Stuttered and Fluent Speech Production: An ALE Meta-Analysis of Functional Neuroimaging Studies

Steven Brown,[1] Roger J. Ingham,[2] Janis C. Ingham,[2] Angela R. Laird,[1] and Peter T. Fox[1]

[1]*Research Imaging Center, University of Texas Health Science Center at San Antonio, Texas*
[2]*Department of Speech and Hearing Sciences, University of California, Santa Barbara, California*

Abstract: This study reports an activation likelihood estimation (ALE) meta-analysis of imaging studies of chronic developmental stuttering in adults. Two parallel meta-analyses were carried out: (1) stuttered production in the stutterers; (2) fluent production in the control subjects. The control subjects' data replicated previous analyses of single-word reading, identifying activation in primary motor cortex, premotor cortex, supplementary motor area, Rolandic operculum, lateral cerebellum, and auditory areas, among others. The stuttering subjects' analysis showed that similar brain areas are involved in stuttered speech as in fluent speech, but with some important differences. Motor areas were over-activated in stuttering, including primary motor cortex, supplementary motor area, cingulate motor area, and cerebellar vermis. Frontal operculum, Rolandic operculum, and anterior insula showed anomalous right-laterality in stutterers. Auditory activations, due to hearing one's own speech, were essentially undetectable in stutterers. The phenomenon of efference copy is proposed as a unifying account of the pattern activation revealed within this ALE meta-analysis. This provides the basis for a stuttering system model that is testable and should help to advance the understanding and treatment of this disorder. *Hum Brain Mapp 25:105–117, 2005.* © 2005 Wiley-Liss, Inc.

Key words: ALE; developmental stuttering; brain imaging; efference copy

INTRODUCTION

Speech is the most distinguishing and complex motor activity that humans engage in, requiring smooth coordination of processes related to respiration, phonation, and articulation. Syllable production, in particular, involves rapid and precisely controlled transitions between open and closed configurations of the vocal tract. Speech requires fine control of physiological processes extending from the lungs to the lips, made all the more complicated because components of the vocal system also serve critical functions unrelated to speech (e.g., breathing, feeding, and facial expression).

Like any complex motor activity, speech is subject to disruptions at many levels due to both congenital and acquired deficits, including those leading to syndromes like dysarthria, apraxia, dysphonia, and stuttering [Kent, 2000]. Chronic developmental stuttering is a speech disorder characterized by involuntary syllable repetitions and prolongations, especially during connected speech, thereby impairing normally fluent speech. This disorder provides a fascinating disease model of speech production not only because of its high prevalence in the population (approximately 1%) but because of its marked gender ratio (3:1 ratio of men:women), probable genetic basis, and responsiveness to environmental stimuli [Bloodstein, 1995]. There is a high rate of recovery in

*Correspondence to: Roger J. Ingham, Department of Speech and Hearing Sciences, University of California Santa Barbara, Santa Barbara, CA 93106. E-mail: rjingham@speech.ucsb.edu

Received for publication 7 February 2005; Accepted 8 February 2005
DOI: 10.1002/hbm.20140
Published online in Wiley InterScience (www.interscience.wiley.com).

children, but stuttering that persists into adolescence or adulthood is much more resistant to recovery [Ingham, 2001a]. Although the core pathology underlying developmental stuttering remains poorly understood, much research has effectively excluded the peripheral vocal system as the cause of the disorder and has instead placed the focus on the central nervous system (CNS). One of the main pieces of evidence for this is that stuttering can be eliminated almost immediately although temporarily by simple manipulations that have no direct effect on the vocal system itself but that almost certainly affect a central planning mechanism. These manipulations, known as fluency-inducing conditions, include oral reading along with another speaker (so-called chorus reading), auditory masking, singing, reading to the accompaniment of a real or imagined rhythmic stimulus, among several others [Bloodstein, 1995]. Importantly, the most effective fluency-inducing mechanisms involve either auditory stimulation or changes to the customary speech pattern [Ingham, 1984]. The fact that simple manipulations like hearing another speaker say the words to be read are so effective in eliminating stuttering strongly suggests that the pathology can be neither with the vocal organ itself nor with the proximal motor mechanism but instead at a locus closer to the level of vocal planning and initiation. Finally, stuttering is distinct from other speech-motor disorders in being more or less specific for speech, in comparison to syndromes such as dysarthria that tend to be part of generalized syndromes affecting motor control throughout much of the body [Kent, 2000]. The cause of chronic developmental stuttering remains unknown, resulting in a plethora of competing theories [Ingham, 2001a].

Neuroimaging studies have provided focus to the debate regarding the causation of stuttering by identifying functional and structural differences between the brains of stutterers and nonstutterers. Three general classes of functional neuroimaging findings have emerged: (1) overactivation of cortical motor areas, such as the primary motor cortex and supplementary motor area; (2) anomalous lateralization, such that speech-related brain areas that typically have left-hemisphere dominance in fluent speakers are active bilaterally or with right-hemisphere dominance in stutterers; and (3) auditory suppression such that primary and secondary auditory areas that are normally active during speech production are not activated [Fox, 2003; Ingham, 2001b]. Finally, anatomical imaging methods have pointed to structural abnormalities in the left hemisphere of developmental stutterers occurring in regions such as the superior temporal gyrus [Foundas et al., 2001] and Rolandic operculum [Sommer et al., 2002], again supportive of suggestions that stuttering may have a genetic basis. Stuttering can therefore provide a unique opportunity for understanding the neural basis of speech production by permitting the examination of correlations between speech production, brain activity, and brain anatomy [Fox, 2003].

Meta-analysis is an important means of examining the concordance of results across a corpus of studies and extracting the most significant and best-supported findings from these studies. Imaging studies of stuttering have been relatively few in number and have been mainly restricted to the oral reading of sentences or paragraphs rather than the types of spontaneous speech behaviors that prompt stuttering in everyday situations. Ingham [2001b] attempted to find regional commonalities among five positron emission tomography (PET) studies using a traditional tabulation of label-reported regional activations and deactivations from these studies. This analysis found partially overlapping abnormal activations in three of five studies in the supplementary motor area (SMA) and anterior insula, as well as abnormal deactivations in auditory association areas. A second meta-analysis, that included performance-correlation analyses of PET studies and more restrictive comparison criteria [Ingham, 2004], found partial overlap in these regions but greater agreement when task and image-analysis methods were matched across studies. Both studies were limited methodologically being tabular, "label-based" meta-analyses. Tabular meta-analyses suffer from poor spatial precision and high variability in labeling brain regions in different publications [Laird et al., 2005b]. Coordinate-based, voxel-wise meta-analysis [Chien et al., 2002; Turkeltaub et al., 2005; Wager et al., 2003] offers a powerful alternative to label-based meta-analyses by deriving statistical whole-brain images of convergence across a corpus of studies. These methods have been applied to normal speech production [Chien et al., 2002; Turkeltaub et al., 2002], but have not been applied previously to studies of abnormal subjects and more specifically have not been applied in stuttering.

We apply the activation likelihood estimation (ALE) method to stuttered speech production and concurrently to fluent speech production, using data published on normal control subjects in the stuttering literature. None of the normal-subject data had been utilized previously in meta-analyses of speech production [Fiez and Petersen, 1998; Indefrey and Levelt, 2000, 2004; Turkeltaub et al., 2002], offering a replication of these meta-analyses and a within-study control for stuttering subjects. The objective of these parallel analyses is to understand the neurophysiological basis of stuttering by reference to normal speech. An additional, more technical reason for carrying out voxel-wise meta-analyses of stuttered and fluent speech production is to use the high spatial resolution of these methods (compared to label-based meta-analyses) to define volumes of interest (VOIs) that can then be used to constrain network models of these systems. By limiting the data sets to data-driven VOIs, network-oriented analytical techniques can be applied to raw data (e.g., using structural equation modeling) [McIntosh and Gonzalez-Lima, 1994] and to coordinate-based meta-data (e.g., using replicator dynamics and related methods) [Neumann et al., this issue; Lancaster et al., this issue]. This has special relevance for pathological conditions such as stuttering [Fox, 2003] in which the breakdown of function most likely occurs at the level of functional systems rather than at the level of individual brain areas.

