



Brain imaging studies of developmental stuttering[☆]

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Abstract

This paper reviews recent brain imaging research on stuttering against a background of studies that the writer and colleagues have been conducting at the University of Texas Health Science Center in San Antonio. The paper begins by reviewing some pertinent background to recent neuroimaging investigations of developmental stuttering. It then outlines the findings from four brain imaging studies that the San Antonio group has conducted using $H_2^{15}O$ positron emission tomography (PET). Finally, some of the principal findings that are emerging across brain imaging studies of stuttering are reviewed, while also highlighting — and attempting to resolve — some apparent across-study inconsistencies among the findings. Research on stuttering using magnetoencephalography (MEG) and transcranial magnetic stimulation (TMS) is also considered. The findings increasingly point to a failure of normal temporal lobe activation during speech that may either contribute to (or is the result of) a breakdown in the sequencing of processing among premotor regions implicated in phonologic planning.

Learning outcomes: As a result of this activity, the participant will become familiar with some recent neurophysiological correlates of stuttering and what they suggest about the nature of this disorder. © 2001 Elsevier Science Inc. All rights reserved.

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1. Introduction

A brief comment on the origins of much of the San Antonio group's neuroimaging research on stuttering may help to understand the direction of the research program that colleagues and I have been following. This program actually emerged from some studies on the "chorus reading effect" that colleagues and I were conducting during the 1970s (Ingham & Carroll, 1977; Ingham & Packman, 1979). The chorus reading effect is the well-documented dramatic reduction in stuttering that occurs when an accompanist and a stuttering speaker read aloud the same material at the same time (Barber, 1939; Johnson & Rosen, 1937). While conducting these studies, it became apparent that the chorus reading effect had to rely on much more than just an induced speech-pattern change. During the 1970s — and even in recent years — this was the generally accepted explanation for the chorus reading effect (Wingate, 1969). Yet, every attempt to confirm that the effect is due to an induced speech pattern has essentially failed (Adams & Ramig, 1980; Ingham & Packman, 1979; Stager, Denman, & Ludlow, 1997; Stager & Ludlow, 1998). There is simply no compelling evidence that the effect depends on the speaker using an unusual speech pattern. It seemed to be the case then — and it still does — that whenever chorus reading is introduced and withdrawn, its remarkable effectiveness must be due to "something" that is literally switched "on" and "off" within the brain. However, it was not until the late 1980s that the then-evolving neuroimaging technologies made it possible to investigate the neurologic processing of that effect in stuttering speakers. Colleagues and I also speculated that imaging this effect might make it possible to identify concomitantly changing neural regions that might have functional control over stuttering.

2. Some relevant history

2.1. *Cerebral Dominance Theory*

The notion that chronic stuttering is due to an abnormal neurologic system is certainly not new; it has had a long and checkered history. Beginning with observations by Sam Orton and Lee Travis during the 1920s (Orton, 1927; Orton & Travis, 1929), this notion was then fostered by their well known Cerebral Dominance Theory (Travis, 1931, 1978). Actually, it was a theory of *failed* cerebral dominance, or nondominance, because it argued that stuttering was the direct consequence of a developmental failure to achieve lateral dominance of the speech centers. This theory waxed and waned in popularity, but somehow it survived because its central proposition — that stuttering is functionally related to failed lateralization — was never thoroughly repudiated.

2.2. Curry and Gregory (1969)

From time to time, Cerebral Dominance Theory was revitalized by some interesting findings. Arguably, the most influential of these emerged from Curry and Gregory's (1969) dichotic listening study. This study involved 20 dextral adult stuttering speakers (19 males and 1 female) and 20 matched controls. The customary right-ear preference in right-handed individuals on this task was found for 75% of the nonstuttering control subjects (reflecting a presumed left-hemisphere dominance for speech processing). Among the stuttering speakers, by contrast, only 45% displayed a right-ear preference — a strong suggestion that stuttering is associated with relatively less pronounced hemispheric dominance. However, the problem with this suggestion — and indeed Cerebral Dominance Theory — is that this conclusion was rather counterintuitive. Why? Because, on average, females also show relatively less hemispheric dominance than males (McGlone, 1980; Witelson, 1991), yet chronic stuttering is definitely *not* more common in females. What may be important ultimately, however, is that Curry and Gregory's findings were based on the processing of an auditory stimulus — a factor that appears to have taken on much more significance in the light recent neuroimaging studies.

2.3. Early EEG and brain stimulation studies

Subsequently, some neurologically oriented studies then suggested that it was the relative *degree* of hemispheric lateralization that might have functional control over stuttering. For instance, an EEG study by Boberg, Yeudall, Schopflocher, and Bo-Lassen (1983) showed that not only was there disproportionate right hemisphere alpha-wave activity across a group of 11 adult stuttering speakers (nine males and two females), but that this activity tended to shift to the left hemisphere after a treatment reduced their stuttering. Essentially similar effects were reported by Moore (1984) within a single-subject EEG experiment. Unfortunately, EEG is very prone to movement artifacts and so it is very difficult to be sure that the source of experimental effects within these studies was due entirely to CNS speech processing.

Earlier brain research had shown that areas of the cortex, basal ganglia, and thalamus are integral to speech and language function. But there were also interesting suggestions within these early studies that some of these areas are implicated in stuttering. For instance, in the early 1950s, Penfield and Welch (1951), and later Ojemann and Ward (1971), reported that direct electrical stimulation of the supplementary motor area (SMA) and the ventral lateral thalamic regions could produce stuttering-like behavior. By contrast, during the late 1980s, there were some extraordinary reports that direct thalamic stimulation could actually *reduce* acquired stuttering (Bhatnagar & Andy, 1989). These findings generally aligned with the position of a number of theorists (e.g., Crosson, 1985; Penney & Young, 1983) who argued that a cortico-striato-

pallido-thalamo-cortical loop is involved in language production and that disordered speech motor behavior reflects a dysfunction in that loop. Of course, it was well established that many of these disorders involve the classic regions such as Broca's and Wernicke's areas. But with the advent of techniques for measuring cerebral blood flow (CBF) it is now known, not surprisingly, that many other areas may also be implicated — including, for example, the anterior part of insula (Bennett & Netsell, 1999; Dronkers, 1996).

