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Towards a functional neural systems model of developmental stuttering

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Abstract

This paper overviews recent developments in an ongoing program of brain imaging research on developmental stuttering that is being conducted at the University of Texas Health Science Center, San Antonio. This program has primarily used $H_2{}^{15}O$ PET imaging of different speaking tasks by right-handed adult male and female persistent stutterers, recovered stutterers and controls in order to isolate the neural regions that are functionally associated with stuttered speech. The principal findings have emerged from studies using condition contrasts and performance correlation techniques. The emerging findings from these studies are reviewed and referenced to a neural model of normal speech production recently proposed by Jürgens [Neurosci. Biobehav. Rev. 26 (2002) 235]. This paper will report (1) the reconfiguration of previous findings within the Jürgens Model; (2) preliminary findings of an investigation with late recovered stutterers; (3) an investigation of neural activations during a treatment procedure designed to produce a sustained improvement in fluency; and (4) an across-studies comparison that seeks to isolate neural regions within the Jürgens Model that are consistently associated with stuttering. Two regions appear to meet this criterion: right anterior insula (activated) and anterior middle and superior temporal gyri (deactivated) mainly in right hemisphere. The implications of these findings and the direction of future imaging investigations are discussed.

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Educational objectives: The reader will learn about (1) recent uses of $H_2{}^{15}O$ PET imaging in stuttering research; (2) the use of a new neurological model of speech production in imaging research on stuttering; and (3) initial findings from PET imaging investigations of treated and recovered stutterers.

Keywords: PET brain imaging; Persistent; Treated and recovered stutterers; Jürgens Model

In recent years positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and magnetoencephalography (MEG) studies have provided converging evidence regarding the neural regions that are implicated in speech production. For the most part this research has served to verify some of the classic models of the neural regions involved in speech production—models that were largely derived from lesion studies. The origin of many models of the regional interaction system supporting speech production can be traced to Wernicke's (1874) observations on aphasia. These observations were ultimately extended by Geschwind (1979) and formed the basis of the Wernicke–Geschwind Model—arguably, the most influential model of speech production. This model identified a sequence of brain regions that play a critical role when, for example, individuals read aloud single words [primary visual area (V1) → angular gyrus → Wernicke's area → Broca's area → M1-mouth]. Inevitably, increasing knowledge about the neural regions and structures associated with speech production, especially subcortical structures, meant that this basic model had to be expanded in a number of important ways. An especially important expansion occurred when it was established that cerebral cortex links with the basal ganglia via input structures that receive direct input from the cerebral cortex, and via output structures that project back to the cerebral cortex via thalamus (Alexander & DeLong, 1985a, 1985b). These multiple loops, which came to be known as cortico-basal ganglia–thalamo–cortical circuits (see Alexander, DeLong, & Strick, 1986), have been found to be involved in speech production. Indeed, certain speech–motor disorders, such as dysarthria, appear to reflect a dysfunction in that loop (Crosson, 1985; Penney & Young, 1983). Not surprisingly, therefore, there is interest in determining if other speech disorders, such as developmental stuttering, are byproducts of a fundamentally dysfunctional neural system.

Major improvements to the understanding of the regions and systems that participate in speech production occurred in the mid-1980s with the arrival of PET imaging of the brain (Ter-Pogossian, Phelps, Hoffman, & Mullani, 1975; Ter-Pogossian, Raichle, & Sobel, 1980). The subsequent groundbreaking $H_2{}^{15}O$ PET experiments by Petersen, Fox, Posner, and Raichle (1988) and Petersen, Fox, Posner, Mintun, and Raichle (1989) yielded the first distinctive images of neural activity during reading and during the production of single words. Other researchers using PET in conjunction with various speech tasks soon replicated and refined Petersen et al.'s findings, identifying a group of regions that were generally active during speech

production (mainly single word production tasks). Across nine of these early PET studies Fiez and Petersen (1998, p. 914) reported that

> . . . the results converge to reveal a set of areas active during word reading, including left-lateralized regions in occipital and occipitotemporal cortex, the left frontal operculum, bilateral regions within the cerebellum, primary motor cortex, and the superior and middle temporal cortex, and medial regions in the supplementary motor area and anterior cingulate.

The variability in regions reported across the studies reported by Fiez and Petersen, however, also prompted arguments about their validity (see Démonet, Fiez, Paulesu, Petersen, & Zatorre, 1996; Poeppel, 1996) and ignited attempts to identify the sources of this variability (Hickok, 2001). That variability was also evident in a much larger meta-analysis of imaging studies of speech production by Indefrey and Levelt (2000). Their review of the findings of 58 word production studies showed the expected variation in regions activated because of experimental task differences (Grabowski & Damasio, 2000). Nevertheless, Indefrey and Levelt provided a valuable summary of the regions that are principally associated with oral reading. Their review did not consider studies of continuous speech or continuous oral reading, but it did highlight a group of relatively broad regions that might be implicated in connected speech. A reasonable conclusion from Indefrey and Levelt's tabulated findings (see Indefrey & Levelt, 2000, pp. 855–858) is that most regions they identified were essentially identical to those reported by Fiez and Petersen (1998). Refinements to these regions continue to occur. For instance, a recent synthesis of lesion and imaging studies by Price (2000) concluded that left anterior insula might have a much greater role in speech planning than Broca's area. A recent meta-analysis of single word reading PET studies compared with fMRI findings by Turkeltaub, Eden, Jones, and Zeffiro (2002) highlighted the functional roles of specific areas of thalamus (left ventrolateral thalamus) and cerebellum (lobules VI and VII) during speech. This compilation of findings is gradually identifying regions that must be implicated in normal speech production—a necessary prerequisite to the understanding of the regions that must be implicated in abnormal speech production such as occurs during chronic developmental stuttering.