TABLE I. Studies included in the meta-analysis

Reference	Modality	n	Gender	Vocal task	Control	Stutter
Fox et al., 1996	PET	10/10	M	Paragraph reading	Rest	Yes
Braun et al., 1997	PET	18/20	M/F	Spontaneous narrative + Sentence construction	Orolaryngeal control	Yes
				Correlations w/dysfluency		Yes
Fox et al., 2000	PET	10/10	M	Correlations w/stutter rate		Yes
De Nil et al., 2000	PET	10/10	M	Word reading	Silent reading	No
De Nil et al., 2003	PET	13/10	M	Word reading	Visual baseline	No
Neumann et al., 2003	fMRI	16/16	M	Sentence reading	Visual baseline	No
Preibisch et al., 2003	fMRI	16/16	M	Sentence reading	Visual baseline	No
Ingham et al., 2004	PET	10/10	F	Correlations w/stutter rate		Yes

Eight studies were included in the two ALE meta-analyses. For n, the first number represents the number of *stutterer* subjects, and the second number represents the number of fluent *control* subjects. All studies except that of Braun et al. [1997] had subjects of one gender. Three studies [Braun et al., 1997; Fox et al., 2000; Ingham et al., 2004] include performance correlations with stuttering/dysfluency rate. Only half of the studies elicited stuttering in the stuttering subjects. Those happened to be the ones that employed the more extensive reading/speaking tasks, such as paragraph reading or spontaneous narration. For Braun et al. [1997] and Ingham et al. [2004], the correlation data contributes exclusively to the stuttering meta-analysis. For Fox et al. [2000], positive correlations with syllable rate are used for the control subjects as well.

MATERIALS AND METHODS

Inclusion Criteria for Articles

Two parallel meta-analyses of eight studies were carried out using ALE analysis, one with the stutterer subjects and one with the control subjects (Table I). The same set of tasks and contrasts was used for both groups, making the two analyses overall comparable (but see caveats in following paragraph). None of these studies had been included in the three previous meta-analyses of speech production [Fiez and Petersen, 1998; Indefrey and Levelt, 2000, 2004; Turkeltaub et al., 2002]. Although the stuttering literature is quite small, several articles were excluded from the meta-analysis. Our inclusion criteria were that: (1) the studies presented coordinate-based analyses of the data; (2) all or most of the brain was imaged; and (3) overt speech was used as part of the task. Using these criteria, the following stuttering articles had to be excluded: Wu et al. [1995] and Van Borsel et al. [2003] because neither reported spatial coordinates for brain locations; De Nil et al. [2001], because only a fraction of the brain was imaged; and Ingham et al. [2000], because only covert speech was employed. As an aside, gender was not a factor in this meta-analysis. Most articles looked at male subjects in both groups (see Table I), and so the meta-analysis has a disproportionate emphasis on male brains. As stuttering mechanisms seem quite variable across the genders [Ingham et al., 2004], it will be important that future studies address gender effects in greater detail.

In addition to including foci for brain activations, the meta-analyses include voxels showing positive correlations with either stuttering rate (stutterers) or syllable rate (controls) during connected speech. For Fox et al. [2000], comparable correlation data was present for both groups. For Braun et al. [1997] and Ingham et al. [2004], correlation data was presented only for the stutterers. Because Braun et al. [1997] included activation data (but not performance correlations) for the controls, it contributed coordinates to the analysis of the controls. The study of Ingham et al. [2004], based on correlations only, was the one article that contributed coordinates exclusively to stutterers and not controls. Finally, no deactivations or negative correlations were examined in this study, mainly because the number of foci across the eight studies was insufficient to do a reliable analysis.

ALE Analysis

Coordinates from conditional contrasts or performance correlations were taken from the original publications. Montreal Neurological Institute (MNI) coordinates were converted to Talairach coordinates using the Brett transform [Brett, 1999]. ALE meta-analysis was carried out on this data as described by Turkeltaub et al. [2002], using a full-width at half-maximum (FWHM) of 10 mm as based on a modification of Laird et al. [2005b]. Statistical significance was determined using a permutation test of randomly distributed foci. Five thousand permutations were computed using the same FWHM value and the same number of foci used in computing the ALE values. The test was corrected for multiple comparisons using the false discovery rate (FDR) method [Genovese et al., 2002]. All data processing was carried out using an in-house Java version of ALE developed at the Research Imaging Center (available at http://brainmap.org/ale). The ALE maps presented in Figure 1 are shown overlaid onto an anatomical template generated by spatially normalizing the International Consortium for Brain Mapping (ICBM) template to Talairach space [Kochunov et al., 2002].

Between-Group ALE Comparison

To create a comparison between the ALE maps for the stutterers and controls, their respective ALE maps were subtracted from one another and a permutation test was run on the subtracted maps to obtain the appropriate threshold

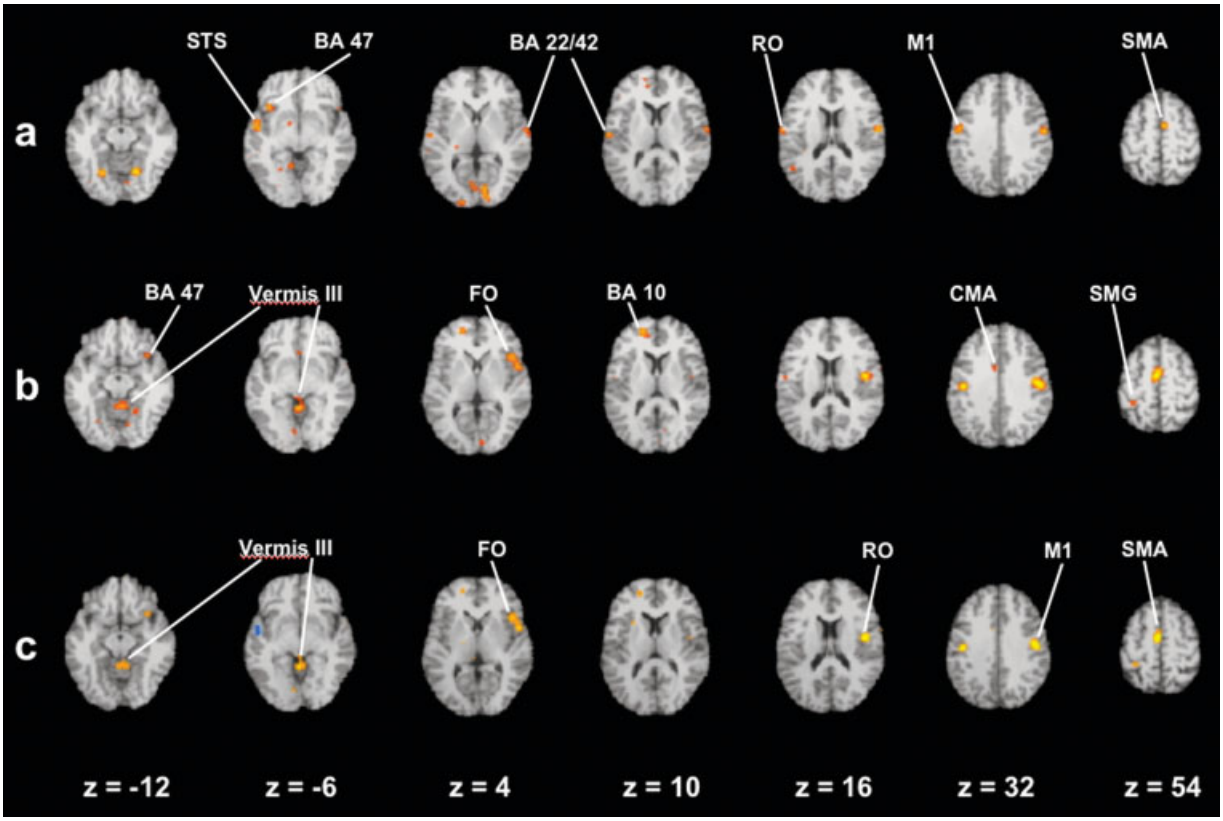

Figure 1.