2.4. Arrival of CBF techniques

It has been known since the early exploratory work of Sherrington (1906) that increases in neuronal firing are associated with local increases in CBF. For example, one of first demonstrations that CBF may directly reflect localized neural processing was an elegant study by John Fulton (1928). This is a superb early example of a single-subject research that was conducted on an unfortunate individual named “Walter K.” Walter had an operation to remove a large collection of congenitally abnormal blood vessels overlaying his occipital cortex, but he was left with a surgical defect over the occipital lobe — actually, a gauze-covered opening to the lobe. After that Walter noticed that whenever he began to read, or went from a dark to an illuminated room, he heard “a loud, coarse, pulsating sound” coming from the back of his head. Fulton actually audio-recorded this “pulsating sound” and determined that it was, quite literally, the sound of CBF rushing to the occipital lobe. Furthermore, he not only documented this CBF effect in a series of ABA experiments, but he was the first to demonstrate a CBF task-habituating effect. This phenomenon, which has only recently been verified in positron emission tomography (PET) studies (e.g., Raichle et al., 1994), is the gradual reduction in the magnitude (and area) of CBF activation that occurs as a task becomes familiar.

However, CBF really became a serious source of investigation through the use of radioactive tracers. The history of this development is well documented by Posner and Raichle (1994). Early CBF investigators relied on relatively primitive tracers (some isotopes were actually injected directly into the carotid artery) and cameras. In fact, in 1980, Wood, Stump, McKeehan, Sheldon, and Proctor reported using an early nontomographic procedure and Xenon (unspecified) as a CBF tracer to study two right-handed adult stuttering speakers. Both were scanned before and after taking the drug haloperidol to reduce their stuttering. The investigators reported finding inadequate left cerebral dominance for speech production among their subjects that was partially rectified after haloperidol reduced their stuttering. Unfortunately, this imaging procedure could only detect CBF close to the surface of the brain — but it was a limitation that soon disappeared with the advent of more sophisticated imaging technologies.

The current advances in neuroimaging are now generally traced to the mid-1970s when Ter-Pogossian, Phelps, Hoffman, and Mullani (1975) and Ter-Pogossian, Raichle, and Sobel (1980) developed tomographic representations

of the annihilation of positron emissions from radioactive tracers. These tracers are injected into the blood stream and then recorded as they flow throughout the brain. This advance was quickly followed by the development of a variety of tracers, especially FDG (F-18 deoxyglucose) and ^{15}O . However, the spectacular advances began in the 1980s with the use of H_2^{15}O PET and the discovery that CBF showed activity in regions that were functionally associated with speech and language. This was demonstrated in the now-classic study by Petersen, Fox, Posner, and Raichle (1988), which showed the regional activations associated with passively viewing a word, hearing a word spoken, saying that word, and generating a verb from that word.

2.5. PET or fMRI

In her excellent review of PET and fMRI, Dr. Feiz has also pointed out the reasons why PET has been favored in speech research and, quite obviously, in stuttering research. Some of the most exciting developments are with hybrid systems, such as fMRI combined with magnetoencephalography (MEG) recording, which appears to improve the temporal resolution of fMRI images. In addition, a new generation of PET cameras is about to become available to researchers. These will permit huge improvements in PET's investigative potential (Fox, personal communication). There is also a lot of interest in transcranial magnetic stimulation (TMS) as a technique for identifying connectivity throughout the brain and also *modifying* CBF in specified regions of the brain (see Fox et al., 1997; Hallett, 2000). But more on TMS later in this paper.

2.6. Evaluation using condition contrasts (subtraction designs) or performance correlation

The most common experimental design used in PET studies is the classic "subtraction design," which researchers then convert to "condition contrasts." Typically, this means that a subject is scanned while resting in order to establish a CBF base rate, and then one activation task (such as speaking normally) is performed during some other scans, while a second activation task (such as speaking rapidly) is performed during another set of scans. All areas that are significantly activated or deactivated during either speech condition are first identified by contrasting each task with the resting state. The two speech conditions are then contrasted so as to identify differences in regional activation patterns between tasks, thereby identifying changes in brain activity that might be functionally associated with, say, speaking rapidly.

It is obvious that the strength of the subtraction design hinges on the extent to which it is possible to argue that there was only one essentially "pure" variable that distinguished between the two activation tasks (i.e., they are identical in all other respects). That is not always an easy proposition to defend. Petersen, van Mier, Fiez and Raichle (1998, p. 854) have provided a succinct account of the

hazards involved in assuming that this one variable is always a “pure insertion” within the subtraction design. As they cogently argue, this is especially problematic for PET studies that use strong cognitive tasks such as verb generation versus another speaking task. For that reason, other approaches are being employed, including task–performance correlations with CBF (e.g., Braun et al., 1997; Fox et al., 2000). The advantage of the performance correlation technique is that it exploits any variance in the behavior being studied. This makes this technique very suitable for stuttering research because the frequency of stuttering from scan to scan can be directly correlated with regional CBF activations and deactivations.

3. San Antonio PET study investigations of stuttering

3.1. $H_2^{15}O$ PET functional activation study (Fox et al., 1996, 2000)

Both the condition contrast and the performance correlation method have been employed in our PET studies. As mentioned above, this research program has mainly used chorus reading in conjunction with $H_2^{15}O$ PET because it can be used to almost entirely remove stuttering temporarily without producing non-normal sounding speech. Its disadvantage is that it can only be used with oral reading — and its “insertion” within a subtraction design is made less “pure” because it must be accompanied by an auditory stimulus. Another procedure we are using is training phonation interval (PI) modification (Gow & Ingham, 1992; Ingham, Montgomery, & Ulliana, 1983). Although it is not as efficient as chorus reading, PI modification does have the advantage of being suitable for spontaneous speech and does not require the addition of an auditory stimulus. However, our PET studies with PI modification have only just begun and so the experiments described below only involve oral reading and chorus reading.

