ABSTRACT

Title of Dissertation: SELF-MONITORING AND SENSORY FEEDBACK IN DISORDERED SPEECH PRODUCTION

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The precise contribution and mechanism of sensory feedback (particularly auditory feedback) in successful speech production is unclear. Some models of speech production, such as DIVA, assert that speech production is based on attempting to produce auditory (and/or somatosensory targets; e.g. Guenther et al. 2006), and thus assign a central role to sensory feedback for successful speech motor control. These models make explicit predictions about the neural basis of speech production and the integration of auditory and somatosensory feedback and predict predict basal ganglia involvement in speech motor control.

In order to test the implications of models depending on the integration of sensory feedback for speech, we present neuroimaging studies of two disorders of speech production in the absence of apraxia or dysarthria - one acquired (Foreign Accent Syndrome; FAS) and one developmental (Persistent Developmental Stuttering; PDS). Our results broadly confirm the predictions of the extended DIVA (Bohland et al. 2010) model, and emphasize the importance of the basal ganglia, especially the basal ganglia-thalamic-cortical (BGTC) loops. I argue that FAS should be thought of as a disorder of excessive speech sensory feedback, and that fluency in PDS depends on successful integration of speech sensory feedback with feedforward control commands.

SELF-MONITORING AND SENSORY FEEDBACK IN DISORDERED SPEECH PRODUCTION

by

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Speech Motor Control

The precise relationship between speech sensory input/feedback and the motor control needed for the production of speech has been a subject of a great deal of research (Perkell et al. 1997; Houde and Jordan 1998; Kent 2000). While debate rages (e.g. Fadiga and Craghiero 2003; Watkins et al. 2003 Galantucci et al. 2006) about the extent to which motor systems are involved in the successful perception of speech, this disagreement is obviously not possible when it comes to the production of speech. To speak successfully, a speaker must be engaging both motor systems - to actually produce the necessary gestures - and the perceptual system - to monitor their production for errors and to guide production (although there is debate as to the extent that fluent natural adult speech requires constant involvement with the perceptual system; see Perkell 2010). In the absence of relevant sensory input, speech production eventually degrades, as has been well-documented in the case of acquired deafness (Binnie et al. 1982; Cowie and Douglas-Cowie 1992), so it is beyond dispute that sensory feedback plays some role in successful speech production. However, two major issues remain – the nature of the goals of the process of speech production, and the mechanisms by which feedback can influence production.

The first of these is the divide between articulatory (Browman and Goldstein 1992; McMahon et al. 1994) and auditory/phonetic (Coleman 1998; Flemming 2001; Port and Leary 2005) theories of phonology – should the basic goal of speech production be understood as realizing certain motor gestures or as realizing certain auditory images? This is a problem on the computational level as defined by Marr (1981), since these theories are attempting to solve the same problem (produce comprehensible speech)

while conceptualizing that problem in fundamentally different ways (matching production to a stored auditory target or matching production to a learned series of movements). It does not greatly matter to proponents of a motor-gesture based theory of speech production whether human mirror neurons (a proposed algorithm for speech production; e.g. Fadiga et al. 2004) are in the inferior frontal gyrus or in the anterior insula, or whether human mirror neurons are gesture-specific or goal-specific. Their only relevance to the argument between articulatory and auditory theories of phonology is whether they allow the storage, retrieval, and production of phonological sequences specified in motor terms. The goal of the system is to produce the appropriate series of articulatory gestures. Similarly, whether Heschel's gyrus or the temporal-occipital-parietal junction is the critical locus of phonological processing necessary for guiding speech production is irrelevant to this question; it is enough that these are primarily auditory areas that are critical in successfully speaking, as the goal of the system is to produce the appropriate series of sounds. The balance of the literature (Coleman 1998; Callan et al. 2000; Kent 2000; Postma 2000; Galantucci et al. 2006), however, has tended to conclude that speech production relies on auditory targets rather than gestural targets, and most explicit models of speech production have adopted the auditory approach (Guenther et al. 2006, Ventura et al. 2009, Hickok et al. 2011).

Given auditory targets, how does the speech motor system achieve those targets? It is not enough to say that sensory feedback guides production; this is true if the targets are auditory and the system is to respond to feedback at all. There has been a general recognition of the utility of analysing speech disorders in the context of theoretical frameworks of speech production (Van der Merwe, 1997; Ziegler 2002),

especially in dealing with speech disorders that clearly engage language-specific systems rather than motor control more narrowly (Ziegler 2002). This dissertation follows from that recognition.

What is needed is concrete proposals of how this is done by the brain in attempting to achieve the goal of producing speech sounds matching auditory targets. Such a proposal does not need to specify the exact transformations into neural commands that are relayed into neuromuscular junctions, since the actual biophysics of articulation *per se* are non-trivial. Such a proposal must, at a minimum, fulfill the following criteria:

1) The model must have some representation of the auditory characteristics (as this is the basic goal of the system) of phonetic targets (whether they are specified in terms of sounds or distinctive features) that is consistent (not necessarily identical) in all instances of the same phonological context. In other words, the representation of /k/ might depend on whether it is followed by a front vowel, but it should not depend on whether /d/ is the last or first sound of the word. Predictable phonetic variation is thus permissible.

2) The model must reliably send the same sequence of commands to the articulators for the same phonological target in the same phonological context. For example, a word-initial /k/ followed by a high vowel should not be produced in radically different physical ways from one instance to the next, all things being equal.

3) The model must be able to adjust its output based on changing auditory

feedback, which must come in a form known to be available either as a Fourier transform of the signal or as the result of well-characterized neural processing.

These criteria are more than fulfilled by the most well-known speech production model in the literature, the DIVA model (Guenther et al. 2006). DIVA has been subjected to many experimental confirmations (described below) of its predictions and basic structure, and as such we will summarize it in some detail. The name stands for Directions Into Velocities of Articulators, which hints at the basic output of the model, namely an 8-dimensional vector specifying the positions of the articulator elements of a Maeda synthesizer (an independently derived method of generating sounds from articulators). Since the model produces output with this specificity, it can and has been implemented in forms that produce plausible speech sounds (see Guenther et al. 2006 for details of simulations), but this is not a strict requirement of the criteria above. Note that the Maeda synthesizer element is not an integral part of the DIVA model; it simply provides a convenient and implementable transformation from the auditory state output (described below) to an actual waveform.

The DIVA Model

Below is a graphical representation of the DIVA model (Guenther et al. 2006). Each of the boxes in the diagram is a set of nodes in what is essentially a large and structured neural network. Each of these sets of nodes is thought to be responsible for a particular set of representations, referred to as “maps”. These “maps” have specific

anatomical correlates that have been posited on the basis of previous neuroimaging and electrophysiological work (see Appendix A for a full listing of the empirical base of the DIVA map localizations).

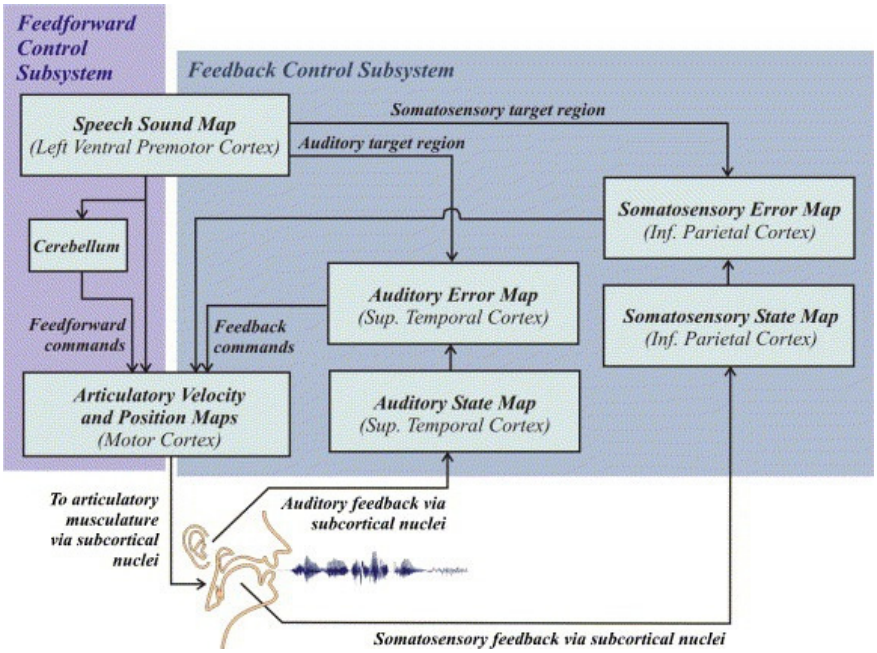

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Figure 1.1 An overview of the DIVA model (Guenther et al. 2006)

DIVA operates in a cyclical fashion, with each cycle corresponding to the production of one target, generally taken to be a syllable (Guenther et al. 2006). Production of an auditory target starts with a particular, consistent pattern of activation of the speech sound map, which has a set of weights connecting it to the auditory and somatosensory error maps, the cerebellum, and the articulator maps. The weights connecting it to these first two produce expected auditory and expected somatosensory consequences of the speech target. After the sound is produced, a transformation is

applied to the resulting spectrogram (as a proxy for cochlear processing) to produce activity in the auditory state map, and a different transformation maps the actual articulator movements to the somatosensory state map. Both state maps are compared to the expectations of the sensory consequences of the production (represented by activity in the auditory and somatosensory error maps), and these expectations are checked against the actual consequences by projections from the sensory state maps to the error maps. New activity created by these state map projections leads to adjustments to ongoing productions via weights from the error maps to the articulator velocity and position maps. Thus, DIVA incorporates both feedback and feedforward control of articulation – from the particular set of motor commands associated with a segment that have been learned over time (the weights between the speech sound map and the articulator velocity and position map) and from sensory error signals and resulting adjustments (caused by discrepancies between sensory expectation and sensory input).

Neurobiological evidence for the DIVA Model

A great strength of the DIVA model is the imaging studies (Bohland and Guenther 2006; Ghosh et al. 2008**;** Tourville et al. 2008**;** Golfinopolous et al. 2010) that have been carried out in order to localize its postulated components. The extensive and obvious behavioral output of a motor control system allows for more behavior-neural function correlations to be made than is at present possible for systems whose workings and output are somewhat more abstract, and DIVA uses this to make specific

hypotheses about where each of its parts is located in the brain. Additionally, since motor control broadly speaking is not limited to humans, single-cell recording work (e.g. Kalaska et al. 1989) in primates has allowed the postulation of correlations between parts of DIVA and specific cell types within these structures, such as the hypothesized correspondence between the articulator velocity map and phasic cells in motor cortex (Tourville and Guenther 2010).

Even where assignment of function to particular cell populations is not possible, localization of the functional components of DIVA still goes beyond simple correlation between regional activity and putative regional function. It is possible to generate model hemodynamic response functions from activity within each map (Ghosh et al. 2008), which serve as a prediction of the fMRI signal in the corresponding voxels when that map is engaged. Thus, DIVA can make genuine quantitative predictions (i.e. how strong should the signal be in a particular area at a particular time) about neural activity (Ghosh et al. 2008) that are directly testable by neuroimaging methods, rather than qualitative predictions (i.e. what areas should be active above baseline during a task). Because speech motor control tasks are physical responses, it is also possible to intervene directly to disrupt production (Tourville et al. 2010), which, combined with those quantitative predictions, allows for causal conclusions to be drawn from neuroimaging experiments (i.e. intervention X was carried out which led *directly* to specific consequences *Y*), as opposed to the correlational logic usually employed in neuroimaging (i.e. stimulus X was presented and consequences Y happened at some time subsequent; see Walsh and Pascual-Leone 2005 for discussion of this distinction in the context of TMS).

DIVA's concrete localizations have also been valuable in modeling disorders of speech production (Tourville et al. 2010). Apraxia of speech, an acquired or developmental specific difficulty in the motor realization of speech sounds, has been associated with left-lateralized lesions or structural abnormalities in frontal operculum, inferior frontal gyrus, and ventral precentral gyrus (Duffy 2005). This falls directly in the neural regions thought to contain the speech sound map in the DIVA model, which explains the chief deficit in AOS quite neatly – disruption of the speech map leads to disrupted motor planning for speech sounds, without significantly affecting motor control more broadly. Persistent developmental stuttering has also been explained using the DIVA model (Max et al. 2004); it has been postulated that it is a disruption of the feedforward control signal reaching the articulator maps, and a consequent overreliance on auditory feedback signals, that is the underlying impairment in stuttering (Max et al. 2004).

State Feedback Control Model

While the DIVA model relies heavily on direct sensory feedback in order to complete the task of speech motor control, other modelers (Ventura et al. 2009, Hickok et al. 2011) have balked at the idea of two separate control systems (feedback and feedforward), and have pursued a state feedback control (SFC) solution. In an SFC system, direct sensory feedback from the environment is not directly compared to the auditory target to produce error signals. Instead, the system compares the incoming auditory with an internal projection of the likely consequences of the set of commands

actually sent to the articulators, providing a kind of internal feedback. It is the difference between the sensory feedback and the internal prediction of consequences that generates error signals, rather than a comparison between sensory feedback and the auditory target. This approach has come to dominate motor control theory in neuroscience (Nakanishi and Schaal 2004; Park et al. 2004; Alexandrov et al. 2005; Shadmehr and Krakauer 2008) outside of the speech domain and has recently been argued to underpin speech motor control as well (Ventura et al. 2009, Hickok et al. 2011)

A major advantage of the SFC model (Hickok et al. 2011) over the DIVA model, independent of theoretical parsimony, is its superior handling of noisy or absent feedback. In DIVA, error signals are directly generated by differences between sensory feedback and auditory targets. When sensory feedback is reasonably clear, this system is adequate – discrepancies between the two will lead to adjustments in the direction of the auditory target. But when sensory feedback is seriously deficient or absent (e.g. in the presence of a loud masking noise), the error signals generated by this approach will be very large, because the available feedback will be remote from the target. Thus, a model like DIVA must predict that speech would very rapidly degrade into incoherence in the environment of a crowded nightclub or noisy bar, since the large error signals would cause gross adjustments in articulator movements and posture in an attempt to reduce the discrepancies caused by impoverished feedback. After all, there is no mechanism for the model as currently constituted to change its predictions about what a speech sound ought to sound like (although this might in principle be added to the model). While it is harder to hear and make oneself understood in very noisy

environments, the slightest bit of practical experience will suggest that people do not generally abandon the normal articulatory movements of their languages in noisy situations.

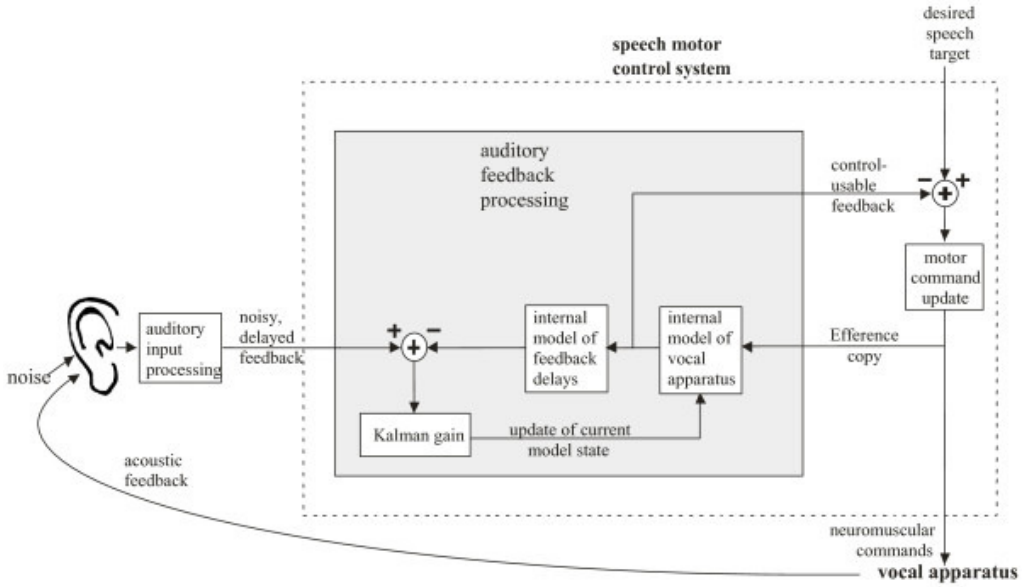

Figure 1.2 State feedback control model of speech (adapted from Ventura et al. 2009)

In an SFC model, sensory feedback is not directly compared to the expected consequences of the auditory target, but passes first through a Kalman filter, a solution to estimating the current state of a time-controlled process that takes into account the current state of the system and the measurement error of the data being received (Kalman 1960; Jacobs 1993). The goal of the Kalman filter is to provide an estimate of the true state of a system of motor controllers, which can then be used to generate future commands to accomplish a system's goals (Kalman 1960). This is an estimate rather than a true picture of the state of the controllers because it is assumed that there is not only noise in the measurements of the controllers' states available to the filter, but noise in the command system that moves those controllers. The Kalman filter is thus a

principled way of compensating for these sources of noise, critical for motor control in any realistic environment.

SFC is not without its own problems. It is critically dependent on having a good observation model, the matrix that relates observations and the estimate of the true state of the vocal apparatus, but this must be hard-coded in current implementations of the model (Ventura et al. 2009) – there is as yet no proposed mechanism for learning them. If the speech system was entirely static, this would not be a serious objection – the model would simply have the parameters that it empirically happened to have, possibly as a result of innate specification. But the vocal tract and articulator configurations of each speaker vary significantly over development, simply due to biological growth, and accounting for how an actual motor control system can learn to adjust when its articulators change in size and relative proportions is a non-trivial problem (Guenther et al. 1998).

DIVA and SFC

In principle, a synthesis between the two models would be desirable, one that combined the strengths of both and had the weaknesses of neither. In practice, this is not truly possible. Each model has a very different conception of the role of feedback in speech motor control, and it is specifying the role played by feedback that poses any difficulty in creating such models. After all, if speech motor control really constituted a set of fixed associations between intended sounds and a set of motor commands, with no further influences, creating a model system would be trivial.

In the DIVA model, the feedback system operates by minimizing the difference

between predictions about the sensory consequences of speech targets and the actual consequences themselves. The difference between prediction and consequence is used to generate adjustments to motor plans supplied by a learned association between the targets and previously efficacious commands. In the absence of significant error signals, feedback is irrelevant to the speech production process. Thus, DIVA is truly a feedforward control model, with feedback playing, at best, a modulatory role; the system will function to some extent even in its absence (even if not well).

By contrast, feedback in the SFC system is conceptualized as attempting to predict and/or update an internal model of the vocal tract. It is this internal model of the vocal tract that is actually responsible for producing the commands sent to the musculature. The particular identity of the speech target determines the function that will map the vocal tract onto its configuration at the next time step, but without the input of the internal model (that is a part of the feedback mechanism), there cannot be motor commands at all. The state-dependent nature of the Kalman filter means that the internal model can be updated in the absence of useful sensory input (these estimates will just be dominated by the product of the control-input vector and the control matrix from the last time step), but the filter itself cannot be disconnected from the model without wrecking it completely.

In this sense, then, DIVA and SFC models are fundamentally different approaches. DIVA cannot be made into an SFC system simply by adding a Kalman filter at some point in the process – it is simply not compatible with the framing of the task assumed by the system. Similarly, SFC cannot learn all of its necessary weightings in the same way that DIVA does – without a reasonably good observation model, it cannot

generate useful estimates of the current state of the vocal tract, and thus cannot update the internal model in a constructive way. The limitations described on these systems are a consequence of the basic architecture of the systems, and any “synthesis” of the two would involve removing most of the components and features of one or the other.

As presently constituted, SFC models will generally cope better with feedback than DIVA, and the SFC is certainly a more principled approach to speech motor control in the sense of primarily relying only on one control mechanism, as opposed to DIVA's feedback/feedforward hybrid (Hickock et al. 2011). However, for the purposes of providing a framework for the interpretation of findings from speech disorders, the DIVA model is superior for three primary reasons. First, DIVA makes very specific neural predictions about the localization of its functional components (Tourville et al. 2010), whereas at present SFC models have only committed to the primary auditory cortex as the location of the Kalman filter (Houde et al. 2007). This obviously makes DIVA more relevant to and easier to evaluate from the context of neuroimaging studies of speech. Second, the fact that it makes these very specific predictions means that it has a larger base of empirical support behind it, in the form of psychophysical (Villacorta et al. 2007; Tourville et al. 2008; Nikizolek 2010) and neuroimaging studies (Bohland and Guenther 2006, Ghosh et al. 2008; Tourville et al. 2008, Golfinopoulos et al. 2010). SFC models are a more recent innovation, and although they may in time accumulate such a body of evidence, such evidence is lacking at the moment. Finally, the DIVA model has fewer hard-coded specifications than SFC, as it learns the relationship between particular sound targets and the motor commands needed to produce them reliably (Guenther et al. 1998). SFC cannot function without a specific

observation matrix, since it cannot relate sensory input to its projection of the state of the vocal tract, and no learning function has yet been proposed for this observation matrix to be induced on the basis of data.