1. The Jürgens Model of speech production

A recent model of the neural basis of speech production proposed by Jürgens (2002) has attempted to synthesize current knowledge about the neurologic foundations of speech production. This elaborate "box and arrow" model of neural regions and structures participating in speech production is derived from a careful integration of findings from lesion, invasive brain stimulation, single-unit recording and brain imaging studies. The model builds on currently known structural connections between and within neural locations. The Jürgens Model provides only partial information on the sequence with which particular regions participate

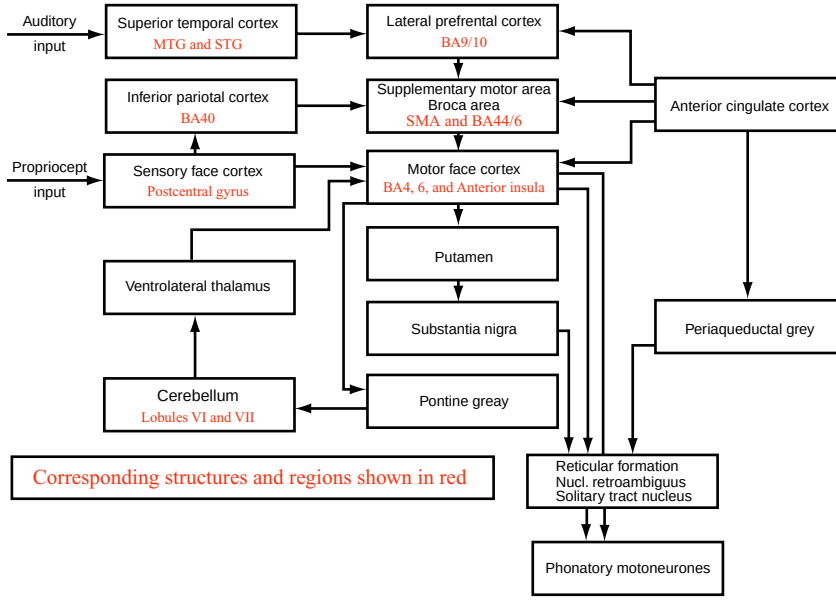

Fig. 1. A description of the Jürgens Model. This figure, as described by Jürgens (2002, p. 251), summarizes the most important structures for which there is evidence from lesion, stimulation, single-unit recording, and brain imaging studies that they are involved in speech production. The arrows identify anatomically confirmed direct connections. There may be more than one structure in a box, but the structures shown within a box are directly connected with each other. The added regions within boxes (shown in red) were confirmed as relevant and accurate by Dr. Jürgens (personal communication).

in different speech tasks, but it does make it possible to locate patterns of regional innervation that characterize different speech tasks. And, of more relevance to stuttering research, it helps to focus the search for regions that are relatively inactive or overactive during the speech of individuals with developmental stuttering.

Fig. 1 reproduces the Jürgens Model with some additions (e.g., specific BA regions) that were derived by analyzing the results of studies that Jürgens used to develop this model. Those additional labels have been confirmed as accurate by the author (Jürgens, 2003, personal communication).

In this figure “Auditory input” refers to input from an individual’s own speech and the speech of others. “Proprioceptive input” emanates from the larynx, articulatory organs and pulmonary stretch receptors. In many respects, therefore, the Jürgens Model has a lot in common with Fairbanks’s (1954) servosystem model of speech production, but supplements it with the principal neural systems that might be necessary to perform its error-correcting functions.

MEG studies of the sequence of neural responses during speaking tasks generally offer support for the Jürgens Model. For instance, Salmelin, Hari, Lounasmaa, and Sams (1994) found that when individuals name a picture their initial occipital

response (not shown in Jürgens Model) moves to left MTG within 200 ms, then reaches Wernicke's area by 275–400 ms and ultimately reaches Broca's Area (and maybe SMA) at 400–600 ms. Sensori-motor cortex responding occurs at about 600 ms. Couple that evidence with Kuriki, Mori, and Hirata's (1999) finding that 120–320 ms prior to an utterance, there was activity around left anterior insula, then this suggests that there is linear signal transmission through to Broca's area. Parallel processing evidence was detected by Dhond, Buckner, Dale, Marinkovic, and Halgren (2001) during a word stem task. The task response signal reached the left BA 37 region by about 180 ms, Wernicke's area by 210 ms, and then moved, via insula, to Broca's area, reaching there by 370 ms.[1] Concurrent posterior middle and superior temporal gyri responses appeared at about 200–245 ms. Dhond et al. also found that novel word stems produced activity *reductions* in prefrontal and anterior temporal regions over a 365–500 ms period.

The processes involved in connected speech are very obviously different than those involved in saying a single word. Typically 4–7 syllables per second (Kent, 1994) are produced during connected speech, which implies that these neural region activations must occur in parallel or that some regions are simply not involved. Unfortunately, MEG cannot identify subcortical activity and so these studies provide a rather incomplete depiction of the time-course of activations or responses in different regions. Nonetheless, normal speech production obviously requires task-dependent arrangements of parallel activity and reduced activity or gating of signals (Gusnard & Raichle, 2001) in the motor and auditory regions. This certainly accords with PET imaging studies that have shown, for instance, that BA 44/6 is not always active during articulation (Etard et al., 2000; Wise, Greene, Buchel, & Scott, 1999). In short, oral reading or spontaneous speech tasks might *not always* recruit all regions that are known participants in vocalization according to the Jürgens Model. Consequently, at best, the model only highlights regions that could be activated and/or deactivated during imaging studies involving different speaking tasks. Its value to the understanding of disordered speech is to highlight the regional activations that differ from those that occur during normal speech and then use the model's "pathways" to predict the effect that these differences might have on neighboring regions and, ultimately, on behavior.

