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Individual differences in neural regions functionally related to real and imagined stuttering

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ABSTRACT

Recent brain imaging investigations of developmental stuttering show considerable disagreement regarding which regions are related to stuttering. These divergent findings have been mainly derived from group studies. To investigate functional neurophysiology with improved precision, an individual-participant approach ($N = 4$) using event-related functional magnetic resonance imaging and test–retest reliability measures was performed while participants produced fluent and stuttered single words during two separate occasions. A parallel investigation required participants to *imagine* stuttering or not stuttering on single words. The overt and covert production tasks produced considerable within-subject agreement of activated voxels across occasions, but little within-subject agreement between overt and covert task activations. However, across-subject agreement for regions activated by the overt and covert tasks was minimal. These results suggest that reliable effects of stuttering are participant-specific, an implication that might correspond to individual differences in stuttering severity and functional compensation due to related structural abnormalities.

1. Introduction

Despite more than two decades of brain imaging research on developmental stuttering there appears to be little consensus regarding the nature of the neurological basis of this disorder. There is ample evidence that persons who stutter (PWS) display signs of abnormal neuroanatomy and neurophysiology (see Ingham, Cykowski, Ingham, & Fox, 2008). However, no specific neural region or system has been consistently found to be functionally related to stuttered speech. There is certainly promise in recent diffusion tensor imaging (DTI) studies, which suggest that stuttering is associated with abnormal white matter integrity in the left superior longitudinal fasciculus as well as other regions including the corpus callosum (Chang, Horwitz, Ostuni, Reynolds, & Ludlow, 2011; Chang, Synnestvedt, Ostuni, & Ludlow, 2010; Cykowski, Fox, Ingham, Ingham, & Robin, 2010). However, considerably less agreement exists with respect to regional activations and deactivations that typify the neurophysiology of PWS (Chang, Kenney, Torrey, Loucks, & Ludlow, 2009; De Nil et al., 2008; Ingham, Grafton, Bothe, & Ingham, 2012; Jiang, Lu, Peng, Zhu, & Howell, 2012; Lu et al., 2010).

Previous imaging studies (see Brown, Ingham, Ingham, Laird, & Fox, 2005) report increased activations in R anterior insula, L premotor cortex, and cerebellum brain regions, along with decreased activation in L superior temporal cortex, as functionally related to stuttering. Nevertheless, functional imaging studies of stuttering are also characterized by considerable variability among participants, possibly due to contributing structural abnormalities (see Ingham et al., 2012). For instance, a recent fMRI study by Kell et al. (2009) on PWS determined that patterns of activation produced during persistent stuttering appeared as an attempt to compensate for contralateral structural anomalies. This is consistent with a recent positron emission tomography (PET) investigation by Ingham et al. (2012) that obtained results that had very little in common with earlier findings, other than strong activations in premotor cortex.

The continuing difficulty in locating consistently activated or deactivated neural regions in PWS is rather surprising. It is certainly true that stuttering is characterized by considerable variability across and within PWS populations, but it is also true that stuttering shows large and predictable responses to a number of so-called fluency-inducing conditions. For instance, the substantial reductions in stuttering during certain procedures, such as rhythmic speech or chorus reading (Bloodstein & Ratner, 2008), can almost be considered a diagnostic feature of the disorder. The immediacy with which stuttering can be essentially "turned on and off" by introducing and removing these procedures strongly suggests the presence of a common neural system that not only controls the occurrence of stuttering, but also a system that can

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be shut down by such procedural manipulations. However, given that high variability in functional activation across studies of PWS is reported in the literature, then an analysis at the individual subject-level might provide the precision necessary for isolating specific patterns of functional activation related to persistent stuttering that is not possible with group studies.

Investigations of speech, particularly stuttered speech, using fMRI presents some special challenges (Gracco, Tremblay, & Pike, 2005). One control over the effects of movement artifacts in individual fMRI studies of motor behaviors has been to consider the use of motor imagery as a surrogate for an overt motor behavior. There is considerable evidence that imagining motor activities, such as an arm or finger movement, produces similar neural activations to those that occur during actual movement execution (e.g., Deiber et al., 1998; Grafton, Arbib, Fadiga, & Rizzolatti, 1996; Lotze et al., 1999). A previous PET study by Ingham, Fox, Ingham, and Zamarripa (2000) introduced a method by which stuttered and fluent utterances might also be investigated using motor imagery. In this study four adult PWS *imagined* stuttering while reading aloud, and then *imagined* not stuttering while reading aloud when accompanied by a recording of a fluent speaker reading the same passage (a condition in which their overt reading was fluent). Consistent with previous motor imagery tasks, activation foci present as PWS imagined stuttering were found in those areas that the same participants activated during overt stuttering on the same task, including the supplementary motor area (SMA), L BA 46, R anterior insula, and R/L cerebellum. Further, imagined fluent speech during the chorus reading condition led to a pattern of activation similar to that observed in their own fluency during overt chorus reading and in normally fluent control participants. Because overt speech production is a source of considerable articulation-induced motion artifact in functional MRI, these results highlight the potential utility of using covert speech production to identify the functional neurophysiology related to stuttering. This in turn has potential clinical benefits. One application, for example, is to emulate imagery strategies that have been used to achieve pain control (see, for review, deCharms, 2008). In such fMRI studies an analog signal is arranged to show in real time the level of neural activation within a pre-established functional site; the patient is then trained to reduce perceived pain by controlling activation at that site using imagery and real time fMRI feedback.

Here we propose a method for isolating regions at the individual participant level for PWS during the overt and *imagined* production of fluent and stuttered speech during the simultaneous collection of blood oxygen level-dependant (BOLD) data using functional magnetic resonance imaging (fMRI). This, however, is neither a straightforward nor an uncomplicated task. There is ample evidence (Brown, 1937; Soderberg, 1967; Wingate, 1984) that PWS have a high probability of stuttering on certain words and sounds, but as these same studies revealed, this is not a consistent or general phenomenon among PWS. It means, therefore, that each participant requires a tailored, pretested list of words that have a high probability of being stuttered or spoken fluently during scanning conditions. And as mentioned previously, articulation-induced movement artifacts present another challenge. These untoward effects are likely to be induced to a higher degree on severely stuttered utterances relative to fluent utterances. Therefore, perhaps a solution to the problem of noise introduced during overt speech production is to scan the same participants while they covertly *imagine* stuttering on a "stutter-prone" word, or while they covertly *imagine* speaking a "nonstutter-prone" word fluently.

The present event-related fMRI study was conducted having two principal aims: (1) to test whether regional activations associated with stuttering are similar or dissimilar for overt and covert tasks within and across the individual PWS; (2) to identify the regional activation effects of stuttered speech (relative to fluent speech) that are common to both overt and covert speech for each individual. Both aims were met by restricting comparisons to reliable and consistent voxel-wise activations found by repeating the entire overt-covert scanning tasks with each participant. The consistency of within-subject experimental effects is a prominent concern in neuroimaging (see Bennett & Miller, 2010) that has never been addressed in any study using PWS.