Even without these advantages over the SFC, DIVA would be the preferred model for interpreting results from speech disorders because it has been productive in modelling work (Max et al. 2004) on one of the disorders that will be considered below. Based explicitly on an integrative model of speech motor control like DIVA, Max et al. (2004) proposed two separate hypotheses about the cause of stuttering, both of which posit a weakness of the auditory feedback system. The first of these hypotheses is that people who stutter (PWS) have unstable internal models of speech, in the sense that they are updated too rapidly by incoming sensory information. This leads to constantly changing mappings between articulatory intentions and motor action, and thus lead to inaccurate or inadequate feedforward commands. This would lead to constant mismatches between expected sensory outcomes and sensory feedback, and lead to frequent adjustments in feedforward commands, presumably producing the primary symptoms of persistend developmental stuttering (PDS). Under this hypothesis, PWS successfully avoid stuttering by relying more heavily on feedback signals for motor control, and since these signals occur at a 10-25 millisecond (Schroede and Foxe 2002) delay relative to the motoric gestures that produced them as a simple physical consequence of sound and nerve conduction occurring at finite speeds, anything that increases the duration of speech would be expected to be helpful for stutterers (Max et al. 2004). It should be added here that the same logic would predict that anything making speech less automatic would help, as the contribution of the feedforward system

would necessarily be weaker under unusual, unlearned conditions. Simulations confirm the plausibility of this approach to PDS (Max et al. 2004), and excessive feedback monitoring ameliorated by distractors forms the basis of some proposals of stuttering (e.g. Vasic and Wijnen 2005).

The second hypothesis is that PWS rely excessively on feedback control signals without any particular instability in their feedforward control system, and that it is this reliance on feedback that causes the primary symptoms of stuttering. This hypothesis rests on the idea that a motor control system depending largely on feedback signals will be relatively unstable due to the inherent lag between movement and feedback, and that this will produce unwanted oscillations in the system. This hypothesis contends that PWS rely on feedback because they have weak projections from the feedforward control system, and so feedback reliance is less a compensatory strategy and more a characteristic of their neural anatomy (Max et al. 2004). State feedback control models, comprising only one control pathway, cannot capture the conflict between two systems that these hypotheses rest on. Testing these hypotheses requires assuming something very much like DIVA.

The DIVA framework will also be adopted for the interpretation of the experimental studies I present below. Despite the advantages of the DIVA model, it remains a model of single syllable production, starting from the representation of a syllable and ending with the syllable being produced by the articulators. It does not in any way represent planning of speech, or the mechanism by which speech sounds are released to the articulators for realization. It thus cannot account for much of the behavioral and imaging data in the speech production literature (see Indefrey and Levelt

2004 for a review). However, a computationally explicit implementation and extension of the model exists for the production of phonological sequences as well as syllables in isolation. This extension is known as the GODIVA model (Bohland 2007; Bohland et al. 2010).

Unlike in DIVA, GODIVA does not represent speech sounds simply as a set of sensory consequences; rather, it employs an abstract, segmental representation to allow for planning of future segments in serial order (Bohland 2007). This abstract representation has been implemented to date in a segmental fashion, and thus might be most obviously interpreted phonemically, but these segments can be implicitly coded in such a way as to capture featural similarity between phonemic categories (Bohland et al. 2010). These segmental representations are also organized into syllables, primarily on the basis of speech error (Shattuck-Hufnagel 1979; Treiman and Danis 1988) and priming (Sevald, Dell and Cole 1995) findings.

GODIVA continues the approach of DIVA in also postulating specific neural counterparts to each functional unit within its network. The neural areas added to DIVA include the prefrontal cortex, medial frontal cortex (supplementary motor area and pre-SMA), and the basal ganglia, specifically basal ganglia-thalamic-cortical (BGTC) loops (Bohland et al. 2010). The interface between the planning and serial order components added by GODIVA and the original DIVA areas is thought to be in the speech sound map, usually localized left ventral premotor cortex and/or posterior IFG (Guenther et al. 2006). GODIVA provides syllable targets to the speech motor control system instantiated by DIVA; its contribution is to take inputs from lexical/semantic systems representing words or short phrases and render them into executable syllables.

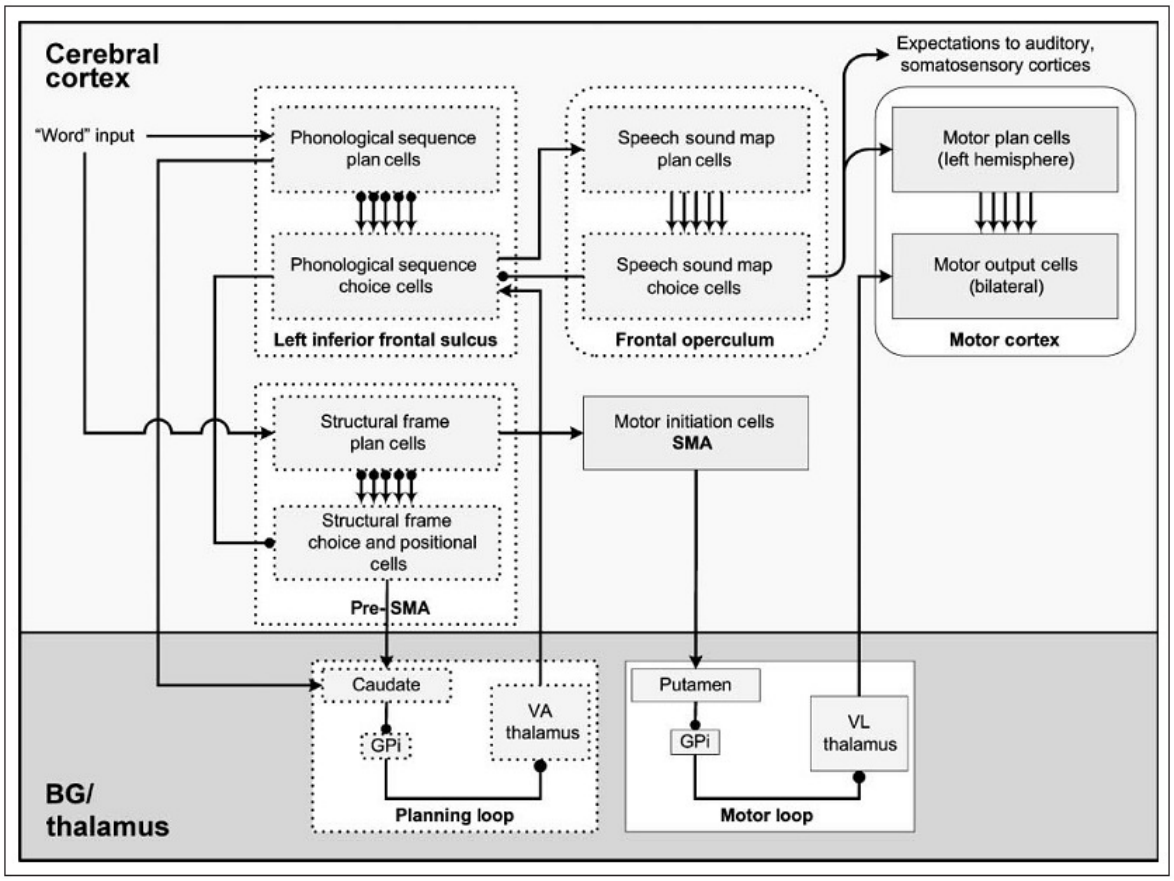

Figure 1.3 The GODIVA model (Bohland et al. 2010).

The above areas are labelled with their basic functions, apart from the basal ganglia loop. The basal ganglia-thalamo-cortical (BGTC) loop containing the caudate passes information about potential syllable positions along to the "choice" layers, which actually select the appropriate phonemic representation for insertion into those abstract syllable frames. This caudate loop corresponds to the associative or "cognitive" loop well-described in the human neuroanatomical literature (Alexander and Crutcher 1990). The BGTC loop containing the putamen has a "motor release" function, i.e. it

determines when incoming planned utterances can be released to the primary motor cortex for production, once some criteria are fulfilled. Since multiple possible planned utterances can be active at any one time (representing different possible motor plans for realizing the planned utterance), this selection process is competitive, and GODIVA postulates active bidding for selection from each plan, modulated by inputs from the supplementary motor area. The characterization of this BGTC loop as a "motor" loop is also well-supported by the neuroanatomical literature (DeLong 1990).

GODIVA thus provides a computationally explicit model of speech sequence planning that also makes specific predictions as to the involvement and function of particular neural areas. Since it also interfaces with DIVA, the combined system provides a computationally explicit model of speech with similarly specific neural predictions, and it is this framework that will guide interpretation of the neuroimaging studies presented below. Specifically, neural regions found to be involved with speech in the these studies will be assumed to be carrying out the functions presented in these frameworks, and regions associated with disordered behavior will be taken as suggesting that the functions those regions subserve are impaired in these disorders.

Disordered Speech

The essential logic of examining this question of sensorimotor interactions in speech production through studying disorders of speech is that neural activity associated with disordered speech will be neural activity associated with speech *per se*. In other words,if the disordered behavior is disordered speech, then any activity strongly correlated with it will be strongly correlated with speech. This logic requires that the disorder be a speech disorder rather than a disorder at a lower level (such as basic motor control) or a disorder of a higher level (such as semantic representations, as in Wernicke's aphasia). The disorder must not impair the ability to move one's articulators outside of speech contexts, and the patient must be able to form coherent propositions and grammatical sentences. The patients should also have normal hearing, since a disorder at the level of the cochlea, while it may have knock-on effects for speech, is not really a disorder of speech. The problem must come in the speaking of a message, not in the hearing or creating of it, as might be the case in Wernicke's or Broca's aphasia (Caramazza and Zurif 1976) .

Another distinction to be made between language disorders is between acquired and developmental disorders, each of which might have a different sort of effect upon the neural circuitry recruited for speech. Both sorts of disorders can be argued as offering a better window into understanding normal functioning. An acquired disorder might be taken as a superior object of study because the

subjects had ostensibly typical brains for many years prior to whatever accident caused the disorder, and so their patterns of neural organization might be more typical away from the particular locus of injury. However, the very fact that their brains were sufficiently injured to produce a diagnosable condition might weaken their relevance to normal functioning. The ways in which healthy neural tissue interacts with diseased or seriously damaged tissue, and how the system as a whole compensates for such damage, is not well understood (e.g. Guido et al. 1992). Furthermore, especially in the acute stages of disorders, on-going reorganization might lead to an unstable pattern of recruitment that makes clear conclusions difficult (Finger and Almli 1985).

Developmental disorders, on the other hand, do not suffer from the interpretative problem of injury. The neural organization of those with these disorders is not the result of sudden accident, and thus will reflect a more stable pattern typical for the subject. Of course, this stable but unusual organization is exactly the drawback of basing conclusions on developmental disorders - there is no guarantee that the pattern in a developmentally disordered population resembles normal functioning . Thus, it cannot be said that either sort of disorder is better for illuminating normal functioning; they are complementary, and each has advantages and disadvantages. Critically, a disorder being characterized as developmental does not preclude the existence of environmental triggers or causes or imply that it is experience-independent (Karmiloff-Smith et al. 2002). Persistent developmental stuttering can thus be a developmental disorder while

still having a distinct onset in childhood (Bloodstein and Bernstein-Ratner 2008).

Below I present two experimental studies of disorders of speech production, one of which is acquired (foreign accent syndrome; FAS) and one of which is developmental (persistent developmental stuttering; PDS). Both are disorders diagnosed on the basis of speech behavior, and both disorders are thought to be independent of basic articulator motor control, so they are speech-specific. The extent to which higher-level linguistic function is impaired in these disorders, particularly PDS, is unclear (cf. Bloodstein and Bernstein-Ratner 2008 for a review), but these impairments, to the extent that they exist, are not the primary symptom in either disorder. The challenge facing patients with both disorders is not formulating what to say, but in planning the utterance itself or actually getting the words out (Bloodstein 2001), like a native speaker in the case of FAS, or at all in the case of PDS.

The two studies below also use two different neuroimaging technologies, functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). Consistencies across the two studies are thus particularly striking, given the different strengths of the two methods, and the differences between the two disorders. Findings from both studies will be interpreted in the framework of DIVA-based models of speech motor control, and will be explained in terms of speech feedback and self-monitoring.

It should be noted that self-monitoring in the context of this dissertation

refers to an automatic, non-consciously driven process of altering motor plans based on a percept of current speech production. DIVA-based models, while based on the idea that a feedback pathway for speech motor control exists, makes absolutely no claims about the extent to which a speaker is conscious of error signals. Adjustments on the basis of altered feedback certainly do not require conscious awareness, as has been demonstrated previously with covert feedback alterations (Tourville et al. 2008). Metalinguistic awareness of speech is not a part of these models. It is not possible to make general statements about precisely which segmental errors will trigger the largest error signals in a DIVA-based model, as these are complex neural networks without pre-determined error map - articulator map weights. It does not refer to deliberate strategies requiring conscious attention.

DIVA-based models are also much more focused on external sensory feedback than internal model-state predictions, which are more important in SFC models (Ventura et al. 2009), so feedback here refers to conflicts between predicted and observed perceptual consequences of speech production, not to conflicts between predictions of internal model states and actual model states.

Acquired Speech Disorders: Foreign Accent Syndrome

Introduction

Foreign accent syndrome (FAS; Blumstein and Kurowski 2006) is an acquired neurological condition most often seen following strokes, but it has also been reported following trauma (Monrad-Krohn 1947, Nielson and McKeown 1961, Aronson 1990, Moonis et al. 1996), and as an unusual presentation in the course of other neurological diseases (Luzzi et al. 2008; Villaverde-Gonzalez et al. 2003). The syndrome is by definition characterized by a "foreign accent" to the patient's speech recognized by all native speakers of the patient's native language or dialect (usually including the patients themselves), but without this "accent" being phonetically consistent with any actual foreign accent (native speaker judgments as to what particular accent the patient might have are typically contradictory and inconsistent; Blumstein and Kurowski 2006). Thus, the patient essentially acquires a 'generic foreign accent' (Blumstein et al. 1987, Ingram et al. 1992). Furthermore, to be considered FAS, this generic foreign accent must be previously unlearned and not have been a part of the patient's pre-morbid linguistic competence, eliminating cases in which patients have resumed previously acquired accents (Roth et al. 1997).

Beyond this basic criterion, the pattern of symptoms observed in FAS is extremely heterogenous between patients. FAS patients have been reported with specific problems in an extremely broad range of segments (i.e. phonemes) that form no linguistically-motivated natural class (cf. Graff-Radford et al. 1986, Gurd et al. 2001,

Avila et al. 2004, Fridriksson et al. 2005 Van Borsel et al. 2005, Scott et al. 2006). These deficits are not consistent across patients, suggesting FAS is probably not fundamentally a disorder of segmental representation or production. In contrast to some other disorders of speech, the segmental errors in FAS are generally patterns that are observed in natural human languages (e.g. unlike the more disordered productions of severe apraxia of speech, Kent and Rosenbek 1983). Above the segmental level, most cases of foreign accent syndrome involve a prosodic disturbance of some kind, though precisely what form this takes in an individual patient can still vary (see Blumstein and Kurowski 2006 for a review). Furthermore, not all FAS patients show disturbed prosodic patterns (Verhoeven and Marlen 2010).

The neuroanatomical correlates of FAS have not been much clearer. Lesions leading to FAS are typically focal, but not confined to one consistent neural area, having been reported with lesions of cortical (Ardila et al. 1988, Berthier et al. 1991, Carbary et al. 2000, Graff-Radford et al. 1986, Moonis et al. 1996, Roth et al. 1997, Takayama et al. 1993, Abel et al. 2009) and subcortical (Blumstein et al. 1987, Gurd et al. 1988, Ingram et al. 1992, Kurowski et al. 1996, Fridriksson et al. 2005) grey matter and white matter (Graff-Radford et al. 1986, Blumstein et al. 1987, Berthier et al. 1991, Kurowski et al. 1996, Avila et al. 2004).

At present, there are three major etiological theories of foreign accent syndrome in the literature. The simplest of these models argues that FAS is not a unique syndrome per se, but simply a particularly mild form of apraxia of speech (AOS; Aronson 1990, Duffy 1995) or even just a perceptual epiphenomenon (Edwards et al. 2005). While it is true that there is a great deal of heterogeneity in the symptoms of FAS

patients, there are still broad similarities, such as prosodic disturbances (Blumstein and Kurowski 2006) between FAS cases sufficient to conclude that it is not merely an epiphenomenon. The specificity and mildness of the problem compared to the more global and severe deficits typically found in AOS suggest that, if this theory is correct, FAS must be at the very least a distinct subtype of AOS.

Two other theories suggest more tangible mechanisms for FAS. One is that FAS is the result of an abnormal speech posture or tense speech musculature (Graff-Radford et al. 1986, Ingram et al. 1992, Moen 2000, Ryalls and Whiteside 2006), suggesting that the neuroanatomical substrate is in motor areas associated with the face or tongue. More recently, it has been proposed that FAS is a disturbance of linguistic prosody (in contrast to affective prosody; Blumstein and Kurowski 2006), involving primary motor cortex and connections to other cortical and subcortical areas.

Since these theories are largely motivated by behavioral measures of patients due to the paucity of neuroimaging data, it is unsurprising that in the present study, we find that none of these theories predicts our results in a straightforward way. On the basis of these results, we hypothesize that FAS may be better understood as a disorder of speech sensory feedback.

Here we report a case of FAS in a 42 year-old woman along with results of a functional magnetic resonance imaging (fMRI) study examining the functional networks associated with error production during spontaneous speech. Our study is not the first to use fMRI in conjunction with a case of foreign accent syndrome. Fridriksson et al. (2005) reported fMRI results with an object naming task in a patient with foreign accent syndrome compared with normal controls. Their patient had a small left putamen lesion

(a very different structure from the patient in the present study), and the differences between normal controls and their patient were limited to increased activity in central sulcus and ventral angular gyrus, consistent with the authors' idea that destruction of the putamen led to recruitment of cortical areas to assist with the processing load (Fridriksson et al. 2005).

However, despite object naming being a classic neurolinguistic task, it may not be especially well suited to eliciting the disordered speech typical of FAS, since FAS patients typically (Scott et al. 2006) produce far fewer errors in individual word naming than in spontaneous connected speech, (and in fact RV's disorder was barely detectable when reading object names from a list). Furthermore, rather than comparing activation against a baseline, it may be informative to examine the modulation of brain activity by task performance (Buchel, Holmes, Rees, & Friston, 1998) when the dynamic range of errors is sufficiently broad. Demonstrating that activity in a certain area varies in line with error rates may be a stronger index of the relevance of this activity to error than baseline subtraction methods. If activity is positively modulated by error, then that activity is likely either driving the error or is compensating for it.

For this reason, we chose to use a cued spontaneous narrative task (described below) to increase the processing demands upon RV (and thus increase the variability of her performance to allow for the parametric modulation analysis) and to provide a more ecologically valid task (thus allowing imaging of a condition closer to real-world linguistic situations).

Methods and Materials

Subject

RV is a 42 year-old right-handed female who is a native speaker of American English from the mid-Atlantic United States. Following a cerebrovascular accident at her workplace in 2006, she awoke the next morning totally unable to speak. Her ability to speak returned over the next few days, but she now speaks in a way that sounds "foreign" to other native speakers of English. RV has never lived overseas and does not speak any other languages. She is aware of the change in her manner of speaking and is distressed by it. Her current manner of speaking stabilized within a month of her cereberovascular accident and has persisted ever since. A video existed of RV reading a written text before her cerebrovascular accident, and we asked that she read the text again for a post-morbid recording. A reduction in pitch variation was observed between pre-morbid and post-morbid recordings of the same scripted utterance, which is consistent with the pitch disturbances usually reported in FAS (Blumstein and Kurowski 2006).

Imaging Parameters

A time series of T2*-weighted BOLD fMRI images were acquired on a General Electric 3T Signa HDxt scanner (GE Healthcare, Waukesha, WI, USA) using an 8-channel HR brain coil and a single-shot gradient-echo EPI sequence. The scanning parameters were as follows: TR (repetition time) = 2000 ms, TE (echo time) = 30 ms, flip-angle = 90º; 64×64 matrix, FOV (field of view) = 240 mm; whole brain coverage with 27 sagittal slices, slice thickness = 5 mm; total volumes = 304 (excluding the 4 volumes at the beginning of acquisition). In additional to the functional data, T1-weighted high-resolution structural images were acquired sagittally using a magnetization-prepared rapid gradient-echo (MPRAGE) sequence.

Task Paradigm

Narrative speech was elicited by asking RV to describe eight different picture sequences from the *Narrative Story cards* (Helm-Estabrooks & Nicholas, 2003). Each sequence consisted of three pictures forming the onset, middle, and end of a story. The pictures in the story cards were presented to the subject as digitalized images on a computer using *E-Prime* software (Psychology Software Tools, 2002). Prior to data acquisition, the subject was trained to be familiar with the storyline of each sequence. During the fMRI session, all the visual stimuli were projected on a translucent screen in front of the MRI scanner using a DLP projector. The subject was able to see the stimuli on the screen through a reflection mirror mounted on the brain coil.