2. The San Antonio studies: an overview

Over the course of a series of $H_2{}^{15}O$ PET studies conducted in the Research Imaging Center at the University of Texas Health Science Center, San Antonio, the authors and colleagues have sought to systematically isolate the neural regions that

[1] The evidence of a signal response moving from Wernicke's area (located within the Superior Temporal Gyrus box in Jürgens Model) to insula and then to Broca's area is not consistent with the model as shown in Table 1. Obviously the model's box and arrow arrangement needs to reflect this pathway. Indeed, there is also reason to suggest that anterior insula may have a more fundamental role than Broca's area in speech planning (Price, 2000).

are functionally associated with developmental stuttering. These studies have been confined to right-handed participants and include adult stutterers of both genders, plus controls matched for age and sex. The findings of these studies have been reported in a series of published papers—and other as yet unpublished papers. One set of studies has investigated the regions associated with oral reading; using accompanied (chorus) reading and unaccompanied (solo) reading to contrast non-stuttered and stuttered oral reading within condition contrast experiments (using eyes-closed rest as a control) (Fox et al., 1996; Ingham, Fox, Ingham, Collins, & Pridgen, 2000). These studies have been accompanied by performance correlation analyses (Silbersweig et al., 1995) showing, for the most part, that the major regional abnormalities identified in the condition contrast studies also show modest but significant correlations with stuttering frequency (Fox et al., 2000; Ingham et al., in press). It has also been shown that the abnormal regional activations and deactivations associated with stuttered speech in these studies did not depend on overt stuttering; they also appeared when stuttering during oral reading was imagined, and they diminished when stutter-free oral reading was imagined (Ingham, Fox, Ingham, & Zamarripa, 2000). More recently, unpublished counterpart studies have imaged the effects of stutter-free spontaneous speech produced by stuttering speakers who have partially completed a stuttering treatment program (Ingham et al., 2001). Currently studies are being conducted on recovered stutterers, the initial group being male stutterers who recovered from stuttering in early adulthood, without formal treatment, and claim to have been recovered for at least 10 years. [Each participant in these studies was identified via their participation in behavioral studies on recovery from stuttering in adulthood conducted by Patrick Finn (1996, 1997).] In addition, studies are being conducted using MEG and event-related fMRI in order to cross validate some of the prominent findings from PET investigations of stuttering.

The following sections of this paper provide an overview of research thus far completed in the San Antonio research program and an attempt to place previous and current findings within the framework of the Jürgens Model. Those sections will provide (1) a reanalysis of an earlier study; (2) the results of a comparison between persistent stutterers, controls and late recovered stutterers; (3) a comparison between the effects of treatment-induced reduced stuttering and reduced stuttering during chorus reading; and (4) an across-study comparison of findings with respect to the Jürgens Model. All the reported studies describe the results of $H_2{}^{15}O$ PET studies using condition contrasts. In each scanning session there were nine **40 s scans (3 scans during 2 different speaking tasks and 3 during an eyes-closed rest condition). PET and MR images for each subject were spatially normalized relative to the Talairach and Tournoux (1988) brain atlas using software developed by Lancaster et al. (2000). Brain dimensions were obtained from the MR images and then applied to the PET images. The images were then transformed into 3-D, spatially-normalized images using 2 mm × 2 mm × 2 mm voxels. Some of the implications of the emerging trends across these studies for a functional neural systems model of developmental stuttering will be discussed.

3. Research studies

3.1. Study 1: neural region activations by stutterers and controls during oral reading

This section uses the framework of the Jürgens Model to reanalyze the findings of the Fox et al. (1996) study. Fox et al. used PET to investigate the neural region effects of chorus reading on stuttering.

3.1.1. Method and subjects

This study involved 10 adult dextral male stutterers and 10 matched controls. Each participant orally read passages during 6 scans, three with and three without a recording of a fluent speaker reading the same passage. Reanalysis of the resulting imaging data was accomplished by identifying the significantly activated and deactivated voxel clusters (15 voxels) within the 32 regions (16 right and 16 left hemisphere) included in the Jürgens Model. Two subcortical regions that appear within the model, periaqueductal grey and pontine grey, were not included because PET scanning in this study (and subsequent studies) did not extend to these brainstem sites. No attempt is made here to address the connections between the regions. Instead, the aim is to identify the regions that are consistently distinguished as present or absent during stuttering.

3.1.2. Results

Fig. 2 shows the total number of significantly activated voxels during solo oral reading (minus rest); that is, when stuttering was present for the stutterers during each 40 s scan. In general, it is noteworthy that the control group did not display significantly activated voxel clusters in all regions within the Jürgens Model; indeed fewer were activated in controls than in the stuttering group (13/32 versus 18/32). The results reported here are the products of using a more conservative analysis system than was used in the original Fox et al. (1996) paper. This data analysis employs voxel clustering (Xiong, Gao, Lancaster, & Fox, 1995), a technique now employed in all San Antonio studies in order to identify major condition effects—but voxel clustering also slightly modified the size (but not regional) effects reported in the Fox et al. (1996) paper. In addition, of course, the focus within this paper on regions that are of interest in the Jürgens Model meant that some areas (e.g., cerebellum) are only partially represented (e.g., lobules VI and VII in cerebellum). However, as Fig. 2 shows, the principal differences reported by Fox et al. between stutterers and controls with respect to cerebellum, right temporal lobe and right anterior insula region are present. Other differences appeared, but across different PET studies with different participants these additional differences have not remained consistent. Some evidence in support of that claim emerges in Studies 2 and 3 presented here.

For clarity only the CBF activation data are presented in Fig. 2. Strong deactivations were observed in numerous regions, but for the persistent stuttering group the most extensive deactivations occurred in STG and MTG.