The first study reviewed was reported in 1996 (Fox et al., 1996). It involved 10 right-handed adult males (mean age, 32 years), who displayed mild to severe stuttering, and 10 right-handed, adult male, normally fluent controls (also with a mean age of 32 years).

Table 1 shows the scanning order completed by these subjects. Each subject completed nine scans under three different conditions. Three were eyes-closed rest (which are labeled *Rest*), three were reading aloud (hereafter labeled *Solo*), and three were chorus readings (which are labeled *Chorus*). These conditions were presented in one of two counterbalanced sequences. During Solo and Chorus conditions, subjects read aloud the same passage from a video screen, with potential adaptation effects controlled by casual conversation with the subject during the 15-min period between each scan. During Chorus conditions, subjects were accompanied by an audiorecording of the same passage being read at an individualized comfortable rate. That recording was heard via an earphone

Table 1

The scanning order and task conditions followed by the 10 adult stutterers and 10 controls in the Fox et al. (1996) study

Order 1	Order 2
1. Rest	1. Rest
2. Solo reading	2. Chorus reading
3. Chorus reading	3. Solo reading
4. Rest	4. Rest
5. Chorus reading	5. Solo reading
6. Solo reading	6. Chorus reading
7. Rest	7. Rest
8. Solo reading	8. Chorus reading
9. Chorus reading	9. Solo reading

Half of the subjects in each group followed Order 1 and half followed Order 2.

inserted in the subject's left ear. The resulting PET data were then averaged across the three scans in each condition.

The speech performance data were the number of 4-s intervals during the 40-s scan that were judged to contain stuttering (i.e., the number out of 10), the number of syllables read aloud and the mean rating of speech naturalness on a scale of 1 to 9 for each 40-s scan. The results, summarized in Table 2, show that during Solo all stuttering speakers displayed stuttering, whereas during Chorus no stuttering was judged to have occurred. Also, during the Chorus conditions the stuttering speakers' and controls' speech rates were not significantly different — and this was also the case for ratings of their speech naturalness.

The differences between the neural regions that were most significantly activated during the Solo and Chorus conditions are summarized in Fig. 1 which is derived from the Fox et al. (1996) data. The bar graphs reflect the volume of significantly activated voxel clusters in regions of the brain during Solo conditions — shown in the left half of the figure — and then for Chorus reading

Table 2

Mean number of 4-s stuttered intervals, syllables spoken per 40-s scan, and speech naturalness rating (1 = *highly natural sounding*; 9 = *highly unnatural sounding*) during Solo and Chorus reading conditions

Group	Solo	Chorus
<i>Stutterers (n = 10)</i>		
Stuttered intervals	6.2 (1–10)	0.0
Syllables spoken	113 (82–154)	143.7 (121–173)
Speech naturalness	5.46 (3–9)	2.50 (1–4)
<i>Controls (n = 10)</i>		
Stuttered intervals	0.0	0.0
Syllables spoken	146.8 (124–188)	145.6 (121–181)
Speech naturalness	2.40 (1–4)	2.53 (1–4)

Range shown in parentheses.

VOLUME OF REGIONAL ACTIVATION

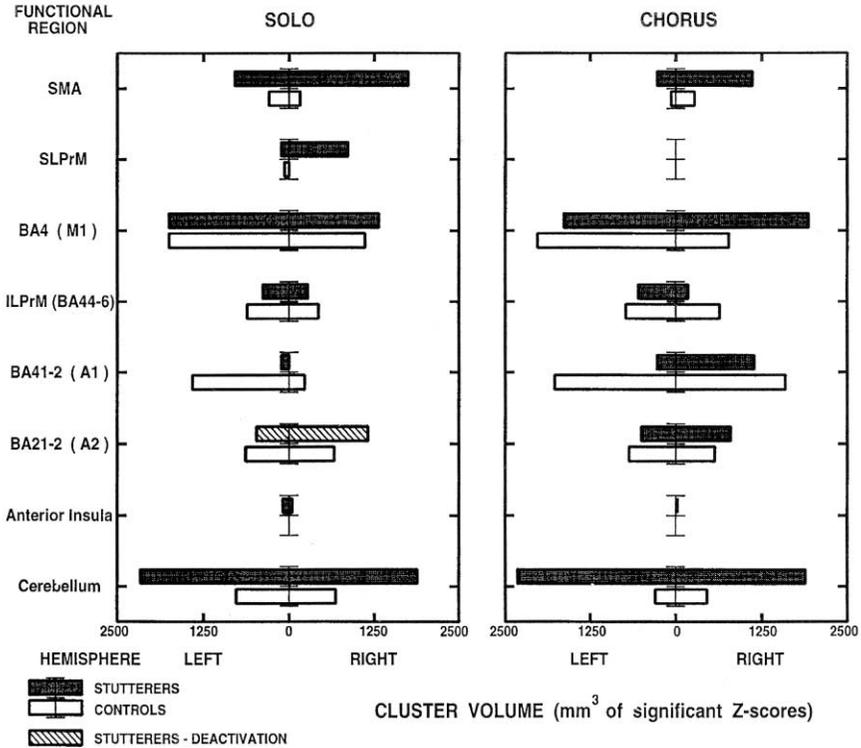


Fig. 1. Bar graph display of significantly activated and deactivated voxel clusters per region and per hemisphere for stutterers ($n = 10$) and controls ($n = 10$) during Solo (-Rest) and Chorus (-Rest) oral reading conditions. Regions include cerebrum and cerebellum. This bar graph is derived from data reported by Fox et al. (1996).

conditions in the right half of the figure. The regions were identified by the Talairach coordinates (Talairach & Tournoux, 1988) of the peak activated or deactivated voxel within a cluster. For each region, the stuttering speakers are graphed in the upper bar in black, while the controls are in the lower bar in black with white stripes. All deactivations are shown in gray.