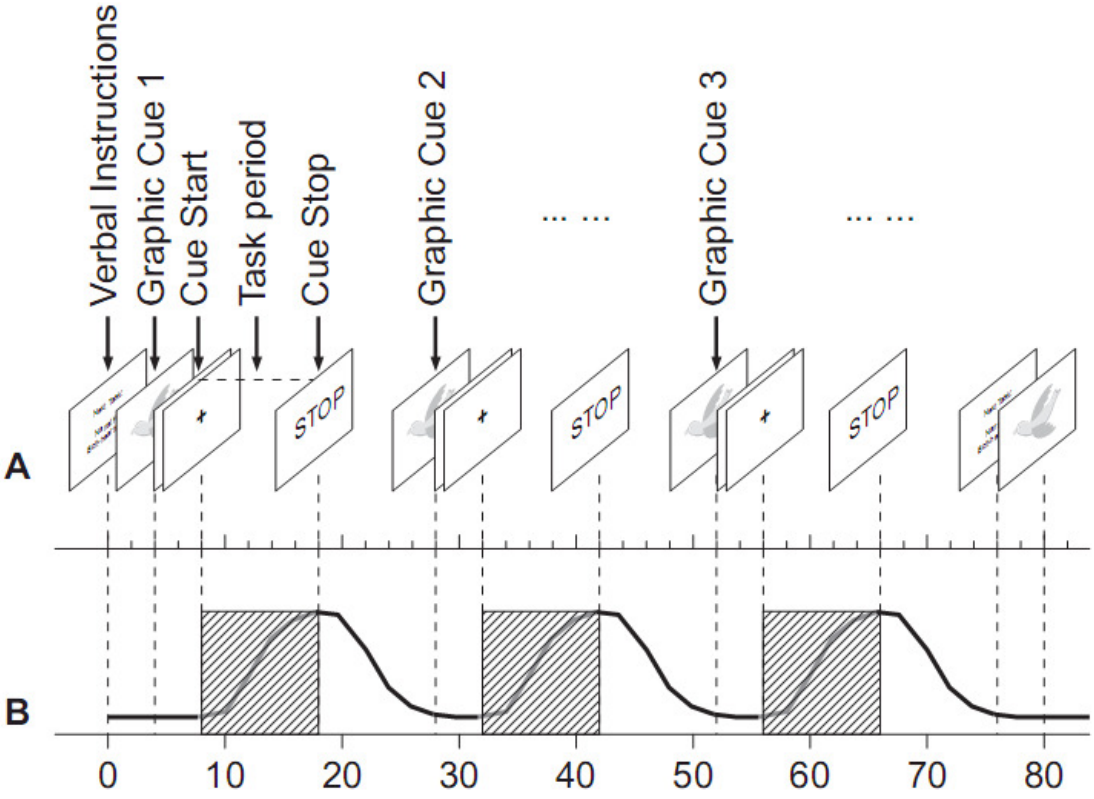

Figure 2.1. An illustrative diagram for the task paradigm in fMRI. (**A**) The sequence and timing of stimulus presentation: each slide indicates a display change on the screen. The slide containing the "START" sign is obscured by the slide for the task period (fixation sign). (**B**) The modeled hemodynamic response curve shown on the same time scale. The shaded areas indicate the portions (5 volumes per task period) that were susceptible to movement artifacts and discarded during image analysis.

For each picture sequence (Figure 1), a verbal cue was first presented for 4 seconds to inform the title of the story. After the verbal cue, each picture in the sequence was presented for 3.5 seconds to prepare the subject for story-retelling. Then the picture was turned off and a "START" sign was presented for 0.5 second to cue the subject to start producing the story. The duration of narrative production after each picture was 10 seconds, during which a fixation sign was presented at the center of the screen. A 'STOP" sign was presented at the end of this period and stayed on for 10 seconds to cue the subject for resting. The 10-14 s duration of on-off task cycles were designed to maximize functional contrast while minimizing motion artifacts during task periods (Birn, Cox, & Bandettini, 2004; Soltysik & Hyde, 2006). The speech signal produced by the subject was recorded continuously with FOMRI™ II noise canceling microphone (Optoacoustics, Or Yehuda, Israel) and digitized at 44.1 kHz using *Audacity* software (Audacity Developer Team, 2006).

Speech Analysis

RV's task-related utterances while being scanned were analyzed by a phonetically-trained native speaker of American English. A 5 kHz low-pass filter was

applied to the utterances using Praat (Boersma 2001) to eliminate scanner noise, but sufficiently high in frequencyto avoid major effects from ringing artifacts in the frequencies of interest. Each ten second block of narrative production was transcribed in broad IPA transcription, and on the basis of the recordings and this transcription, the number of words containing segmental or suprasegmental errors was recorded for each ten second utterance. Two other phonetically-trained listeners naïve to the purpose of the experiment also rated the data in the same fashion. Inter-rater reliability was assessed across all words with two categories (error and non-error) via Fleiss's kappa ($\kappa = 0.96735$). This result suggests exceptionally good agreement by standard benchmarks (Landis and Koch 1977).

Image Analysis

Image analysis was performed using AFNI (Cox, 1996). The reconstructed images were first processed using a combination of rigid-body volume registration and in-plane image registration to remove both the slow drift motion and the transient motion within sagittal planes caused by speech production. This technique involved four steps: a 3D volume registration for computing rigid-body alignment parameters, followed by a 2D image registration for aligning each corresponding slice across volumes, followed by the correction for slice timing difference within each volume, and finally another 3D volume registration for fine-tuning the whole head alignment. The resulting images were spatially smoothed with a 6 mm FWHM Gaussian kernel for voxel-wised regression analysis. To account for serial correlation errors in general linear model, we adopted the restricted maximum likelihood (REML) estimate of an autoregressive moving average

(ARMA) model (Box, Jenkins, & Reinsel, 2008). In addition to modeling the mean task (zero-order) effect using a box-car function, the number of words with errors in each 10 s narrative production block was modeled as a linear (first order) modulation effect using a mean-centered step function (Buchel, Holmes, Rees, & Friston, 1998). Both functions were convolved with a canonical hemodynamic response function (HRF) to be used as regressors in the general linear model. Rigid-body alignment parameters were used as nuisance covariates to model the residual susceptibility effects due to head motion (Friston et al., 1996; Lund et al., 2005; Lund et al., 2006). To minimize the susceptibility artifacts generated by articulator movements, the images during each 10 s production period were discarded in the regression analysis (Birn et al., 2004).

Results

Speech Analysis

Table 1 is a summary of RV's errors while producing speech in the cued narrative task. The "prosodic errors" column is the sum of lexical stress and sentence-level prosody categories, collapsed together due to the low incidence of lexical stress errors produced by RV.

Block	# of words	# of words with errors	consonant errors	vowel errors	lexical stress	sentence-level prosody	prosodic errors
10	18	2	1	1	0	2	2
11	23	2	3	3	0	3	3
12	31	3	4	3	0	2	2
16	24	2	2	2	0	2	2
17	25	4	3	4	1	3	4
18	27	2	0	2	1	2	3
28	24	7	2	3	2	1	3
29	23	2	3	2	0	3	3
30	23	3	0	3	0	1	1
34	28	4	1	4	1	0	1
35	27	3	2	3	0	2	1
36	31	4	5	2	0	0	0
49	25	2	1	3	0	0	0
50	27	3	0	3	2	2	4
51	25	6	3	1	2	1	3
52	19	3	4	2	0	0	0
53	30	4	1	4	2	1	3
54	20	5	2	3	1	1	2
55	23	4	3	4	0	0	0
56	27	3	2	3	0	2	2
57	22	5	0	2	0	3	3
58	28	6	2	1	0	2	2
59	25	5	0	6	2	1	3
60	24	3	3	0	0	0	0

Table 1. Breakdown of linguistic errors in the narrative condition, by imaging block.

Imaging Results

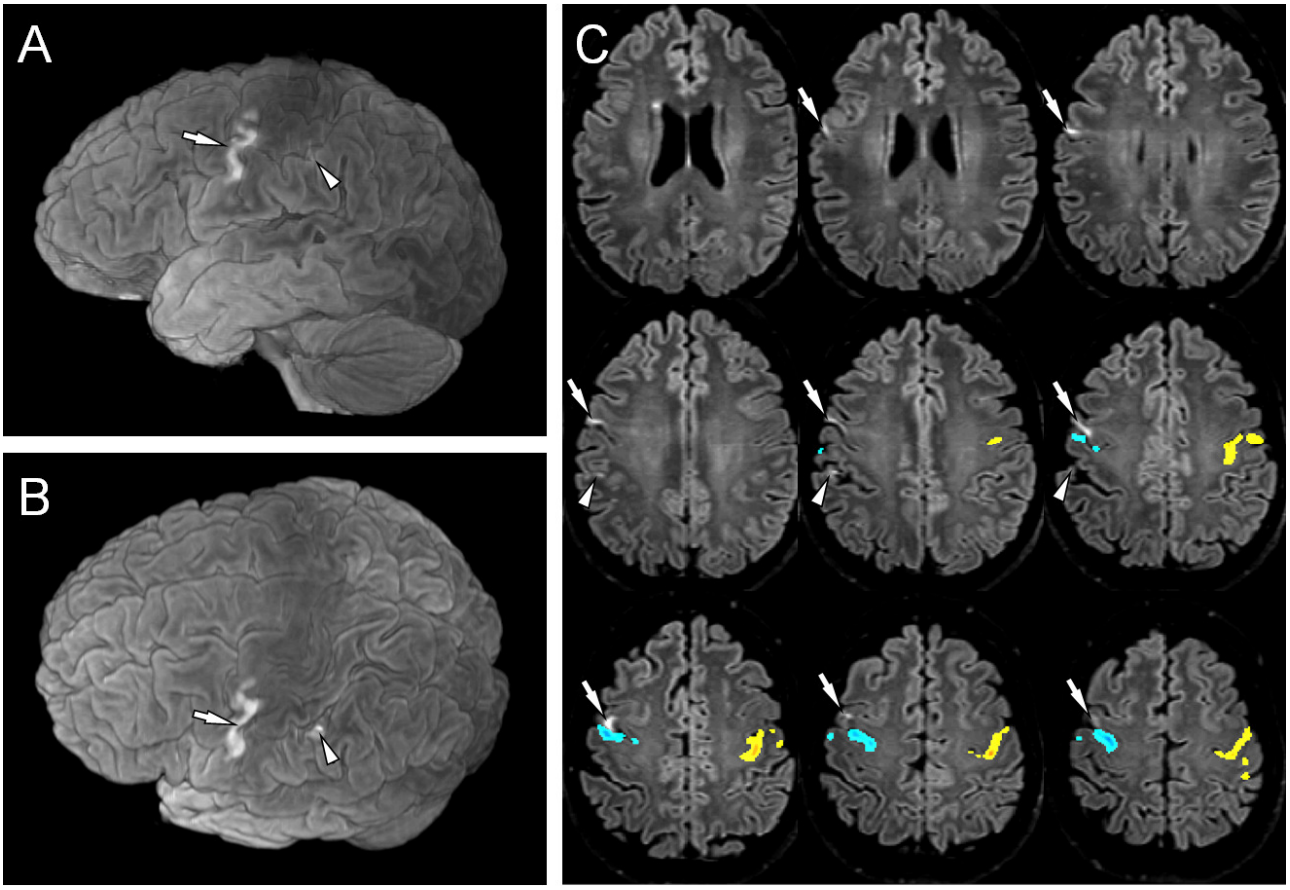

Figure 2.2. Extent of cortical laminar infarct *(white arrows, A-C)* in the expected location of the face representation of the motor strip and focal cortical infarct in the parietal lobe *(white arrowheads, A-C)*. Left lateral *(A)* and left supero-lateral *(B)* views of volume rendered 3D FLAIR MRI demonstrate the extent of cortical laminar infarct as hyperintense signal confined to the precentral gyrus involving the expected location of the face representation on the motor strip. BOLD fMRI activations *(C)* from fingertapping task alternating between the right (*blue*) and left (*orange*) hands superimposed on contiguous 3 mm FLAIR sections confirm that the hand representation is superior to the region of laminar cortical infarct involving the motor strip. Neurologic convention, slices are viewed from above with patient L = figure L.

Figure 2.2 illustrates the brain areas in which activity was positively modulated by production error in the spontaneous narrative task. The *t*-statistic map was thresholded at one-tailed $p < 0.025$ for each voxel using the ARMA (1,1) model (Forman et al. 1995).

Initial clustering based on family-wise error (FWE) alphasim methods produced a huge cluster connecting functionally heterogenous areas and was thus deemed inappropriate. We instead resampled the image to small voxels (1x1x1) and choose an arbitrary spatial cluster threshold of 350-mm^3 corresponding to the size of five raw voxels (3.75x3.75x5 mm^3). This corresponds to a whole-brain FWE rate of 0.5 according to Monte Carlo Simulation.

The lack of modulated activity in the primary motor cortices is of particular interest, and the positively modulated activities are substantially left-lateralized. In B, it can be seen that the main foci positively modulated activity are localized in primary auditory cortex (specifically Heschel's gyrus), the length of STS, and the anterior portion of STG.

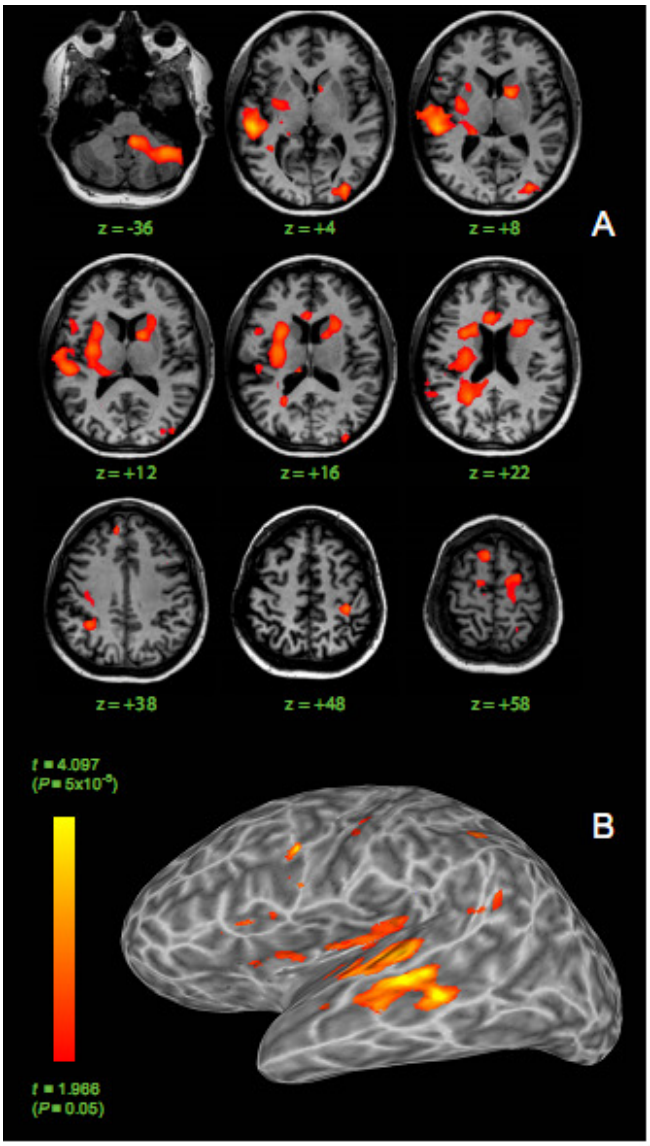

Figure 2.3. BOLD activation modulated by the number of word errors in each narrative production block (showing positive modulation only). All images are thresholded at one-tailed $p < 0.05$. P-values were corrected for family-wise error via the false discovery rate (FDR) procedure. (**A**) Axial slices showing the activations in left dentate and lateral cerebellum (z = -36), left temporal regions (anterior-temporal area, insula, and superior temporal sulcus; z = +4, +8, +12, +16), bilateral caudates (z = +12, +16, +22), anterior cingulate (z = +22), left premotor area and IPL (z = +38), right postcentral area (z = +48), and SMA/preSMA (z = +58). (**B**) The left temporal error-related modulations shown on an inflated cortical map of RV's left hemisphere: superior temporal sulcus, transverse temporal sulcus, and circular sulcus of insula.

Table 2 contains the locations, Brodmann's area (if cortical) and t-scores for brain areas showing activity positively modulated by production error in the narrative condition.

Region	BA	t-score	x	y	z	t-score	x	y	z
Subcortical									
Cerebellum									
Dentate		-	-	-	-	2.64	17	-42	-26
Hemisphere		-	-	-	-	2.89	29	-51	-32
Basal Ganglia									
Caudate		2.65	-19	9	22	2.35	15	7	16
Anterior Putamen		3.49	-28	5	10	-	-	-	-
Posterior Putamen/claustrum		3.43	-32	-6	5	-	-	-	-
Neocortical									
Frontal									
SMA proper	6	2.33	-15	-8	62	2.44	14	-5	59
pre-SMA	6	2.47	-10	16	57	-	-	-	-
PMd/IFG	44/6	2.58	-55	3	29	-	-	-	-
Temporal									
STS	21/22	2.12	-52	-30	0	-	-	-	-
Anterior STG	22	2.21	-52	-14	2	-	-	-	-
Heschel's Gyrus	41	2.84	-54	-18	7	-	-	-	-
Parietal									
TPO Junction	39/40	2.26	-57	-49	24				
IPL/IPS	40/7	2.62	-33	-46	38	2.69	31	-32	47
Proisocortical									
Insula						-	-	-	-
Anterior Insula		2.41	-29	13	13	-	-	-	-
Posterior Insula/Claustrum		2.98	-32	-8	12				
Cingulate									
Anterior Cingulate	32	2.19	1	26	21	-	-	-	-

Mesial Temporal										
Parahippocampal Gyrus	36	2.6	-21	-25	-8		3.05	25	1	-15

Table 2. Modulation of BOLD signal by dysfluency in FAS. SMA - supplementary motor area, pMD – prefrontal dorsal motor cortex IFG – inferior frontal gyrus, STS – superior temporal sulcus, STG – superior temporal gyrus, TPO – temporal-parietal-occipital, IPL/IPS – inferior parietal lobule/sulcus. Left hemisphere regions are in the left columns, and right hemisphere in the right columns.

In the spontaneous narrative task, we found positive modulation effects in a broad, primarily left-lateralized network encompassing cortical and subcortical regions, including temporal speech perception areas, frontal premotor areas (but not primary motor), proisocortical premotor areas, including left cingulate and insular cortices, as well as basal ganglia, cerebellum, and parahippocampal gyri. No significant negative modulation was observed in any area.

Discussion

The symptoms observed in RV are broadly typical of FAS (Blumstein and Kurowski 2006). She displayed sporadic segmental errors, while not consistently producing any particular segment erroneously. Likewise, she produced sporadic suprasegmental errors, but there was no prosodic context in which RV displayed uniformly disordered intonation. A majority of analyzed segments and utterances were produced without obvious error, but errors were sufficiently frequent to produce the impression that RV was a non-native speaker of English, albeit one with fluent production.

A set of regions containing the cerebellum, the basal ganglia (caudate and putamen), frontal motor areas (SMA, pre-SMA, IFG), superior temporal areas (STG,

STS, Heschel's gyrus), anterior parietal areas (TOP junction, IPS) the insula, the anterior cingulate, and the parahippocampal gyrus showed activity positively modulated by production error in RV. No such activity was observed in unlesioned portions of the primary motor cortex or primary somatosensory cortex. This particular set of regions is consistent with the idea that FAS may be a disorder of auditory feedback rather than a purely motor deficit.

A novel model of FAS is needed to account for this network, as it is not entirely consistent with existing models of FAS. We propose specifically that FAS is a disorder of speech sensory feedback, in the same sense as the speech sensory feedback loops instantiated in the DIVA model of speech production (Guenther et al. 2006). This model incorporates a number of areas that serve to detect any drift from acoustic targets in the speaker's own speech, and generate and deliver feedback signals to correct these erroneous deviations.

Normal Speech

Some of the areas in which activity was positively correlated with error production are known to be involved in the production of speech in healthy subjects. A meta-analysis examining 82 imaging studies of speech production (Indefrey and Levelt 2004) reveals, for example, that portions of the inferior frontal gyrus play a role in syllabification, while retrieval of the phonological form of words from memory reliably activates areas such as left anterior insula and left posterior STG and MTG. Importantly, the Indefrey and Levelt (2004) meta-analysis showed that phonological self-monitoring may be subserved by STG bilaterally, a result supported by a recent fMRI study demonstrating superior

temporal activation common to speech and non-speech articulator movement, even when this movement was silent (Dhanjal et al. 2008). This role for STG as a generator of auditory feedback signals, which we suggest are inappropriately large in RV's case, is also postulated in the GODIVA phonological sequencing model (Bohland et al. 2010).