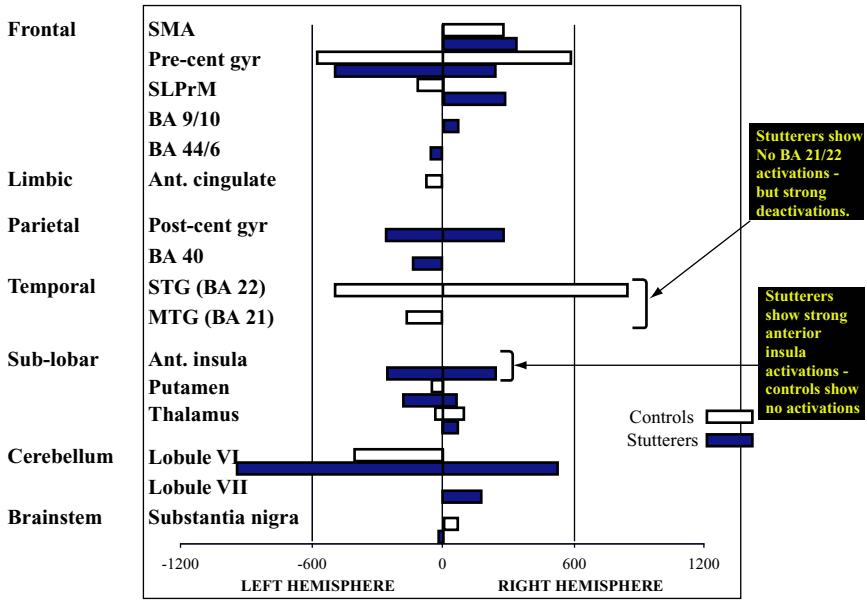

Fig. 2. Shows for each of 16 regions (in both hemispheres) within the Jürgens Model the number of significantly activated voxels that occurred on average for the adult male persistent stutterers ($n = 10$) and controls ($n = 10$). These data were derived from oral reading (minus rest) conditions within the Fox et al. (1996) study.

3.2. Study 2: a comparison between neural activations of stutterers, late recovered stutterers and normally fluent controls

Study 2 is an initial report on an investigation designed to identify the differences among the neural regions activated during spontaneous speech by adult male stutterers, late recovered stutterers and normally fluent controls. By studying late recovered stutterers, especially those who recovered without formal treatment, it is expected to be possible to determine if successful recovery of fluency is associated with the establishment of normal neural processing of speech. The premise for this research is that successful self-managed recovery in adulthood most likely means that the individual's self-managed therapy has succeeded (maybe as much as is possible) in modifying the aberrant neural systems that constitute the basis of chronic stuttering. This is not meant to diminish the importance of studying those who recovered from stuttering in early childhood. However, recovery at an early age is less likely to be similar to recovery from a chronic condition in adulthood because complete neural reorganization in children is more likely than in adults (Muller et al., 1999).

An overarching goal of this research is to study "fully recovered" developmental stutterers in order to formulate a neurophysiological measure of recovery.

Conceivably this measure could also become a neurophysiological measure of treatment outcome. Durable stutter-free speech cannot be replaced as a measure of recovery, but stutter-free speech that is *not* associated with normal neurologic processing may differ in its post-treatment durability (and possibly in other ways) from speech that *is* associated with normal neurologic processing.

3.2.1. Method and subjects

This preliminary study reports a PET imaging investigation of three groups of adult male dextral participants. Each group contained four participants (ultimately, each group will contain 10 same-sex subjects): persistent stutterers (30–46 years), recovered stutterers (31–50 years), and controls (28–50 years). The persistent stutterers percent syllables stuttered on the monologue task during the PET scans ranged from 2.3 to 9.8.

3.2.2. Results

Fig. 3 shows the total number of significantly activated voxels (in clusters of 15 or more) throughout the principal neural regions (in both hemispheres) identified within the Jürgens Model. It is immediately obvious that not all regions were significantly activated—none at all in the parietal lobe or substantia nigra. Overall,

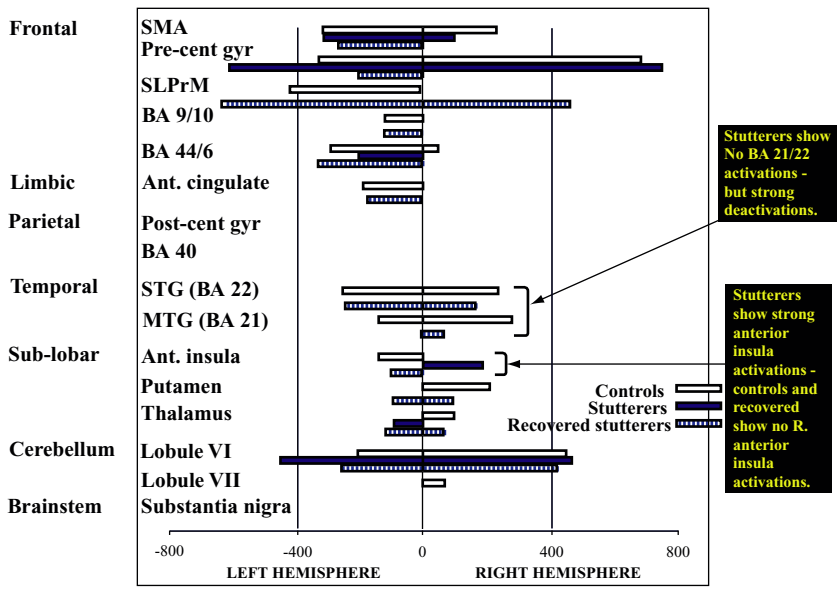

Fig. 3. Shows for each of 16 regions (in both hemispheres) within the Jürgens Model the number of significantly activated voxels that occurred on average for the adult male persistent stutterers ($n = 4$), late recovered stutterers ($n = 4$), and controls ($n = 4$). These data were derived from three monologue (minus three rest) conditions during an unpublished PET study.