Axial slices demonstrating major ALE foci from the two meta-analyses. **a:** Major ALE foci for the fluent controls. Principal sites of activation are labeled; bilateral cortical activations are labeled on only one side of the brain. **b:** Major ALE foci for the stuttering subjects. The labels highlight activations seen uniquely in the stuttering group. **c:** Group comparison of the ALE foci from the two groups. For this panel only, orange indicates stutterers > controls, and blue indicates controls > stutterers (the latter seen only for the superior temporal sulcus). Labels highlight the vocal-motor areas shown by the meta-analysis to have large cross-laboratory concordance. The bilateral auditory areas, present in controls but absent in the stutterers, are below threshold in the group comparison. The Talairach coordinates for the slices are shown at the bottom of the figure. The same set of seven slices is shown in all three panels. The left side of a slice is the left side of the brain. The threshold for all analyses is $P < 0.05$. STS, superior temporal sulcus; RO, Rolandic operculum; M1, primary motor cortex; SMA, supplementary motor area; Vermis III, the medial portion of lobule III of the cerebellum; FO, frontal operculum/anterior insula; SMG, supramarginal gyrus; CMA, cingulate motor area.

for significance ($P < 0.05$), as described in Laird et al. [2005b].

Region-of-Interest Analysis of ALE Clusters

Once the two ALE meta-analyses for the studies were complete, the BrainMap database (www.brainmap.org) was searched to determine the foci from the original datasets that were located within a region-of-interest (ROI) that was defined by the extent of various clusters from the two meta-analyses. Eleven clusters that showed interesting between-group differences were subjected to ROI analysis. The bounding box of the ROIs was obtained from the ALE map ($P < 0.05$). Once the coordinates that fell within the bounding box were determined, they were inspected to verify the ones that actually fell within the appropriate cluster border.

RESULTS

Two ALE meta-analyses were carried out using activation data or performance correlations for the same tasks in both groups (but see caveats in the Methods section). In total, 154 foci were analyzed for stutterers and 73 for controls. This markedly larger number of foci for stutterers compared to that for controls is in agreement with virtually all imaging studies in the stuttering literature, showing more areas of activation and a wider distribution of these areas for stutterers relative to controls when performing the same tasks. Such differences are seen even when behavioral performance is equated across groups, such as when fluency-inducing manipulations (e.g., chorus reading and treatment programs) are employed to eliminate stuttering [Fox et al., 1996; Ingham et al., 2003; Neumann et al., 2003].

TABLE II. Major ALE foci for the fluent control subjects

Lobe	Region	x	y	z	ALE ($\times 10^3$)	Size (mm^3)
Frontal						
Left	Primary motor cortex (4/6)	−49	−9	32	13.43	2,128
	Inferior frontal gyrus (47)	−36	19	−6	8.15	408
	Prefrontal cortex (10)	−12	49	12	6.90	248
Right	Primary/premotor cortex (4/6)	54	−10	34	11.90	2,312
	Rolandic operculum (4/43)	56	−8	20	11.80	SC
	Supplementary motor area (6)	5	−2	57	11.91	664
Temporal						
Left	Superior temporal sulcus (22/21)	−51	−3	−5	9.19	888
	Superior temporal gyrus (42)	−58	−13	11	8.55	792
Right	Superior temporal gyrus (22)	62	−8	8	7.90	SC
Occipital						
Left	Cuneus (17)	−18	−94	1	7.27	488
	Lingual gyrus (19)	−10	−51	−3	8.13	432
	Lingual gyrus (18)	−4	−75	4	7.19	336
	Lingual gyrus (19)	−24	−57	−4	6.65	104
Right	Lingual gyrus (17)	11	−84	5	8.24	752
Cerebellum						
Left	Lobule VI	−22	−63	−16	12.33	1,096
Right	Lobule VI	18	−62	−15	13.48	1,128
	Vermis VI	4	−71	−15	7.05	344

The 17 principal ALE clusters derived from the analysis with the control subjects. After each anatomical name in the region column is the Brodmann area (BA) in parentheses. The columns labeled as x, y, and z are the Talairach coordinates for the weighted center of each cluster. The ALE score shown is the true value multiplied by 10^3. The right column shows the size (in mm^3) of each cluster. The two right-hemisphere clusters labeled as SC in the size column (namely, 57, −9, 20 and 62, −8, 8) are derived from the right primary motor cortex cluster at 54, −10, 34, having a cluster size of 2,312 mm^3. The Rolandic operculum is listed here in the frontal lobe, although it is listed for the stuttering subjects in the parietal lobe due to a slight difference in the location of the weighted center of the cluster.

Fluent Controls

ALE images for the fluent controls are presented in Figure 1a, and the ALE scores and cluster sizes for these locations are presented in Table II. The analysis shows that most core areas of the vocal-control system highlighted in the previous meta-analyses of single-word oral reading are present, even though the analyses have no overlap in the literature covered. The main areas include the primary motor cortex, SMA, premotor cortex, Rolandic operculum (Brodmann area [BA] 4/43), left inferior frontal gyrus (BA47), cerebellar hemispheres (principally lobule VI), and bilateral auditory association areas. Primary and secondary visual areas (BA17/18/19) were also seen, reflecting the use of written text as a stimulus. No activity was seen in the frontal operculum or anterior insula. Finally, the one part of the basal ganglia showing a significant ALE score was the inferior part of the left globus pallidus (seen in Fig. 1a at slice level $z = -6$). This focus is not listed in Table II because it did not meet our cluster-volume criterion of 100 mm^3.

Stutterers

The results with the stutterers performing the same tasks are shown in Figure 1b and Table III, and a color-coded comparison between the stuttering group and control group is shown in Figure 1c. From a qualitative standpoint, virtually all areas seen in the ALE analysis with fluent controls were present in the analysis with stutterers, including the primary motor cortex, premotor cortex, SMA, Rolandic operculum, cerebellar hemispheres, visual association cortex, and prefrontal cortex (BA10). At a basic level, the same set of core areas involved in vocal production of read text was therefore seen in parallel in both meta-analyses. Within that core most vocal-motor areas showed larger ALE scores and cluster sizes in stutterers compared to that in controls, as highlighted in Figure 1c. Such was the case in the SMA, primary motor cortex (BA4/6), right Rolandic operculum, and cerebellar vermis (lobule VI). In fact, the strongest and largest focus in the entire analysis was seen in the right primary motor cortex for the stutterers. It was both larger and stronger than was that for the controls, and larger and stronger than the left-hemisphere coordinates were for the primary motor cortex for either group.

Next, a series of brain areas not seen in the fluent controls was found to have large concordance in the stutterers, most notably the right frontal operculum/anterior insula, left cingulate motor area, cerebellar vermis of lobule III, supramarginal gyrus bilaterally, and frontal eye fields (BA8). The most striking of this group was the right frontal operculum bordering on the anterior insula (BA45/13), which achieved both a large ALE score and a large cluster size in stutterers but had no counterpart in the control subjects. In addition, the absence of activation in the auditory association cortex (BA22/42) bilaterally in

TABLE III. Major ALE foci for the stuttering subjects

Lobe	Region	x	y	z	ALE ($\times 10^3$)	Size (mm^3)
Frontal						
Left	Supplementary motor area (6)	−2	−5	54	16.40	1,664
	Primary motor cortex (4)	−45	−16	31	15.70	1,016
	Prefrontal cortex (10)	−16	49	9	13.37	1,008
	Cingulate motor area (24)	−6	8	35	9.16	256
Right	Primary motor cortex (4)	48	−12	32	18.18	4,112
	Frontal operculum/insula (45/13)	47	13	2	14.14	1,904
	Inferior frontal gyrus (47)	35	16	−15	11.88	384
	Superior frontal gyrus (8)	17	24	47	10.37	616
	Premotor cortex (6)	35	13	46	8.62	432
	Anterior cingulate (32/24)	0	21	−8	8.21	184
Parietal						
Left	Supramarginal gyrus (40)	−31	−40	55	9.21	216
	Rolandic operculum (43/4)	−54	−7	15	8.50	192
Right	Rolandic operculum (43/4)	44	−6	16	17.40	SC
	Supramarginal gyrus (40)	36	−38	49	10.52	296
Occipital						
Left	Lingual gyrus (18)	−7	−75	−7	9.65	240
Right	Fusiform gyrus (19)	20	−55	−14	9.16	288
	Lingual gyrus (17)	5	−86	5	8.18	200
Temporal						
Left	Superior temporal gyrus (22)	−56	−24	1	8.84	208
Cerebellum						
Left	Lobule VI	−37	−62	−25	12.54	912
	Lobule VI	−24	−64	−17	11.98	712
Right	Vermis III/IV	3	−46	−11	14.45	2,304
	Lobule VI	12	−68	−17	13.91	848
	Vermis VI	0	−70	−25	10.37	440