The latter study may be relevant in that it demonstrated a suppression of activity in somatosensory areas in speech relative to articulator movement alone (Dhanjal et al. 2008), suggesting that part of the role of the speech sensory feedback network is suppression of the automatic somatosensory signals associated with articulation. This is broadly consistent with the present study, in which we did not find activity in primary somatosensory cortex correlated with error production, and thus not producing articulator error signals. However, correlated activity was found in paracentral lobule, an area known to be active in response to attended somatosensory stimuli (Forss et al. 1996). The fact that activation was found in the present study but not in Dhanjal et al. (2008) may be the direct consequence of the impairment of inhibitory function of RV's sensory feedback network. This lack of regulation of feedback means that activity is not suppressed in this region, as it would be in normal participants.

Cortical Areas

Audiological deficits per se have not been reported as a feature of FAS, and RV's awareness of her own problem and ability to hear that her speech has changed makes a general auditory deficit an unlikely cause of the syndrome. However, since auditory input is a logically necessary component of a speech sensory feedback network, the

involvement of a primary auditory area like Heschl's gyrus is unsurprising.

In addition, higher level auditory association areas involved in speech perception and language comprehension, such as anterior and posterior STG and STS are implicated in our patient. The role of these regions in processing and monitoring of complex sounds is well-supported by the experimental literature. Anterior STG is known to respond more to frequency-modulated sounds than tones (Binder et al. 2000), broadband noise sufficiently regular to induce a pitch percept (Griffiths et al. 2001), and homologous structures in macaques are known to preferentially respond to complex sounds (Phillips 1993, Steinschneider et al. 1995, deCharms et al. 1998). Successful detection and processing of these features are crucial to successful self-monitoring of speech, since vowels are primarily distinguished by differences in their formant structure (i.e. modulations of their frequency), and consonantal segments in human language are acoustically complex sounds (Ladefoged 2005).

Left superior temporal sulcus and gyrus have been shown in PET studies to be activated by the sound of the speaker's own voice (Wise et al. 2001), and left anterior superior temporal areas in particular have been shown in fMRI to be selective for human voices (Bellin et al. 2000) and prefer natural native-language vowels to a variety of non-speech stimuli, even showing spatial segregation in BOLD response based on the vowel category in question (Obleser et al. 2008). Finding activation of STS or STG in a speech versus resting baseline condition is an uncontroversial finding, and it is typical of fMRI studies of speech to find STS activation for speech versus non-speech controls (cf. Hickok and Poeppel 2007 for a review). Simply having the appropriate phonetic properties of speech is not enough to maximally drive activity in STS, as it

appears to be sensitive to the intelligibility of the speech presented (Spitsyna et al. 2006). Higher order classification of incoming stimuli as speech or non-speech also appears to impact STS activity (Möttönen et al. 2005), suggesting that the computations performed by STS cannot be entirely determined by the properties of the incoming stimulus. In the present network, STS is likely recruited as a self-monitoring center (McGuire et al. 1996) functionally specialized for speech.

Ventrolateral PMC and SMA are known to be strongly connected to primary motor cortex in humans (Guye et al. 2003), and it is by these projections that their outputs are conveyed to the part of cortex that will actually produce motor commands. This area, along with the SMA and pre-SMA, appears to be organizing and planning the linear sequence of motor commands prior to the initiation of speech movements originating from M1. Pre-SMA is not directly connected to primary motor cortex, so its contribution must be via its connections with SMA (Luppino et al. 1993). Additionally, SMA is the target of robust projections from putamen (Alexander 1990) which itself receives projections from auditory cortex (McGeorge and Faull 1989). This indirect but robust link between SMA and auditory cortex provides an anatomical pathway by which incoming speech information can act as feedback, as discussed below.

The present study found reliable error-modulated activity within the insula, which has been implicated in motor conditions relevant to speech, and in a study of patients with apraxia of speech anterior insula proved to be the area of greatest overlap of their lesions (Dronkers 1996). Bilateral damage to insula in at least one case lead to a form of mutism (Habib et al. 1995). In the context of FAS considered as a deficit of auditory speech feedback, the insula is likely to act as an auditory-motor interface within our

network as it is known to have a significant auditory input (Mesulam and Mufson 1982) in addition to its motor involvement (Augustine 1996). If our network is to carry out its function, there must be a linkage between auditory feedback and the motor system, and we propose that the insula is a significant site for that linkage as part of its role coordinating the articulators.

The anterior cingulate cortex (ACC) has been shown in humans to be crucially involved in error-detection and compensation (Gehring and Knight 2000, Luu et al. 2000) and motor control (Paus et al. 1993, Badgaiyan and Posner 1998, Turken and Swick 1999) making it relevant to any sort of feedback task. The motor portion of the ACC, the so-called cingulate motor area is also implicated in speech phonation (Barrett et al. 2004, Schulz et al. 2005, Loucks et al. 2007), and is associated with the sequencing of complex motor movements more generally (Roland and Zilles 1996).

The parahippocampal cortex, among its many other functions (Fyhn et al. 2004), appears to play a specific role in auditory monitoring. For example, it has been noted that patients with resections of parahippocampal cortex have abnormal judgments regarding dissonant music, finding it far less offensive and troubling than normal controls, despite their retention of their ability to detect these musical errors (Gosselin et al. 2006). This suggests that parahippocampal cortex's role in the network we are proposing may not be strictly the detection of errors, but rather generating a judgment or weighting, such as a negative affective response in the case of dissonant music or the relative weighting of diverse feedback signals in the case of speech.

Subcortical Areas

The idea that FAS is in part a disorder of sensory speech feedback is consistent with the characteristics of the subcortical areas in which activity correlated with error production in our patient. These regions may constitute nodes in the anatomical networks that couple sensory and motor areas of the cortex, providing essential mechanisms for fine-grained feedback modulation. These include, for example, the right cerebellar hemisphere (which is anatomically connected to forebrain structures within the left hemisphere in which activity was similarly correlated with error production).

Cerebellar activation in articulatory and auditory contexts is long-established, having been implicated in tasks as diverse as novel word responses (Price et al. 1996), auditory localization (Weeks et al. 1999), and consonant discrimination based on stop closure time (Mathiak et al. 2002). Tasks involving auditory processing with a strong temporal component (like speech) appear to reliably engage the cerebellum, and a role for the cerebellum in sensory speech feedback is supported by the computational modeling literature, as for example in the many versions of the DIVA model of speech production (Guenther and Perkell 2004). As noted above, this computationally explicit model specifically includes the cerebellar hemispheres as part of a network that adjusts for unexpected auditory error signals that come from the on-line monitoring of speech output. This model, has been supported by an fMRI study that examined responses to speech produced by subjects with altered auditory feedback (a perturbed speech condition) versus normal feedback, and found right cerebellar activity specifically elevated for the contrast of perturbed versus non-perturbed speech feedback (Tourville et al. 2007). All of this evidence would predict right cerebellar involvement in a

condition affecting the ability to monitor auditory speech feedback, and this is what can be inferred in RV's case.

The basal ganglia are classic extrapyramidal motor areas, but there is substantial evidence that they also act to “gate” sensory inputs, in other words to selectively inhibit sensory inputs irrelevant to the organism’s current task (Schneider et al. 1986, Tinazzi et al. 2000). This selective, task-dependent inhibition may be necessary for any system selecting motor responses from a behavioral repertoire. Most importantly for a complex task requiring the coordination of so many regions, the basal ganglia are very well-positioned to serve in a coordinating capacity by their extensive anatomical connections with a wide range of cortical areas (Alexander 1990).

The areas of the basal ganglia associated with error production in patient RV included the anterior and posterior putamen as well as the body of the caudate nucleus. Both the caudate and putamen have been implicated in reports of speech deficits, following structural damage (Pickett et al. 1998) or direct intraoperative stimulation (Vanburen 1963). The putamen has specifically been shown to be active during automatic performance of previously learned motor sequences, a process that should be necessary for adjusting speech gestures to incoming error signals.

Functional imaging studies have clarified the role that may be played by the putamen in regulating activity of the larynx and oral articulators. fMRI studies have shown frequency-dependent activation of the putamen in a syllable repetition (Wildgruber et al. 2001), for syllable repetition in response to click trains (Riecker et al. 2006) and for silently-mouthed speech versus inner speech (Nota and Honda 2004). These studies together suggest a role for this region in articulatory control, perhaps

glottal control specifically (cf. Schulz 2005). Caudate activity has also been shown to be modulated in response to speech stripped down to its intonation contour (Meyer et al. 2002), and by artificially induced monotonous speech (Barrett et al. 2004), suggesting that the caudate's role in the speech sensory feedback network may well involve pitch-monitoring, fitting well with RV's marked pitch disturbance.

A Novel Model for FAS

If the present findings were simply a comparison of speech to a rest or non-speech baseline, they would be wholly unremarkable. But we examined modulations of the strength of the BOLD signal (and, by inference, level of neuronal activity) by the severity of FAS (as reflected in the number of errors) moment-to-moment (or at least block-to-block), which may make it possible to draw functional conclusions regarding the role of these regions. That is, the neural processes that precipitate symptoms in this disorder (at least in this patient) should be subserved by areas in which activity is modulated by the number of errors produced.

The primary motor cortex represents the final common pathway for commands to motor neurons that control the articulators. RV's lesion directly affected only a circumscribed portion of this area, and since RV is still able to speak, the motor commands conveyed to the articulators must pass through unlesioned portions of the primary motor cortex, which are themselves active during speech. Crucially, this activity was not modulated by error production in RV, as it did showed no correlation with the severity of production errors, which is inconsistent with the idea that FAS is a pure

motor deficit.

Instead, error production in RV strongly modulated activity in neocortical areas involved in perception/comprehension (superior temporal areas) as well as premotor areas associated with speech motor control (SMA, ventral and dorsal lateral premotor areas, anterior insula), consistent with the idea that symptoms of FAS in RV are instead associated with dysfunction in a network of regions that play a role in self-monitoring, detection and correction of speech errors.

In this model, since the focal lesion in M1 does not actually prevent RV from speaking, damage to this region must have a more subtle effect. It is likely that implementation of small, precise adjustments dictated by the feedback system – effective modulation of speech output – is interrupted by RV's lesion. This is consistent with the role assigned to the primary motor cortex in the GODIVA model of speech sequence production (Bohland et al. 2010), in which motor cortex is responsible not only for the final output of motor commands, but for the integration of planning and control signals from the rest of the speech motor network. In GODIVA, these two functions, output and integration, are functionally separated, and the absence of non-speech motor impairment of RV's articulators suggests that her lesion has disrupted this integration function rather than the output function of primary motor cortex. While the preservation of the output function of primary motor cortex allows for unimpaired non-speech movements, the weakness in final integration of motor speech plans caused by the focal lesion leads to the sporadic and heterogenous speech errors observed in RV.

The regions included in this model are summarized in Table 3: the left superior temporal areas are engaged in self monitoring and play a critical role in complex sound and speech sound processing, while the lateral premotor cortex, SMA and insula are upstream regions that organize corrective adjustments, relaying commands to the primary motor areas that regulate speech. The dorsal ACC provides further on-line error correction and the cerebellum may supply additional fine-grained motor control required for effective feedback generation. The basal ganglia might assist in sensory driven feedback adjustments while other regions such as the claustrum and parahippocampal cortex may be responsible for coordinating interactions within this network. Finally, the primary motor cortex provides precise regulation of speech sensory feedback, without which the network becomes excessively active.

While the existing theoretical explanations of FAS (e.g. Duffy 1995, Blumstein and Kurowski 2006, Ryalls and Whiteside 2006) do not obviously predict our findings, it is not the case that our findings are entirely inconsistent with any of these theories. Our network includes the insula, which is often thought to be one of the main loci of dysfunction in AOS (Dronkers 1996), as an auditory feedback-motor linkage, and many of the areas in the present network have a role in the control of articulators, meaning that there may well be an “abnormal vocal tract posture” of the sort proposed by Ryalls and Whiteside (2006) in some patients with FAS. Finally, parahippocampal cortex and caudate are known to be play a role in pitch monitoring (Meyer et al. 2004, Gosselin et al. 2006) and so might be the subcortical areas postulated by the general linguistic prosodic disturbance hypothesis.

The DIVA model in general predicts the involvement of regions that were

correlated with error production in the present study: the classic auditory speech perceptual areas in superior temporal cortex and lateral and medial neocortical and proisocortical premotor areas, provide the necessary conditions for a sensory feedback network - perceptual and motor regions that respectively monitor and modulate the speech signal, at either end of such a circuit. The cerebellum and basal ganglia may provide the anatomical mechanisms that couple the neocortical areas, enabling the fine-grained sensorimotor interactions required for effective feedback modulation.

Region	Function in the speech feedback control network
Auditory areas (Heschel's gyrus, STS, anterior STG)	Auditory monitoring of speech
Insular cortex	Auditory-motor interface
Caudate Nucleus	Pitch monitoring
Putamen	Control of phonation/glottal control
Cerebellum	Sensory control of motor activity
Anterior cingulate cortex	Error detection
Parahippocampal gyrus	Error response generation
Premotor areas (preSMA, PMCv, SMA)	Movement generation and sequencing
Primary motor cortex	Movement implementation

Table 3. Summary of areas implicated in the proposed network

The present study used only a single subject with FAS. Although attempts were made to recruit more individuals with FAS, chronic FAS is a relatively rare disorder (Blumstein and Kurowski 2004), however common it might be transiently following stroke. We would predict that other FAS participants would show a similar pattern of activity to RV; our hypothesis is meant to be general. Non-disordered control participants were not recruited for this study because it was explicitly a study of the neural basis of the symptoms of FAS, and as such control

participants would not have produced the behavior that was of interest during the scan. While control participants could have completed the task, the question of interest in the present study was not the activation involved in the task *per se*, but rather the activation associated with errors in completing the task. Control participants would not have produced the same kind of errors, leaving no obvious behavior with which to correlate activity. The network we have identified does not overlap a great deal with previously-described "default" networks (Raichle and Snyder 2007) in speech conditions (van de Ven et al. 2009), suggesting that we have not simply observed activity associated with incidental increases in scanner noise.

A single case-study is in no way definitive. Further studies might include diffusion tensor imaging and covariance analyses in this and other FAS patients in order to examine anatomical and functional connections within the proposed network and its normal operation in healthy, age-matched controls. Finally, since the symptoms of FAS are often transient, a longitudinal study would be useful in order to examine reorganization within this network to determine how this correlates with recovery of speech function.

The results of the present study are not directly predictable from any of the existing accounts of FAS, and the anatomical hypotheses associated with those theories do not bear much relation either to the lesion pattern that we have observed in RV or the error-modulations observed in our fMRI results. While the variability in lesion patterns is a hallmark of FAS as discussed above, the lack of correspondence between existing accounts of FAS and our functional results is striking. The functional network

identified in the present study, in which activity was correlated with the severity of RV's errors in a spontaneous and ecologically valid speech task, suggests that FAS may a disorder of sensory speech feedback control and implementation.

Developmental Speech Disorders (Persistent Developmental Stuttering)

Persistent developmental stuttering is a fluency disorder that affects approximately 1% of the general population (Andrews et al. 1983). It is characterized by sporadic difficulties in producing fluent speech in the absence of apraxia or other orolaryngeal impairments (Bloodstein and Bernstein Ratner 2008). In this sense the disorder is language-specific. The disorder's behavioral consequences are often variable between persons and can fluctuate in severity in the same person from day to day. People who stutter (PWS) mostly share a small set of symptoms, namely repetition or "blocking" of syllables (Wingate 1964), excessively tense speech musculature tension while speaking (Freeman and Ushijima 1978), and unusually prolonged sounds(Van Riper 1982). A host of secondary behaviors are often observed in stuttering, usually the consequence of attempts to avoid or mitigate the primary symptoms (Van Riper 1982; Buchel and Sommer 2004). The severity of stuttering is not uniform across all speech conditions, and certain circumstances can temporarily ameliorate the problem, generally involving unusual articulatory patterns or speech conditions (e.g. speaking with a metronome or delayed auditory feedback; Bloodstein and Bernstein Ratner 2008).

The present study focuses upon the role of the basal ganglia in the pathophysiology of PDS.Their involvement is expected for several reasons, including increased striatal dopamine synthesis in PWS (Wu et al. 1997) and success with alleviating stuttering symptoms with dopamine antagonists

(Macguire et al. 2004; Stager et al. 2005).PWS are also reported to have changes in fluency after the onset of Parkinson's disease (Shahed and Jankovic 2001) and deep brain stimulators have been reported to alleviate stuttering symptoms (Burghaus et al. 2006).Basal ganglia involvement is also hypothesized on theoretical grounds (Alm 2004), given their involvement in computational models of speech motor control (Tourville and Guenther 2010) and stuttering in particular (Max et al. 2004). Since, as discussed below, changes in activity of the basal ganglia have also been directly associated with PDS in functional neuroimaging studies, and may occasionally have dramatic effects on fluency (Braun et al. 1997, Fox et al. 1996), basal ganglia dysfunction likely plays a major role in the pathophysiology of this disorder.

As mentioned above, persistent developmental stuttering is an impairment of speech without any accompanying deficit in non-speech motor control. Since PWS only stutter when producing language, it has also been argued that dysfluency in stuttering involves a failure to integrate non-motor language-specific neural systems with the speech motor system (Watkins et al. 2006).Specifically, structural abnormalities in the brains of PWS have been interpreted as reflecting a failure of linguistic sensorimotor integration (Sommer et al. 2002; Watkins et al. 2006).The basal ganglia, via distinct BGTC circuits discussed below, may represent a mechanism that effects such integration, as it is known to play a role in sensorimotor integration generally (Brown et al. 1997). Abnormal interactions within and between these BGTC circuits may underlie stuttering symptoms, and successful language-motor integration may depend on

regulation of these interactions. Thus, interactions between these circuits and the motor and non-motor linguistic regions may enable fluent speech.

The beneficial effects of unusual articulatory conditions noted above in PDS suggests that the interaction between BA 44/45 and the insula –perhaps mediated by the basal ganglia– may be critical in the production of dysfluent speech. BA 44/45 in particular comprises classical Broca's area and is usually seen as subserving more cognitive aspects of speech production (Poldrack et al. 1999), such as verbal working memory (Rogalsky et al. 2008), serving as an area for articulatory rehearsal (Chen and Desmond 2005). The insula's contribution to speech production is thought to be the motoric coordination of articulators since lesions there reliably lead to apraxia of speech (Dronkers 1996), especially in more automatic conditions (van Turennout et al. 2003). Direct communication between the insula and frontal operculum may represent the transmission of a pre-rehearsed articulatory plan directly to a cortical area governing the execution of that plan, without input from other brain regions – e.g. the BGTC circuitry–that normally regulate speech. This sort of unregulated, direct communication may play a causal role in the production of dysfluent speech.

Certain conditions have been shown to temporarily reduce the frequency of stuttering behavior that may implicate auditory feedback mechanisms in the pathophysiology of this disorder. For example, behavioral symptoms are less pronounced when PWS read a text aloud, or when they are engaged in choral reading (Fox et al. 2000), speaking with a metronome (Brady 1969) or in an unusual voice (Bloodstein and Bernstein Ratner 2008), or under delayed auditory

feedback conditions (Kalinowski et al. 1996), although response to these conditions is not uniform across PWS (Bloodstein and Bernstein Ratner 2008). A common thread between many of these fluency-evoking conditions is a disruption in the normal, automatic feedback loop between speech and its sensory consequences. This suggests a number of potential causes of dysfluency in PDS.

Direct alteration of auditory feedback appears to induce greater fluency (at least transiently), regardless of what type of alteration is carried out (Stuart et al. 1997), or even if different varieties of feedback are combined (Macleod et al. 1995), although this effect may be limited to a subset of PWS (Foundas et al. 2001).For example, a manipulation that alters formant frequencies is very different from a temporal slowing of feedback, but both seem to have similar effects. Thus, the insensitivity of fluency improvement to the details of feedback alteration suggests that the disruption of normal feedback conditions is more important than the particular form of feedback *per se*. Therefore the locus of stuttering behavior may lie in a general impairment of the relationship between the motor speech act and its associated auditory and somatosensory features.

Inadequate left lateralization has long been hypothesized as a possible explanation for PDS. It has been argued that when NS speak, they do so in a manner dominated by their left cerebral hemispheres, and that is when the left hemisphere fails to dominate cerebral activity in PWS that stuttering occurs (Travis 1978). The issue is still unresolved and is complicated by functional

neuroimaging evidence described below, so abnormal lateralization remains a possible cause of dysfluency in PDS.