The Solo half of the figure shows that stuttering is associated with quite distinctive pattern of brain activity. Firstly, the stuttering speakers show very prominent right hemisphere Brodmann’s Area 6 (BA 6). It should be noted that SMA and the superior lateral premotor region (SLPrM) are both in BA 6. The stuttering speakers’ BA 6 activations are much greater than the controls’ BA 6 activations. Differences between the stuttering and nonstuttering speakers’ activations were also evident for primary auditory areas (BA 41/42), anterior

insula, and cerebellum. It was particularly noteworthy that the primary auditory areas (BA 41/42) for the stuttering speakers were relatively inactive — while in contrast to the controls, the stuttering speakers' auditory association area (BA 21/22) was hugely deactivated, especially on the right.¹

On the right half of Fig. 1, it can be seen that the Chorus conditions reduced many of the observed differences between the stuttering and nonstuttering speakers. It certainly diminished the relatively excessive right hemisphere BA 6 (SMA/SLPrM) and left hemisphere anterior insula activations by the stuttering speakers. The effect of chorus reading is also shown most prominently in the premotor system, where the right lateralized activations in SMA and SLPrM were either reduced or normalized. At the same time, it is clear that the stuttering speakers still continue to show relatively larger cerebellum activations than do the controls. The Chorus condition did produce more normally intense activations in the stuttering speakers' temporal lobe, especially on the right, but that was an expected (and validating) effect because the chorus reading audio signal was delivered to the left ear.

From these data, our group concluded that developmental stuttering (at least in right-handed adult males) was characterized by extensive hyperactivity of the premotor system — with some (though not excessive) right lateralization. In addition, we deduced that the surprising levels of deactivation in the temporal lobe may have severely compromised the stuttering speakers' ability to adequately monitor their speech — at least during oral reading.

Incidentally, these were not simply group effects. The regional activations and deactivations that were observed during stuttering also showed remarkable intersubject agreement. For example, the stuttering speakers' activations in SMA, SLPrM, and anterior insula were present for between 7 and 10 of the 10 subjects.

Recently, these conclusions were fortified by a performance correlation reanalysis of the same data (Fox et al., 2000). This reanalysis involved correlating all regional CBF values with the frequency of stuttering (stuttered intervals) and then with the number of syllables spoken per 40 s. The goal was to identify the regions that correlated significantly with stuttering and regions that correlated with speaking rate. Table 3 summarizes the findings with respect to stuttering frequency and shows, in essence, that the condition contrasts and performance correlation findings complement each other quite well. On the left are the regions that were found to have significantly correlated with stuttered-interval frequency.

It will be noticed that some regions, notably the thalamus and basal ganglia, that emerged as important within the condition contrasts (see Fig. 1), actually failed to correlate with changes in stuttering. While others, such as M1 (mouth)

¹ In Fox et al. (1996), it is indicated that BA 21/22 was deactivated on the left. This was an error in the original analysis of the deactivated voxel data. The deactivations in BA 21/22 were in the right hemisphere. This correction is reflected in the performance correlation analysis reported in Fox et al. (2000).

Table 3

Results of performance correlation analysis between the frequency of stuttered intervals and regional CBF measures (from Fox et al., 2000)

	Hemisphere	Sign	Correlation (<i>r</i> range)
SMA	Bilateral	+	.35–.42
M1-mouth	Right	+	.34
ILPrM	Right	+	.34
Anterior insula	Right	+	.35–.37
Superior temporal	Right	–	.35
Cerebellum	Left	+	.34–.42
Cerebellum	Right	+	.34–.51

and cerebellum, that had shown little activation change across conditions, were significantly correlated with stuttering. The correlations are modest — generally around .3 or .4 — but they served to highlight the areas that appear to be mainly changed during Chorus Reading. In all probability, this pattern of activations and deactivations will be shown to be peaks in a system of regional interactions that form the neurophysiological basis of stuttering.

3.2. A PET functional lesion study (Ingham et al., 1996)

This section reports the results of an analysis that we made only on the Rest condition data — that is, when subjects were instructed to just close their eyes and rest. These data made it possible to conduct what is termed a *functional-lesion study*. Functional lesion PET studies seek to identify regional physiological abnormalities that are disorder-specific, but are not due to gross structural abnormalities. Actually, this study — also reported in 1996 (Ingham et al., 1996) — was prompted, in part, by an earlier SPECT brain imaging study (Pool, Devous, Freeman, Watson, & Finitzo, 1991). That study, which analyzed CBF only within a single thin brain slice, reported that stuttering speakers show abnormal neural asymmetries (right > left) in the anterior cingulate gyrus, superior temporal gyrus, and middle temporal gyrus — even when they were NOT speaking.

Our findings can be summarized quite simply: We found that when subjects were NOT speaking, there were literally *no* differences between stuttering and nonstuttering speakers for any of the regional CBF values. Indeed, there was not even a trend towards differences between these groups in the regions that had been reported to differ between stuttering and nonstuttering speakers. In short, these findings do *not* support suggestions that developmental stuttering is necessarily associated with abnormal neurophysiology. Instead, the brain physiology of stuttering speakers appears to be different only when they are speaking — or perhaps when they imagine they are speaking. Of course, the absence of neurophysiological differences cannot be interpreted to mean the absence of neuro-anatomic differences. Nevertheless, the finding that CBF activity in stuttering

speakers does not differ from CBF activity among controls when both are NOT speaking appears to be reliable; the same finding was also obtained in a 1997 PET study by Braun et al.

3.3. A PET study of imagined stuttering (Ingham, Fox, Ingham, & Zamarippa, 2000)

One other recent study from our lab (Ingham, Fox, Ingham, & Zamarippa, 2000) has investigated whether overt stuttering is a prerequisite for the abnormal or stutter-associated activations and deactivations that were found in the Fox et al. (1996) study. It has been argued that these unusual activations could be merely byproducts of the unusual speech-motor movements of stuttering during scanning (e.g., Ludlow, 1999). Consequently, we decided to investigate this issue by rescanning 4 of the original 10 stuttering speakers and their four controls. We then carefully repeated the original PET study, but with one crucial difference: Subjects were instructed not to read aloud, but only to *imagine* that they were reading aloud. During the Solo conditions, therefore, the stuttering speakers were asked to *imagine* that they were also stuttering while reading the passage. While in the Chorus condition they were instructed to listen to the recorded passage and *imagine* they were reading aloud but NOT stuttering — exactly as they had done during the previous experiment. The controls merely had to imagine that they were reading aloud as they had in the previous Solo and Chorus conditions.