2. Method

2.1. Participants

Four male young adults (P1 = 21yrs; P2 = 25yrs; P3 = 19yrs; P4 = 19yrs.) who were developmental stutterers volunteered to participate in this study, which was approved by the University of California, Santa Barbara (UCSB) Human Subjects Committee. Each PWS was a UCSB student; only one had received any form of therapy for stuttering and that was five years prior to this study. Each was paid for time involved in this study. All had English as their first language, and all had been stuttering since at least elementary school. All reported normal vision and were able to read all words correctly. All were strongly right-handed as confirmed by 10/10 right-handed scores on the Edinburgh Handedness Inventory (Oldfield, 1971).

Prior to the experiment, stuttering was assessed using three 3-min self-selected speaking tasks (oral reading, monolog, and telephone conversations) during within-clinic assessments, which were administered by a research assistant trained on the Stuttering Measurement System (SMS; Ingham, Bakker, Ingham, Kilgo, & Moglia, 1999). Table 1 shows the percent syllables stuttered (%SS), syllables spoken per minute (SPM) and average speech naturalness (NAT) scores obtained from audio-visual recordings for each participant during each of the within-clinic assessments. This confirms that all four participants produced stuttering during the oral reading task, which is most relevant to the present study. Table 1 also shows that although small in number, the participants displayed a considerable range of stuttering severity.

2.2. Pretesting sessions

Prior to the experiment, each participant was individually pretested during a number of audiovisual recorded sessions in order to identify a corpus of 30–40 words (mono- and multi-syllable) that were reliably either stuttered or fluent. Initially, each participant read aloud from a list of approximately 150 words that were constantly changed to include words that either the experimenter

Table 1
Pre-experiment speech performance data produced by four individual participants. Shown are percent syllables stuttered (%SS), syllables spoken per minute (SPM), and mean speech naturalness rating per minute (Na: 1 = highly natural; 9 = highly unnatural) during three 3-min speaking tasks: oral reading, monolog, and telephone conversation.

	P1	P2	P3	P4
Reading				
%SS	12.4	8.6	1.6	2.1
SPM	84.4	116.1	258.4	205.6
Na	6.3	8.6	4.0	3.3
Monolog				
%SS	15.7	2.2	0.9	1.4
SPM	79.3	178.7	255.8	162.5
Na	8.0	3.3	3.0	3.3
Telephone				
%SS	13.0	1.9	2.1	2.3
SPM	65.2	189.7	173.1	139.7
Na	5.6	2.3	3.0	3.7

or the participant expected would be stuttered. These words were then repeatedly presented on a computer monitor at 20 s intervals (the time between word presentations during the actual scanning sessions) until the experimenter and an independent judge agreed that the participant would orally read and stutter consistently on approximately half of the words and read fluently the other half. In some cases this required up to 14 iterations of each participant's word list. The final number of selected words varied across participants (range: 30–44 words, mean: 37 words) with few words that were common among participants.

2.3. fMRI test sessions

Each participant completed four separate imaging sessions on four separate days. The first two sessions, herein referred to as Set A, consisted of an overt session and a covert session that were completed two days apart. Participants returned to the lab after a delay of at least 3 weeks and completed Set B, which followed the same procedure as Set A. Each imaging session lasted for approximately one hour.

2.3.1. Overt task

Participants were instructed to read aloud each individual word that appeared for 4 s on a visual display, which was then followed by a 20 s interval during which participants viewed a static fixation cross. Participants were instructed to speak at a comfortable level consistent with everyday discourse, and not to try to talk over the acquisition noise produced by the MRI scanner. Overt speech was recorded using an MRI-compatible microphone (see below). Each word was from the participant's corpus of consistently stuttered (stutter-prone) and consistently fluent (not stutter-prone) words, and they were presented in alternating order The participant's corpus of words was repeated following a 120 s pause for up to three occasions. This was necessary in order to ensure that 12 unambiguously stuttered and 12 unambiguously fluent words could be identified from the recorded speech for subsequent analysis.

2.3.2. Covert task

The covert task began outside the scanner by having the participant practice imagining as vividly as possible the task words as either stuttered or fluent. Participants were instructed to judge if the word was imagined vividly and to set a personal threshold in order for a word to be considered vividly imagined. After the participant and experimenter were satisfied with training performance the covert scanning session began.

During each fMRI session participants were instructed to imagine reading aloud the same pre-selected words that had been produced overtly, which were visually presented for 4 s and separated by a 20 s interval, during which participants viewed a fixation cross. A total of eight such scan epochs were collected, and within each epoch set participants were presented with 6–7 different words from their individually selected lists. Odd-numbered scan epochs presented words that were previously identified as participant-specific "stutter-prone words" and even-numbered scan epochs presented words that were previously identified as "not stutter-prone words." The visual presentation of each word served as the imperative to imagine reading aloud, and depending on the condition, either doing so fluently or while stuttering. The experimenter checked at the end of each epoch set whether the participant had vividly imagined each word in accordance with the instructed condition. Words that the participant judged not to be imagined vividly were noted and modeled separately in each respective design matrix (see below). Following the completion of the initial four scan epochs, participants received a 120 s rest, and then repeated the procedure during scan epochs 5–8 using the identical words.

2.4. Behavioral apparatus

Stimulus presentation was controlled with a laptop computer running MATLAB 7.1 (Mathworks, Natick, MA) and the Cogent 2000 toolbox (Wellcome Department of Imaging Neuroscience, London, UK). During the overt task, a shielded, MRI-compatible microphone (Shure: Model SM93) was affixed to the inside of the head-coil and positioned within the participant's breathstream – a location that produced the clearest and least ambiguous speech signal (see Section 2.5).

2.4.1. Imaging procedures

Functional MRI images were acquired using a 12-channel phased-array head coil inside a 3.0 T Siemens Trio (Erlangen. Germany). Participants lay supine in the scanner and were fitted with additional padding in order to reduce head motion. For each scan epoch, a single-shot echo planar imaging (EPI) sequence that is sensitive to BOLD contrast was used to acquire 37 slices per repetition time (TR = 2000 ms, 3 mm thickness, 0.5 mm gap), echo time (TE) of 30 ms, flip angle of 90°, field of view (FOV) of 192 mm, and 64 × 64 acquisition matrix. The in-plane resolution for the functional scans is 3×3 mm^2. Before the collection of the first functional epoch, a high-resolution T1-weighted sagittal sequence image of the whole brain was acquired (TR = 15.0 ms; TE = 4.2 ms; flip angle = 9°, 3D acquisition, FOV = 256 mm; slice thickness = 0.89 mm, acquisition matrix = 256 × 256).

2.5. Data analysis: behavior

Overt speaking was recorded and further processed offline using Audacity 2.0® software (Version 1.2.5. http://audacity.sourceforge.net) in order to filter scanner-related noise from that of the speech signal. Reliability of stuttered and fluent overt speech was confirmed by arranging for two of the experimenters (R.J.I. and J.C.I.) to listen independently to the audio filtered recordings of each word spoken during scanning. Only those words that both experimenters agreed independently to be unambiguously stuttered or fluent were included in the final analyses, thus pinpointing the 12 stuttered and 12 fluent words that were analyzed for each participant.

