present study suggests a possible link between reducing the frequency of relatively short PIs and reductions in the level of putamen activity. The mean % reduction in the shortest PIs between PT and the end of E was consistently larger than 50% for PG (based on MPI or PS treatment), but never exceeded 40% for FG. In other words, treatments such as the MPI or PS (which necessarily reduces the frequency of short PIs in the process of prolonging/extending the duration of phonation) that achieve such reductions appear to be reducing putamen activation. This would seem to be a promising direction for further research into factors that may assist treatment outcome.

The most puzzling finding of the present study concerns the link between the changes in activation levels in the REST data from *Pretreatment* to the end of *Establishment*. There were strongly correlated CBF changes in three pairs of brain regions during READ conditions [R. putamen $\times$ L. posterior insula, $r = .91$; R. BA 6 (6, 4, 60) $\times$ R. BA 6 (58, −8, 38), $r = .94$; L. claustrum $\times$ R. CBM lobule VI, $r = .94$]. During MONO and REST conditions there were similar or even higher positive correlations between these three pairs of regions. In other words, neural activity associated with overt speech was also present in the absence of speech. Rather similar findings were reported in an earlier PET study that required four AWS to imagine they were reading aloud and stuttering (Ingham, Fox, Ingham, & Zamarripa, 2000), but the similarities were much less impressive during a similar task with four AWS in a recent fMRI study (Wymbs et al., 2013). On the other hand, other recent imaging studies with AWS (Ingham et al., 2012; Xuan et al., 2012) have also made comparisons between resting and speaking activations; and also report strong similarities in activations in speech-related regions. These findings, however, should not be all that surprising given the results reported by Sidtis, Strother, and Rottenberg (2004) from a PET study of resting state effects. They reported a block design study in which 11 healthy adult volunteers completed simple tasks ("finger opposition, syllable repetition, sustained phonation, and repetitive lip closure") with the scanning of each task alternating with a REST condition. As they reported the "results of this study show that the pattern of brain activity during a resting state is significantly affected by the behavioral task with which it is temporally paired." (Sidtis et al., 2004, p. 1411).

The Sidtis et al. (2004) findings may also have relevance to the present study for another reason. Sidtis et al suggested that the behavioral task's effect on rest may result in the inducement of a "set," or readiness to produce the task, via neural metabolism that enhances or supports a sustained change in behavior. In the present study the "set" may interact with putamen (which Sidtis et al. also found) and thereby help to sustain the altered manner of speech production necessary for fluent speech.

Obviously, the clinical significance of the present findings can only be realized through an investigation of the long-term behavioral and neurologic outcomes of the AWS participants in this study. Systematic replication of this work through investigations

using stuttering treatments other than those used in the present study could also be enlightening. Nevertheless, the present study is the first to demonstrate a possible functional relationship between changes in a specific neural region and sustained positive responsiveness in AWS to a behavioral stuttering treatment.

Acknowledgments

This study was completed with the support of RO1 Grant DC007893 from the National Institute on Deafness and Other Communication Disorders awarded to the first author. Special thanks are offered to Peter Fox for providing the facilities for this study and for his continuing support for imaging research on developmental stuttering. Thanks are also due to Robin Selman Hampton, Krystal Purkheiser, Annie New, Kate Paolini, Gina Pecile, Amanda Petros, and multiple graduate assistants at the University of Georgia for their assistance in gathering data and background material.

Appendix A. The 46 regions sampled for the present study, including the local maxima coordinates