the controls produced activations in 19 regions, the recovered stutterers in 17 regions and the persistent stutterers in 9 regions. Of the 19 regions activated by the controls, the recovered stutterers also activated 14, but only 7 regions activated by the persistent stutterers were identical to those activated by the controls (the recovered and persistent stutterers shared 6 regions). The differences between the persistent stutterers and controls, while not identical to those obtained in the Fox et al. study (likely due to the difference between oral reading and monologue tasks), are generally similar to that study (see Fig. 2). More regions in the frontal lobe were activated in the persistent stutterers and controls. But some of the strong between-group differences were present: the persistent stutterers displayed a larger volume of activations in CBM than the controls, and the persistent stutterers again displayed a complete absence of significantly activated voxels in STG and MTG, plus significant activations in right anterior insula where the controls showed none.

The regional activations by the recovered stutterers had much more resemblance to those of the controls—and much less resemblance to the persistent stutterers' regional activations. For instance, the recovered stutterers and controls showed generally similar magnitudes of activation in CBM, MTG (though not in STG), and left anterior insula. By contrast, the persistent and recovered stutterers showed striking differences in many regions, including the temporal lobe and right anterior insula—the latter differences are highlighted in Fig. 3. They did retain some similarities with the stutterers, however, including little or no MTG activation, no lobule VII activation in cerebellum and left ventrolateral thalamus activation (although the absence of left hemisphere activations in the controls is unexpected in view of recent meta-analytic studies—see above).

3.3. Study 3: identifying neural regions that distinguish between temporary and sustained improvements in fluency by persistent stutterers

Previous studies (Fox et al., 1996, 2000; Ingham et al., 2000) investigated the effect of chorus reading in order to isolate the neural region activations that are modified when stuttering behavior decreases or ceases during this well-known fluency-inducing procedure. Chorus reading is not generally considered to be a therapeutic strategy because its fluency-inducing effects are temporary—they cease almost immediately when the chorus reading condition is removed (Ingham, 1984). More recently investigations have shifted towards attempting to identify the principal neural regions that are activated and deactivated during a stuttering treatment procedure that *does* produce sustained improvements in fluency. The goal is to identify neural region changes that might distinguish between improvements in fluency that are temporary and those that are maintained.

3.3.1. Method and subjects

The stuttering treatment employed in this project is the Modified Phonation Interval (MPI) program developed by the senior author (Ingham, Moglia, Kilgo, & Felino, 1997). The program's effectiveness in producing sustained treatment

benefits has been documented in a recent treatment outcome study (Ingham et al., 2001). Details of this computer-based and largely self-managed program are described elsewhere (Ingham, 1999). The program initially trains speakers to reduce the frequency of relatively short intervals of phonation via a biofeedback arrangement—a strategy that has been shown to functionally control stuttering (Gow & Ingham, 1992; Ingham, Montgomery, & Ulliana, 1983). Basically, the MPI program involves three consecutive therapy phases—Establishment, Transfer, and Maintenance—all with speaking tasks designed initially to establish stutter-free speech in clinic conditions, and then ultimately to transfer and maintain those gains in fluency in beyond-clinic conditions.

An initial investigation into the effect of the Establishment Phase of the MPI program on the neural regions associated with speech production was conducted with male and female persistent stutterers. Nine dextral male and eight dextral female persistent stutterers participated. Their stuttering frequency before this study ranged from 1.3 to 32.3% SS for the males and 3.6 to 29.4% SS for females during a monologue task. Each participant then completed part of the MPI Establishment Phase that ultimately required a 3-min monologue to be completed without stuttering, below a target PI frequency, and with a rating of 3 or less on the 9-point Speech Naturalness scale (Martin, Haroldson, & Triden, 1984). At that point each person participated in a PET scan session and completed three eyes-closed rest and three monologue speaking tasks.[2] For comparative purposes nine dextral male and eight dextral females served as controls. They were age matched and completed the same monologue speaking task during the PET scan conditions.

3.3.2. Results

The right side of Fig. 4 shows the regional activations results of the male and female groups during the monologue task when all stutterers had partially completed the MPI treatment's Establishment Phase and had achieved stutter-free speech. The left side of Fig. 4 shows the chorus minus rest condition contrast data for the 10 male stutterers and 10 controls in the Fox et al. (1996) study and counterpart data from a replication of the Fox et al. study using 10 female stutterers and 10 controls (Ingham, 2001; Ingham et al., in press). During this oral reading task all male stutterers achieved stutter-free speech and 7/10 females achieved that level; the three remaining females produced at least 80% reductions in stuttering frequency in the chorus condition.

One of the main findings is highlighted within Fig. 4. This shows that the persistent stutterers of both sexes produced bilateral BA 22 activations during MPI-treatment and chorus reading conditions. Also highlighted is the absence of right anterior insula activations during chorus reading for both sexes and in the

[2] Three additional scans were also completed. During these scans the stuttering participants were instructed to try to increase their target PI frequency counts so as to briefly restore stuttering (see Ingham et al., 1983), but this proved to be problematic for most participants. In both gender groups most participants could not perform this task or displayed "forced" rather than genuine stuttering.