2.6. Data analysis: fMRI

Preprocessing and parameter estimation of functional imaging data were conducted with Statistical Parametric Mapping (SPM5, Welcome Department of Imaging Neuroscience, London, UK). Functional images were realigned, coregistered to the native T1, normalized to the MNI-152 template with a resolution of $2 \times 2 \times 2$ mm, and then smoothed with a Gaussian kernel of 8 mm full-width at half-maximum. In order to account for potential fluctuations of signal intensity due to motion and other noise artifacts, the functional images were rescaled by the inverse of the variance at each time point using robust weighted least squares estimation (Diedrichsen & Shadmehr, 2005). The FSL software package (Version 4.1.9. http://fmrib.ox.ac.uk/fsl) and custom MATLAB code were used to extract region-based functional imaging statistics. Further, the cluster command line function in FSL was used for the identification of contiguous voxel clusters from linear contrasts between stuttered and fluent speech conditions. In order to maintain consistency with previous experiments with PWS (e.g., Ingham et al., 2012), region-based local maxima are reported in Talairach coordinates (Talairach & Tournoux, 1988) using the MNI-to-TT transformation supplied by the GingerALE software package (Laird et al., 2010; Lancaster et al., 2007).

Cortical regions were demarcated based on the Brodmann region template supplied with MRICron (Rorden, Karnath, & Bonilha,

2007) with the exception of the insula (BA13), which was selected from the Talairach atlas supplied with AFNI. This region was converted to MNI-152 space using a 9-DOF affine transformation. The following Brodmann areas were included in the current analysis: 1–10, 13, 21–23, 24, 32, 38–47. The basal ganglia (globus pallidus, caudate, putamen) and the thalamus were demarcated using Freesurfer (Fischl et al., 2002, 2004), while cerebellum regions were demarcated using the spatially unbiased cerebellum template supplied with SUIT (Diedrichsen, 2006). In order to isolate condition specific components of BOLD, participant-level design estimations were made with a general linear model. A separate design matrix was created for each scan session, so that overt and covert sessions from Sets A and B were modeled separately. This made it possible to identify reliable changes in BOLD intensity associated with fluent and stuttered speech. All trials were modeled using vectors that contained the onset and duration of each unambiguously categorized word (stuttered or fluent) as well as its temporal derivative. For the overt condition, separate columns were created for all agreed fluent and stuttered events, as well as an additional column for all events that were not agreed to be either fluent or stuttered. For the covert condition, separate columns were included for all vividly imagined fluent and stuttered events, as well as an additional column for events that the participant stated were not vividly imagined. Blocking factors of noninterest were included so as to mark the boundaries between adjacent scan runs.

2.7. Selection of areas reliably associated with fluent and stuttered speech

In order to fulfill the two principal aims of this study it was necessary to identify, separately for each participant, brain regions that were consistently recruited during the overt and covert production of fluent and stuttered speech in both Sets A and B. The entire procedure that was then followed is shown graphically in Fig. 1. Independent linear contrasts (fluent > baseline) and (stutter > baseline) were first performed for each overt and covert session (set at $p < 0.001$, uncorrected for multiple comparisons). A region based approach to assess the agreement levels across Sets A and B was then implemented. This was accomplished by counting the number of above-threshold voxels contained in each region of interest (see above for a description of the regions) separately for each contrast. This resulted in separate condition-specific voxel counts for Sets A and B. A conjunction between the Set A and B contrasts for each condition ($p < 0.001$, uncorrected for multiple comparisons) identified the common above-threshold voxels across A and B. All regions containing at least 10 adjacent above-threshold voxels were included in the conjunction analysis of A and B. In order to identify those regions consistently recruited for each condition, a replication percentage for each region was then calculated by dividing the number of common voxels within a region by the total number of voxels from both Sets A and B. A conservative threshold for replication was set at 60%. In this manner, a region was considered to be reliable for a particular condition only if 60% (or more) of aggregate above-threshold voxels were shared between A and B. This level of agreement was selected by taking into account the levels of "satisfactory" reliability as reported by Bennett and Miller (2010) in their review of reliability within fMRI studies. The reliability metric selected was voxel cluster overlap using the "Dice" formula described by Rombouts et al. (1997). This produced an average agreement indice of 0.467 for cluster overlap across 13 studies (see Bennett & Miller, 2010, p. 142). Therefore, we elected to use a relatively conservative 0.6 overlap between voxel clusters in across two scanning occasions as the minimal level of agreement.

From this analysis, a replication mask was generated for each condition (i.e., fluent overt, fluent covert, stutter overt, stutter covert), including any overlapping voxels that were found within those regions that survived the replication threshold. These replication masks were then applied to all between-condition contrasts detailed below.

2.8. Differential effects of fluent and stuttered speech

The first aim of this study was to assess the differential effects of stuttered speech relative to normally fluent speech for each participant. In order to determine the patterns of increased activation found during stuttering, the linear contrasts (stutter > fluent) and (fluent > stutter) were performed separately for each overt and covert session separately for each participant (set at $p < 0.05$, uncorrected for multiple comparisons). The initial goal was to highlight individual similarities and differences in PWS separately for the both overt and covert speech. To do so, a hard overlap of the contrasts performed separately for Sets A and B identified common activation patterns between conditions. In this manner, only those voxels found to be differentially active in both Sets were considered. Each overlap was further restricted to those voxels identified using a replication mask (described above) so as to ensure that the contrasts reflected those regions that were found to be reliably activated across Sets A and B for a given individual. Only those voxels that were reliably above baseline for either fluent or stuttered speech (or both) were included. This restricted effects to be above baseline for at least one condition, and excluded effects due to contrasting below-baseline parameter estimates.

The second aim was to identify the effects of stuttered speech (relative to fluent speech) that were common to both overt and covert speech for each individual. In order to isolate speech modality-independent activation, a hard overlap was performed between the contrasts for both overt *and* covert conditions in order to identify those voxels that were commonly activated for the contrast (stutter > fluent) across both Sets A and B (set at $p < 0.05$, uncorrected for multiple comparisons). In other words, this overlap approach identified voxels that were reliably greater for stuttering compared to fluent speech (across Sets A and B) for both the overt and covert conditions. A replication mask limited results to those regions that were reliably above baseline for both overt and covert stuttered speech. The identical procedure was carried out for the contrast (fluent > stutter).

3. Results

3.1. Overt stuttered and fluent speech

Individual analyses for evidence of activations associated with stuttered or fluent speech was confined to voxel clusters that displayed 60% or greater overlap across Sets A and B. In order to measure differential and reliable effects of fluent and stutter-related activation, additional analyses were carried out using statistical contrasts between the fluent and stuttered conditions. These were restricted to those voxels that were common to Sets A and B.