The 23 principal ALE clusters derived from the analysis with the stuttering subjects. After each anatomical name in the region column is the Brodmann area in parentheses. Columns labeled as x, y, and z are the Talairach coordinates for the weighted center of each cluster. The ALE score shown is the true value multiplied by 10^3. The right column shows the size (in mm^3) of each cluster. The right parietal cluster labeled as SC in the size column (namely, 44, −6, 16) is derived from the right primary motor cortex cluster at 48, −12, 32, having a cluster size of 4,112 mm^3. The Rolandic operculum is listed here in the parietal lobe, although it is listed for the control subjects in the frontal lobe due to a slight difference in the location of the weighted center of the cluster.

the stutterers was notable. This absence can be seen in comparing the stutterers and controls in Figures 1b and 1a, respectively; however, this difference did not achieve significance in the group comparison, as shown in Figure 1c. Finally, the weak left globus pallidus activation seen with controls was not seen with stutterers, nor was any other part of the basal ganglia seen to be active. Overall, the comparison of the two meta-analyses demonstrates the presence of a common core of vocal-motor areas for both groups but with the additional occurrence in stutterers of the following: (1) overactivations in these areas; (2) anomalous right-dominant lateralization in these areas; (3) additional areas of activation (motor and nonmotor) not seen in the controls (e.g., frontal operculum and vermis III); (4) an absence of auditory activations bilaterally; and (5) an absence of basal ganglia activations.

Region-of-Interest Analysis

Table IV presents an ROI analysis of the significant ALE foci for stuttering subjects with regard to each of eight studies included in the meta-analysis. Eleven major clusters showing significant between-group differences were analyzed. As can be seen at the top of the table, four major laboratories contributed to this literature, as represented by city: San Antonio, Bethesda, Toronto, and Frankfurt. The critical finding from this analysis is that most of the core vocal areas, including the primary motor cortex, frontal operculum, Rolandic operculum, cingulate motor area, and cerebellar vermis III, have contributions from three of four lab groups. This is also the case for the right-lateralized motor activations in the primary motor cortex, frontal operculum, and Rolandic operculum. SMA activation was seen by only two groups; it was not scored for Braun et al. [1997] because their SMA activation sat 10 mm lateral to the peak coordinate in our analysis.

In contrast to this picture, activation in several areas outside of the core vocalization centers came principally from one or two groups, perhaps reflecting specific features of their design or analysis. As shown in the lower part of Table IV, areas such as the frontal eye fields (BA8), supramarginal

TABLE IV. Region-of-interest (ROI) analysis for the stuttering data

	San Antonio			Bethesda	Toronto		Frankfurt	
Region	Fox (1996)	Fox (2000)	Ingham (2004)	Braun (1997)	De Nil (2000)	De Nil (2003)	Prebeisch (2003)	Neumann (2003)
L motor cortex	+		+			+		
R motor cortex	+	+	+			+	+	+
SMA	+	+	+		+			
R frontal operculum	+	+	+			+	+	+
R Rolandic operculum	+	+				+	+	+
Cerebellar vermis III	+	+		+		+		
Cingulate motor area			+		+			
R frontal eye field				+			+	+
R inferior frontal (BA47)							+	+
L prefrontal (BA10)				+				
L supramarginal							+	

The eleven principal ALE foci from the stuttering analysis in the left column and the eight publications contributing to the meta-analysis along the top of the remaining columns. The eight publications come from four different laboratories, as shown by the city names listed along the top of the figure. A plus sign (+) indicates that a given publication registered an activation in the brain area listed in that row. SMA, supplementary motor area.

gyrus (BA40), and anterior inferior frontal gyrus (BA47) came principally from the Frankfurt group. Likewise, the prefrontal cortex (BA10) came exclusively from Braun et al. [1997], perhaps reflecting their unique use of formulated narratives rather than reading tasks, thereby activating brain areas for working memory and language generativity.

DISCUSSION

The results of these two ALE meta-analyses shed light on the neural basis of normal speech production and on differences between the underlying mechanisms of fluent and stuttered speech. In the case of stuttering, the use of a voxel-based meta-analysis method provides a statistical rigor and spatial precision not attained by the previous tabular meta-analyses of stuttering. This should serve as a stimulus for future investigations into interactions among ROIs identified by the meta-analyses, using network analyses such as structural equation modeling [McIntosh and Gonzalez-Lima, 1994] and replicator dynamics [Neumann et al., this issue; Lancaster et al., this issue]. In the following discussion, the meta-analysis findings are considered with respect to fluent speech and stuttered speech in sequence.

Fluent Speech: Core Areas for Speech Production

The meta-analysis with the fluent subjects presented a picture of the brain areas important for normal speech production very similar to that seen in the two previous label-based meta-analyses of single-word reading [Fiez and Petersen, 1998; Indefrey and Levelt, 2000, 2004] as well as one voxel-based meta-analysis [Turkeltaub et al., 2002]. In fact, an inspection of the Talairach coordinates of activations in motor cortex, SMA, cerebellum, and auditory areas in our meta-analysis showed a substantial overlap with those of Turkeltaub et al. [2002] for these regions, despite the fact that no studies were common between the two analyses. These findings add support to our contention that there is a set of core areas critically important for speech production. The primary motor cortex, premotor cortex, SMA, frontal operculum, anterior insula, Rolandic operculum, cingulate motor area, basal ganglia (putamen and globus pallidus), and quadrangular lobule (lobule VI) of the cerebellum thus comprise a highly consistent set of areas activated for speech production. Likewise, the primary and secondary auditory cortices are activated reproducibly in overt reading tasks. Interestingly, this same overall set of areas is activated during wordless singing [Brown et al., 2004; Perry et al., 1999; Riecker et al., 2000], thus arguing that these areas play a general role in the control of voluntary vocalization rather than in speech alone. Based on the results of these four meta-analyses of speech production, it seems unlikely that other brain areas beyond those described herein will be found to be major components of the motor-sensory system for vocalization. Other areas seen to be active in the current meta-analysis are most likely related to nonvocal aspects of the reading tasks analyzed. For example, primary and secondary visual areas are most likely related to the use of read text as the stimulus for speech. Moreover, the activation in left BA47 might be related to lexical rather than vocal aspects of the task, as this area has been found to be active in covert picture-naming and verb-generation tasks [e.g., Thompson-Schill et al., 1999] as well as in general semantics tasks [Dapretto and Bookheimer, 1999; Preibisch et al., 2003]. In addition, BA47 is not a consistent area of activation across the four meta-analyses of speech production (see below).

Stuttering: Concordance Across Studies

As this is the first coordinate-based meta-analysis of stuttered speech, the parallel comparison with fluent speech

provides an unprecedented opportunity to examine the pathology of stuttering. The stuttering neuroimaging literature is relatively small, yet a high degree of concordance across studies emerged when meta-analysis was carried out, thereby paving the way for establishing neural signatures of stuttering. In addition, these findings show more consistency than the earlier label-based analyses do, while at the same time validate the earlier observations of abnormal activation in the right frontal operculum/anterior insula and cerebellum coupled with deactivation in right auditory association areas [Ingham, 2001b, 2004]. The following examines a series of effects related to the neurobiology of stuttering. The most general effect is the overall increase in the number of activated brain areas in stutterers compared to that in fluent subjects carrying out the same tasks, and the more widespread distribution of these activated areas in the brain. Although such an observation does not lend itself readily to interpretation, it does show that the meta-analysis provides an accurate picture of what virtually all the imaging studies have demonstrated individually.