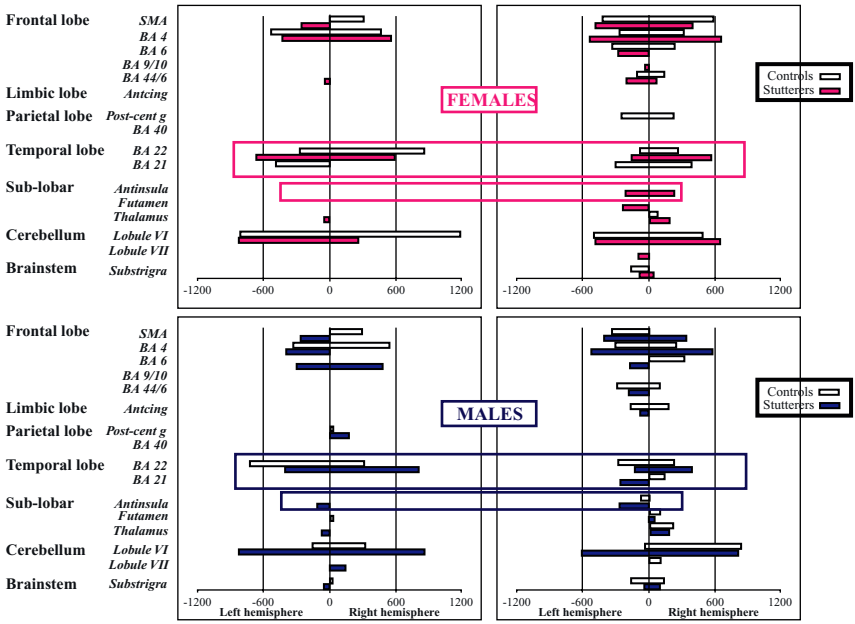

Fig. 4. Shows a comparison between neural activations by MPI-treated speakers and by speakers during chorus reading. The left column shows, for each of 16 regions (in both hemispheres) within the Jürgens Model, the number of significantly activated voxels that occurred on average for the adult female persistent stutterers ($n = 8$) and controls ($n = 8$), and adult male persistent stutterers ($n = 9$), and controls ($n = 9$). These data were derived from three monologue (minus three rest) conditions during an unpublished PET study in which the persistent stutterers had completed part of the MPI-treatment program (Ingham et al., 2001). The right column shows parallel data from adult female and male persistent stutterers ($n = 10$; 10) and controls ($n = 10$; 10) during chorus reading conditions. These data were derived from three chorus reading (minus three rest) conditions during the Fox et al. (1996) and Ingham et al. (in press) PET studies. The boxed areas highlight BA 21/22 and anterior insula and show that during fluency-inducing conditions both areas were largely normalized.

males during MPI-treatment. Bilateral anterior insula activations were, however, still evident in the MPI-treated female persistent stutterers. These findings form a direct contrast with those reported in Studies 1 and 2. In Study 1 BA 22 activations *were not* present and right anterior insula activations *were* present in the male persistent stutterers during solo reading (see Fig. 2). A similar result has been found for females (see Ingham, 2001). Study 2, while it involved only four persistent stutterers, indicated that similar effects are likely to occur among untreated male persistent stutterers during a monologue task (see Fig. 3). PET imaging of stuttered monologue speech by female persistent stutterers is not presently available. Thus, it appears that the major aberrant features of stuttering in persistent male and female stutterers (activation of right anterior insula and absence of activation—including

Table 1
The total number of neural regions within the Jürgens Model that were significantly activated by stutterers and controls when completing monologue and oral reading tasks during PET

	Females		Males	
	MPI (monologue)	Chorus reading	MPI (monologue)	Chorus reading
Treatment				
Stutterers	19	9	17	14
Controls	18	8	19	9
	Monologue	Solo reading	Monologue	Solo reading
Nontreatment				
Stutterers		13	9	18
Controls	18	18	19	13

The upper half of the table shows the total number of activated regions during PET imaging studies involving "Treatment," that is MPI or chorus reading. These data were derived from Study 3 (see Fig. 4). The lower half of the table shows the total number of activated regions during monologue and oral reading tasks within PET scan studies that did not involve treatment ("Nontreatment"). These data were derived from Studies 1 and 2 as well as from Ingham (2001).

deactivation—of auditory association cortex) were at least partially normalized by the fluency-inducing effects of chorus reading and the MPI program.

There are some rather prominent differences between the regions activated during MPI treatment and chorus reading that may help to explain the different fluency-producing effects of both procedures. These differences may be quantified in various ways, but for purposes of this broad review they have been analyzed at the simplest possible level: the number of regions within the Jürgens Model that were activated during each task. Table 1 shows that MPI-treated speech (monologue) consistently activated more regions than chorus reading within the Jürgens Model for the persistent stutterers of both genders. The controls did not receive MPI treatment, but they were exposed to chorus reading. Conceivably, part of the difference might be due to more regions being activated during a monologue than during oral reading. However, in the lower half of Table 1 it is evident (from across the studies reported here) that such large differences between monologue and oral reading are not expected among controls. The female and male controls produced significantly fewer activated regions during chorus reading than during solo reading (Chi Square $= 15.0$; $P < 0.001$). Thus, it appears that chorus reading activates consistently fewer speech-related regions than is the case for MPI-treatment. We would hypothesize, therefore, that chorus reading might have only transient beneficial effects on the fluency of persistent stutterers because other aberrant neural interactions associated with stuttered speech remain unaffected by chorus reading and would, therefore, return when chorus reading ceases. By contrast, the MPI-treated speakers achieve fluency while using almost all of the regions that are used by controls—and presumably in a much less dysfunctional fashion than before treatment. It is freely acknowledged that this is a very simple interpretation

of the differences between the chorus reading and MPI-treatment data; nonetheless, it may help to explain why chorus reading is likely to have far less therapeutic potential when compared with MPI-treated speech.