3.1.1. Overt stuttered and fluent speech and previous findings

A major focus of this study was to address whether stutter-related activation patterns are common across individual PWS, and if the identified patterns of activation are consistent with findings from previous studies. Table 2 shows the centers of mass (COM) and the number of voxels for identified clusters of activation (Cl) for each of the four participants for which there is greater activation for stuttered relative to fluent production. See Fig. 2 for a depiction of these individual activation clusters. Of

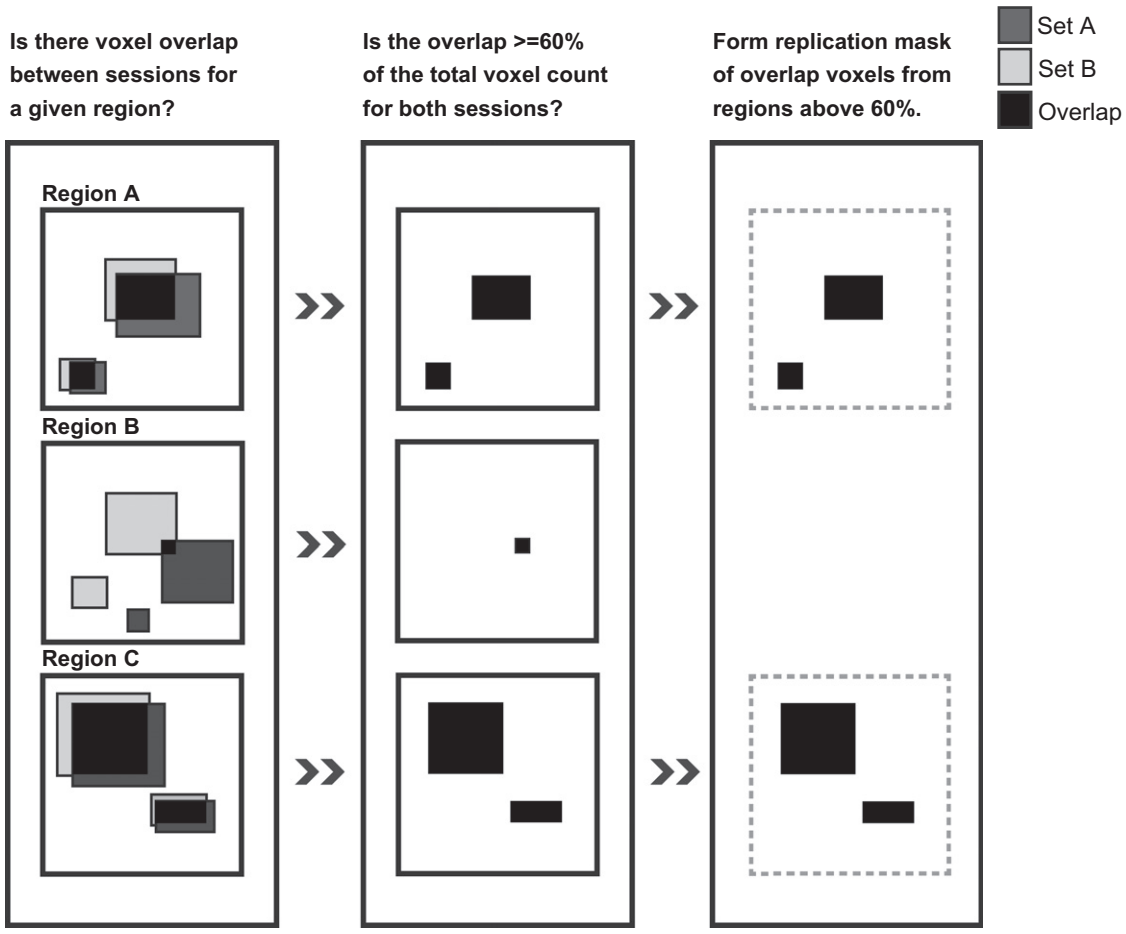

Fig. 1. The process used for determining which regions are reliably activated during speech conditions. Independent linear contrasts corresponding to a given condition relative to baseline (i.e., stutter > baseline; $p < 0.001$, uncorrected for multiple comparisons) are first carried out for both Sets A and B. Shown in the left column, the number of above-threshold voxels for Set A and Set B contrast images, and the overlap showing common voxels between the contrast images are counted within each a priori region of interest. As can be seen from this example, each region (A–C) contains individual clusters of activation that differ in size and in the amount of overlap between the two occasions. Activation clusters from regions that have $\geqslant$60% overlap among all the voxels from Sets A and B are selected and then included in a replication mask. Shown in the middle column, overlap is isolated for each region and evaluated for% overlap. Regions A and C have more than 60% overlap, but Region B does not (right column). The large perimeter rectangle is a representation of the whole brain, and the three squares that it contains represent individual regions of interest. Dashed region boundaries (right column) indicate that the replication mask is restricted to those clusters that are found within reliable regions and not the entirety of a reliable region.

critical importance, there is considerable disparity between the four participant's (P) stutter-related regional activations. In fact, as shown in Fig. 2, locations of inter-participant agreement only occurred between P2 and P4 [L precentral gyrus (BA 4/6), R anterior insula (BA 13), L cerebellum lobule IV], and between P3 and P4 [R pre-supplementary motor area (preSMA, BA 6), R precentral gyrus (BA 4/6)]. It is notable, however, that all participants produced at least some activations within regions that Brown et al. (2005) had earlier identified as the neural signatures of stuttering (increased activations in anterior insula, premotor cortex, and cerebellum brain regions, along with lack of activation in superior temporal cortex).

There were few regions where the activation for fluent words was greater than that of stuttered words. Table 2 shows that this only occurred in three regions and across only two participants. The lack of strong results suggests that the voxel locations identified for the fluent > stutter contrasts from Sets A and B do not overlap. Further, as revealed by Table 4, there were fewer regions that survived the replication threshold for the contrast (overt > baseline) for fluent speech with respect to the same replication contrast performed for stuttered speech. This suggests that there are relatively fewer regions that demonstrate consistent overt fluent activation across Sets A and B. This finding was consistent across all participants. For instance, P1 had 33 regions that were in common across Sets A and B for overt stuttered speech, but only 23 regions for overt fluent speech. Further, a ratio of regions that survive the 60% threshold from the total number of regions in common across Sets A and B was greater for stuttered relative to fluent overt speech in 3 of the 4 participants. These results suggest that overt fluent speech demonstrated relatively weak reliability across Sets A and B, and because of this, led to the small number of activation foci for the overt (fluent > stuttered) contrast.

3.1.2. Overt and covert stuttered and fluent words – similarities and differences

Comparisons were made between the regional locations where stuttered words produced significantly stronger activations than fluent words during each participant's overt and covert productions. The results (as shown in Tables 3a and 3b) are, once again, illuminating because they highlight the considerable differences across participants among their overt and covert stuttered word productions. The lack of consistency across participants in the direction of these differences is exemplified by P2, who activated only six regions during overt stuttered words (note that activations for overt stuttered words are those reported in Table 2), but 24 during his covert stuttered word production. By contrast, P4

Table 2
Sites related to overt stuttered speech (stutter > fluent) and fluent speech (fluent > stutter) during the production of single words. Shown are the cluster sizes (Cl) for regions containing a minimum of 10 common voxels and the centers of mass of each cluster in Talairach space for the four participants.