Functional neural differences in PWS have been examined with the use of functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) techniques (see De Nil 2003 for a review). While fMRI offers a higher spatial resolution, the signal it measures is highly sensitive to movement on the part of the subject (Birn et al. 2004). It is difficult to use fMRI to examine naturalistic speech tasks, when the primary symptoms shown in PWS are evident, since they entail continuous speech movement. By contrast, more artificial tasks like picture naming (e.g. Lu et al. 2009) and single-sentence reading (e.g. Watkins et al. 2006) involve brief, intermittent speech and thus are less likely to pose a challenge to PWS.

PET is less sensitive to motion artifacts than fMRI (LaPointe 2005), and as such remains a preferable method for tasks that require subjects to produce continous speech. Since, as noted, continuous speech conditions pose the greatest challenges to PWS and produce the most stuttering behavior, this makes PET a superior method to fMRI for the purposes of examining the neural basis of dysfluent behavior. For the present study, we use PET to exploit these advantages.

Previous PET literature on stuttering has found activity correlated with stuttering severity in a wide range of cortical and subcortical areas.The cortical areas can be grouped into two major functional categories: 1) pre-rolandic motor

outflow regions (BA 44/45, BA 47 the insula) and primary motor/sensorimotor cortex and 2) posterior perisylvian regions (medial temporal gyrus and angular gyrus) and superior temporal gyrus.. We predicted that all of these areas would show activity associated with stuttering, and that correlations in activity between these groups of areas should weaken with increasing stuttering severity. (Wu et al. 1995; Fox et al. 1996). Since many of these posterior perisylvian areas have been implicated in auditory speech processing (e.g. Price et al. 1996), stronger correlations between these areas should reflect stronger auditory-motor integration.

The basal ganglia are prominent among subcortical areas implicated in previous PET work on PDS. These structures are well-connected with many regions of the brain with which they interact in reliable and well-defined networks (Alm 2004). We expected that these interactions (correlations in activity between regions) may play a primary role in the pathophysiology of PDS. Specifically, previously reported correlations between severity of dysfluency and basal ganglia activity, especially in the putamen (Braun et al. 1997, Giraud et al. 2008) led us to predict that altered interaction between the basal ganglia and cortical areas outlined above would be associated with stuttering severity.

We expect the interaction between the basal ganglia and cortical areas to be mediated by two of the well-described basal ganglia-thalamo-cortical loops(BGTC; Alexander and Crutcher 1990): 1) the motor loop which links the putamen and the ventrolateral thalamus with the supplementary motor area (DeLong 1990) and which plays a role in organization and sequencing of motor

behaviors and 2) the prefrontal or associative loop connecting the caudate nucleus with the prefrontal cortex and dorsomedial thalamus, which may play a role in organizing and sequencing cognitive behaviors, including language. Correlations of these loops with motor outflow regions would be taken as evidence of better integration within the motor systems, and stronger correlations between these loops and the posterior perisylvian areas mentioned above would be taken as evidence of stronger auditory-motor integration, specifically auditory feedback integration (Tourville et al. 2008).

Functional neuroimaging evidence has been equivocal on the question of hemispherical lateralization in PWS. When PWS are contrast with NS, more activity is observed in the left hemisphere in the NS and more activity is observed in the right hemisphere in PWS (De Nil et al. 2001). However, when only PWS are considered, left hemisphere activity has been shown to be associated with increased stuttering severity, while right hemisphere activity has shown to be associated with attenuated stuttering symptoms (Braun et al. 1997), reflecting a reduction in auditory-motor integration. The picture is further complicated by evidence of a lack of left-lateralized activity and deactivation of frontal and temporal areas during chorus reading, which suppresses stuttering symptoms (Fox et al. 1996). As simple association between hemisphere activity and stuttering severity appears inadequate to address this question, we predicted that greater interaction between the left and right hemisphere (a better proxy for left hemisphere dominance, as regions that do not communicate cannot dominate one another, would be associated with increased fluency within PWS.)

In the present study we apply a connectivity analysis to task-related neural activity indexed by PET to understand these interactions. In this approach, neural activity over the course of a particular task is analyzed as a dynamic, interacting network (Bullmore and Spoorns 2009) than a grouping of static neural isolates. Following previous suggestions in the neuroimaging literature (e.g. Lu et al. 2010), we hypothesize that it is altered patterns of connectivity that determines stuttering behavior, rather than abnormal activity in isolated regions.

Most connectivity analyses that have been carried out in stuttering (Lu et al. 2010) have compared patterns of correlation between brain regions in PWS and people who do not stutter (NS). This is not ideal, because differences that emerge from that contrast could be due to the very different linguistic experiences of PWS and NS, rather than being directly related to fluency or stuttering behaviors; since PWS have had long experience with dysfluency, they are likely to engage in a wide range of behaviors and strategies while speaking in an attempt to avoid such dysfluency. The present study therefore compares correlation patterns in people who stutter when they are not experiencing dysfluency, people who stutter when they are experiencing dysfluency, and controls who do not stutter.

As an experimental probe, we use a cued sentence-generation task (Braun et al. 1997) designed to induce a moderate degree of dysfluency in PWS participants but not prove so difficult that none of them will be able to avoid stuttering. PET is ideal for such a paradigm, because the majority of its signal is generated during the 10 second period immediately following arrival of the tracer

in the brain, triggering scan onset. Thus, as long as some PWS participants stutter during this critical window and some PWS participants do not, these groups can be reliably compared.

Regions of interest were selected based on the areas identified as likely to be involved in stuttering above. Our stuttering participants were divided into two transitory groups, depending on whether or not they happened to stutter during the task. For each group of participants, we applied a linear regression model to the activity in each region of interest to assess the significance of its correlation with every other region of interest. Significant correlations between regions of interest were taken to indicate functional connectivity between those regions. We then determined whether or not those significant correlations differed between participant groups by determining the significance of a group x region interaction term in the linear regression model for each region of interest.

This allowed differentiation of patterns associated with fluency and dysfluency in PWS. Nevertheless, while dysfluency is the behavioral hallmark of persistent developmental stuttering, the findings of structural differences (Foundas et al. 2001, Somer et al. 2002, Watkins et al. 2006, Cykowski et al. 2010) suggest that there may be differences between PWS and NS even when PWS are not experiencing dysfluency. Therefore we also compared connectivity patterns in order to disambiguate “trait” (differences between participants based on whether they are PWS or NS) and “state” features (differences between participants based on whether or not they experience dysfluency during a task) of stuttering.

The results of all of these analyses can be enriched by the application of the tools of social network analysis (Wasserman and Faust 1994), a technique originating in the field of sociology but which has been successfully applied to a wide range of problems in a number of disciplines (Knoke and Yang 2008). Simply put, social network analysis allows for the quantification of properties of interest in a network, so that intuitive judgments about how "cohesive" a network might be or how "central" a particular node is can be instead computed objectively. In the present study it permits us to make principled statements about how critical particular regions are in achieving or failing to achieve fluency in PDS.

A social network concept that has been previously applied in the neuroimaging literature is small world analysis (cf. Basset and Bullmore 2006 for a review). Small world networks have desirable properties, such as a reasonably high efficiency of communication for a relatively low cost (Latora and Marchiori 2001), and a well-functioning network might be expected to have small world character (Spoorns and Honey 2006). We applied this analysis and expected that correlation patterns associated with dysfluency will have less small world character and lower communicative efficiency, while those associated with fluency will have greater small world character and greater efficiency.

In general, we predicted that functional interactions of regions identified as being part of associative and motor BGTC circuits would be associated with stuttering severity. Specifically, we predicted that greater coupling within and between these circuits would be associated with an increase in fluency in

PWS,reflecting more effective integration between cognitive-language and speech motor control systems. Additionally, we predicted that increased fluency in PWS would be associated with altered interactions between these central nodes within circuits, especially putamen and SMA, and cortical motor regions, including BA 44/45, insula, and primary motor cortex, representing more efficient regulation of motor outflow by the basal ganglia under these conditions. Insula and BA 44/45 interactions were predicted to be associated with dysfluency, as they represented articulatory automaticity, the disruption of which generally contributes to fluency in PWS.

We also predicted that increased fluency in PWS would be associated with stronger interactions between the posterior perisylvian areas, especially STG, and other brain regions, reflecting more effective integration of auditory feedback. Additionally, We predicted altered lateralization patterns - a greater degree of left-right hemisphere interaction and left lateralization of correlated activity - would be associated with fluent speech production. Social network and small world analysis allow us to characterize these interactions as communicative networks and identify critical regions in a principled way.

The present study was designed to shed light on the moment of dysfluency in PDS as a speech motor phenomenon, rather than to find long-term trait features in PWS. We attempt to separate the activity associated with PDS in the long term from the activity associated with dysfluency itself by comparing PWS who happen to be stuttering and PWS who happen not to be stuttering. As a result, our analysis will primarily yield neural patterns of recruitment associated

with failing or succeeding in avoiding dysfluency in PWS, rather than underlying non-speech motor causes of the disorder. The primary speech motor symptom of the disorder must have some neural cause *qua* speech motor symptom, and it is that aspect of PDS that the present study investigates.

Methods

Subjects

This study was approved by the NINDS/NIDCD Institutional Review Board of the National Institutes of Health, Bethesda. Informed consent was obtained from all subjects after the risks, hazards, and discomfort associated with these studies were explained. Control subjects included eight females aged 24-50 years, and 11 males aged 23-47 years. Stuttering subjects included eight females aged 23-51 years and 9 males aged 23-50 years. All subjects were free of medical or neuropsychiatric illnesses which might affect brain function on the basis of history and physical examination, baseline laboratory evaluation, and MRI. The diagnosis of developmental stuttering conformed to DSM-IV criteria. Typical stuttering severity was determined with the Stuttering Severity Instrument outside of the scanner. None of the stuttering subjects were enrolled in speech therapy, and all subjects were free of medications at the time of the scan.

Scanning methods

PET scans were performed on a Scanditronix PC2048-15B tomography (Uppsala, Sweden) which has an axial and in-plane resolution of 6.5 mm. Fifteen planes, offset by

6.5 mm (centre to centre) were acquired simultaneously. Subject's eyes were patched, and head motion was restricted during the scans with a thermoplastic mask. For each scan, 30 mCi of $H_2{}^{15}O$ were injected intravenously. Speech tasks were initiated 30 s prior to injection of the radiotracer and were continued through the scanning period (Fig 2.X). Scans commenced automatically when the count rate in the brain reached a threshold value (~20 s after injection) and continued for 4 min. Studies were separated by 10-min intervals. Emission data were corrected for attenuation by means of a transmission scan. Arterial blood was sampled automatically during this period, PET scans were registered and analysed using statistical parametric mapping (SPM) software (MRC Cyclotron Unit, Hammersmith Hospital,London,UK).The 15 original PET slices were interpolated and spatially registered in order to minimize the effects of head movement.

Images were smoothed with a Gaussian filter (20x20x12mm in the x, y and z axes)to accommodate intersubject differences in anatomy, and stereotaxically normalized to produce images of 26 planes parallel to the anterior–posterior commissural line in a common stereotaxic space (Friston et al.1989) cross-referenced with a standard anatomical atlas (Talairach and Tournoux 1988). Differences in global activity were controlled for by analysis of covariance (Friston et al.1990)**.** Proportional normalization (ratio) for global counts and pooled variance was used for the test statistics generation (Worsley et al., 1992). Normalization was accomplished by dividing each voxel by the average of all gray matter voxels for each PET volume.

Dysfluency-evoking task

Speech dysfluency was evoked by means of a sentence construction task. In this task, subjects were instructed to produce a series of novel sentences using verbs that were assigned shortly before the onset of the scan (e.g. *calculate, evaluate, understand*). Speech rate, rhythm and intonation were normal during the task, and semantic content was relatively constrained. Subjects were instructed to avoid using any behaviors (circumlocution, word substitution) which might prevent the expression of stuttering symptoms

Speech Recording

The subjects' speech output was recorded along with a computer-generated signal, identifying the state of the $H_2{}^{15}O$ scan. The data were digitized with a sampling rate of 5000 Hz, using an antialiasing filter of 2000 Hz. Using MITSYN software, the leading edge of the computer generated signal was identified, and the digitized speech sample (from 20 s before to 40 s following the state of the scan) was played back and dysfluent symptoms were scored as present or absent in 2-s epochs. Repetitions, prolongations, and obvious blocks were tallied and counted as stuttering. PWS subjects who scored 0 for each epoch in the sentence generation task were assigned to the Fluent group, while those who scored 1 for at least 1 epoch were assigned to the Dysfluent group.

We did not separate Dysfluent participants based on the average number of errors per epoch, as a multiplicity of Dysfluent groups would result, each with a very small *n.* This would be problematic from a statistical perspective as it would significantly increase the proportion of noise in the signal for each of these small Dysfluent groups

and complicate comparison with the much larger Fluent group. Thus, all the potential Dysfluent groups were collapsed together.

Because of the tracer kinetic behavior of the H215O in brain tissue, the observed change in the PET signal depends upon when during data acquisition the dysfluencies occur. Thus, stuttering events occurring within the first 10s following the arrival of the H2 15O bolus in the brain will affect the final PET image to a greater extent than events occurring 40s later. We therefore calculated a weighting function which describes these changes in the PET signal. It was derived by (i) solving the Kety flow model (Kety 1951) for predicted tissue activity in the case of changing flow, (ii) calculating the sensitivity (derivative) of the predicted PET tissue activity to the flow at each second during the period sampled and (iii) normalizing the resultant sensitivity curve by setting this to an integral of 1.0.The sensitivity curves from 20 independently derived H215O scans were averaged to generate the final weighting function, which was then shifted –5s from the start of scan to account for the approximate haemodynamic response time.

Linear Regression Model

Normalized regional values were further processed in SAS with PROC GLM, and regions of interest selected were based on the GLM contrast. For every pair of regions of interest a multiple regression model of the following form was applied:

$$\text{RegionA} = \beta\,0 + \beta 1\,\textit{RegionB} + \beta 2\,\textit{Group} + \beta 3\,\textit{RegionB} \times \textit{Group}$$

Where β1 represented the main effect of a second region on the region in question, β2 represented the effect of group membership (Fluent, Dysfluent or Control) on the region in question, and β3 represented the interaction between the second

region main effect and the group membership effect.

A series of follow-up tests were applied to highlight cases where there is a relationship between brain regions for a given group (e.g. fluent individuals) and a difference in this relationship across groups (e.g., fluent versus dysfluent). The follow-up tests were calculated by multiplying the p-value for the interaction term of the combined model with the slope parameter of the region term for the group specific model. There are a wide range of methods for combining p-values for independent statistical tests (Loughin, 2004). However, in the current case the tests are not dependent, and as a result these standard measures are not appropriate. Instead, cut-offs for the p-value were simulated based on a null model assuming that the scores for each of the 2 regions and 2 groups came from independent standard normal distributions given the same number of observations as the actual data. 100,000 simulated data sets were created and for each data set a combined p-value was calculated. The cut-off was then defined as the one half the 5th percentile and 1st percentile of the simulated combined p-values (0.0021 and 0.00014). The cut-off values were divided by two to account for the two tests performed on each region pair: one test for the fluent group and one test for the dysfluent group.

Social Network Analysis

For each neural region that participated in any significant correlations that significantly differed between groups, based on the above analysis, the sum of the number of correlations between that region and all other regions was calculated. In other words, the number of significant β1s were counted for each region in each group.

This was the “degree” score, i.e. the number of other regions a given region was connected to.

All significant correlations between regions of interest in each group were scored for betweenness and closeness using GEPHI (Bastian et al. 2009). Betweenness is a measure derived from the number of regions that are joined by a shortest path passing through a given region (Wasserman and Faust 1995). The higher the betweenness score, the more interactions in which the region serves as an intermediate. In cognitive terms, if information is travelling from one region to another, betweenness offers a rough measure of how frequently a given node is contributing to the processing of that information as it flows between the two regions. Higher betweenness regions are involved in the intermediate processing of information flows between many regions, whereas lower betweenness regions tend not to be involved in the interactions of other regions in the network.

Closeness is a measure derived from the inverse of the sum of the shortest path distances from a given region to all other regions in the network (Wasserman and Faust 1995). The fewer intermediate regions there are separating the two, the higher the closeness score will be. In cognitive terms, if information is travelling from one region to another, closeness offers a rough measure of how many areas contribute to the processing of that information as it flows between the two regions. Higher closeness regions pass their information more directly on to the regions they interact with, whereas lower closeness regions interact with other regions through several intermediate

processing steps.

All betweenness and closeness scores were normalized within each group to be between 0 and 1.

Small World Analysis

Small world analysis was applied to the set of correlations for each participant group that was significant regardless of whether they were significantly different from the correlations of other participant groups. In other words, small world analysis was applied to all regional pairs with a significant β1 associated with a particular group. Small-world measures were calculated on the basis of the method described by Latora and Marchiori (2001). Correlations were imported into GEPHI, an open source network visualization and analysis program (Bastian et al. 2009), and the average path length and clustering coefficient were calculated.

The average clustering coefficient for a random graph with an equivalent number of nodes and edges were taken to be (K/N)/N and the average path length was taken to be ln N/ ln (K -1), where K is the number of edges in the graph and N is the number of nodes. The ratio of the average clustering coefficient of each network to the average clustering coefficient of an equivalent random graph is gamma, and the ratio of the average path length to the average path length of an equivalent random graph is lambda. Gamma and lambda for each network are reported below. If the ratio of gamma to lambda is greater than

1, the network is thought to have significant small world character (Basset and Bullmore 2006).

Additionally, we calculated an alternative measure of global network efficiency described by Latora and Marchiori (2001) that does not assume that all nodes in a network are connected to all other nodes.

Results

Analysis of speech produced by PWS participants during the task revealed that 8 participants stuttered and nine participants did not stutter during the critical 10 seconds after scan onset. This meant that approximately half of the PWS participants had shown stuttering behavior during the time period responsible for most of the PET signal, and half had not. Those who had stuttered were assigned to the “Dysfluent” group (PWS who had stuttered during the relevant part of the task) and the “Fluent” group was defined as PWS who had not stuttered during the relevant part of the task. This group assignment was based solely on speech produced during the task, and on the basis of no other criteria.

The linear regression model described in the Methods section above was applied to all pairs of regions of interest in all three groups (Dysfluent, Fluent, and Control). The follow-up tests described in the Methods section above was used to calculate conjoint probabilities for the Dysfluent v. Fluent contrast. All correlations for each group with a significant β3 coefficient and at least one associated significant β1 coefficient are reported. Conjoint p-values from the null-

model simulation described above are also reported; p-values significant at the .05 level are marked with one asterisk, and p-values significant at the .01 level are marked with two.

Table 4 below shows the results of the simulations used to determine conjoint probabilities.

BGTC-BGTC	BGTC region A	BGTC region B	B1 Fluent	B1 Dysfluent	B3	Conjoint
Fluent>Dysfluent	LEFT HEM					
	Putamen	SMA	1.2009	-0.1503	-1.3512	0.002*
	SMA	Caudate	1.0268	0.0652	-0.9616	0.0001**
	BILATERAL					
	R SMA	L Putamen	1.4631	-0.1845	-1.6476	0.00001**
	R SMA	L Caudate	1.2461	0.2251	-1.021	0.00001**

BGTC-BGTC	BGTC region A	BGTC region B	B1 Fluent	B1 Dysfluent	B3	Conjoint
Dysfluent>Fluent	RIGHT HEM					
	DMT	VLT	0.3712	1.2114	0.8402	0.0004

BGTC-Motor	BGTC region	Motor region	B1 Fluent	B1 Dysfluent	B3	Conjoint
Fluent>Dysfluent	LEFT HEM					

	Putamen		45	-1.8739	0.6648	2.5387	0.0013*
	Putamen	M1/S1		-1.4055	0.7346	2.1401	0.0005*
	SMA		45	-2.7453	0.8614	3.6067	0.0001**
	SMA	M1/S1		-2.08	0.8906	2.9706	0.00001**
	Caudate		45	-2.7724	1.0557	3.8281	0.00001**
	Caudate	M1/S1		-1.7326	0.9992	2.7318	0.0002*
	BILATERAL						
	R VLT	L 45		-2.5346	0.1753	-2.4559	0.00001**
	R SMA	L 45		0.7177	0.7177	-3.3641	0.00001**
	RIGHT HEM						
	Caudate		44	-0.8727	0.1948	1.0675	0.0002*

BGTC - Motor	BGTC region	Motor region	B1 Fluent	B1 Dysfluent	B3	Conjoint
Dysfluent>Fluent						
	RIGHT HEM					
	Caudate	M1/S1	-0.6245	0.6124	1.2369	0.0001**
	Putamen	M1/S1	-0.78	0.9769	1.7569	0.0001**

PERISYLVIAN - BGTC	PS region	BGTC region	B1 Fluent	B1 Dysfluent	B3	Conjoint
Fluent>Dysfluent	LEFT HEM					
	STG	SMA	-0.7668	0.2138	0.9806	0.0001**
	STG	Putamen	-1.242	-0.1472	1.0947	0.00001**
	BILATERAL					
	R MTG	L PFC	1.3929	-0.0664	-1.4594	0.0002*
	L STG	R SMA	-0.6947	0.0636	0.7583	0.0005*

PERISYLVIAN - BGTC	PS region	BGTC region	B1 Fluent	B1 Dysfluent	B3	Conjoint

Dysfluent>Fluent	LEFT HEM						
	ANG	PFC		0.0349	1.1826	1.1477	0.0008*
PERISYLVIAN - MOTOR	PS region	Motor region		B1 Fluent	B1 Dysfluent	B3	Conjoint
Fluent>Dysfluent	LEFT HEM						
	STG	Insula		-0.6178	0.3743	0.9921	0.0008*
	STG	M1/S1		1.9859	-0.0971	-2.0831	0.0001**
	MTG		45	1.6392	-0.246	-1.8852	0.0002*
	Insula	ANG		-2.7918	-0.2601	2.5317	0.0002*
	BILATERAL						
	L STG	R 45		1.6174	-0.1678	-1.7852	0.0012*
	R MTG	L Insula		-0.5854	0.2063	0.7917	0.0005*
PERISYLVIAN - MOTOR	PS region	Motor region		B1 Fluent	B1 Dysfluent	B3	Conjoint
Dysfluent>Fluent	LEFT HEM						
	ANG	M1/S1		0.3973	-1.1022	-1.4995	0.0015*
MOTOR - MOTOR	Motor region A	Motor region B		B1 Fluent	B1 Dysfluent	B3	Conjoint
Fluent>Dysfluent	LEFT HEM						
	Insula		45	-1.5252	1.1539	2.679	0.0162
MOTOR - MOTOR	Motor region A	Motor region B		B1 Fluent	B1 Dysfluent	B3	Conjoint
Dysfluent>Fluent	LEFT HEM						

	45	Insula		-0.1026	0.5379	2.679	0.0013*
Caudate			45	-2.7724	1.0557	3.8281	0.00001**
	44	Insula		0.3949	1.0727	0.6778	0.002*

Table 4. Correlations that are significant in the Fluent group than the Dysfluent group and vice versa. B1 Fluent = β1 coefficient of the relevant linear regression equation in the Fluent group, B1 Dysfluent = β1 coefficient of the relevant linear regression model in the Dysfluent group, B3 = β3 coefficient of the relevant linear regression equation, and conjoint = the simulated conjoint probability. Significance at the p = .05 level is indicated by one asterisk, and significance at the p = .01 level is indicated by two. Left Hem = left hemisphere, Right Hem = right hemisphere, Bilateral = correlations involving a right and left hemisphere region. BGTC = basal ganglia-thalamo-cortical circuit areas.