The series of core areas comprising the vocal system in the fluent controls was also seen in the meta-analysis of stuttering, including the primary motor cortex, premotor cortex, SMA, Rolandic operculum, and cerebellum (hemispheres and vermis of lobule VI). Stuttered speech therefore depends, at least to a large degree, on the same series of core areas important for speech in general. This is in contrast to a model in which stuttering might occur through some alternative vocalization route (e.g., cingulate vocalization areas). But beyond this general level of commonality, three points of difference are observed. First, compared to the results with the fluent controls, there is an increase in activation in lateral vocal-motor areas (especially in the right hemisphere) and decrease in activation in auditory areas (bilaterally). Second, this is accompanied by a laterality shift that brings the balance of activity toward the right hemisphere, i.e., through a reduction of activity in left-hemisphere areas (primary motor cortex, auditory cortex, and Rolandic operculum) and an increase in activity in right-hemisphere areas (frontal operculum and Rolandic operculum). This general pattern of brain activity emerges as a rightward shift in cerebral activation. This is consistent with the findings of numerous preimaging studies of developmental stuttering [see Moore, 1993]. Finally, there is prominent overactivity in three medial motor structures: SMA, cingulate motor area, and cerebellar vermis (both lobules VI and III).

An important objective of a meta-analysis is not only to provide a picture of concordance across a corpus of studies but a sense of which studies find activations in which areas, and to attempt to correlate them with task-specific effects [see Laird et al., 2005a]. The critical finding from the ROI analysis was that most core vocal areas, including the primary motor cortex, frontal operculum, Rolandic operculum, cingulate motor area, and cerebellar vermis, had contributions from three of four lab groups. Importantly, this was also the case for the right-lateralized motor activations in the primary motor cortex, frontal operculum, and Rolandic operculum. SMA activation was seen by only two groups; it was not scored for Braun et al. [1997] because their SMA activation sat 10 mm lateral to the peak coordinate in our analysis. In contrast to this picture, activation in several areas outside of the core vocalization centers came principally from one or two groups, including the prefrontal cortex (BA10), the frontal eye fields (BA8), supramarginal gyrus (BA40), and anterior inferior frontal gyrus (BA47). Activity in right BA47, in particular, was argued by Preibisch et al. [2003] to be a negative correlate of stuttering severity. Comparable activity in this area was seen by them in both a visual semantics task and a reading task, therefore arguing that the role of right BA47 was tied more closely in with semantics function than with vocalization (see above). In any case, this area did not show strong concordance across the studies in the meta-analysis.

The overall picture from the ROI analysis was a robust concordance across laboratories in the core motor areas and lesser concordance outside of these areas. This is perhaps the most desirable outcome that the meta-analysis could have provided for the stuttering field. This result was not influenced by the presence or absence of stuttering in a particular study. The effect was seen in studies that both elicited stuttering (the San Antonio and Bethesda studies) and those that did not (the Toronto and Frankfurt studies). The meta-analysis was thus more successful at providing a general picture of a stutterer phenotype than at pinpointing a profile of activity uniquely associated with stuttered speech. Clearly, a much larger corpus of studies is needed to dissect such effects.

Neural Signatures of Stuttering

Whereas several of the stuttering effects described above involved relative changes in activity or laterality between stutterers and fluent controls, the meta-analyses highlighted three neural signatures that seemed more or less specific to the stuttering group: (1) overactivation in the right frontal operculum/anterior insula; (2) absence of activation in auditory areas bilaterally; and (3) overactivation in the vermal region of lobule III of the cerebellum. These three signatures will now be described in more detail.

Activity in the right frontal operculum/anterior insula (BA45/13) stood out as being unique in our analysis in two respects. First, unlike other lateral motor areas such as the primary motor cortex and Rolandic operculum, activity was found exclusively in the right hemisphere. Second, again unlike the primary motor cortex and Rolandic operculum, activity was found uniquely in the stutterers. In the dataset of Fox et al. [1996], activation in the frontal operculum/insula was much higher during stutter-filled solo reading than during stutter-free chorus reading. Moreover, in the treatment study of Neumann et al. [2003], activation was present before treatment but was eliminated after treatment. Activity in this right-hemisphere region during reading tasks therefore may be a strong marker of stutterer status.

Although the frontal operculum of the left hemisphere has well-established functional linkages with speech [Ackermann and Riecker, 2004] and language processes [Friederici et al., 2000], and even with manual imitation [Iacoboni et al., 1999], the functional role of the right frontal operculum is far more elusive. Results from several lines of research suggest that one common link may be the processing of vocal fundamental frequency during both production and perception. Activity in the right frontal operculum and anterior insula are prominent during wordless singing tasks [Perry et al., 1999; Riecker et al., 2000], including vocal imitation of pitch sequences [Brown et al., 2004]. Regarding speech, activity in the right frontal operculum and anterior insula is associated most closely with prosody tasks. For example, Hesling et al. [2004] found right-sided BA44 activity when they contrasted "expressive" presentation of a 30-s reading passage with a "flat" presentation in which the fundamental frequency contours were reduced greatly. Likewise, Meyer et al. [2004] demonstrated activation in the right frontal operculum (BA44) when subjects listened to degraded speech stimuli that preserved the intonational (melodic) properties but not segmental properties of speech, as contrasted to normal speech. Wildgruber et al. [2004] found bilateral activations in the frontal operculum on discrimination tasks for both affective and linguistic prosody; their right-hemisphere activations were located in BA45/46. Much neuropsychological evidence suggests that the right hemisphere may be dominant for production and perception of affective speech prosody [reviewed in Wymer et al., 2002]. Production and perception of vocal fundamental frequency therefore seems mediated, at least in part, by the right frontal operculum/anterior insula. Abnormal activity in this region might contribute to aberrant phonological processing in stuttering. Another point relevant to aberrant phonology is the strong inhibition of auditory areas during oral reading (see below). In classical models of speech production, the frontal operculum is the recipient of projection fibers originating in the posterior part of the superior temporal gyrus that travel through the superior longitudinal (arcuate) fasciculus to the frontal lobe [Catani et al., 2002]. Overactivation of the right frontal operculum coupled with inhibition of right (and left) auditory areas therefore might represent a disrupted functional connectivity between auditory and motor areas during speech planning in stutterers. Another reason for highlighting the importance of frontal operculum/anterior insula to stuttering is the evidence that it is also abnormally active (bilaterally) in Tourette's syndrome and that tic frequency may correlate with activity in this and other speech-related regions [Stern et al., 2000]. Tourette's syndrome has been related frequently to developmental stuttering because of its similar developmental pattern, responsiveness to related stimuli, and comorbidity with stuttering [Comings and Comings, 1994; Abwender et al., 1998].