		P1				P2				P3				P4			
		Cl	X	Y	Z	Cl	X	Y	Z	Cl	X	Y	Z	Cl	X	Y	Z
Overt stuttered word activations (stutter > fluent activations)																	
Frontal																	
L	SMA (6)	89	−8	−13	57												
	GPrCs (6)	52	−54	−4	28												
	GPrC (4)	28	−46	−15	54	16	−40	−19	41					602	−49	−13	42
	GPrC (4)					53	−58	−13	33								
	GFm (9)													28	−52	9	37
	GFm (10)									246	−37	49	17				
	GFi (44)													56	−56	8	21
	GFi (47)													104	−46	18	1
R	Pre−SMA (6)									141	4	2	69	935	1	12	47
	SMA (6)													52	2	−10	66
	GPrCs (6)									278	44	−7	53	32	58	−1	19
	GPrC (4)									22	59	−9	23	480	48	−15	42
	GFm (9)													99	34	39	37
	GFm (9)													50	33	28	35
	GFm (10)													35	42	44	21
	GFi (47)													123	45	21	−5
Limbic																	
L																	
R	GC (32)									34	1	10	37				
	GC (32)									15	15	33	17				
Parietal																	
L	GPoC (3)													103	−59	−18	23
	PCu (7)	10	−29	−67	37									24	−7	−79	52
	LPs (7)													322	−29	−66	52
	LPi (39)													31	−48	−62	43
	LPi (40)													195	−53	−53	35
	LPi (40)													20	−60	−43	33
R	PCu (7)									253	5	−78	50				
	LPs (7)									119	33	−69	51				
	LPi (40)									103	49	−48	48				
Temporal																	
L	GTs (22)									86	−52	7	0				
	GTs (42)									25	−60	−22	12				
R	GTT (41)	28	45	−32	7												
	GTm (21)									19	62	−37	−4				
	GTs (22)													72	60	−38	9
Sub lobar																	
L																	
R	Cl	27	35	6	6												
	Ant INS (13)					653	40	19	1					206	33	21	7
	Pos INS (13)									135	47	−37	20				
CBM																	
L	Cr I	46	−43	−62	−31												
	Lobule IV	21	−20	−58	−26	146	−26	−62	−22	80	−1	−50	0	34	−10	−64	−15
	Lobule VI	18	−40	−41	−26												
	Lobule VI	16	−32	−53	−32												
R	Cr I	89	42	−53	−35									58	44	−59	−26
	Lobule VI					185	27	−67	−21								
						12	7	−68	−15								
Overt fluent word activations (fluent > stutter activations)																	
Parietal																	
L																	
R	GPoC (2)					10	62	−18	25								
	LPi (40)									115	48	−39	50				
CBM																	
L																	
R	Cr I					12	48	−50	−28								

activated 21 regions during overt production, but only seven during covert productions. And, then again, P3 activated 14 regions during the overt and 14 during the covert conditions – but only two were in similar regions during both conditions.

These findings need to be weighed against the levels of agreement among voxel clusters between Sets A and B for each participant. Table 4 addresses this issue by showing the total number regions (with 10 or more clustered voxels) that had some level of overlap across Sets A and B. Among those regions with voxel clusters satisfying the $\geqslant$60% criterion for consistency, their mean percentage overlap across occasions ranged from 67% to 79% (see Table 4, far right column). Table 4 also shows, for example, that P2 had relatively poor agreement for overt stuttered words (only 26% of regions showing $\geqslant$60% agreement), but very good

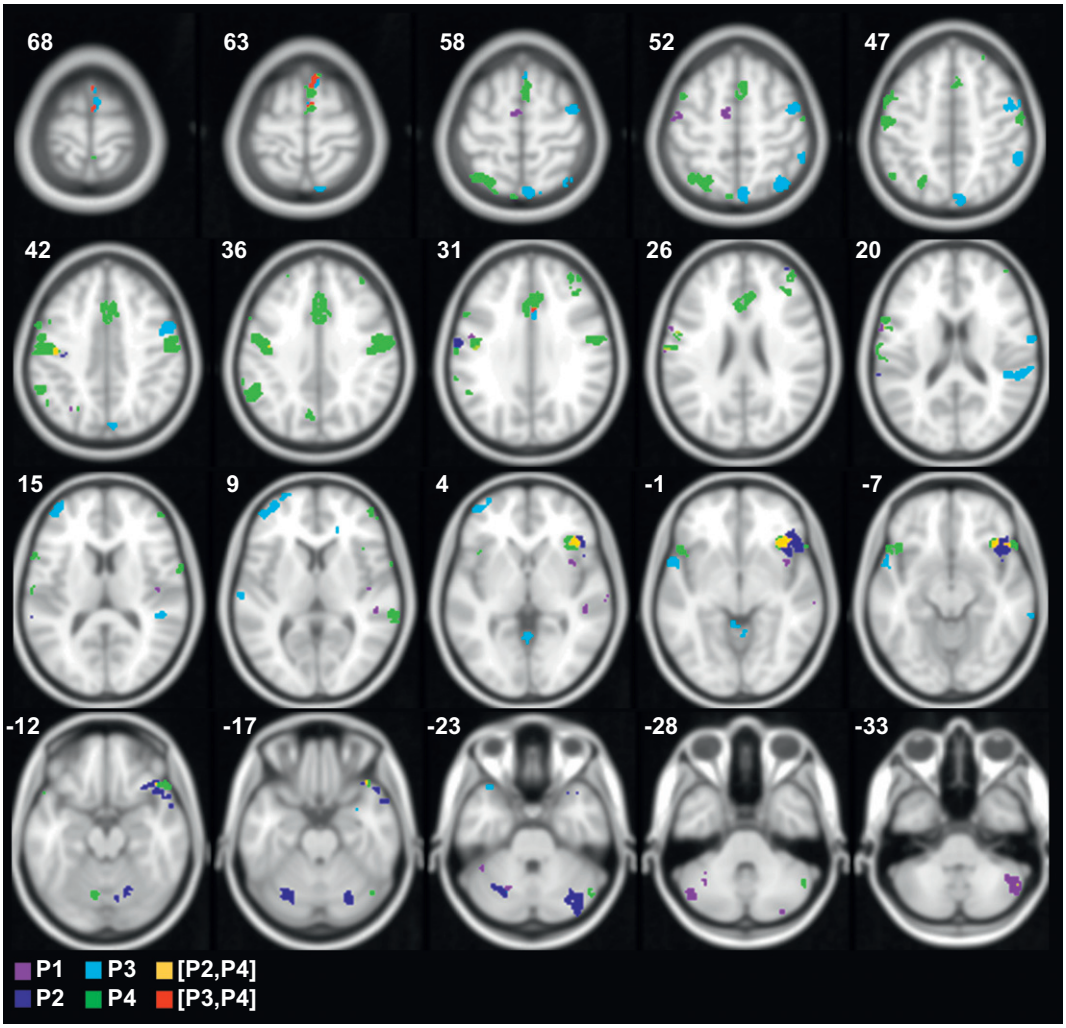

Fig. 2. Consistent participant-specific locations showing increased activation during stuttering on single words, as revealed by the contrast (stutter > fluent). Voxels are color coded for each participant. Results are constrained to those regions with ⩾60% agreement between Sets A and B, and displayed using an uncorrected threshold of $p < 0.05$ (see Section 3.1.3). R = R; L = L.

agreement for covert stuttered words (83% of regions showing ⩾60% agreement). By contrast, the other three participants had near 50% of identified regions with ⩾60% agreement across occasions for both overt and covert stuttered responses. In short, poor across-occasion agreement makes it difficult to interpret P2's overt stuttering data and should therefore be interpreted with caution.[1]

3.1.3. Overt and covert stuttered words – regional activation overlap

The identification of regions showing overlap between overt and covert production was confined to stuttered words using the contrast (stutter > fluent). No overlap was found between overt and covert fluent word activation using the opposite contrast (fluent > stutter). As mentioned above, the regional overlap of overt and covert stuttered words was examined only for those regions with reliability at 60% or greater between Set A and Set B. It is clear from Table 5 and Fig. 3, however, that relatively few regions demonstrated greater activation for stuttered speech during both overt and covert production. Indeed, using a threshold set to $p < 0.005$, there appeared to be no overlap between overt and covert stuttered speech, a result that was interpreted as potentially including Type II error because of previously reported similarities (Ingham et al., 2000). For that reason these data were analyzed using a less conservative threshold of $p < 0.05$, fully recognizing the potential for Type I error but allowing comparisons with previous research, especially the findings reported by Brown et al. (2005).