Correlations Distinguishing Fluent and Dysfluent

The correlations that differentiated Fluent and Dysfluent groups involving those BGTC circuits and motor outflow and perisylvian posterior regions are visualized below. All correlations are depicted on a map of the regions of interest, following the schematic in Figure 3.1. Distinguishing correlations are reported regardless of whether their conjoint probability met the simulated cut-off value.

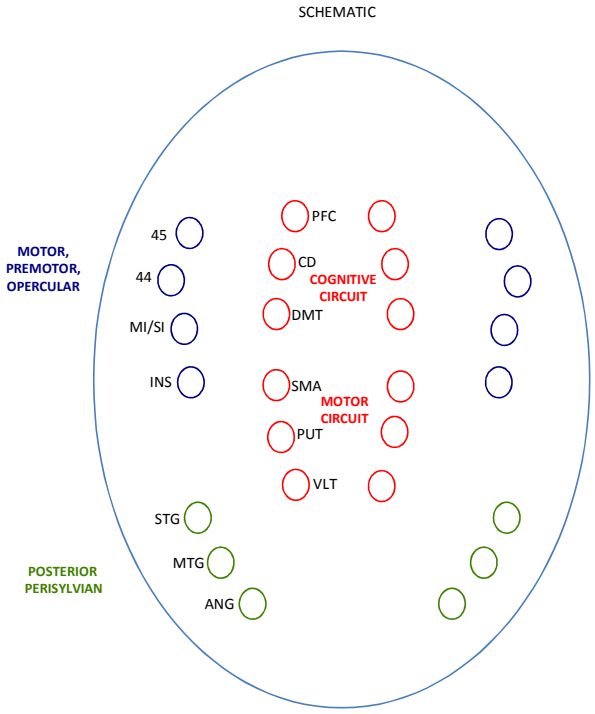

Fig 3.1 Schematic of the correlation maps displayed below. Left hemispheric regions are on the left side of the figure, right hemispheric regions are on the right. Each broad group of regions is assigned a specific color. Red = BGTC cognitive and motor circuits, blue = motor outflow regions, and green = posterior perisylvian regions. Regions have been arranged for ease of visualization and illustration of functional connections and not anatomic accuracy. Numbered regions correspond to the appropriate Brodmann's area. M1/S1 = primary motor/sensorimotor cortex, INS = insula, STG = superior temporal gyrus, MTG = medial temporal gyrus, ANG = angular gyrus, PFC = prefrontal cortex, CD = caudate, DMT = dorsomedial thalamus, SMA = supplementary motor area, PUT = putamen, and VLT = ventrolateral thalamus. Red lines indicate positive correlations, and blue lines indicate negative correlations.

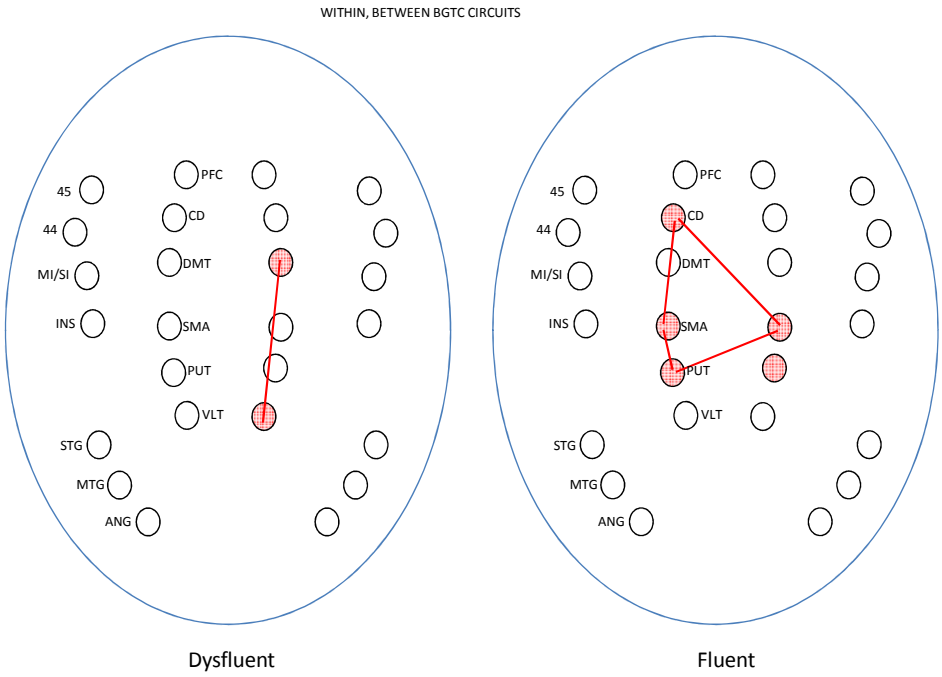

Figure 3.2.Correlations distinguishing the Fluent group (right) from the Dysfluent (left) that are between and within BGTC loop regions. Layout follows Figure 3.1.

The BGTC circuits and their connections are the focus of the present study. When connections within and between the motor and cognitive circuits themselves are evaluated, differences between Fluent and Dysfluent groups are apparent. In the Fluent group, the motor and cognitive circuits are coupled, and all participating BGTC loop areas are linked via the SMA (see Figure 2.2). Both ipsilateral and contralateral correlations are observed. The only direct coupling between these circuits distinctive to the Dysfluent group is an ipsilateral connection between dorsomedial and ventrolateral thalamus in the right hemisphere, and the conjoint probability of this correlation does not meet the simulated cut-off..

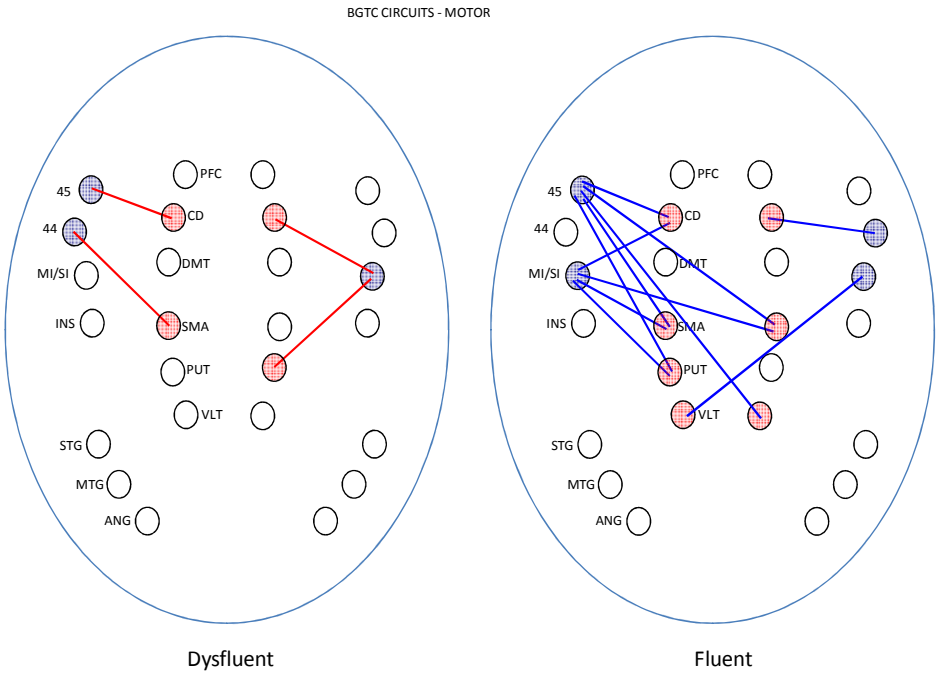

Figure 3.3 Correlations distinguishing the Fluent group (right) from the Dysfluent (left) involving BGTC loop regions and motor outflow regions. Layout follows Figure 3.1.

The cognitive and motor circuits were also coupled with cortical motor outflow regions in ways that differentiated fluent and dysfluent groups. In the Fluent group, distinctive correlations between the BGTC loops and motor-outflow regions are primarily left-lateralized, and the motor outflow regions in communication with the circuits are left BA 45 and left M1/S1 (see Figure 2.3). The Fluent group also shows contralateral correlations between these sets of regions, with left BA 45 and MI/SI communicating with R SMA, and left VLTH communicating with right M1/S1. In the Dysfluent group, distinctive correlations between these sets of regions are sparser, and no contralateral correlations are

observed. Crucially, distinctive correlations in the fluent group are entirely negative while those in the dysfluent group are positive.

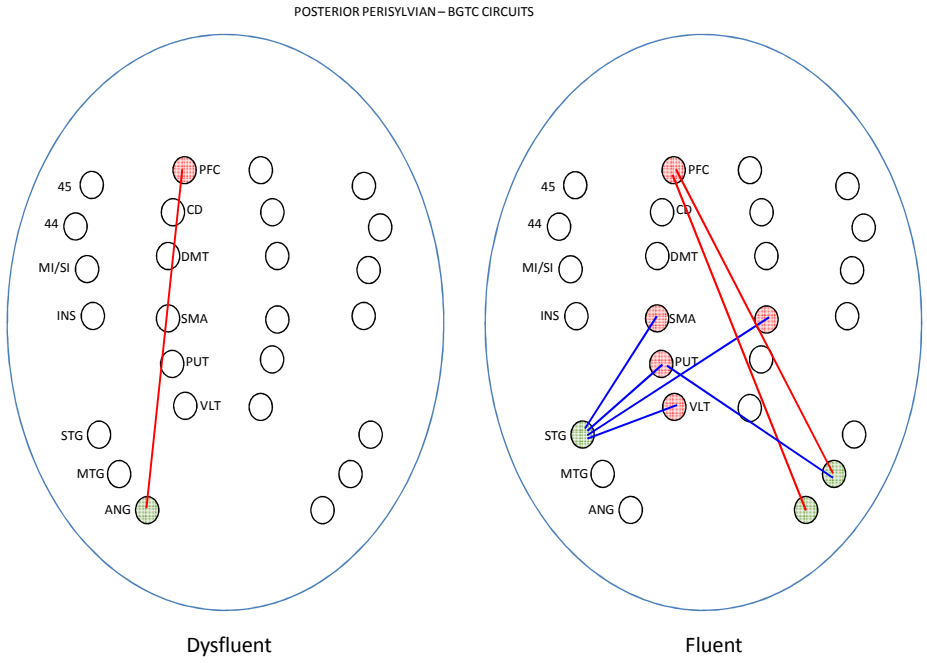

Fig 3.4 Correlations distinguishing the Fluent group (right) from the Dysfluent (left) involving BGTC loop regions and posterior perisylvian regions. Layout follows Figure 3.1

Group differences were also apparent in the connections of posterior perisylvian regions and the BGTC circuits. In the Fluent group, distinguishing correlations between the BGTC loops and the posterior perisylvian regions include negative interactions between the motor circuit and the left STG (see Figure 3.4). Again, distinguishing correlations in the Fluent group were both ipsilateral and contralateral (including connections between left PFC and right MTG and right ANG). In the Dysfluent group, the only distinguishing interaction between these sets of regions was ipsilateral, linking left angular gyrus and the

left PFC, and the conjoint probability of this correlation does not meet the simulated cut-offs

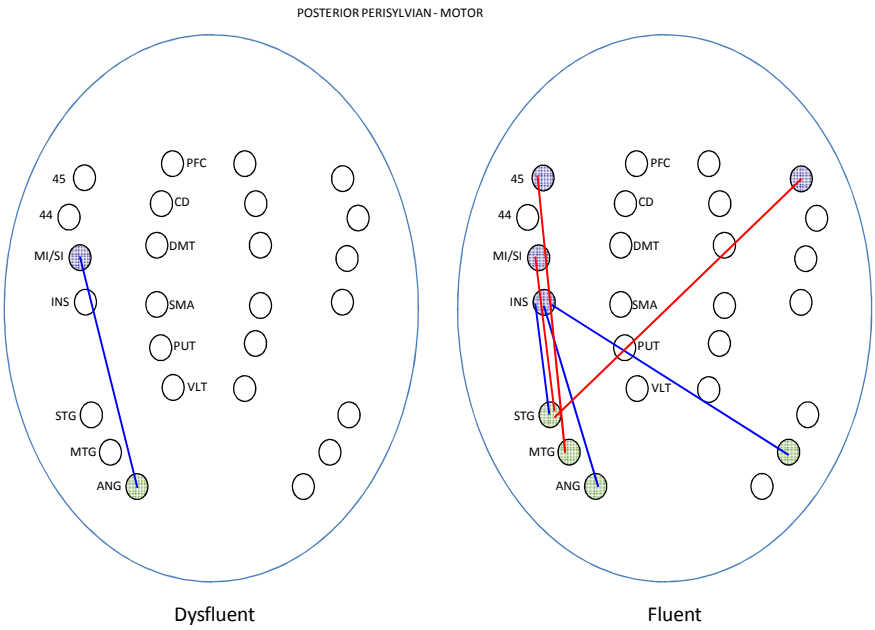

Fig 3.5 Correlations distinguishing the Fluent group (right) from the Dysfluent (left) posterior perisylvian regions and motor outflow regions. Layout follows Figure 3.1

Correlations between posterior perisylvian and motor outflow regions also demonstrated differences between the Fluent and Dysfluent groups (see Figure 3.5). The Fluent group has a large number of such correlations, while the Dysfluent group has only one with a non-significant conjoint probability. In the Fluent group, the connections between the insula and posterior perisylvian regions are entirely negative, while the correlations between BA 45 and M1/S1 and these regions are positive. These regions once again participate in contralateral correlations in the Fluent but not the Dysfluent group.

Individual Regions

To determine the relative importance of each region in the set ofdistinctive correlations for the Fluent and Dysfluent group, the “degree” of each region (the number of significant correlations involving that region) was calculated for each set of distinctive correlations. “Degree” is a social network analysis measure indicating the number of correlations in which a given region participates.

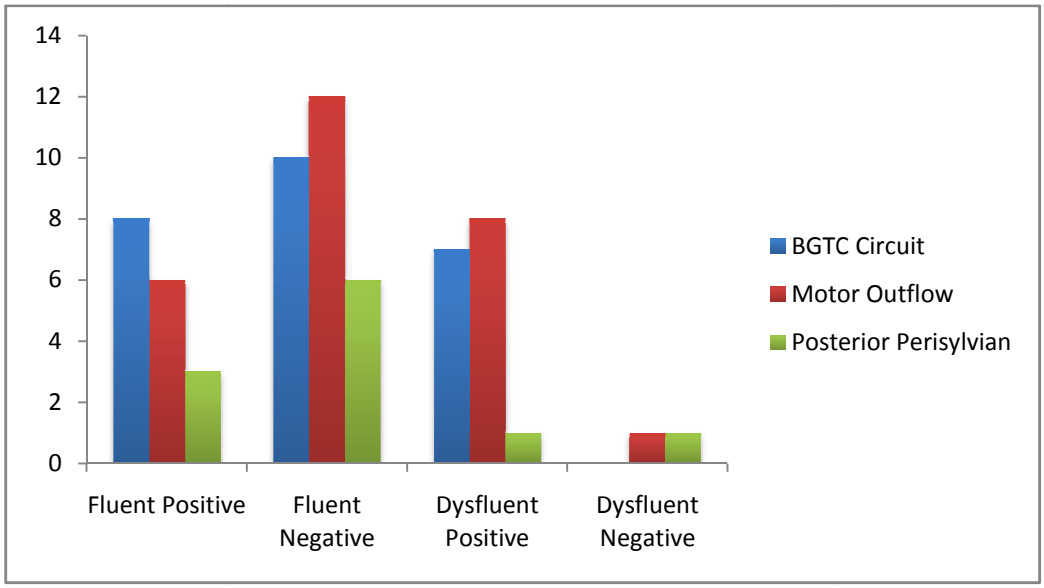

Figure 3.6 Total degree for each set of regions in the distinctive Fluent and Dysfluent correlations. As with the maps, blue = BGTC circuit regions, red = motor outflow regions, and green = posterior perisylvian regions.

The degree data also show that regional categories do not contribute equally to correlations differentiating Fluent and Dysfluent groups (see Figure 3.6). The motor outflow regions were dominant, followed by the BGTC circuit and posterior perisylvian regions. Importantly, in every regional category, negative

correlations exceeded positive correlations for the Fluent group. The reverse was true for all regional categories in the Dysfluent group, with the exception of posterior perisylvian regions (where positive and negative correlations are equal).

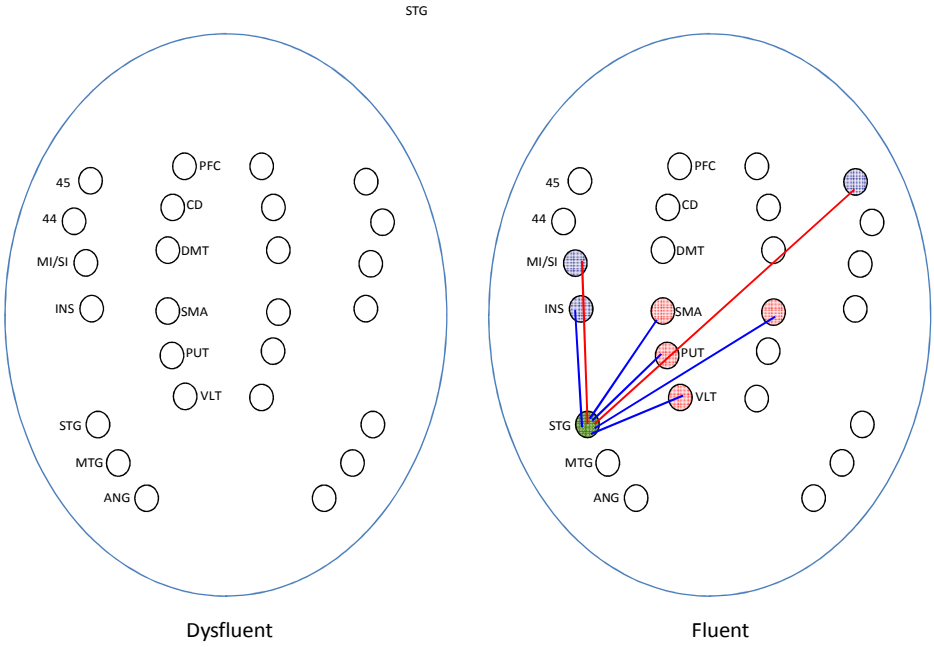

Fig 3.7 Significant correlations of the left superior temporal gyrus in the Fluent (right) and Dysfluent (left) group. Layout follows Figure 3.1

The left STG in the Fluent group (see Figure 3.7) participated in at least one correlation with every category of regions both ipsilaterally and contralaterally (excluding other posterior perisylvian regions), including both the cognitive and motor BGTC loops. The relative balance of negative and positive correlations reflects a complex pattern of modulation of other brain regions by auditory cortex. Left STG did not participate in any significant correlations in the Dysfluent group.