#	x	y	z	Hemisphere	Lobe	Gyrus	Region
1	−8	20	64	L. Cerebrum	Frontal	Middle frontal	BA 6
2	−50	12	10	L. Cerebrum	Frontal	Precentral	BA 44
3	59	−4	12	R. Cerebrum	Frontal	Precentral	BA 43
4	60	−6	16	R. Cerebrum	Parietal	Postcentral	BA 43
5	−42	−40	16	L. Cerebrum	Temporal	Superior Temporal	BA 41
6	−30	−10	11	L. Cerebrum	Sub-lobar	Claustrum	Claustrum
7	22	−6	−2	R. Cerebrum	Sub-lobar	Lentiform Nucleus	Lateral GIobus Pallidus
8	26	−12	0	R. Cerebrum	Sub-lobar	Lentiform Nucleur	Lateral GIobus Pallidus
9	43	−30	22	R. Cerebrum	Sub-lobar	Posterior Insula	BA 13
10	−12	−80	21	L. Cerebrum	Occipital	Cuneus	BA 18
11	−2	−32	−18	L. Cerebellum	Anterior		Lobule III
12	−24	−74	−21	L. Cerebellum	Posterior		Lobule VI
13	−24	−76	−16	L. Cerebellum	Posterior		Lobule VI
14	40	−74	−20	R. Cerebellum	Posterior		Lobule Cr l
15	10	−78	−10	R. Cerebellum	Posterior		Lobule VI
16	8	−72	−7	R. Cerebellum	Anterior lobe		Lobule VI
17	8	−58	−30	R. Cerebellum	Anterior	Nodule	Lobule IX
18	−41	0	42	L. Cerebrum	Frontal	Precentral	BA 6
19	−44	2	44	L. Cerebrum	Frontal	Middle Frontal	BA 6
20	10	11	56	R. Cerebrum	Frontal	Superior Frontal	BA 6
21	60	−20	10	R. Cerebrum	Temporal	Transverse Temporal	BA 41
22	−19	14	−9	L. Cerebrum	Sub-lobar	Lentiform Nucleus	Putamen
23	−29	−23	20	L. Cerebrum	Sub-lobar	Claustrum	Claustrum
24	30	−28	18	R. Cerebrum	Sub-lobar	Posterior Insula	BA 13
25	32	−28	14	R. Cerebrum	Sub-lobar	Posterior Insula	BA 13
26	−4	−86	0	L. Cerebrum	Occipital	Lingual	BA 18
27	22	−82	30	R. Cerebrum	Occipital	Cuneus	BA 19
28	−28	−54	−44	L. Cerebrum	Posterior		Lobule VIIIA
29	31	−59	37	R. Cerebrum	Parietal	Sub-Gyral	BA 39
30	−8	−4	64	L. Cerebrum	Frontal	Superior Frontal	BA 6
31	−58	−17	35	L. Cerebrum	Frontal	Precentral	BA 4
32	6	4	60	R. Cerebrum	Frontal	Medial Frontal	BA 6
33	58	−8	38	R. Cerebrum	Frontal	Precentral	BA 6
34	58	−12	38	R. Cerebrum	Frontal	Precentral	BA 6
35	−10	−80	18	L. Cerebrum	Occipital	Cuneus	BA 18
36	−6	−76	32	L. Cerebrum	Occipital	Cuneus	BA 19
37	6	−70	−38	R. Cerebellum	Posterior		Lobule VIII
38	40	−64	−20	R. Cerebellum	Posterior		Lobule VI
39	−28	−6	18	L. Cerebrum	Sub-lobar	Claustrum	Claustrum
40	−30	−8	20	L. Cerebrum	Sub-lobar	Posterior Insula	BA 13
41	−28	−28	24	L. Cerebrum	Sub-lobar	Posterior Insula	BA 13
42	−22	−14	24	L. Cerebrum	Sub-lobar	Caudate	Caudate Body
43	18	0	0	R. Cerebrum	Sub-lobar	Lentiform Nucleus	Lateral Globus Pallidus
44	11	−88	34	R. Cerebrum	Occipital	Cuneus	BA 19
45	13	−87	30	R. Cerebrum	Occipital	Cuneus	BA 19
46	−4	−24	−14	L. Brainstem	Mid brain	–	Red Nucleus

References

Abbey, E. (1975). *The monkey wrench gang*. New York: Avon Books.

Alm, P. A. (2004). Stuttering and the basal ganglia circuits: A critical review of possible relations. *Journal of Communication Disorders, 37*, 325–369.

Alm, P. A. (2007). The dual premotor model of cluttering and stuttering: A neurological framework. In *Proceedings of the 1st World Conference on Cluttering*, Katarino, Bulgaria (May).

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society Series B (Methodological), 57*, 289–300.

Bloodstein, O., & Ratner, N. B. (2008). *A handbook on stuttering* (6th ed.). San Diego: Singular.

Boberg, E., Yeudall, L. T., Schopflocher, D., & Bo-Lassen, P. (1983). The effect of an intensive behavioral program on the distribution of EEG alpha power in stutterers during the processing of verbal and visuospatial information. *Journal of Fluency Disorders, 8*, 245–263.

Bothe, A. K., Davidow, J. H., Bramlett, R. E., & Ingham, R. J. (2006). Stuttering treatment research, 1970–2005: I. Systematic review incorporating trial quality assessment of behavioral, cognitive, and related approaches. *American Journal of Speech-Language Pathology, 15*, 321–341.

Brown, S., Ingham, R. J., Ingham, J. C., Laird, A. R., & Fox, P. T. (2005). Stuttered and fluent speech production: An ALE meta-analysis of functional neuroimaging studies. *Human Brain Mapping, 25*, 105–117.