Given the problems mentioned above in interpreting P2's data (see Section 3.1.3), comments on the overlap findings are confined to the other three participants. Comparisons between participants demonstrated some commonalities between P1 and P3. For instance, P1 and P3 both produced overt and covert stuttered words that were associated with activations in the SMA and in BA 22,

[1] As shown in Table 4, for P2 50 regions contained a minimum of 10 above-baseline voxels ($p < 0.001$) separately for Sets A and B. However, only 13 of these regions (26% of the total) had at least 60% of their voxels overlap across Sets A and B, indicating that there were a relatively low number of regions were stable across the two occasions. The goal of this study was to highlight *regions* that were reliably activated across occasions for an individual, and not necessarily whether the *individual* should be considered reliable. However, due to the low percentage of regions that were reliable across Sets A and B, the results for P2 should be interpreted with caution. Considering that agreement was better for overt fluent speech regions (38% of total regions), it is unlikely that general fluctuations in signal-to-noise or participant state of mind could be the culprit. On the other hand, it is conceivable that fluctuations in signal-to-noise were present during *stuttering* trials across the two occasions. This is compounded by the fact that stuttering can lead to increased articulation-induced motion artifact during fMRI and that the severity of stuttered utterances is variable from trial to trial. Evidence for this point also comes from the observation that 75% of the identified regions during *imagined* stuttering were stable for P2 across Sets A and B. Nevertheless, given our emphasis on conservative reliability, it seems logical to express caution regarding what conclusions can be drawn from P2's overt stuttering results.

Table 3a
Stuttered word activations greater than fluent word activations for overt and covert production conditions for P1 and P2.

		P1 OVERT				P1COVERT					P2 OVERT				P2 COVERT			
		Cl	X	Y	Z	Cl	X	Y	Z		Cl	X	Y	Z	Cl	X	Y	Z
Frontal										*Frontal*								
L	SMA (6)	89	−8	−13	57	660	−3	−6	59	L SMA (6)					1278	0	−10	66
	GPrCs (6)	52	−54	−4	28	21	−32	−10	53	GPrC (4)	16	−40	−19	41	548	−46	−11	49
	GPrC (4)					17	−40	−12	61	GPrC (4)	53	−58	−13	33				
	GPrC (4)	28	−46	−15	54	64	−59	−2	20	GFm (9)					112	−42	35	34
	GPrC(4)					53	−53	−8	45	GFm (9)					33	−35	50	26
R	GPrC (6)					160	43	−6	53	R GPrC(4)					252	16	−29	65
	GFm (9)					90	28	37	35	GPrC(4)					52	42	−13	45
	GFm (10)					70	13	61	16	GFi (47)					60	48	16	2
Parietal										*Limbic*								
L	PCu (7)	10	−29	−67	37	12	−16	−60	54	L								
	LPs (7)					123	−23	−71	46	R GC (24)					69	10	0	47
R	PCu (7)					60	9	−72	44									
	LPi (40)					25	60	−34	30	*Parietal*								
	LPi (40)					22	60	−22	22	L GPoC (3)					196	−19	−31	61
										PCu (7)					160	−9	−81	46
										LPs (7)					107	−41	−58	52
										R LPs (7)					40	37	−55	49
Temporal																		
L	GTs (22)					245	−51	5	−2									
	GTs (22)					109	−47	−46	20	*Temporal*								
R	GTT (41)	28	45	−32	7					L GTs (22)					236	−49	12	−1
	GTs (22)					504	51	−38	7	GTs (22)					51	−54	−43	16
										R GTm (22)					64	55	−45	1
										GTs (42)					45	59	−33	16
Sub lobar																		
L	Ant INS (13)					104	−41	4	6									
R	Cl	27	35	6	6					*Sub lobar*								
	Ant INS (13)					1410	40	12	6	L Ant INS (13)					101	−40	1	7
										Th					59	−19	−31	14
CBM										Th					47	−14	−20	10
L	Cr I	46	−43	−62	−31	968	−31	−61	−27	Th					147	−1	−15	12
	Lobule IV	21	−20	−58	−26					Pu					209	−22	0	8
	Lobule VI	18	−40	−41	−26					R Ant INS (13)	653	40	19	1				
	Lobule VI	16	−32	−53	−32					Th					38	11	−20	10
R	Cr I	89	42	−53	−35													
										CBM								
										L Lobule IV	146	−26	−62	−22	88	−25	−36	−23
										Lobule V					48	−27	−33	−37
										R Lobule VI	185	27	−67	−21				
										Lobule VI	12	7	−68	−15				

albeit in opposite hemispheres. P4 showed a distinct pattern of activation relative to the others, with activation localized to the left BA 44, bilateral BA 9, and the left parietal lobe (BA 7). Although clear speech modality-independent similarities and differences were observed between the participants, the exact functional significance of the identified regions cannot be addressed by these findings. The difference between previous findings (Ingham et al., 2000) and those reported in this study may, for example, be a byproduct of using PET (enabling connected speech) and fMRI (requiring uncustomary short utterances). Nonetheless, it is evident that efforts to take advantage of regions that are functionally important for stuttering – perhaps for clinical purposes – will need to take into account the highly individualized but consistent activations associated with individual PWS.

4. Discussion

The neural basis of stuttering has been gradually elucidated through the ongoing implementation of neuroimaging techniques that began during the early years of neuroimaging (Wood, Stump, McKeehan, Sheldon, & Proctor, 1980), gathered pace in the 1990s with FDG and ^{15}O PET studies and has continued forth via the surge in popularity of fMRI and DTI (see Ingham et al., 2008 for a review). A previous meta-analysis (Brown et al., 2005) suggested that there was sufficient consistency among earlier group imaging studies that it was possible to identify some neural signatures of stuttering. However, as Ingham et al. (2012) observed, the findings from more recent studies (e.g., Chang et al., 2009; De Nil et al., 2008; Jiang et al., 2012; Lu et al., 2010) are disappointingly inconsistent with the previously identified neural signatures.[2]

Arguably, the variability among these findings may be a byproduct of white matter structural abnormalities among PWS, identified using DTI (Brown, Li, Boyd, Delaney, & Murphy, 2007; Caroni, Donato, & Muller, 2012), which could induce functional changes during the production of speech with ongoing neurological impairment. This variability became strikingly obvious in

[2] Jiang et al. (2012) reported that PWS may differentially process different types of stuttering events in different parts of the brain. They reported that "more typical" types of stuttering events (e.g., prolongations of onset sounds) activated L BA 44/45 and L precuneus (BA 7). However, "less typical" types of stuttering events (e.g., multiple word or phrase repetitions) activated the L/R putamen, R lateral globus palidus, and cerebellum L lobule VI. The present study did not subdivide stuttering events. However, if these regions are functionally related to occurrences of stuttering, then it might also be expected that they should be associated with stuttering (albeit more or less typical) for all or most participants in the current study. In fact, there was some overlap between the areas associated with stuttering in the Jiang et al. and the current study, but it was not consistent across participants: cerebellum L. lobule VI was activated by three participants, and L precuneus and L BA 44 were activated by one participant. No participants activated the basal ganglia regions.