3.4. Study 4: an across-study analysis of regional activations

One obvious problem among the findings from the studies reported above is that they do not display a consistent pattern of regional activations as might be predicted within the Jürgens Model. In none of the reported studies, for example, is there evidence that the controls displayed activations in *all* of the regions specified in the model which, in turn, could raise legitimate doubts about either the validity of the imaging findings or even the model. However, if it is the case that not all neural regions and structures are expected to be active in every speaking task, then all of the regions and structures would only be expected to display concurrent activity in a study that utilizes all possible speaking tasks. For that reason an additional analysis of the findings from the San Antonio studies was conducted by making comparisons across published and recent studies in order to identify regions and structures that were active (irrespective of magnitude) or inactive (displaying no significantly activated voxels with a cluster size of 15 or more). Its purpose was to use across-study comparisons to test the validity of the Jürgens Model and to help isolate the regions that are functionally associated with stuttering.

3.4.1. Method and subjects

This analysis was conducted on controls and persistent stutterers of both genders, during oral reading and monologue tasks. The data for this analysis were derived from Fox et al. (1996), Ingham et al. (in press), and Study 2 (all described above).

3.4.2. Results

The results of this synthesis study are summarized in Table 2. The first finding of interest is that almost all regions specified within the Jürgens Model were activated by the controls in at least one of the San Antonio studies on stuttering. The notable exception was BA 40 within the inferior parietal lobe. This region has been found to be correlated with fluent speech production (Kircher, Brammer, Williams, & McGuire, 2000) and associated with the production of short phrases (e.g., Wise et al., 2001) and so it is somewhat surprising that it did not appear among activations reported in the controls used in the San Antonio studies.

The contrast between regions significantly activated or not significantly activated for the controls and persistent stutterers was, as shown in Table 2, quite striking. Notable was the absence of activation in anterior cingulate and MTG (BA 21), and the presence of activations in right anterior insula and left BA 40, all relative to the controls. These differences are made even sharper by relating the findings to performance correlation analyses of the regional activations and deactivations by the male (Fox et al., 2000) and female (Ingham et al., in press)

Table 2
The results of a comparison across PET studies conducted at the University of Texas Health Science Center, San Antonio, for regions activated within the Jürgens Model

Lobe	Region (BA)	Total Cont		Total Stut	
		L	R	L	R
Frontal	Supplementary motor area (6)	X	X	X	X
	Precentral gyrus (4)	X	X	X	X
	Premotor cortex (6)	X	X	X	X
	Prefrontal (9/10)	X	X	X	X
	Frontal operculum (44/6)	X	X	X	X
Limbic	Anterior cingulate	X	X		
Parietal	Postcentral gyrus	X	X	X	X
	Inferior parietal lobe (40)			X	
Temporal	Superior temporal gyrus (22)	X	X	X	X*
	Middle temporal gyrus (21)	X	X		
Sub lobar	Anterior insula	X		X	X
	Putamen	X	X	X	X
	Thalamus (ventrolateral)	X	X	X	X
Cerebellum	Quadrangular lobule (VI)	X	X	X	X
	Quadrangular lobule (VII)		X		X
Brainstem	Substantia nigra	X	X	X	X

The comparison involved oral reading (minus rest) and monologue (minus rest) tasks across four studies that included either male or female controls (Cont) or persistent stutterers (Stut). X indicates that the region was activated on at least one occasion across the four studies. X* was from the Ingham et al. (in press) study which also showed that all activated voxels by the female persistent stutterers were negatively correlated with stuttering frequency.

persistent stutterers. These studies showed that for both genders only two regions distinguished between the persistent stutterers and controls in the present analysis and also correlated with the frequency of stuttering: deactivation of right BA 21 and activation of right anterior insula. There was no evidence that anterior cingulate or left BA 40 showed any sign of a positive or negative correlation with stuttering frequency. However, as the table asterisk indicates, right BA 22 was also significantly negatively correlated with the frequency of stuttering in the male and female persistent stutterers. Consequently, it seems reasonable to suggest that overactivation in right anterior insula and deactivation in right BA 21/22 tend to distinguish between persistent stutterers and normally fluent speakers during speech production.

4. Discussion

The San Antonio studies constitute a program of brain imaging research that is designed to isolate the neural regions that are consistently associated with stut-

tering and its frequency during connected speech. Beginning with the Fox et al. (1996) study it was observed that stuttering was associated with unusual overactivation in the right hemisphere with abnormal activations in motor cortex, subcortical regions, and cerebellum. There was an absence of activation—even strong deactivation—in the temporal lobe. In the subsequent studies these distinctive activations and deactivations have been winnowed until it is evident that a cluster of regions regularly appears as functionally related to stuttering across the speaking tasks and genders. The regional effects reported by Fox et al. (1996) became more focused with performance correlation (Fox et al., 2000) and were largely replicated in female persistent stutterers (Ingham et al., in press). Common to both genders were excessive activations in right anterior insula and deactivations (negative correlates) in right BA 21/22 and left inferior frontal gyrus. There were, however, gender-related regional effects: only male persistent stutterers showed abnormally large CBM activations; only female persistent stutterers showed bilateral activations in anterior insula and basal ganglia. The abnormal right anterior insula activations and right BA 21/22 deactivations also occurred when male persistent stutterers imagined stuttering and they were normalized when these DSs imagined speaking fluently (Ingham et al., 2000). The results of more recent studies are summarized in this paper. They have also shown that these particular regions are essentially normalized in male recovered stutterers and during the MPI treatment with both genders. In addition, the findings of these studies have now been reanalyzed with reference to the regions in the Jürgens (2002) Model in order to determine the areas of dysfunction within that model.