Fluent	**Total**	**Positive**	**Negative**	**Dysfluent**	**Total**	**Positive**	**Negative**
Region	Degree	Degree	Degree	Region	Degree	Degree	Degree
Left Hemisphere							
L SMA	6	3	3	L IFG (BA 45)	2	2	2
L STG	5	1	4	L Insula	2	2	0
L Putamen	6	3	3	L IFG (BA 44)	2	2	0
L IFG (BA 45)	6	1	5	L ANG	2	1	1
L Insula	4	1	4	L DMT	1	1	0
L M1/S1	5	1	4	L M1/S1	1	0	1
L Caudate	4	2	2	L SMA	1	1	0
L PFC	2	2	0	L PFC	1	1	0
L VLT	1	0	1				
L MTG	1	1	0				
L ANG	1	0	1				
Right Hemisphere							
R SMA	4	2	2	R M1/S1	2	2	0
R MTG	3	1	2	R DMT	1	1	0
				R VLT	1	1	0
				R Putamen	1	1	0
				R Caudate	1	1	0

Table 5 Degree scores for region s participating in the distinctive Fluent (left) and Dysfluent correlations (right), Degree was calculated as an unweighted sum of the number of distinctive correlations involving each region of interest (see Methods). Regions are ranked by degree.SMA = supplementary motor area, STG = superior temporal gyrus, IFG = inferior frontal gyrus, M1/S1 = primary motor/sensorimotor cortex, PFC = prefrontal cortex, VLT = ventrolateral thalamus, MTG = middle temporal gyrus, ANG = angular gyrus, DMT = dorsomedial thalamus.

The Fluent group has by far the largest number of high degree regions, maximal in SMA and STG. (see Table 3.1). The degree values of the Fluent group are dominated by negative correlations and these are clustered in the left hemisphere. In the Dysfluent group, degree scores are lower and are found in both left and right hemispheres; only three areas participate in negative correlations.On the basis of these data, maps depicting correlations between

individual regions and other brain areas (presented below, Figures 3.7-3.11) were restricted to regions with the highest degree scores: left STG, SMA, putamen, BA 45 and insula.

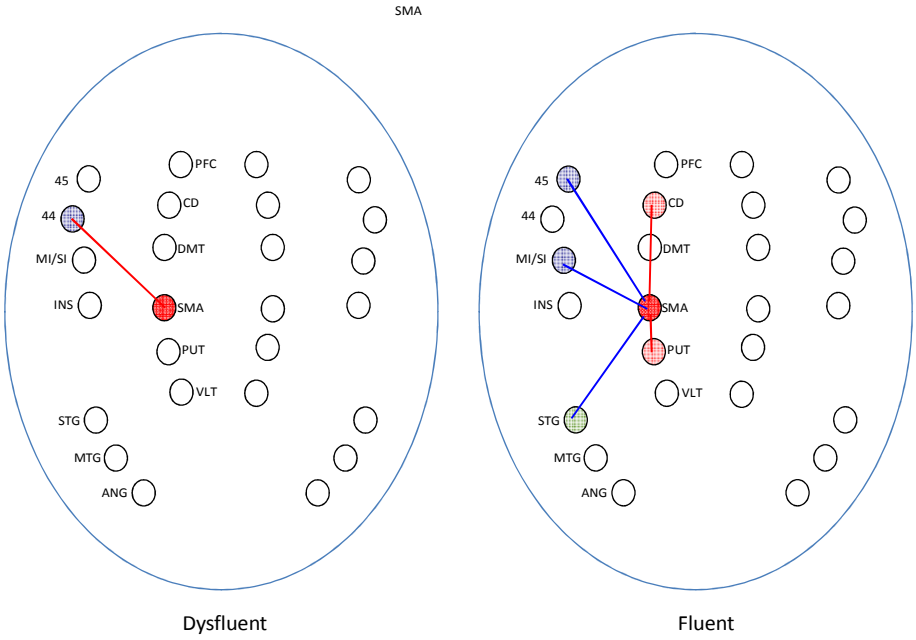

Fig 3.8 Significant correlations of the left supplementary motor area in the Fluent (right) and Dysfluent (left) group. Layout follows Figure 3.1.

The left SMA was linked to all categories of regions in the left hemisphere in the Fluent group (see Figure 3.8). All of the distinguishing correlations between the left SMA and other BGTC loop regions are positive while all of the distinguishing correlations between the left SMA and motor outflow and posterior perisylvian regions are negative. There is only a single positive distinguishing correlation between SMA and BA 44 in the Dysfluent group.

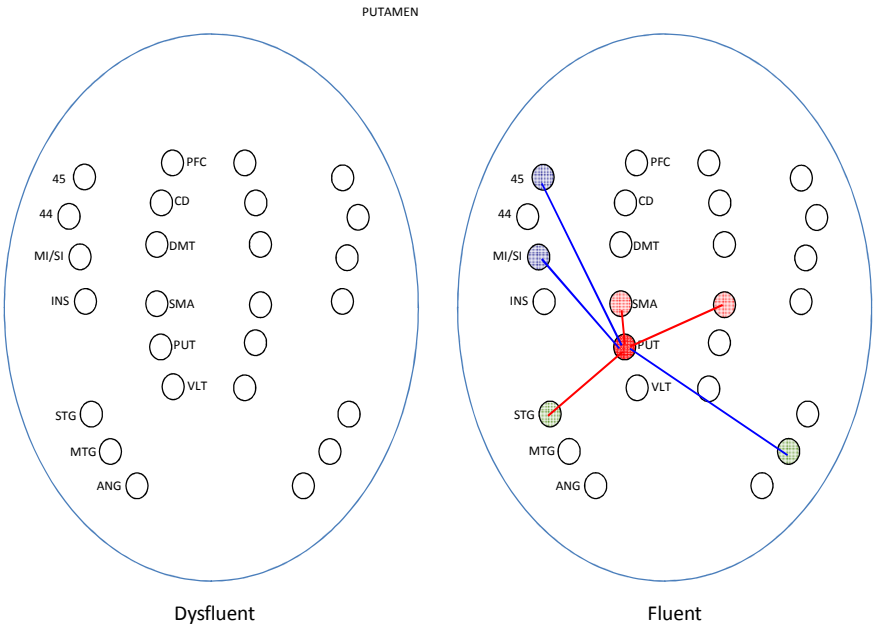

Fig 3.9 Significant correlations of the left putamen in the Fluent (right) and Dysfluent (left) group. Layout follows Figure 3.1.

Distinguishing correlations involving the left putamen (see Figure 3.9) are similar to those seen for the left SMA (see Figure 3.9) in the Fluent group. The left putamen is linked with right SMA rather than left caudate within the BGTC loops, and it has a contralateral correlation with right MTG not associated with the left SMA. The left putamen does not participate in any distinguishing correlations in the Dysfluent group.

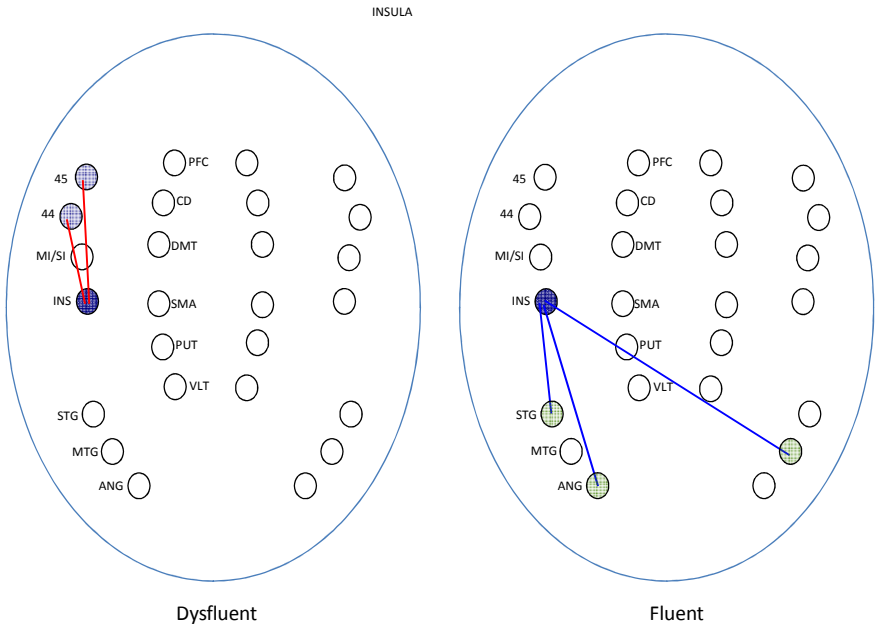

Figure 3.10 Significant correlations of left insula in the Fluent (right) and Dysfluent (left) groups. Layout follows Figure 3.1.

Left insula is positively correlated with left BA 44 and BA 45 in the Dysfluent group, and is connected with the motor and cognitive loops via these regions (see Figure 3.10, left). This interaction between the insula and 44 and 45 in particular is entirely unique to the Dysfluent group. The insula is coupled with BA 45 in the Fluent group, but this correlation does not reach conjoint significance (see Table 4). It instead interacts negatively with contralateral posterior perisylvian areas (see Figure 3.10, right). All of the correlations of the insula are positive in the Dysfluent group, and negative in the Fluent group.

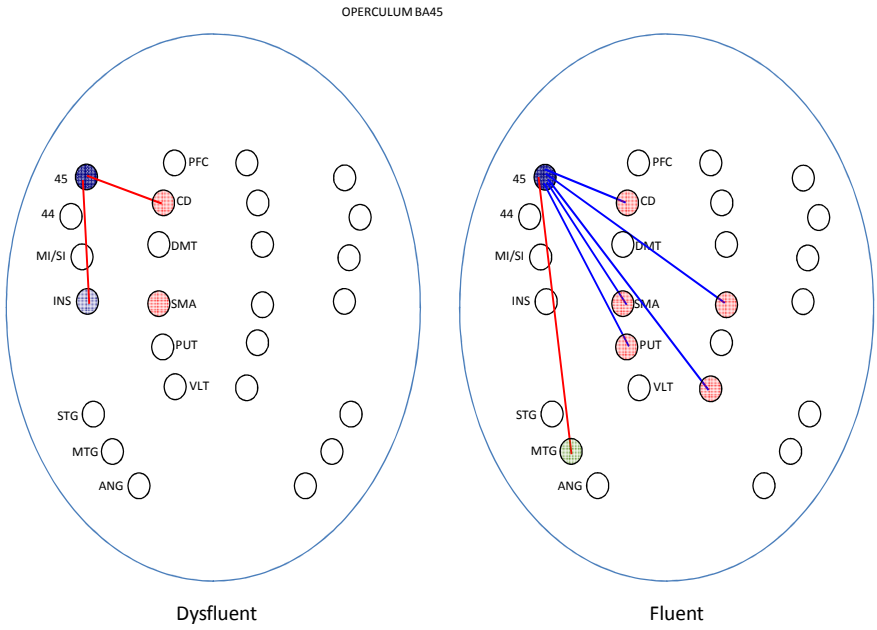

Figure 3.11 Significant correlations of left BA 44/45 in the Fluent (right) and Dysfluent (left) groups. Layout follows Figure 3.1.

In the Dysfluent group, BA 45 is linked with the insula, and has links with the cognitive BGTC circuit (see Figure 3.11). In the Fluent group, left BA 45 participates in primarily negative correlations, and is linked in this way to both cognitive and motor BGTC loops. The Fluent group also shows a positive correlation between MTG and BA 45, which may represent coupling of classical Wernicke's and Broca's areas.

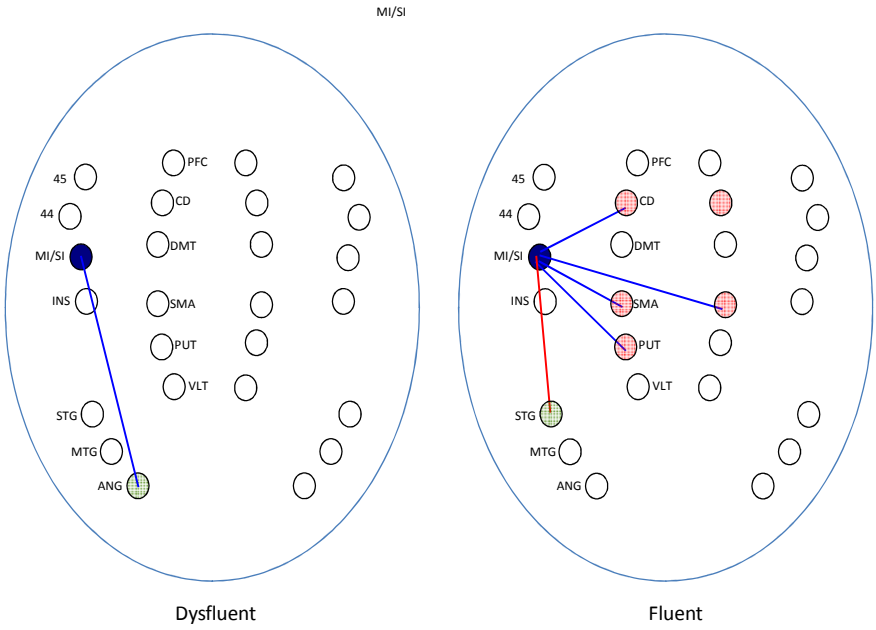

Figure 3.12. Significant correlations of left M1/S1 in the Fluent (right) and Dysfluent (left) groups. Layout follows Figure 3.1.

Primary motor/sensorimotor cortex was linked with both BGTC circuits and posterior perisylvian regions in the Fluent group, but only with left ANG in the Dysfluent group (Figure 3.12). In the Fluent group, M1/S1 participates in negative correlations with all the BGTC circuit regions and a positive correlation with left STG. Left M1/S1 also participates in a contralateral connection in the Fluent but not in the Dysfluent group.

Trait, State, and Normalization

As noted in the Methods, significant inter-regional correlations (B1 values) that did not differ significantly between the Fluent and Dysfluent group, but that did differ significantly from the Control group are the correlations would be direct

evidence of “trait” stuttering, i.e. a pattern of neural activity common to PWS regardless of whether or not they are stuttering. No such correlations were found, and so the present study offers no evidence of “trait” neural activity specific to people who stutter. Thus, group differences in correlations must correspond to “state” stuttering, i.e. whether or not PWS happened to stutter during the scan, because they cannot be attributed to “trait” stuttering.

Differences between the two PWS groups could either involve the Fluent group correlations becoming more like controls or adopting a pattern of correlations that differed from controls. Fluent PWS could thus either show a pattern of correlations more like the pattern found in the Control group than like the Dysfluent group, or they could show a pattern of correlations different from both the Control and Dysfluent group. Significant inter-regional correlations (β1 values) shared between the Fluent and Control group that in each case significantly differed from the Dysfluent group would be evidence of “normalization”. In other words, they would be similarities between the Fluent and Control group that they did not share with the Dysfluent group. Only a single instance of this was found, a correlation between right primary motor/somatosensory cortex and right putamen. Thus, the present study found only marginal evidence for a pattern of “normalization” of neural activity with respect to controls in PWS speaking fluently.

Since the vast majority of the significant correlations in the Fluent group could not be attributed to “trait” stuttering or “normalization” as noted above,

these state-related patterns can be attributed to “compensation,” i.e. a pattern of neural connectivity observed only PWS successfully avoided dysfluency.

Certain correlations were shared between all three groups, characteristic of speech production in controls and PWS, whether fluent or dysfluent. They shared positive contralateral correlations between regions within the BGTC loops. More specifically, left caudate nucleus, left putamen, left dorsomedial thalamus and left supplementary motor area were all linked to their homologous counterparts in the right hemisphere.

Small World Analysis and Centrality Measures

Small world and centrality measures from social network analysis offer a more quantitatively rigorous set of measures to characterize how regional linkages varied between groups, as well as to reinforce degree as a measure of relative regional importance. As noted above, these measures must be applied to “networks” of regions that are fully connected in order to produce useful results. Since there are inter-regional correlations in both sets of distinctive correlations that did not differentiate Fluent and Dysfluent groups from each other, these tools cannot be used with the distinctive Fluent and distinctive Dysfluent correlations presented in Figures 3.2- 3.11. Instead, these tools are applied to the whole set of significant correlations associated with each group (i.e. all significant β1 values), regardless of the significance of the group interaction or conjoint p-values. These “networks” were densely inter-connected, allowing for successful application of the relevant measures.

Network	Gamma	Lambda	Gamma/Lambda	Global Efficiency
Fluent	4.52	2.67	1.69	0.0000719
Dysfluent	5.98	4.65	1.28	0.0000445
Control	5.48	3.06	1.79	0.0000668

Table 6. Small world analysis measures as applied to all significant B1 values associated with the Fluent, Dysfluent, and Control networks. Gamma is the ratio of the clustering co-efficient of each "network" to the clustering co-efficient of a random network of the same size. Lambda is the ratio of the average path length of each "network" to the average path length of a random network of the same size. Two nodes that are directly linked have a path length of 1 between them, and each node lying between two given nodes adds one to the path length. A "network" is considered to have small world character when the ratio of gamma to lambda is greater than 1. Small world character is thus associated with networks that have tightly-linked clusters that are joined by topologically short connections.The global efficiency measure is described in Latora and Marchiori (2001) and is a measurement of the communicative efficiency of the "network."

All of the sets of significant correlations had appreciable small-world character (see Table 5), which is typical of well-functioning biological and non-biological networks (Basset and Bullmore 2006). However, the Fluent and Control groups have approximately 30% more small world character than the Dysfluent group, and they are both approximately twice as globally efficient.

Additional social network analysis measures were applied to these correlations. Our analysis focused on centrality, another metric for the importance of individual regions and their functional role within networks. Specifically, we used two measures, betweenness and closeness. More disagreement between these measures indicates a less efficient network, since a greater match between measures will give a network more small world character and lead to greater global efficiency scores (cf. Basset and Bullmore 2009). Small-world character is a property of networks with tight clusters that are

sparsely connected, meaning that regions with high betweenness should also score high on closeness. Deviations from this match between measures will lead to lesser small world character. While it is unsurprising to find many regions with closeness scores but a zero betweenness score (since the regions may be connected to others but just happen not to fall on a shortest path between two other regions), the opposite cannot occur, since any intermediate region must be connected to at least two other regions.

Unlike the global scores generated by the small world analysis, the ROI-based mismatch between betweenness and closeness makes it possible to determine the precise contribution of individual regions to a network's global efficiency.The BGTC circuit, cortical motor, and posterior perisylvian regions that ranked highest on both measures for the Fluent and Dysfluent groups are presented below.

Dysfluent		Fluent	
Closeness	Betweenness	Closeness	Betweenness
Right Putamen	Right DMT	Left Putamen	Right Putamen
Right Caudate	Left DMT	Left VLT	Right Caudate
Left Caudate	Left PFC	Left Caudate	Right DMT
Left VLT	Left SMA	Left PFC	Left Putamen
Right VLT	Right SMA	Right Putamen	Left Caudate

Table 3.4 Top five highest-scoring BGTC circuit regions on closeness and betweenness measures for the Dysfluent group (left) and Fluent group (right). DMT = dorsomedial thalamus, VLT = ventrolateral thalamus, PFC = prefrontal cortex, SMA = supplementary motor area.

A mismatch between closeness and betweeness scores is observed in the Dysfluent group, as the top five closeness regions do not correspond to any of the top five betweeness regions (see Table 3.4). Left and right putamen and left caudate appear as highly-ranked regions on both measures in the Fluent group, however, suggesting better agreement between the centrality measures.

Dysfluent		Fluent	
Closeness	Betweenness	Closeness	Betweenness
Left BA 45	Left BA 45	Left M1/S1	Left BA 45
Right BA 45	Right BA 45	Left Insula	Left Insula
Right M1/S1	Right M1/S1	Left BA 45	Right M1/S1
Left M1/S1	Left M1/S1	Right BA 45	Left M1/S1
Right BA 44	Right BA 44	Right BA 44	Right BA 45

Table 3.5 Top five highest-scoring cortical motor regions on closeness and betweenness measures for the Dysfluent group (left) and Fluent group (right). M1/S1 = primary motor/sensoirimotor cortex.

Closeness and betweenness rankings form a good match in both Fluent and Dysfluent groups in cortical motor areas, with all top five in both groups consistent between measures (see Table 3.5). This suggests that the cortical motor areas in both group is not detracting from the small-world character of either network.

Dysfluent		Fluent	
Closeness	Betweenness	Closeness	Betweenness
Right MTG	Right ANG	Left STG	Left STG
Left MTG	Left ANG	Right MTG	Right MTG
Right ANG	Right MTG	Right ANG	Right ANG

Table 3.6 Top three highest-scoring posterior perisylvian regions on closeness and betweenness measures for the Dysfluent group (left) and Fluent group (right). MTG = middle temporal gyrus, ANG = angular gyrus, STG = superior temporal gyrus.