Table 3b
Stuttered word activations greater than fluent word activations for overt and covert production conditions for P3 and P4.

		P3 OVERT				P3 COVERT						P4 OVERT				P4 COVERT			
		Cl	X	Y	Z	Cl	X	Y	Z			Cl	X	Y	Z	Cl	X	Y	Z
Frontal										*Frontal*									
L	GFm (10)	246	−37	49	17					L	SMA (6)					16	−41	5	56
R	Pre−SMA (6)	141	4	2	69						GPrC (4)	602	−49	−13	42				
	SMA (6)					1042	4	−5	59		GFm (8)					97	−44	17	46
	GPrCs (6)	278	44	−7	53						GFm (9)	28	−52	9	37	48	−54	7	36
	GPrC (4)	22	59	−9	23						GFi (44)	56	−56	8	21	55	−54	7	19
											GFi (47)	104	−46	18	1				
										R	Pre−SMA (6)	935	1	12	47				
Limbic																			
R	GC (32)	34	1	10	37						SMA (6)	52	2	−10	66				
	GC (32)	15	15	33	17						GPrCs (6)	32	58	−1	19	158	39	10	45
											GPrC (4)	480	48	−15	42				
											GFm (9)	99	34	39	37	137	29	37	33
Parietal																			
R	GPoC (3)					108	42	−18	49		GFm (9)	50	33	28	35				
	PCu (7)	253	5	−78	50						GFm (10)	35	42	44	21				
	LPs (7)	119	33	−69	51						GFi (47)	123	45	21	−5				
	LPi (40)	103	49	−48	48														
										Parietal									
										L	GPoC (3)	103	−59	−18	23				
Temporal																			
L	GTs (22)	86	−52	7	0	118	−52	4	0		PCu (7)	24	−7	−79	52				
	GTs (42)	25	−60	−22	12						LPs (7)	322	−29	−66	52	162	−24	−63	50
R	GTs (22)					13	52	−5	6		LPi (39)	31	−48	−62	43				
	GTm (21)	19	62	−37	−4						LPi (40)	195	−53	−53	35				
											LPi (40)	20	−60	−43	33				
Sub lobar										*Temporal*									
L						43	−41	−3	7	L									
						35	−16	−6	25	R	GTs (22)	72	60	−38	9				
R	Cl					168	30	−2	14										
	Ant INS (13)					13	33	21	8										
	Pos INS (13)	135	47	−37	20					*Sub lobar*									
	Th					52	11	−10	16	L									
						43	2	−8	8	R	Ant INS (13)	206	33	21	7				
CBM																			
L	Lobule IV	80	−1	−50	0					*CBM*									
	Lobule VI					28	−27	−49	−28	L	Lobule IV	34	−10	−64	−15				
	Lobule VI					801	−29	−65	−26	R	Cr I	58	44	−59	−26				
	Lobule VI					15	−41	−42	−35										
R	Lobule VI					849	20	−68	−24										

recent PET findings reported by Ingham et al. (2012), which reported results that were substantially different from those found in a series of earlier studies that used a similar protocol to investigate oral reading (Fox et al., 1996, 2000). Indeed, this evidence suggests that there is reason to believe that previous group imaging studies may have unknowingly masked substantial and potentially important individual differences. Sensitive neuroimaging techniques, such as event-related fMRI appear to be better suited for the identification of individual differences. With one exception from a recent MEG study by Sowman, Crain, Harrison, and Johnson (2012), little attention has been paid to the individual participant neural system in PWS. However, the interpretation of the results from Sowman et al. (2012) is problematic; the speech data were "successful vocalizations" (saying "I" or "O") and "unsuccessful vocalizations," with the latter being events where the "subject indicated that blocking had occurred." Interestingly, their investigation revealed activations associated with "successful vocalizations" that incorporated BA 47/12, a site related to stuttering by Kell et al. (2009). Unfortunately, Sowman et al. (2012) failed to make clear whether "successful vocalization" in their study was associated with stuttered or non-stuttered events aside from the absence of blocking, making it difficult to confidently attribute the BA 47/12 to one or the other event. The present study showed very clearly that the stuttered word production was associated with distinctive and reliable differences across the four participants. In this regard it suggests that considerable variability in regions associated with stuttering is to be *expected*. Importantly, this does not exclude the possibility that variability is influenced by the considerable differences among the four participants in their customary frequencies and severities of stuttering (see Table 1).

In addition to examining individual differences, the present study was also designed to test for consistency with findings from an earlier PET study that compared overt and covert (imagined) speech in PWS (Ingham et al., 2000). In that regard, the present study is also the first report on the consistency with which the activations of imagined stuttered and nonstuttered words could be activated across scanning occasions. There is a more fundamental reason, however, as to why it is important to establish the stability of an individual's sites of activation that are associated with overt and covert stuttering. For instance, a site that is commonly activated during overt and covert stuttering could have considerable functional value. If it is the case that the overlapping sites show consistent changes from stuttered to fluent utterances during an individual's overt and imagined stuttering (relative to fluent), then it is conceivable that the direct manipulation of activation at those sites – perhaps by using transcranial magnetic stimulation (Wagner, Rushmore, Eden, & Valero-Cabre, 2009) or real time fMRI feedback (deCharms, 2008) – could modify the occurrence of

Table 4
Shown is the total number of regions with common voxels that replicate across the two separate scan sessions for each condition. Condition replication was derived from overlap of the within-session contrasts, each with respect to baseline (e.g., overt stutter > baseline) at $p < 0.001$, uncorrected. Column 4 data are the mean percentage overlap of the subset of regions that have $\geqslant 60\%$ agreement on voxel overlap.

		Total regions	>60% rep	Ratio (above thresh/total)	Mean% rep (above thresh regions)
P1					
FLUENT	OVERT	23	10	0.43	0.79
FLUENT	COVERT	42	22	0.52	0.70
STUTTER	OVERT	33	17	0.52	0.73
STUTTER	COVERT	55	45	0.82	0.77
P2					
FLUENT	OVERT	42	19	0.45	0.72
FLUENT	COVERT	44	22	0.50	0.73
STUTTER	OVERT	50	13	0.26	0.67
STUTTER	COVERT	65	54	0.83	0.76
P3					
FLUENT	OVERT	31	11	0.35	0.72
FLUENT	COVERT	43	29	0.67	0.73
STUTTER	OVERT	54	28	0.52	0.75
STUTTER	COVERT	54	32	0.59	0.76
P4					
FLUENT	OVERT	32	12	0.38	0.68
FLUENT	COVERT	19	6	0.32	0.68
STUTTER	OVERT	53	40	0.75	0.74
STUTTER	COVERT	27	14	0.52	0.70

Table 5
Modality-independent sites (see previous comments re: use of this term) of activation related to stuttered speech as revealed through the overlap of the contrast (stutter > fluent) for both overt and covert production. Shown are the voxel cluster sizes for regions containing a minimum of 10 common voxels and the center of mass (COM) of each cluster in Talairach space.