All subjects were carefully trained before the scanning session to the point where each reported he could clearly imagine reading aloud and stuttering, or not stuttering, without moving any part of the speech musculature. Their reading rates in this study also partially validated the procedure, because three of the four stuttering speakers actually read fewer words during the scanned Solo conditions than they did during the scanned Chorus condition (the fourth read about the same amount in both conditions). In other words, there was a reduction in reading rate when stuttering was imagined that paralleled the reduction that occurred when the stuttering speakers read aloud and stuttered.

The results for these two groups of four subjects are shown in Fig. 2. In this bar graph figure, we have reproduced their significant activation and deactivation volumetric data during the original or overt speech conditions. These data are compared with their volumetric data during imagine speech conditions, or when they imagined they were reading aloud. It is clear from these findings that the prominent activations in the SMA, anterior insula, and cerebellum that occurred in the stuttering speakers during overt speech also occurred when they were imagining that they were speaking and stuttering. Equally important was the finding that the deactivations in A2, the auditory association area (BA 21/22), that occurred when the stuttering speakers read aloud also occurred when they imagined reading aloud and stuttering.

Finally, there is another interesting finding that is captured in Fig. 3. It shows that the stuttering speakers' abnormal activations also diminished when, during

STUTTERERS AND CONTROLS - SOLO

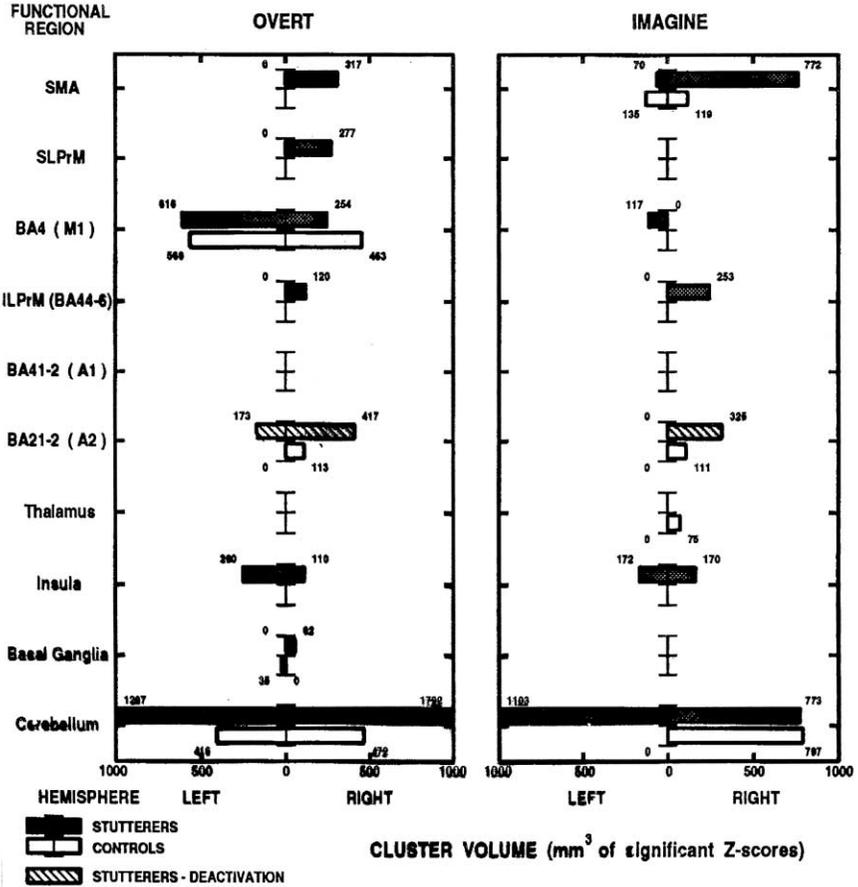


Fig. 2. Bar graph display of significantly activated and deactivated voxel clusters per region and per hemisphere for stutterers ($n=4$) and controls ($n=4$) during Overt-Solo and Imagine-Solo conditions. Regions include cerebrum and cerebellum. This bar graph is derived from data reported by Ingham, Fox, Ingham, and Zamarripa (2000).

the Chorus condition, the stuttering speakers imagined reading fluently. The increase in A2 activation was obviously due to the audiorecording.

Incidentally, the similarity between neural activations that occur when behavior is performed and when it is imagined is well-established (see Roland, Larsen, Lassen, & Skinhoj, 1980; Schnitzler, Salenius, Salmelin, Jousmaki, & Hari, 1997). Nonetheless, this is the first time that empirical observations indicate that this is also true of stuttering.