The second important signature of stuttering is the reduction in activity in auditory areas during vocalization tasks, especially because all previous meta-analyses of vocal production, as well as our own meta-analysis with the control group, showed prominent and generally bilateral activations during overt speech. The inhibitory effect in stutterers was difficult to assess with the ALE meta-analysis, because it did not include deactivations or negative correlations [Ingham, 2001b]. It is therefore important to consider the literature suggestions of a fundamental abnormality in auditory areas during overt reading tasks, as compared to fluent controls. Fox et al. [1996] was the first study to show that stutterers have marked reductions in superior temporal lobe activations, and even deactivations, during reading tasks. This was followed up by data showing negative correlations between stuttering rate and auditory activations in male [Fox et al., 2000] and female [Ingham et al., 2004] cohorts. Braun et al. [1997] showed not only bilateral deactivations in auditory areas in stutterers during dysfluency-inducing tasks but strong negative correlations between dysfluency and activation in right hemisphere auditory areas. In a study not included in the meta-analysis because it did not report coordinates, Van Borsel et al. [2003] found an absence of activations bilaterally in auditory areas in stutterers on an overt speech task for which controls demonstrated strong activations bilaterally. In De Nil et al. [2000], for the contrast of oral reading minus silent reading, nonstutterers showed only left auditory activations (BA22) whereas stutterers showed only right auditory activations, and the group comparison of nonstutterers minus stutterers had significant signal in left auditory association cortex. For the functional magnetic resonance imaging (fMRI) studies of Neumann et al. [2003] and Preibisch et al. [2003], only group comparisons were reported and thus it is more difficult to assess task-dependent auditory effects within groups. Neumann et al. [2003] reported that bilateral BA22 was more active in people who stuttered less severely than it was in those with more severe stuttering (based on clinical assessment), demonstrating that auditory activations seem to correlate negatively with stuttering severity. Stager et al. [2003] showed that activity in auditory areas bilaterally was greater during fluency-inducing than during dysfluency-inducing conditions, a result that parallels findings by Fox et al. [1996] on chorus reading. The only study to provide no indication of an auditory effect in stutterers is the treatment study of De Nil et al. [2003]. The nonstuttering control subjects in that study showed neither primary motor nor auditory activations during overt reading, and so the data with the stutterers might be equally difficult to interpret. Looking at the group comparison in the meta-analysis (Fig. 1c), the area that showed the largest inter-group difference (at z of -6) is a part of the superior temporal sulcus situated just anterior to those areas found to have voice-selective auditory representations [Belin et al., 2000, 2002]. In sum, the published literature supports a robust auditory inhibitory effect in stutterers, which is consistent with the meta-analysis results. The inhibition of auditory activity seems amplified by the amount of stuttering during a reading task and by clinical assessment of stuttering severity, and seems ameliorated by fluency-inducing manipulations and perhaps treatment. This might be one of the most distinctive markers of stut-

tering in the neuroimaging literature [Ingham, 2001b]. It remains an open question as to whether such auditory inhibitions occur only during self-produced speech or during auditory perception in general.

Third, activity in the vermal part of lobule III stood out as a unique activation in the stuttering group. Cerebellar activations during overt vocalization generally occur in lobule VI (the quadrangular lobule) and the associated vermis [Brown et al., 2004; Perry et al., 1999; Turkeltaub et al., 2002], as was seen in our meta-analysis with the control subjects (see Table II). For Fiez and Petersen [1998], midline cerebellar activity was seen slightly more anteriorly, in lobule V. In contrast to this, activity in lobule III was not generally seen with vocalization tasks in normal subjects; however, it seemed to be found with chronic developmental stutterers. In the dataset of Fox et al. [1996], the principal midline cerebellar activity for the stutterers was in vermis VI during stutter-free chorus reading; activity in vermis III was only seen during stutter-filled solo reading. Likewise, Braun et al. [1997] observed activity in vermis III during their stutter-filled dysfluency tasks but not during their stutter-free fluency tasks; no activity was detected in their control subjects. De Nil et al. [2003] observed activity in vermis III in their stutterer subjects before a treatment program but not at any point after treatment. Control subjects showed activity in lobule VI but not lobule III. These results overall suggest that activity in vermis III might not only be a marker for stutterer status but also one for stuttered speech as well. One point that raises doubts about the significance of vermis III for actual stuttering is that it did not show positive correlations with stutter rate in either the male or female cohorts in the San Antonio datasets [Fox et al., 2000; Ingham et al., 2004]. Correlations with the cerebellar midline were only seen with vermis VI. Vermis VI and the hemispheric portion of lobule VI have known somatotopic representations for the lips and tongue [Grodd et al., 2001]; therefore, their activation during oral reading tasks is readily explainable in terms of a motor map of the cerebellum. In contrast, vermis III does not have any functional properties attributed to it in somatotopy studies [Grodd et al., 2001]; therefore, its unique activation in stutterers during reading tasks is intriguing and in need of further investigation.

A comment about the basal ganglia is in order because this set of structures has been implicated in stuttering for many decades. Alm [2004], in reviewing a large literature about stuttering and the basal ganglia, proposed a model in which the core dysfunction of stuttering was suggested to be an "impaired ability of the basal ganglia to produce timing cues for the initiation" of speech motor activity (p. 325). Unfortunately, this proposal provided no predictions about whether particular nuclei/circuits of the basal ganglia would be over- or underactivated during stuttering. The meta-analysis data did not provide strong indications either favoring or opposing this model. Essentially, a weak globus pallidus activation seen with the controls was eliminated in the stutterers. This absence of basal ganglia effects is surprising given the established role of the left putamen in vocalization, both for speech [Klein et al., 1994; Turkeltaub et al., 2002; Wildgruber et al., 2001] and for song [Brown et al., 2004]. Perhaps the most basal ganglia-specific effect seen in the meta-analysis was the overactivation of the SMA (as well as cingulate motor area) in stutterers. The SMA is associated traditionally with internal generation of motor activity and is often activated during mental imagery tasks, including imagery of stuttered speech [Ingham et al., 2000]. An observation of SMA overactivation must be seen in light of the reading tasks carried out in the studies for the meta-analysis, which were very much externally cued (i.e., by the text to be read). The spontaneous narrative task in Braun et al. [1997] was perhaps the closest thing to an internally-cued speech task in the meta-analysis. They did in fact observe SMA activations (10 mm lateral to the ALE focus for the SMA), although at a reduced level in stutterers compared to that in controls. Although the basal ganglia may certainly be playing a contributing role in stuttering, this role is in need of elucidation in future studies.

Efference Copy: A Unifying Hypothesis

As stated previously, the three most salient characteristics of stuttering to emerge from this meta-analysis were overactivation in the right frontal operculum/anterior insula, absence of activation in auditory areas bilaterally, and overactivation in the vermal region of lobule III of the cerebellum. There are key questions to be addressed. Why are two of the abnormalities hyperactivity, whereas the third is underactivity? Are the three phenomena independent or linked? A tentative answer to both of these questions can be provided by invoking the phenomenon of efference copy, as follows.

Efference copy can be defined as a feed-forward projection of a motor plan, at the movement of movement-plan initiation onto the sensory system(s), in which perceptual feedback is anticipated to occur as a consequence of the movement. Efference copy was proposed initially in the context of perceptual constancy [von Holst and Mittelstaedt, 1950], i.e., that the visual scene remains continuous during eye movements. It has also been cited in explanation of the well-known observation that we cannot tickle ourselves [Blakemore et al., 1999; Weiskrantz et al., 1971]. The signal projected to the perceptual region receiving the efference copy is inhibitory, as the net effect is an attenuation of the perceptual response. For example, in the somatosensory system Leube et al. [2003] showed that "predictions generated in motor areas attenuate sensory areas." In the speech system, Houde et al. [2002], reported that, "during speech production, the auditory cortex (1) attenuates its sensitivity and (2) modulates its activity as a function of the expected acoustic feedback" (p. 1125). Others have reported similar effects using other imaging modalities [Curio et al., 2000; Numminen and Curio, 1999]. Such findings have led to the conclusion that efference copy applies to motor control in general [Haruno et al., 2001]. Max et al. [2004] have also considered its role in stuttering, albeit not as described below.

In stuttering, the most characteristic performance abnormality is the failure to properly initiate the speech-motor plan. This is not likely a defect of motor programming per se, as developmental stutterers do not exhibit dysarthria, oral dyspraxia, or other signs of an incorrect mental model of the desired movement, nor is this an abnormality of the motor execution system (motor cortex, basal ganglia, lower motor neurons), as there is no oral weakness, slowness, spasticity, tremor, or hypophonia. The problem is limited to successful initiation of the motor program. Importantly, stuttering is usually exhibited as a repetition of the initial sound of a word. In the context of efference copy, this would suggest that the perceptual prediction (of speech sounds) is being delivered repeatedly to the auditory system as an inhibitory signal that will attenuate the effects of any successful utterances. Furthermore, if stuttering is sufficiently severe, inhibition of auditory areas below baseline should occur and has been reported [Fox et al., 1996]. Efference copy thus can readily explain the noted lack of speech-related auditory activations in stutterers.