		P1				P2				P3				P4			
		Cl	X	Y	Z	Cl	X	Y	Z	Cl	X	Y	Z	Cl	X	Y	Z
Frontal																	
L	SMA (6)	29	−5	−12	60												
	GFm(9)													14	−53	8	37
	GFi (44)													23	−56	8	19
R	SMA (6)									49	4	−7	72				
	GFm (9)													28	34	39	36
	GFi (47)					21	46	16	2								
Parietal																	
L	LPs (7)													69	−24	−64	50
R																	
Temporal																	
L	GTs (22)									52	−52	7	0				
R	GTs (22)	11	44	−34	8												
Sub lobar																	
L																	
R	Ant INS (13)	19	36	7	5												
CBM																	
L	Cr I	15	−42	−61	−31												
	Lobule VI	16	−32	−53	−32												
	Lobule VI					144	−26	−62	−22								
R	Lobule VI					182	27	−67	−21								
	Lobule VI					11	7	−68	−16								

stuttering during speech. In the present study the within-participant overlap sites were relatively few in number. Further, although the "overlap sites" for P1 and P3 were included among those identified within the Brown et al. (2005) meta-analysis, the overlap sites of P4 failed to agree with any region found in the Brown et al. (2005) meta-analysis.

An important issue of comparisons between real and imagined behavior is the expected level of isomorphism needed in order to validate the relationship between the activations associated with these two classes of behaviors. In other words, what is the extent of resemblance between a real and imagined behavior that is necessary to prove they are related? In order to test for isomorphism it must be assumed that it is possible to produce a behavior that can be precisely replicated when it is being imagined. Obviously it is challenging to address this empirically, and so essentially a sufficient level of isomorphism is inferred within many studies simply because the real and imagined activations show some sign of overlapping in particular neural regions (e.g. Aleman et al., 2005; Shuster & Lemieux, 2005). In the case of the Ingham et al. (2000) PET study, for instance, the overlapping of real and imagined activations was essentially confined to the PWS ($n = 4$) and not the controls. However, the inference of isomorphism was determined by BA region-overlap and not the voxel-overlap technique used in the present study. The huge problems faced when trying to

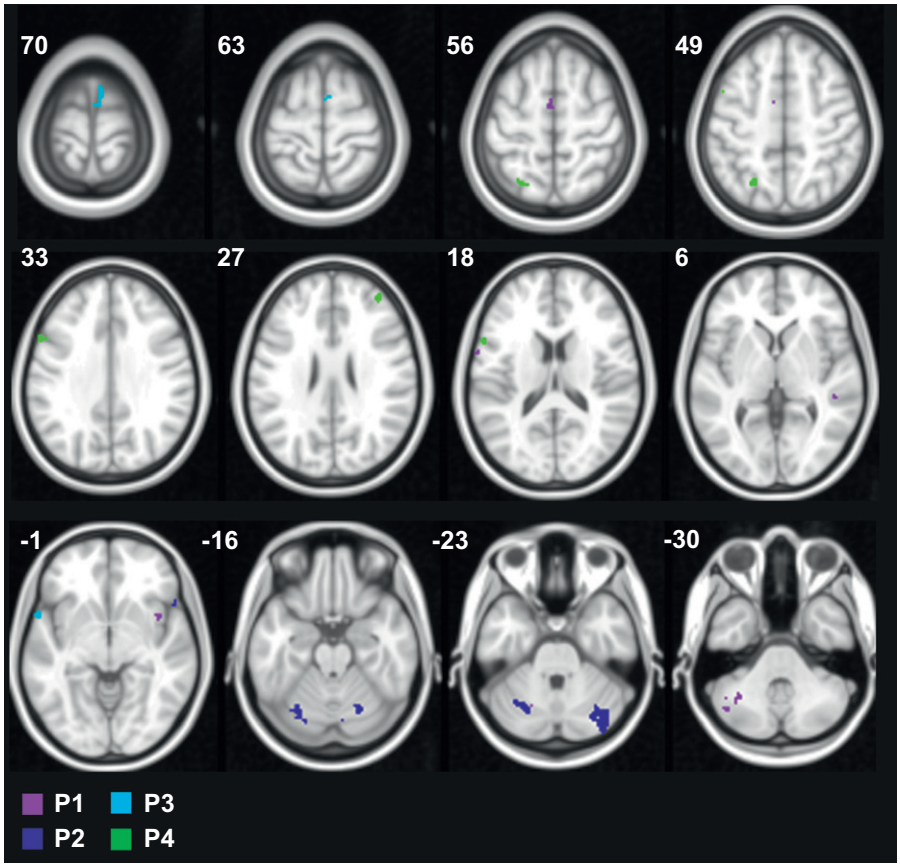

Fig. 3. Modality-independent sites of activation related to stuttered speech as revealed through the overlap of the contrast (stutter > fluent) for both overt and covert production. The voxels are color coded for each participant. Results are constrained to those regions with ⩾60% agreement between Sets A and B, and displayed using an uncorrected threshold of $p < 0.05$ (see Section 3.1.3). R = R; L = L.

ensure that there is a necessary and sufficient resemblance between an overt and covert behavior becomes obvious when attempts are made to match the mental imagery of a motor skill with behavior. Milton, Small, and Solodkin (2008) provided an interesting overview of the methodological problems that are involved in trying to achieve isomorphism associated with expertise in sport and why covert images might be expected to differ from imaged overt behavior. For example, they suggest that it is conceivable that a small amount of overlap still involves the most important and functional regions shared between overt and covert (imagined) motor production. In the context of the present study, the small number of stutter-related regional activations that were similar during overt and covert stuttering may include functionally important regions for individual PWS. On the other hand, this small number may not exceed chance levels of agreement, given the alpha level adjustment that was necessary to find them. This issue might ultimately need to be resolved by techniques designed to modify such regions. They may include, for example, real time fMRI feedback so as to train individual PWS to learn to modify target-region activations and then test for the effect of training on follow-up overt speaking tasks.

In summary, the results of this study provide added support for the emerging argument that individual PWS may use different neural regions during overt stuttering, perhaps in response to neuroanatomic abnormalities (Ingham et al., 2012). The high level of within-participant agreement (67–79%) across separate scanning occasions of the same task suggests that stuttering-associated activations are likely to be stable for an individual. These within-participant percentages actually exceed most overlap percentages reported by Bennett and Miller (2010, see Table 2) for fMRI studies reporting test–retest data calculated as in the present study. The idiosyncratic activations reported in this study may carry many implications, including the possibility that they are related to the different frequencies, topographies and severity levels of stuttering or differing functional strategies for dealing with underlying neuroanatomic abnormalities. Whatever the reason, they highlight the importance of using individual scan data in brain imaging research on developmental stuttering. This would seem to be especially important for evaluating neural system changes within treatment research or locating regions that might be modified for therapy purposes.

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