SOLO AND CHORUS - STUTTERERS

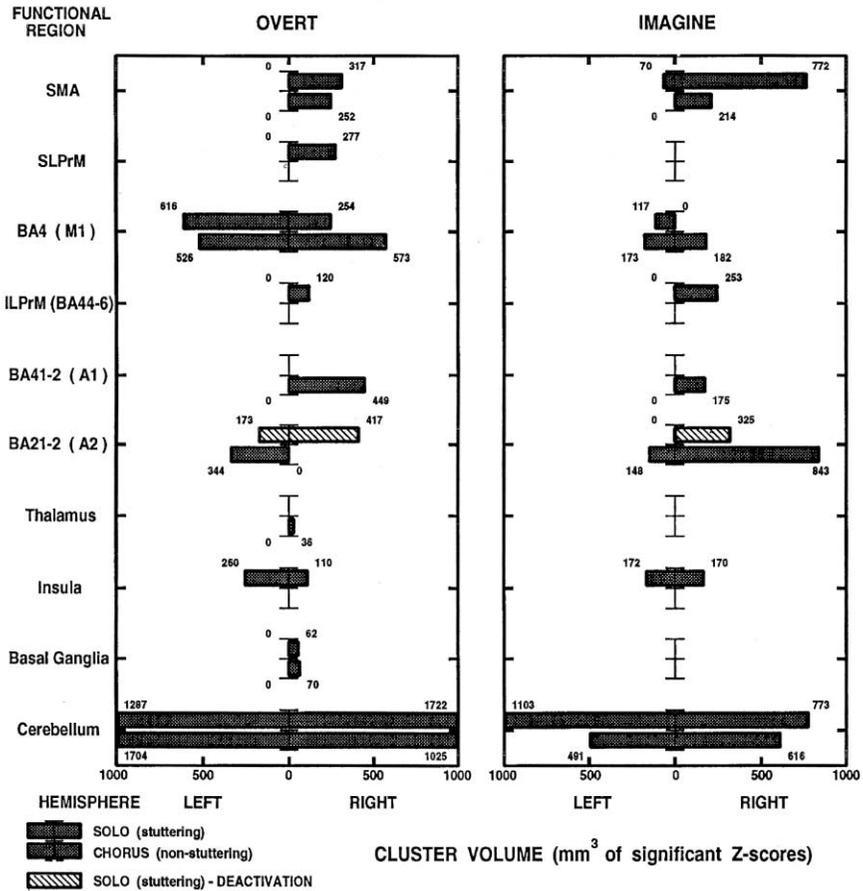


Fig. 3. Bar graph display of significantly activated and deactivated voxel clusters per region and per hemisphere for stutters ($n=4$) showing Solo compared with Chorus tasks. Comparisons are shown when tasks were performed overtly or while they were imagined. Regions include cerebrum and cerebellum. This bar graph is derived from data reported by Ingham, Fox, Ingham, and Zamarripa (2000).

3.4. PET investigation of stuttering in females

One of the recent concerns in brain imaging research on speech has been the effect of gender. This has been a particular issue ever since Shaywitz et al. (1995) reported clear gender differences for regions related to speech production:

During phonological tasks, brain activation in males is lateralized to the left inferior frontal gyrus regions; in females the pattern of activation is very

different, engaging more diffuse neural systems that involve both the left and right inferior frontal gyrus. (p. 607)

For that reason, we have been concerned to determine the extent to which our findings for males may be generalized to females. It is rather intriguing to realize that to the best of our knowledge the study described here, albeit briefly, is the first physiological or neurophysiological study that has been directed solely towards female-stuttering speakers.

Actually, there are many compelling reasons for focussing these particular investigations on female stuttering speakers. We know, for example, that the rate of recovery from stuttering among young stuttering speakers is likely to be much higher among females when compared with males (Yairi & Ambrose, 1999). Conceivably, therefore, chronic stuttering in older aged females may implicate a rather different set of neural regions. There is also evidence that females who stutter will have a significantly higher number of offspring who stutter (Kidd, Heimbuch, & Records, 1981). Consequently, the genetic expression of this disorder at a neurologic level might be expected to be more distinctive among females than among males.

The findings that are emerging from this study appear to suggest that there is considerable overlap between regions that are functionally related to stuttering. In both genders, we have found that the anterior *insula*, is especially active — perhaps much more on the left in females — and that the *auditory association area* (A2) is deactivated. We also appear to have replicated across genders the finding of an unusual lack of activity in A1 (BA 41/42) and very strong deactivation in A2 (BA 21/22). However, the condition contrasts so far reveal at least two other interesting points: (1) unlike the male subjects, there appears to be just as much SMA activation in the controls as in the stuttering speakers — perhaps more, and (2) cerebellum activity appears to be relatively similar in the stuttering speakers and in the controls. The performance correlation analyses on these findings are currently being conducted and so it is too early to know whether these differences will also be shown to be functionally related to the frequency of stuttering and/or syllable production. As mentioned above, the findings from the male subjects show that there may be important differences between the results of conditional contrast and performance correlation analyses.

What is important, however, is whether these findings and the findings from other groups using neuroimaging techniques with stuttering speakers, are replicable. And that is an issue that is beginning to take on some importance.

4. Is it possible to reconcile the inconsistent findings among recent brain imaging studies on stuttering?

Essentially all of the published reports of PET investigations of stuttering have emerged from four groups over the past 5 years (Braun et al., 1997; De Nil, Kroll,

Kapur, & Houle, 1998; Fox et al., 1996; Ingham, Fox, Ingham, & Zamarripa, 2000; Wu et al., 1995). More recently, they have been supplemented by some important MEG findings from Salmelin et al. (1998) and Salmelin, Schnitzler, Schmitz, and Freund (2000) in Finland. In total, therefore, there are relatively few studies, but some intriguing inconsistencies are beginning to emerge.

Inconsistencies among research findings generally invite two possible explanations: (1) either the findings from some studies are simply not replicable, or (2) there are plausible explanations for these inconsistencies. There are, of course, many across-study differences in their reported activations and deactivations that might be expected to occur simply because of technical differences. Among these are differences in imaging techniques ($H_2^{15}O$ or FDG PET; MEG), tasks (e.g., oral reading, spontaneous speech, single words), data processing (e.g., choice of significance level), and even the number of scans per condition (two vs. three). Nevertheless, if the principal effects related to stuttering are robust, then any findings that have been considered theoretically interesting should also be consistently replicated across studies. Some of the more noteworthy that have also been reported inconsistently are stuttering-related activations in (1) SMA, (2) anterior insula, and (3) anterior cingulate, plus (4) deactivations in A2, the auditory association area (BA 21/22). Table 4 summarizes the studies that have reported activations or deactivations in these regions for stuttering speakers during speaking tasks. Are there any reasonable explanations for these inconsistencies?