The motor-system overactivity observed in stuttering has two potential explanations. First, repeated initiation of the speech-motor plan likely repeatedly activates some components of the speech motor system, resulting in overactivation. Second, there is now considerable evidence that increased skill is associated with a concomitant decrease in activation [Jansma et al., 2001; Just et al., 1996; Raichle et al., 1994]. The converse is also true. Disease conditions that result in less competence in task performance are associated with regional over-activation [Bookheimer et al. 2001; Habib, 2000]. In stuttering, it is likely that both effects come into play. The right laterality of the motor region hyperactivity also deserves comment. Studies from two labs have suggested that developmental stuttering might be associated with a structural lesion in the left hemisphere [Foundas et al., 2001, 2003; Sommer et al., 2002]. In the presence of a left-hemisphere dysfunction, the right hemisphere assumes left-hemisphere tasks at which it is intrinsically less competent [Gandour et al., 2003, 2004], resulting in overactivation.

What, then, accounts for cerebellar overactivation? A fundamental aspect of the efference copy concept is that despite attenuation of the received sensory signal (in this instance, speech), there is self-monitoring that routinely compares the expected and the actual. The cerebellum has been implicated in the assessment of match between the predicted action and the actual sensory consequences [Blakemore et al., 2001]. The cerebellum has also been demonstrated to be involved in auditory discrimination [Petacchi et al., 2005]. Consequently, the repeated observation of cerebellar overactivation in stuttering may be associated not only with the motor overactivity (as part of the motor system), but a response to an action–consequence mismatch.

The preceding stuttering system model linking motor overactivity, auditory underactivity, and cerebellar overactivity lends itself to a network-based analysis. This could be accomplished either by structural equation modeling applied to raw data [Büchel et al., 1999; McIntosh and Gonzalez-Lima, 1994] or with one of the newly developed network-modeling strategies intended for meta-analysis [Neumann et al., this issue; Lancaster et al., 2005]. Both offer promising strategies for extending the present meta-analysis. The efference copy mechanism would predict an inverse relationship between right anterior insula and left auditory cortex. It would also predict a direct relationship between the cerebellar activity and the difference between right motor and left auditory cortex (i.e., if the cerebellar activity is the "discrepancy signal"). These effects should be present both on a study-by-study and on a trial-by-trial basis. These are both very testable predictions. In fact, the replicator dynamics [Neumann et al., 2005] and fractional similarity network analysis [Lancaster et al., 2005] methods can be applied to trial-by-trial data (i.e., to raw data) as well as to meta-analysis data.

REFERENCES

Abwender DA, Trinidad KS, Jones KR, Como PG, Hymes E, Kurlan R (1998): Features resembling Tourette's syndrome in developmental stutterers. Brain Lang 62:455–464.

Ackermann H, Riecker A (2004): The contribution of the insula to motor aspects of speech production: a review and a hypothesis. Brain Lang 89:320–328.

Alm PA (2004): Stuttering and the basal ganglia circuits: a critical review of possible relations. J Commun Disord 37:325–369.

Belin P, Zatorre RJ, Lafaille P, Ahad P, Pike B (2000): Voice-selective areas in human auditory cortex. Nature 403:309–312.

Belin P, Zatorre RJ, Ahad P (2002): Human temporal-lobe response to vocal sounds. Brain Res Cogn Brain Res 13:17–26.

Blakemore SJ, Frith CD, Wolpert DM (2001): The cerebellum is involved in predicting the sensory consequences of action. Neuroreport 12:1879–1884.

Bloodstein O (1995): A handbook on stuttering. San Diego: Singular Publishing Group. 596 p.

Bookheimer SY, Sojwas MH, Cohen MS, Saunders AM, Pericak-Vance MA, Mazziotta JC, Small GW (2000): Patterns of brain activation in people at risk for Alzheimer's disease. N Engl J Med 343:450–456.

Braun AR, Varga M, Stager S, Schulz G, Selbie S, Maisog JM, Carson RE, Ludlow CL (1997): Altered patterns of cerebral activity during speech and language production in developmental stuttering: An $H_2{}^{15}O$ positron emission tomography study. Brain 120: 761–784.

Brett M (1999): The MNI brain and the Talairach atlas, Cambridge Imagers. Online at http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html.

Brown S, Martinez MJ, Hodges DA, Fox PT, Parsons LM (2004): The song system of the human brain. Brain Res Cogn Brain Res 20:363–375.

Büchel C, Coull JT, Friston KJ (1999): The predictive value of changes in effective connectivity for human learning. Science 283:1538–1541.

Catani M, Howard RJ, Pajevic S, Jones DK (2002): Virtual in vivo interactive dissection of white matter fasciculi in the human brain. Neuroimage 17:77–94.

Chien JM, Fissell K, Jacobs S, Fiez JA (2002): Functional heterogeneity within Broca's area during verbal working memory. Physiol Behav 77:635–639.

Comings DE, Comings BG (1994): TS, learning, and speech problems. J Am Acad Child Adolesc Psychiatry 33:429–430.

Curio G, Neuloh G, Numminen J, Jousmaki V, Hari R (2000): Speaking modifies voice-evoked activity in the human auditory cortex. Hum Brain Mapp 9:183–191.

Dapretto M, Bookheimer SY (1999): Form and content: dissociating syntax and semantics in sentence comprehension. Neuron 24: 427–432.

De Nil LF, Knoll RM, Kapur S, Houle S (2000): A positron emission tomography study of silent and oral word reading in stuttering and nonstuttering adults. J Speech Lang Hear Res 43:1038–1053.

De Nil LF, Knoll RM, Houle S (2001): Functional neuroimaging of cerebellar activation during single word reading and verb generation in stuttering and nonstuttering adults. Neurosci Lett 302:77–80.

De Nil LF, Knoll RM, Lafaille SJ, Houle S (2003): A positron emission tomography study of short- and long-term treatment effects on functional brain activation in adults who stutter. J Fluency Disord 28:357–380.

Fiez JA, Petersen SE (1998): Neuroimaging studies of word reading. Proc Natl Acad Sci USA 95:914–921.

Foundas AL, Bollich AM, Corey DM, Hurley M, Heilman KM (2001): Anomalous anatomy of speech-language areas in adults with persistent developmental stuttering. Neurology 57:207–215.

Foundas AL, Corey DM, Angeles V, Bollich AM, Crabtree-Hartman E, Heilman KM (2003): Atypical cerebral laterality in adults with persistent developmental stuttering. Neurology 61:1378–1385.

Fox PT (2003): Brain imaging in stuttering: where next? J Fluency Disord 28:265–272.

Fox PT, Ingham RJ, Ingham JC, Hirsch TB, Downs JH, Martin C, Jerabek P, Glass T, Lancaster JL (1996): A PET study of the neural systems of stuttering. Nature 382:158–162.

Fox PT, Ingham RJ, Ingham JC, Zamarripa F, Xiong JH, Lancaster JL (2000): Brain correlates of stuttering and syllable production: a PET performance-correlation analysis. Brain 123:1985–2004.

Friederici AD, Meyer M, von Cramon DY (2000): Auditory language comprehension: an event-related fMRI study on the processing of syntactic and lexical information. Brain Lang 74:289–300.

Gandour J, Dzemidzic M, Wong D, Lowe M, Tong Y, Hsieh L, Satthamnuwong N, Lurito J (2003): Temporal integration of speech prosody is shaped by language experience: an fMRI study. Brain Lang 84:318–336.

Gandour J, Tong Y, Wong D, Talavage T, Dzemidzic M, Xu Y, Li X, Lowe M (2004): Hemispheric roles in the perception of speech prosody. Neuroimage 23:344–357.

Genovese CR, Lazar NA, Nichols TE (2002): Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage 15:870–878.

Grodd W, Hülsmann E, Lotze M, Wildgruber D, Erb M (2001): Sensorimotor mapping of the human cerebellum: fMRI evidence of somatotopic organization. Hum Brain Mapp 13:55–73.

Habib M (2000): The neurological basis of developmental dyslexia: an overview and working hypothesis. Brain 123:2373–2399.

Haruno M, Wolpert DM, Kawato M (2001): Mosaic model for sensorimotor learning and control. Neural Comput 13:2201–2220.

Hesling I, Clement S, Bordessoules M, Allard M (2004): Cerebral mechanisms of prosodic integration: evidence from connected speech. Neuroimage 24:937–947.

Houde JF, Nagarajan SS, Sekihara K, Merzenich MM (2002): Modulation of the auditory cortex during speech: an MEG study. J. Cog Neurosci 14:1125–1138.