Chang, S.-E., Erickson, K. I., Ambrose, N. G., Hasegawa-Johnson, M. A., & Ludlow, C. L. (2008). Brain anatomy differences in childhood stuttering. *Neuroimage, 39*, 1333–1344.

Chang, S.-E., Horwitz, B., Ostuni, J., Reynolds, R., & Ludlow, C. L. (2011). Evidence of left inferior frontal-premotor structural and functional connectivity deficits in adults who stutter. *Cerebral Cortex, 21*, 2507–2518.

Civier, O., Bullock, D., Max, L., & Guenther, F. H. (2013). Computational modeling of stuttering caused by impairments in a basal ganglia thalamo-cortical circuit involved in syllable selection and initiation. *Brain and Language, 126*, 263–278.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences*. Hillsdale, NJ: Lawrence Erlbaum Associates.

Costello, J. M., & Ingham, R. J. (1984). Assessment strategies for children and adult stutterers. In R. Curlee & W. H. Perkins (Eds.), *Nature and treatment of stuttering: New directions* (pp. 303–333). San Diego: College-Hill.

Crick, F., & Koch, C. (2005). What is the function of the claustrum? *Philosophical Transactions of the Royal Society London, 360*, 1271–1279.

Cykowski, M., Fox, P. T., Ingham, R. J., Ingham, J. C., & Robin, D. A. (2010). A study of the reproducibility and etiology of diffusion anisotropy differences in developmental stuttering: A potential role for impaired myelination. *Neuroimage, 52*, 1495–1504.

De Nil, L. F., Kroll, R. M., & Houle, S. (2001). Functional neuroimaging of cerebellar activation during singleword reading and verb generation in stuttering and nonstuttering adults. *Neuroscience Letters, 302*, 77–80.

De Nil, L. F., Kroll, R. M., Lafaille, S. J., & Houle, S. (2003). A positron emission tomography study of short and long term treatment effects on functional brain activation in adults who stutter. *Journal of Fluency Disorders, 28*, 357–380.

Friedman, J. R., Hastie, T., & Tibshirani, R. (2008). *The elements of statistical learning: Data mining, inference, and prediction* (2nd ed.). Heidelberg: Springer-Verlag.

Goldiamond, I. (1965). Stuttering and fluency as manipulatable response classes. In L. Krasner & L. P. Ullmann (Eds.), *Research in behavior modification* (pp. 106–156). New York: Rinehart & Winston.

Ingham, R. J. (1984). *Stuttering and behavior therapy: Current status and experimental foundations*. San Diego, CA: College-Hill Press.

Ingham, R. J. (1987). *Residential prolonged speech stuttering therapy manual*. Santa Barbara, CA: Department of Speech and Hearing Sciences, University of California.

Ingham, R. J. (1999). Performance-contingent management of stuttering in adolescents and adults. In R. Curlee (Ed.), *Stuttering and related disorders of fluency* (pp. 200–221). New York: Thieme.

Ingham, R. J., & Andrews, G. (1973). An analysis of a token economy in stuttering therapy. *Journal of Applied Behavior Analysis, 6*, 219–229.

Ingham, R. J., & Student, F. (2013). *Modifying phonation intervals (MPI) stuttering treatment iOS application*. Stuttgart, Germany: Logera Solutions GmbH.

Ingham, R. J., Bakker, K., Ingham, J. C., Kilgo, M., & Moglia, R. (1999). *Stuttering Measurement System* (SMS software). <http://www.speech.ucsb.edu/> Retrieved 07.04.07.

Ingham, R. J., Cykowski, M., Ingham, J. C., & Fox, P. T. (2008). Neuroimaging contributions to developmental stuttering theory and treatment. In R. J. Ingham (Ed.), *Neuroimaging in communication sciences and disorders* (pp. 53–85). San Diego: Plural Publishing.

Ingham, R. J., Fox, P. T., Ingham, J. C., & Zamarripa, F. (2000). Is overt speech a prerequisite for the neural activations associated with chronic developmental stuttering? *Brain and Language, 75*, 163–194.

Ingham, R. J., Grafton, S. T., Bothe, A. K., & Ingham, J. C. (2012). Brain activity in adults who stutter: Similarities across speaking tasks and correlations with stuttering frequency and speaking rate. *Brain and Language, 122*, 11–24.

Ingham, R. J., Kilgo, M., Ingham, J. C., Moglia, R., Belknap, H., & Sanchez, T. (2001). Evaluation of a stuttering treatment based on reduction of short phonation intervals. *Journal of Speech, Language, and Hearing Research, 44*, 1229–1244.

Ingham, R. J., Moglia, R., Kilgo, M., & Felino, A. (2007). *Prolonged speech treatment program (accompanied by phonation interval recording)*. Santa Barbara, CA: Department of Speech and Hearing Sciences, University of California.