4.1. Inconsistent SMA activations

SMA has been regarded as critical to some recent theories of stuttering (e.g., Webster, 1993). For that reason, there is interest in the strong stuttering-related SMA activations that were reported by De Nil et al. (1998) and Fox et al. (1996, 2000). On the other hand, SMA activations during stuttered speech tasks were not reported by either Braun et al. (1997) or Wu et al. (1995). There appears to be a rather straightforward explanation in the case of the Wu

Table 4

Pattern of significant activations and deactivations in four selected regions across recent PET studies on stuttering

	SMA activations	Anterior insula activations	ACC (cingulate) activations	BA 21/22 (A2) deactivations
Wu et al. (1995)				
Fox et al. (1996)	✓	✓		✓
Braun et al. (1997)			✓	✓
De Nil et al. (1998)	✓	✓	✓	
Ingham, Fox, Ingham, and Zamarripa (2000)	✓	✓		✓

Studies reporting significant activations or deactivations in the selected regions are identified with a check mark (✓).

et al. study: The investigators simply did not scan high enough in the brain to record SMA. The Wu et al. study also did not use a rest-state control condition which, in turn, makes it very difficult to compare this study with the other imaging studies.

Gender effects might be one other possible explanation for the inconsistent SMA findings. The Fox et al. and the De Nil et al. studies involved only male subjects, but Braun et al. (and Wu et al.) used a mixed gender population. As mentioned above, there may be important reasons for arguing that there are gender differences in speech processing and this might apply to female stuttering speakers. For instance, in the study from our group that has just been described, the prominent SMA activations appear to be just as prominent among the female controls as they are among the female stuttering speakers. In other words, any prominent SMA activations might be gender-related rather than stuttering-related.

4.2. Inconsistent anterior insula activations

Following Dronker's (1996) important study, anterior insula has been viewed as crucial to phonologic planning and, therefore, of fundamental importance to normal speech production. Indeed, Dronker's findings may even revive speculations about the relationship between dyspraxia and stuttering (Jones, 1967). Strong and presumably aberrant anterior insula activations during stuttering were reported by De Nil et al. (1998), Fox et al. (1996), and Ingham, Fox, Ingham, & Zamarripa (2000), but not by Braun et al. (1997). Gender effects cannot be used to explain this particular inconsistency because strong anterior insula activations also occurred in our recent study with females.

One possible explanation might be related to the subtraction design that was used in the Braun et al. study. In this study, the activation data were derived first by averaging across two different spontaneous speaking tasks and then they were compared with the averaged activations during two different "dysfluency-reducing" tasks that used very different speaking rates. This across-task averaging was not used in any of the other studies. It is possible, therefore, that any significant anterior insula activations may have been masked by the condition averaging within the Braun et al. study.

4.3. Inconsistent anterior cingulate cortex (ACC) activations

Because of its location it has been theorized that ACC mediates affective and autonomic activities as well as aiding the control of motor responses (Maclean, 1993). Thus, ACC is an area of interest to many theories of stuttering. Strong ACC activations were reported by Braun et al. (1997) and De Nil et al. (1998), but were not found in the Fox et al. (1996) or Ingham, Fox, Ingham, & Zamarripa (2000) studies. One important difference between the studies that found ACC activation and those that did not could reside in the choice of speaking task. Braun et al. employed two different "dysfluency-evoking"

speaking tasks, one of which required production “of novel sentences using a verb that was assigned shortly before the onset of the scan” (Braun et al., 1997, p. 763). ACC activations were obtained in both the stuttering speakers and their controls. De Nil et al. instructed their male stuttering speakers to read aloud different lists of words that were also presented without preview. In this study, though, the ACC activations were not present in the controls. De Nil et al. concluded that this ACC activation “reflects the presence of cognitive anticipatory reactions to stuttering” (De Nil et al., 1998, p. 1038), but it is also possible that the use of this unfamiliar speaking task actually served to activate ACC in the stuttering speakers. Indeed, a number of PET studies with normal speakers have not only demonstrated that this can occur, but it has also been shown that these ACC activations may diminish as task familiarity increases (Petersen et al., 1998; Petersson, Elfgren, & Ingvar, 1999; Raichle et al., 1994). Interestingly, it appears from the same research that as ACC decreases, then there will be a reciprocal increase in insula activation.

By way of contrast, the subjects in the Fox et al. (1996) and Ingham, Fox, Ingham, and Zamarripa (2000) studies were recorded while stuttering on a very familiar continuous oral reading task and, as mentioned, there was no evidence of significant ACC activation. Consequently, if ACC activations always occur when there is stuttering during an *unfamiliar* speech task, but not when there is stuttering during a *familiar* speech task, then it seems more likely that these unusual ACC activations are functionally related to the speaking task rather than to stuttering.

4.4. Inconsistent auditory association area (BA 21/22) deactivations

Perhaps one of the most intriguing findings from the brain imaging studies has been that the auditory processing system in stuttering speakers is either inactive or deactivated during stuttering. This has immense implications for stuttering theories that have argued that audition has a critical role in stuttering. As Table 4 shows, these A2 deactivations were reported by our group (Fox et al., 1996; Ingham, Fox, Ingham, & Zamarripa, 2000), and by Braun et al. (1997), but were not reported by De Nil et al. (1998). In fact, De Nil et al. actually reported a small but significant BA 22 (part of A2) activation. However, one obvious difference between the other studies and the De Nil et al. study is that the latter did not report their CBF deactivation data. This means that it is entirely possible that there were far more substantial and intensive BA 21/22 deactivations that might have offset the reported BA 22 activation (this phenomenon occurred in the Ingham, Fox, Ingham, & Zamarripa, 2000 study).

4.5. Are some inconsistencies due to different technologies?

Some of the inconsistencies among the recent brain imaging studies may be related to differences among their technologies — but those differences are also

informative. A recent series of studies by Salmelin et al. (1998, 2000) used MEG in order to identify the sequence of neural processing during speaking tasks. MEG is capable of making temporal analyses of neural processes — a decided advantage over PET — but this advantage is offset by the limited cortical depth and specificity of MEG signals.