What functions are known to be associated with right BA 21/22 and right anterior insula? Lack of activation in BA 21/22 during speech has important implications. Perhaps the most consistent findings in imaging studies of speech by normal speakers is *activation* of left and right BA 21/22 (see Indefrey & Levelt, 2000; Turkeltaub et al., 2002), with most activation on the left. Belin, Zatorre, Lafaille, Ahad, and Pike (2000) have also shown that regions in the upper bank of L/R STG selectively respond to the speaker's voice. And Jäncke, Mirzazade, and Shah (1999) demonstrated that activations in BA 22 increase when the listener's attention is directed during a speech recognition task; they increase further when listeners try to detect a specific target syllable. Similar effects were reported recently by Hugdahl, Ersland, Rimol, and Niemi (2003). Jäncke et al. also found that activations in L and R BA 22 were almost identical, even when BA 41/42 activations were stronger on the left. Thus it may be, as the San Antonio studies suggest, that persistent stutterers show poor responsiveness to their own speech signal and probably have an impoverished capacity to monitor their own speech.

Overactivation in right anterior insula has numerous implications that need to be carefully disentangled. Paulesu et al. (1996) has argued that left insula cortex forms an anatomic bridge between Broca's and Wernicke's area thereby giving it a critical language function, and right insula cortex seems to be active during

attention and in the modulation of physiological sensation. Interestingly, the insula appears to be activated only when tasks involve articulation of non-repeated and phonologically complex words (e.g., Wise et al., 1999), but not when only automatic or simple articulatory patterns are produced (e.g., Murphy et al., 1997). However, the complex cytoarchitecture of insula has implied diverse functionality. Most speech functions involve dorsal left anterior insula (Price, 2000; Riecker, Ackermann, Wildgruber, Dogil, & Grodd, 2000; Wise et al., 1999); lesions in this region appear responsible for dyspraxia (Dronkers, 1996). Arguably, evidence of disproportionate right hemisphere activity in persistent stutterers during speech may mean that left anterior insula's functions have changed hemispheres in this group.

From another perspective, evidence that right anterior insula is also strongly activated during chronic anxiety (Rauch, Savage, Alpert, Fischman, & Jenike, 1997) might suggest that its activation is a response to anxiety in persistent stutterers. However, there is little (if any) evidence that developmental stuttering is functionally associated with either state or trait anxiety (Ingham, 1984, 1990). Furthermore, the site associated with anxiety (usually state anxiety) consistently occurs in the *ventral* right anterior insula, while the activations found in persistent stutterers consistently occur in *dorsal* right anterior insula (Fox et al., 1996; Ingham et al., 2000, in press). And because stuttering involves unusual speech movements, the activations in dorsal right anterior insula may be consistent with activations found in that area during singing (Riecker et al., 2000), swallowing (Zald & Pardo, 1999), and chronic breathlessness (Banzett et al., 2000).

Finally, an obvious point of interest is whether the Jürgens Model provides additional contributions to our understanding of the neural systems that are functionally related to stuttering. It is not clear that this is necessarily the case, possibly because of some limitations in the exposition of the model. One rather logical prediction from this model, as shown in Fig. 1, is that the consistent lack of activation (and strong deactivation) by persistent stutterers in BA 21/22 should produce reduced activations in BA 9/10. From the data provided in Study 1 that does not appear to be true; in Study 1 right BA 9/10 was activated in the persistent stutterers, but not in the controls—despite the strong BA 21/22 activations in the controls. In Study 2, however, there is some evidence that lack of BA 21/22 activations in the persistent stutterers was associated with lack of significant activation of BA 9/10. The reverse was true, however, for the controls and recovered stutterers. The strong activation in right anterior insula in the persistent stutterers might, according to the model, have also been expected to produce consistent significant activations in putamen or substantia nigra in Studies 1 and 2. But this was not the case. In short, the current findings have not shown that the connections within the Jürgens Model are strong predictors of neural region interactions for chronic developmental stuttering.

Locating the neural connections and ultimately formulating a neural systems model of developmental stuttering will require investigations that employ a variety of imaging techniques and sophisticated analysis methods. Included among

these will be transcranial magnetic stimulation, which is now being explored in San Antonio for the purpose of studying connectivity (Fox et al., 1997; Ingham et al., 2000). A recent study by He et al. (2003), which used within-condition inter-regional covariance analysis to identify the connections that differentiate tongue movements and speech, is one of a number of data analysis strategies that might be useful. In any event, it is the continuing developments in imaging techniques and analysis techniques that will ultimately lead to the development of a functional neural system model of developmental stuttering. This paper provides an interim report on that search as it is being conducted in one laboratory.

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CONTINUING EDUCATION

Towards a functional neural systems model of developmental stuttering

QUESTIONS

1. The Jürgens Model of speech production outlines neural regions that different studies have shown are implicated in speech production. The Model highlights:
   a. regions that participate in all speaking tasks
   b. regions that are activated and deactivated during speech production
   c. the hemisphere in which the regional activations should occur
   d. the sequence of regional activation in response to a speech stimulus
2. Fox et al. (1996) conducted a PET study that compared the neural regions activated by persistent male adult stutterers and controls during oral reading. They reported abnormal activations of cerebral blood flow in:
   a. anterior cingulate
   b. right anterior insula
   c. left temporal lobe
   d. left caudate
3. Initial findings from the PET investigation of late recovered stutterers show that in comparison with normally fluent speakers during spontaneous speaking tasks they show:
   a. similar magnitudes of activation in cerebellum
   b. similar magnitudes of activation in left superior temporal gyrus
   c. similar magnitudes of activation in left anterior cingulate
   d. all of the above
4. The neural region effects of fluency induced in persistent stutterers by chorus reading and by a stuttering treatment procedure (MPI) are:
   a. characterized by differences in the number of regions that are activated within the Jürgens Model
   b. similar in male and female adult persistent stutterers
   c. similar in their effects on Broca's area
   d. similar in their effects on substantia nigra
5. This paper reviewed three different $H_2{}^{15}O$ PET studies on persistent stutterers that are being conducted by the senior author and colleagues. The regions within

the Jürgens Model in which persistent stutterers and controls have consistently shown different activations are:

a. anterior cingulate
b. middle temporal gyrus
c. right anterior insula
d. all of the above