Kell, C. A., Neumann, K., von Kriegstein, K., Posenenske, C., von Gudenberg, A. W., Euler, H., et al. (2009). How the brain repairs stuttering. *Brain, 132*, 2747–2760.

Lancaster, J. L., Rainey, L. H., Summerlin, J. L., Freitas, C. S., Fox, P. T., Evans, A. C., et al. (1997). Automated labeling of the human brain. A preliminary report the development and evaluation of a forward-transform method. *Human Brain Mapping, 5*, 238–242.

Lancaster, J. L., Woldorff, M. G., Parsons, L. M., Liotti, M., Freitas, C. S., Rainey, L., et al. (2000). Automated Talairach atlas labels for functional brain mapping. *Human Brain Mapping, 10*, 120–131.

Martin, R. R., Haroldson, S. K., & Triden, K. A. (1984). Stuttering and speech naturalness. *Journal of Speech and Hearing Disorders, 49*, 53–58.

Neumann, K., Preibisch, C., Euler, H. A., von Gudenberg, A. W., Lanfermann, H., Gall, V., et al. (2005). Cortical plasticity associated with stuttering therapy. *Journal of Fluency Disorders, 30*, 23–39.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 25*, 965–969.

Onslow, M., Costa, L., Andrews, C., Harrison, E., & Packman, A. (1996). Speech outcomes of a prolonged-speech treatment for stuttering. *Journal of Speech and Hearing Research, 39*, 734–749.

Price, C. J. (2010). The anatomy of language: A review of 100 fMRI studies published in 2009. *Annals of the New York Academy of Science, 1191*, 62–88.

Price, C. J. (2012). A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading. *Neuroimage, 62*, 816–847.

Prins, D., & Ingham, R. J. (2009). Evidenced-based treatment and stuttering – Historical perspective. *Journal of Speech, Language, and Hearing Research, 52*, 254–263.

Riecker, A., Ackermann, H., Wildgruber, D., Dogil, G., & Grodd, W. (2000). Opposite hemispheric lateralization effects during speaking and singing at motor cortex, insula and cerebellum. *NeuroReport, 11*, 1997–2000.

Riecker, A., Brendel, B., Ziegler, W., Erb, M., & Ackermann, H. (2008). The influence of syllable onset complexity and syllable frequency on speech motor control. *Brain and Language, 107*, 102–113.

Riecker, A., Kassubek, J., Groschel, K., Grodd, W., & Ackermann, H. (2006). The cerebral control of speech tempo: Opposite relationship between speaking rate and BOLD signal changes at striatal and cerebellar structures. *Neuroimage, 29*, 46–53.

Riecker, A., Mathiak, K., Wildgruber, D., Erb, M., Hertrich, I., Grodd, W., et al. (2005). FMRI reveals two distinct cerebral networks subserving speech motor control. *Neurology, 64*, 700–706.

Schmahmann, J. D., Doyon, J., McDonald, D., Holmes, C., Lavoie, K., Hurwitz, A. S., et al. (1999). Three-dimensional MRI atlas of the human cerebellum in proportional stereotaxic space. *Neuroimage, 10*, 233–260.

Sidtis, J. J., Strother, S. C., & Rottenberg, D. A. (2004). The effect of set on the resting state in functional imaging: A role for the striatum? *Neuroimage, 22*, 1407–1413.

Sommer, M., Koch, M. A., Paulus, W., Weiller, C., & Büchel, C. (2002). Disconnection of speech-relevant brain areas in persistent developmental stuttering. *Lancet, 360*, 380–383.

Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain*. New York: Thieme.

Watkins, K. E., Smith, S. M., Davis, S., & Howell, P. (2008). Structural and functional abnormalities of the motor system in developmental stuttering. *Brain, 131*, 50–59.

Webster, R. L. (1974). *The precision fluency shaping program: Speech reconstruction for stutterers*. Roanoke, VA: Hollins Communication Research Institute.

Weiller, C., Bormann, T., Saur, D., Musso, M., & Rijntjes, M. (2011). How the ventral pathway got lost – And what its recovery might mean. *Brain and Language, 118*, 29–39.

Wymbs, N. F., Ingham, R. J., Ingham, J. C., Paolini, K. E., & Grafton, S. T. (2013). Individual differences in neural regions functionally related to real and imagined stuttering. *Brain and Language, 124*, 153–164.

Xuan, Y., Meng, C., Yang, Y., Zhu, C., Wang, L., Yans, Q., et al. (2012). Resting-state brain activity differs in adult males who stutter. *PLoS ONE, 7*(1), e30570. Epub. 2012 January 20.