Salmelin et al. (1998) first located unusual temporal lobe processing among stuttering speakers that are reasonably consistent with the deactivations reported in our group's studies (Fox et al., 1996, 2000; Ingham, Fox, Ingham, Zamariippa, 2000) and Braun et al.'s (1997) study. However, in a more recent study (Salmelin et al., 2000), these researchers appear to have uncovered an unusual neural processing sequence among stuttering speakers when producing a word (nonstuttered) in response to a stimulus. They found that among controls the stimulus was first processed in Broca's area (where articulatory planning is presumed to occur) and then in the lateral central sulcus and premotor area (where motor preparation occurs). But among stuttering speakers this sequence was reversed; premotor and motor processing occurred before articulatory planning. This may prove to be an extremely important finding with interesting clinical implications. The only difficulty in interpreting the findings from this study is that the data were based on the production of fluent words. For some unexplained reason, the data from stuttered words were not reported. In addition, because MEG only records near to the surface of the brain (12 mm in Salmelin et al.), it is not possible to know what role regions that reside at a deeper level, such as anterior insula or ACC, might have played in this process.

4.6. Do these findings help to narrow the search for an aberrant neural system?

Based on the forgoing, it would appear that the critical and malfunctioning neural system associated with stuttering will very likely involve an interplay between the premotor and the auditory regions of the brain. The aberrant system appears to occur bilaterally, but more dominantly in the right hemisphere. By a judicious blending of current MEG and PET findings, some critical elements of the system are beginning to be isolated. It would appear from these findings that a failure of normal temporal lobe activation may either contribute to (or is the result of) a breakdown in the sequencing of processing between the premotor area — possibly anterior insula — and Broca's area.² This breakdown is obviously intermittent and can be modified by various "fluency-inducing" strategies. Precisely why or how these modifying procedures interact with this system is an issue that will surely have wide-ranging clinical implications.

² Interestingly, in their recent review of neuroimaging studies of stuttering, Sandak and Fiez, (2000) drew similar conclusions, but for some reason failed to recognize the role of the auditory system.

5. The future: can abnormal neural activations be modified?

The clinical implications of these findings are, of course, as important as their theoretical implications. Indeed, in the final analysis, I believe that the findings from this research will only move the field forward if they lead to more effective and efficient methods of changing this problem behavior. This is an almost essential next step if neuroimaging-based research is going to avoid repeating the lack of clinical progress that has resulted from the past two decades of research driven by the speech-motor model of stuttering (Ingham, 1998). At the same time, it is interesting to consider how the neuroimaging findings relate to some known clinical strategies, especially those based on speech-pattern change. In fact, as mentioned earlier, the functional bases of components of prolonged speech are currently being investigated in the San Antonio research program. One interesting possibility is that the effectiveness of the response-contingent stimulation strategies, especially with children, might be because they activate a dormant auditory processing system by “highlighting” (Siegel, 1970) previously unrecognized events. Research on these effects may certainly assist clinical management of stuttering, but it may also be possible to directly modify aberrant neural activations and deactivations.

One of the more radical clinical approaches that the San Antonio group has begun to explore is the use of TMS (George, Wassermann, & Post, 1996) in an attempt to see if it is possible to directly modify the abnormal neural activations that stuttering speakers produce during speech. That technology, which involves direct magnetic stimulation of regions close to the surface of the cortex, is also being used in an effort to identify the interconnections in neural systems associated with fluent and stuttered speech (Fox et al., 1997). There is ample evidence from our investigations that TMS is able to activate particular regions, but thus far we have been unable to deactivate these regions (Ingham, Fox, Ingham, Collins, & Pridgen, 2000). Some recent PET/TMS research does suggest that a particular “stimulus train” may deactivate regions in BA 4 (Paus et al., 1998), but that finding has yet to be replicated. A recent German study (Mottaghy et al., 1999) is promising from another direction. This study found that it may be possible to stimulate and activate the auditory association area (BA 21/22) using TMS. If this proves to be a reliable finding, then this may offer some prospects for directly modifying stuttering.

In conclusion, I believe that the recent neuroscience approach to the investigation of stuttering continues to be an exciting development. It will be interesting to see if some of the insights from this research will actually lead to a long-overdue breakthrough in our understanding of, and especially treatment for, this disorder. I believe that this will most likely emerge from a marriage between neuroscience and genetics — but that is another story entirely. For the time we can only speculate about the exciting progeny that might emerge from that union.

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Appendix A. Continuing education

1. The Cerebral Dominance Theory of developmental stuttering by Orton and Travis argues that
 - a. Stuttering is the direct consequence of complete cerebral dominance of language.
 - b. Stuttering is the direct consequence of no lateral dominance of the speech centers.
 - c. Stuttering seems to be independent of which cerebral hemisphere is dominant for language.
 - d. Stuttering only occurs in individuals who are right hemisphere dominant for language.
2. Studies have shown that direct electrical stimulation of the following brain areas can produce stuttering-like behaviors
 - a. Corpus callosum and the vermis of the cerebellum electrical stimulation
 - b. Direct thalamic and supplementary area electrical stimulation
 - c. Electrical stimulation of Wernicke's area and the vermis of the cerebellum
 - d. Ventral lateral thalamic regions and SMA electrical stimulation
3. Transcranial magnetic stimulation attempts to modify stuttering by
 - a. Decreasing tension in facial muscles associated with anticipatory behaviors
 - b. Stimulating regions close to the surface of the cortex
 - c. Stimulating cranial muscles to distract the person who stutters from anticipatory behavior
 - d. Stimulating regions close to the midbrain
4. It appears that critical and malfunctioning neural systems associated with stuttering will involve an interplay between
 - a. Premotor and auditory regions of the brain
 - b. Thalamic and auditory regions of the brain
 - c. Cerebellar and sensory regions of the brain
 - d. Thalamic and sensory regions of the brain
5. CBF activity in stuttering speakers
 - a. Is decreased from CBF activity among controls when both groups are not speaking

- b. Is increased from CBF activity among controls when both groups are not speaking
- c. Is not different from CBF activity among controls when both groups are not speaking
- d. Has not been measured when subjects are not speaking

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