Iacoboni M, Woods RP, Brass M, Bekkering H, Mazziotta JC, Rizzolatti G (1999): Cortical mechanisms of human imitation. Science 286:2526–2528.

Indefrey P, Levelt WJ (2000): The neural correlates of language production. In: Gazzaniga MS, editor. The cognitive neurosciences (2nd ed.). Cambridge, MA: MIT Press. p 845–865.

Indefrey P, Levelt WJ (2004): The spatial and temporal signatures of word production components. Cognition 92:101–144.

Ingham RJ (1984): Stuttering and behavior therapy: current status and empirical foundations. San Diego: College-Hill Press. 486 p.

Ingham RJ (2001a): Stuttering. In: Blakemore C, Jennett S, editors. The Oxford companion to the body. Oxford: Oxford University Press. p 659–660.

Ingham RJ (2001b): Brain imaging studies of developmental stuttering. J Commun Disord 34:493–516.

Ingham RJ (2004): Emerging controversies, findings, and directions in neuroimaging and developmental stuttering: on avoiding petard hoisting in Athens, Georgia. In: Bothe AK, editor. Evidence-based treatment of stuttering: empirical issues and clinical implications. Mahwah, NJ: Lawrence Erlbaum Associates. p 27–63.

Ingham RJ, Fox PT, Ingham JC, Xiong J, Zamarripa F, Hardies LJ, Lancaster JL (2004): Brain correlates of stuttering and syllable production: gender comparison and replication. J Speech Lang Hear Res 47:321–341.

Ingham RJ, Fox PT, Ingham JC, Zamarripa F (2000): Is overt stuttered speech a prerequisite for the neural activations associated with chronic developmental stuttering? Brain Lang 75:163–174.

Ingham RJ, Ingham JC, Finn P, Fox PT (2003): Towards a functional neural systems model of developmental stuttering. J Fluency Disord 28:297–317.

Jansma JM, Ramsey NF, Slagter HA, Kahn RS (2001): Functional anatomical correlates of controlled and automatic processing. J Cog Neurosci 13:730–743.

Just MA, Carpenter PA, Keller TA, Eddy WF, Thulborn KR (1996): Brain activation modulated by sentence comprehension. Science 274:114–116.

Kent RD (2000): Research on speech motor control and its disorders: a review and prospective. J Commun Disord 33:391–428.

Klein D, Zatorre RJ, Milner B, Meyer E, Evans AC (1994): Left putaminal activation when speaking a second language: evidence from PET. Neuroreport 21:2295–2297.

Kochunov P, Lancaster JL, Thompson P, Toga AW, Brewer P, Hardies J, Fox PT (2002): An optimized individual target brain in the Talairach coordinate system. Neuroimage 17:922–927.

Laird AR, McMillan KM, Lancaster JL, Kochunov P, Turkeltaub PE, Pardo JV, Fox PT (2005a): A comparison of label-based meta-analysis and activation likelihood estimation in the Stroop task. Human Brain Mapp 25:6–21.

Laird AR, Fox PM, Price CJ, Glahn DC, Uecker AM, Lancaster JL, Turkeltaub PE, Kochunov P, Fox PT (2005b): ALE meta-analysis: controlling the false discovery rate and performing statistical contrasts. Hum Brain Mapp 25:155–164.

Lancaster JL, Laird AR, Fox PM, Glahn DE, Fox PT (2005): Automated analysis of meta-analysis networks. Hum Brain Mapp 25:xxx–yyy.

Leube DT, Knoblich G, Erb M, Grodd W, Bartels, Kircher TT (2003): The neural correlates of perceiving one's own movement. Neuroimage 20:2084–2090.

Max L, Guenther FH, Gracco VL, Ghash SS, Wallace ME (2004): Unstable or insufficiently activated internal models and feedback biased motor control as sources of dysfluency: A theoretical model of stuttering. CICSD 31:105–122.

Meyer M, Steinhauer K, Alter K, Friederici AD, von Cramon DY (2004): Brain activity varies with modulation of dynamic pitch variance in sentence melody. Brain Lang 89:277–289.

McIntosh AR, Gonzalez-Lima F (1994): Structural equation modeling and its application to network analysis in functional brain imaging. Hum Brain Mapp 2:2–22.

Moore WH (1993): Hemispheric processing research. Past, present, and future. In: Boberg E, editor. Neuropsychology of stuttering. Edmonton: The University of Alberta Press. p 39–72.

Neumann J, Lohmann G, Derrfuss J, von Cramon DY (2005): The meta-analysis of functional imaging data using replicator dynamics. Hum Brain Mapp 25:165–173.

Neumann K, Euler HA, von Gudenberg AW, Giraud AL, Lanfermann H, Gall V, Preibisch C (2003): The nature and treatment of stuttering as revealed by fMRI: a within- and between-group comparison. J Fluency Disord 28:381–410.

Numminen J, Curio G (1999): Differential effects of overt, covert and replayed speech on vowel-evoked responses of the human auditory cortex. Neurosci Lett 272:29–32.

Petacchi A, Laird AR, Bower J (2005): The cerebellum and auditory function: An ALE meta-analysis of functional neuroimaging studies. Hum Brain Mapp 25:118–128.

Perry DW, Zatorre RJ, Petrides M, Alivisatos B, Meyer E, Evans AC (1999): Localization of cerebral activity during simple singing. Neuroreport 10:3979–3984.

Preibisch C, Neumann K, Raab P, Euler HA, von Gudenberg AW, Lanfermann H, Giraud AL (2003): Evidence for compensation for stuttering by the right frontal operculum. Neuroimage 20:1356–1364.

Raichle ME, Fiez JA, Videen TO, MacLeod AM, Pardo JV, Fox PT, Petersen SE (1994): Practice-related changes in human brain functional anatomy during nonmotor learning. Cereb Cortex 4:8–26.

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.

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

Stager SV, Jeffries KJ, Braun AR (2003): Common features of fluency-evoking conditions in stuttering subjects and controls: an $H_2{}^{15}O$ PET study. J Fluency Disord 28:319–336.

Stern E, Silbersweig DA, Chee KY, Holmes A, Robertson MM, Trimble M, Frith CD, Frackowiak RS, Dolan RJ (2000): A functional neuroanatomy of tics in Tourette syndrome. Arch Gen Psychiatry 57:741–748.

Thompson-Schill SL, D'Esposito M, Kan IP (1999): Effects of repetition and competition on activity in left prefrontal cortex during word generation. Neuron 23:513–522.

Turkelbaub PE, Eden GF, Jones KM, Zeffiro TA (2002): Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. Neuroimage 16:765–780.

Van Borsel J, Achten E, Santens P, Lahorte P, Voet T (2003): fMRI of developmental stuttering: a pilot study. Brain Lang 85:369–376.

von Holst E, Mittelstaedt H (1950): Das reafferenzprinzip (wechselwirkungen zwischen zentralnervensystem und Peripherie). Naturwis-senschaften 37:464–476.

Wager TD, Jonides J, Reading S (2004): Neuroimaging studies of shifting attention: a meta-analysis. Neuroimage 22:1679–1693.

Weiskrantz L, Elliott J, Darlington C (1971): Preliminary observations on tickling oneself. Nature 230:598–599.

Wildgruber D, Ackermann H, Grodd W (2001): Differential contributions of motor cortex, basal ganglia, and cerebellum to speech motor control: effects of syllable repetition rate evaluated by fMRI. Neuroimage 13:101–109.

Wildgruber D, Hertrich I, Riecker A, Erb M, Anders S, Grodd W, Ackermann H (2004): Distinct frontal regions subserve evaluation of linguistic and emotional aspect of speech intonation. Cereb Cortex 14:1384–1389.

Wu JC, Maguire G, Riley G, Fallon J, LaCasse L, Chin S, Klein E, Tang C, Cadwell S, Lottenberg S (1995): A positron emission tomography [18F]deoxyglucose study of developmental stuttering. Neuroreport 6:501–505.

Wymer JH, Lindman LS, Booksh RL (2002): A neuropsychological perspective of aprosody: features, function, assessment, and treatment. Appl Neuropsychol 9:37–47.