Only three posterior perisylvian regions have non-zero closeness and betweenness scores for both groups, so these are the only regions reported in Table 3.6. Another centrality score mismatch is observed in the Dysfluent condition relative to the Fluent condition; while all of the top three betweenness regions in the Fluent group are the same and in the same relative ranking as the top three closeness regions, this is not the case in the Dysfluent group, where only two regions match between scores and the relative rankings of those are inverted (see Table 3.6).

Discussion

Overview

Persistent developmental stuttering is a language-specific disorder of speech with a highly variable symptom profile, between and within individuals (Bloodstein and Bernstein Ratner 2008). A large number of neural regions have been implicated in the disorder, and thus a functional connectivity approach to

understanding the pathophysiology of PDS was pursued in the present study. We presented hypotheses relating to three major theories of stuttering and what patterns of neural connectivity would be associated with dysfluency in PWS. Given that stuttering is a failure of speech/language integration, we hypothesized that greater coupling between linguistic and motor systems would be associated with fluent speech. Since disruptions to normal auditory feedback conditions can temporarily reduce stuttering severity, we predicted that dysfluency would be associated with less integration between auditory and motor systems. Finally, because stuttering symptoms wax and wane with attempts to speak fluently, we hypothesized that PWS would show more left lateralized activity when successfully producing fluent utterances than when utterances contained stuttering events.

As far as speech motor control is concerned, we predicted that the BGTC circuits and their functional connections would be central in patterns of activity associated with fluency in PWS. We expected BGTC circuit involvement for a number of reasons, including their centrality in theories both of speech motor control (Goulfinopolos et al. 2010) and stuttering (Alm 2004), the suspected involvement of dopaminergic systems (Wu et al. 1997; Stager et al. 2005) and previous findings of an association between stuttering severity and basal ganglia activity (Braun et al. 1997, Giraud et al. 2008). Specifically, we predicted more effective coupling within and between the motor and cognitive circuits, reflecting language-motor integration and better coordination between action plan selection and planning in PWS when achieving fluency. In PWS who were fluent during

scanning, we also predicted more effective coupling between BGTC circuits and cortical motor outflow regions, reflecting more effective speech motor control. We also predicted that direct coupling between BA 45 and the insula would be associated with dysfluency, reflecting excessive automaticity in speech production.We further predicted that effective regulation of frontal operculum by BGTC circuits and posterior perislylvian areas – supplanting direct control by the insula - would only emerge during fluent speech production.

The integration of auditory feedback in our two groups of PWS and NS, was of interest because of the auditory-related dysfluency-reducing conditions known to help many PWS noted above and the role of auditory feedback in some theories of stuttering (e.g. Max et al. 2004). We predicted that less robust coupling between STG and other neural regions (BGTC circuit and cortical motor outflow) would be associated with dysfluency. Fluent speech production in PWS was predicted to involve strong coupling between STG and these regions, because STG is the likely origin of auditory error signals and the regions with which it is coupled are those most likely to utilize that feedback for motor control. We hypothesized that the strong coupling between STG and the BGTC motor circuit/cortical motor outflow regions reflected effective integration of auditory error signals in motor plan selection.

Atypical lateralization profiles have long been posited as a cause of stuttering (Travis 1978). Previous neuroimaging work has presented a muddled picture of the extent to which it is important in the disorder due, due to largely contradictory findings (Fox et al. 1996; Braun et al. 1997; De Nil et al. 2001).

Thus, we were interested in assessing lateralization in our participants. We predicted that fluent speech production in PWS would be associated with more effective inter-hemisphere communication (as reflected in more inter-hemispheric correlations, and greater left lateralization as reflected by a greater preponderance of functional connectivity in the left hemisphere). We also hypothesized that the regulation of motor outflow areas by the BGTC circuits, both cognitive and motor, would be strongly left-lateralized in fluent speakers.

PET was chosen in order to allow for a more naturalistic speech task, and to conduct functional connectivity analysis to examine interactions between a wide range of brain regions. We found that the functional connections associated with fluency in PWS were more numerous and more diverse overall than the functional connections associated with dysfluency in a group of PWS who exhibited fluency breakdown during our PET task. As predicted, the Fluent group showed evidence of better coupling within BGTC motor and cognitive circuits, between the BGTC motor and cognitive circuits, and between the two hemispheres.

Motor Control

While the more numerous correlations noted among regions within each of the BGTC circuits of interest in the Fluent group in the present study suggests better functioning of those specific circuits, these circuits were also better coupled with each other. Since this is evidence of stronger coupling between a traditionally cognitive/associative circuit and a motor circuit (Middleton and Strick

2000), we interpret this as better integration of cognitive and motor processing. We identify the cognitive BGTC circuit with language in particular because of findings of grammatical impairments in Parkinson's and Huntington's disease patients (Ullman et al. 1997) and its role in resolving lexical ambiguities (Chenery et al. 2008). A role is assigned to the PFC in connection with the cognitive BGTC circuit by computational models of syllable production (Bohland et al. 2010). Since the same computational models assign the motor circuit a role in the release of articulatory plans from inhibition (Bohland et al. 2010), better coupling between these circuits can be taken to represent more effective language-motor integration. The failure of the Dysfluent group to show any distinguishing correlations that achieved conjoint significance between BGTC regions emphasizes the importance of circuit coupling for fluency.

The most obvious difference between the Fluent and Dysfluent groups with respect to correlations between the BGTC circuits and motor outflow regions is the difference in sign of the correlations involved in each. The uniformly positive correlations between BGTC circuit regions and the motor outflow regions in the Dysfluent group can be explained by a simple feed-forward account. That is, these regions are connected, and activation simply spreads between them, thus producing the correlations. This cannot account for the uniformly negative correlations between these categories of regions in the Fluent group. These functional connections must play a different and more complex role in the Fluent group, perhaps a regulatory function (Blumenfeld et al. 2004). Given the

proposed role of the BGTC circuits in DIVA, we suggest that this is likely, and that these connections represent signals for the release or arrest of motor sequences. An explanation in terms of servomotor control theory is also possible; the Dysfluent group may get stuck in a positive feedback circuit as a result of the connectivity between these areas, while the Fluent group's negative correlations disrupt the formation of this circuit. Both of these accounts are consistent, and the overlap between them will be explored below. That both more and more complex interactions between the BGTC circuits and motor outflow regions are associated with fluency supports our motor integration hypothesis.

In the Fluent group, the left SMA is highly central and connects the BGTC motor and cognitive circuits as well as the left motor outflow regions and the left STG. SMA thus serves as a coupling site for a wide diversity of regions, joining the motor plan selection functions of the BGTC motor circuit with the predictive function of the cognitive circuit (Bohland et al. 2010), together with the execution of those plans via the cortical motor outflow regions. The putamen shows a similar pattern of correlations, which was surprising because previous PET work found that the putamen was highly active in a cohort of PWS relative to NS (Braun et al. 1997). The present study clarifies this association, since the putamen is only significantly coupled with other regions in the distinguishing Fluent correlations (when PWS are speaking fluently), not the distinguishing Dysfluent correlations (when PWS are not speaking fluently). Thus, in PWS experiencing dysfluency, the putamen may be highly active, but its activity is not correlated with activity in other regions, and is not appropriately coupled with

other regions. It is only when PWS generate fluent utterances that the motor circuit is appropriately coupled with other regions; putamen connectivity is an indicator of this stronger integration of the motor circuit and other systems.

One of the few areas within which the Dysfluent group shows more robust connectivity than the Fluent group is within the motor outflow regions, specifically the left motor outflow regions. As noted above, left BA 44/45 and left insula are sufficiently correlated to reach conjoint significance only in the Dysfluent group and they are not participants in the diverse positive and negative correlations seen in the Fluent group. Left BA 45 is very important for the Dysfluent "network" in terms of degree, as is the left insula, so their connections are crucial to understanding the neural basis of dysfluency in PWS in the present study. We suggest that the uniformly positive connections within the left motor outflow region, and the absence of negative correlations with outside regions, represent excessive automaticity in speech motor planning (i.e., an inability to adjust speech plans) in PWS when they fail to achieve fluency. Instead of receiving the widespread modulatory inputs associated with successful compensation for stuttering, the Dysfluent group is instead locked into a positive feedback circuit (Gehring et al. 2000), unable to make effective use of sensory error signals. In the Fluent group, this coupling was disrupted by connections with left and right posterior perisylvian areas, enabling the motor outflow to be in communication with the BGTC circuits.

The connections of the MTG and ANG with BA 44/45 during fluent speech production in PWS represent tighter coupling of Broca's and Wernicke's areas.

These are classical language areas with a long history in neuropsychology and have been reliably found to be connected in functional connectivity analyses (Hampson et al. 2002). That better coupling between these areas should lead to more successful speech is not surprising.

We can be more specific about the function of the connections between these areas, however. The posterior perisylvian regions may play a part in disrupting the conjointly significant correlation between BA 44/45 and the insula seen only in the Dysfluent group, as the perisylvian regions participate in positive and negative correlations with both BA 45 and the insula. Given the well-established role of STG in phonological processing (Buchsbaum et al. 2001, Hickok and Poeppel 2007) and the function attributed to the planumtemporale in the DIVA model, we suggest that phonetic error signals from these regions disrupt the automatic connection between BA 45, a substrate of phonological working memory (Rogalsky et al. 2008) and speech motor planning (Desmond and Chen 2005), and the insula, a substrate of articulatory coordination (Dronkers 1996). Our increased temporal-motor correlation hypothesis is supported by the present study.

Auditory-motor

The efficacy of feedback-altering conditions in temporarily reducing stuttering severity in some PWS led us to hypothesize an association between successful auditory-motor integration and fluent speech in PWS. This would be reflected in the current study in coupling between posterior perisylvian regions,

especially the STG, and the BGTC motor circuit and cortical motor outflow areas. Only the Fluent group shows modulatory or inhibitory coupling of posterior perisylvian regions with the motor circuit; since the most important region that shows such coupling is the left STG, we suggest that this represents the contribution of phonetic error signals to the motor plan selection occurring within the motor circuit. Its absence in the Dysfluent group is likely to reflect the failure to appropriately integrate these signals when not achieving fluency. The left STG is highly important in the broader Fluent "network", with a wide diversity of connections between many regions, both positive and negative. Correlations of particular importance are its linkages with both cognitive and motor circuits and primary motor cortex. We suggest that this diversity of connections represents the regulation of the system as a whole by phonetic error signals, and that the coupling with the BGTC circuits and primary motor cortex in particular reflects the effective use of error signals to guide motor plan selection and execution. The hypothesis of better coupling between the BGTC circuits and posterior perisylvian areas in the Fluent group is supported by the present study.

During fluent but not dysfluent speech production, the left STG was effectively connected to all other regional categories (motor outflow and BGTC circuits) in both hemispheres. It was also negatively connected with the BGTC motor circuit and insula, while being positively connected to the operculum and M1/S1. This suggests that integration of input from the STG is necessary for fluency in PWS; the lack of any correlations whatsoever involving the STG in the Dysfluent group supports this claim. This input should take the form of auditory

or phonological information, and, following previous modeling work, we suggest that more effective STG coupling during the production of fluent speech represents integration of auditory feedback signals. In the context of coupling with the BGTC motor circuit, this feedback is used to satisfy the selection criteria for release of motor plans from inhibition. Additionally, since the STG is positive correlated with one end (the operculum/BA 45) and negatively correlated with the other end (insula) of a correlation that we have argued is strongly associated with dysfluency, we suggest that these error signals may disrupt excessively automatic articulation in successful compensation. When this link is not disrupted by feedback, compensation fails.

In a weak feedforward control model of stuttering, delayed auditory feedback and altered auditory feedback should both serve the same purpose - activating the feedback control pathway to a greater degree and contributing to its dominance over the unreliable feedforward control pathway in people who stutter. This explains relative insensitivity of stuttering to the precise details of feedback alteration or feedback type (Macleod et al. 2005); the mechanism we suggest is broader than this. As a result we do not have specific predictions about which types of feedback with what settings should result in greater fluency, apart from suggesting that alterations of any kind that tend to lead to more weighting of feedback control signals will be helpful on average.

Lateralization

It has been proposed that a lack of left-lateralization plays a role in stuttering (Travis 1978), and so we predicted that fluent speakers would be characterized by a greater degree of left-lateralization. This lateralization hypothesis was supported by the data in the present study. Not only did the Fluent group show far more distinctive left-lateralized correlations than the Dysfluent group, but the Fluent group also had more interhemispheric correlations. Additionally, a substantial proportion of the left hemisphere correlations in the Fluent group were negative connections between the BGTC circuits and cortical motor outflow regions. Since, as discussed above, these connections must play some kind of modulatory or regulatory role, the present study suggests that majority of changes in connectivity that enable fluent speech in PWS are supported by the left hemisphere.

The relative importance of the BGTC circuits and the supplementary motor area for fluent speech, in particular, supports the empirical predictions of the GODIVA framework. These regions are posited to play a crucial role in the release (and effective selection) of motor plans in normal speech (Bohland et al. 2010), and their increased centrality and involvement in the Fluent group relative to the Dysfluent group supports their contribution to successful speech control. GODIVA's interpretation of these regions as important for releasing motor plans that fulfill a certain set of criteria can be enriched by these results; the strong connectivity of STG with the motor circuit suggests that some of these criteria are auditory, possibly a prediction of the phonetic consequences of the motor plan under consideration. These results and the GODIVA model together suggest that the BGTC circuits provide the means for selection among motor plans, and

that the STG provides the basis for that selection.

The importance the GODIVA model assigns to our highest degree regions is reinforced in a principled way by centrality measures, which offer a means of determining precisely how communicatively important each region is. Since these measures make assumptions about the how regions are linked together, we applied these measures to all correlations in each group with significant β1s, regardless of whether those correlations significantly differed between groups. These measures thus also gave us a sense of the importance of each region for the connections of each group as a whole, and not just their importance in the distinguishing connections of each group. The relative agreement of the two centrality measures (closeness and betweenness) also suggest how well-organized each "network" is, since processing should be most efficient when the best connected regions (closeness) are the same regions that serve most frequently as intermediaries (betweenness). Our centrality analysis results support our identification of critical regions by degree, since high degree regions rank highly on both centrality measures in the Fluent group. The Dysfluent group has more of a mismatch between these measures, especially dramatic in the posterior perisylvian regions and the BGTC circuit regions. This suggests that relatively inefficient neural recruitment and suboptimal organization of communicative networks lead to dysfluency in PWS. Suboptimal organization must of course have a cause, but it simply represent a local performance maximum that is not sufficient to achieve fluent speech. Feedback control is inherently less stable than feedforward control due to the lag between motor

commands and perceptual input (Guenther et al. 1998), and so once such a local performance maximum is achieved, it may be very difficult to move away to a greater performance equilibrium without enduring a temporary decrease in fluency. The present study does not allow us to distinguish between cortical or subcortical grey matter itself and connecting white matter tracts, since correlations between regions could either be due to similar computations being performed on the same inputs in both regions or in communication between them during scanning.

The learning mechanism of the DIVA model suggests the outlines of an account of how these circuits might mature in such a way as to produce the breakdown seen in PD, which is unsurprising, as accounting for developmental changes was one of the original motivations for DIVA (Guenther et al. 1998).. The idea of DIVA-based models is that the robust learning mechanism should prevent the need for significant changes in functional organization over the course of development. Individual mappings will change, but the basic flow of information between components will not. Simply put, any deficit in learning that prevents the formation of reliable mappings between the speech sound map and the articulator position and velocity maps could lead to a weakness in feedforward control of the kind posited by the framework we adopt. This problem, in model-theoretic terms, could lie in either the connections directly between the sound maps and the articulator maps, in the connections between these maps and intermediate maps, such as the cerebellum, or potentially in the intermediate maps themselves. Simulations of deficits in the connections between speech

sound maps and articulator maps leading to stuttering behavior are described in Max et al. (2004).

The fit between our results and DIVA-based models is excellent but not perfect. The biggest change our data suggests to DIVA is a more direct linkage between the superior temporal gyrus and the motor-planning BGTC circuit, given the robustness of the connections between the STG and this circuit and its exclusive association with fluency. However, given that our functional connectivity analysis cannot address the temporal dynamics or directionality of information flow, our ability to make specific model suggestions is limited.

Centrality measures offer an assessment of disorganization in the "networks" of dysfluent PWS that is supported by a different technique, small world analysis. Both the Fluent and Control "networks" have more small world character than the Dysfluent "network," suggesting better organization of neural recruitment; the Dysfluent "network" also scores much lower on a measure of global communicative efficiency than either of the other two "networks", suggesting less communicative efficiency. Reduced small world character and global efficiency has been associated with "networks" seen in several forms of neuropathology (Wang et al. 2009; Sanz-Arigita et al. 2010). Thus, the hypothesis that the Dysfluent "network" is less well-organized and less efficient is supported by the present study.

Even though the Dysfluent and Fluent "networks" differ in terms of their organization, there might in principle still be correlations seen between regions in PWS regardless of whether or not fluency was being achieved in a particular task

(distinguishing Fluent *and* Dysfluent correlations). This would represent the trait features of stuttering rather than the state features of stuttering. No such correlations were found. The present study offers no support for trait features in PDS, only state features (associated with achieving fluency or dysfluency alone).

However, the state dependent difference we report could represent two different processes. Distinguishing Fluent correlations might have differed from the Dysfluent correlations in more closely resembling Control correlations. As noted, this could be termed “normalization,” in which case achieving fluency in PWS could be characterized as simply suppressing or altering a pattern of aberrant neural recruitment and achieving a pattern typical of NS. Only one such correlation (shared by the Fluent and Control groups but not by the Dysfluent groups) was found, between right M1/S1 and the right putamen. Since “normalization” cannot account for the majority of the distinguishing Fluent correlations, we suggest that the distinguishing Fluent correlations instead represent a successful, alternative strategy of compensation for stuttering.

Although the Fluent correlations discussed above can be primarily attributed to compensation for stuttering, compensation can be understood in a number of different ways. Based on the particular patterns of connectivity observed in the present study, we can draw specific conclusions about the nature of successful compensation in PWS. Non-motor linguistic and motor systems are better integrated in fluent speech in PWS, and there is a stronger coupling between those same motor systems and auditory regions. Correlated activity is also far more left lateralized during fluent speech in PWS along with more

contralateral connections, suggesting that compensation involves better interhemispheric coordination.

While the Fluent and Dysfluent groupings in the present study were propitious and not pre-planned on the basis of anything known about the subjects, it is possible that some measure of stuttering behavior or severity outside of our task could separate them into the same groups. It is thus possible that we have identified differences between two subtypes of PWS rather than between PWS who are achieving fluency and PWS who are not achieving fluency. If these subtypes differed only in how challenging they found the task of novel verb sentence generation, the generalizability of the results of the present study would be weakened. Future studies could include more stuttering instruments to reduce the possibility that the Fluent and Dysfluent groups are not subtypes of the stuttering population.

Additionally, the present study used only one task and only grouped PWS participants into two categories when many more subtypes have been proposed for the disorder (see Yairi 2007 for a review). Ideally, more tasks would be used and a continuous measure of stuttering performance during the task would be used. Additional tasks might create more gradients of stuttering behavior, and a continuous measure might allow for assessing how our network patterns change with increasing or decreasing stuttering severity.

Finally, we did not discover evidence of any neurological “trait” features of PWS, but this is to be expected because our design was primarily aimed at studying the moment of dysfluency in PWS. Many studies have shown behavioral

and neural differences between PWS and NS independent of fluency (see Bloodstein and Bernstein Ratner 2008 for a review) and even in cases where a speech task is not required, and these must contribute to stuttering behavior. The present study is designed only to address the neural mechanisms of stuttering dysfluency itself, rather than addressing more stable and long-term features of stuttering. This is the natural result of contrasting two equivalent groups of stutterers performing the same task who differed only on transient performance. The moment of dysfluency must ultimately be explained in speech motor terms, even if the ultimate cause lies elsewhere, since the major symptom of stuttering is motoric in nature. The existence of weak feedforward control is entirely consistent with that weak feedforward control being associated with other deficits. Our findings are thus compatible with other observations about stuttering behaviors, particular stuttering behaviors not directly tied to dysfluency itself.

The present study sheds little light on what leads to stuttering behavior in PWS. However, it does show the neural difference between successfully compensating for or avoiding stuttering behavior in PWS. Most importantly, it reveals evidence for a PWS-specific neural recruitment pattern for speaking fluently that does not closely resemble the neural recruitment shown by NS when they achieve the same task. No voxel-based morphometry studies were performed with this group of stuttering participants, and so anatomical asymmetries cannot be assessed. While existing cortical asymmetry data is consistent with our findings, especially that suggesting posterior perisylvian

involvement (Foundas et al. 2001), the present study does not contribute to this literature.

Future studies following up on this finding should thus include more tasks, ideally designed to induce more or less dysfluency than our sentence-generation task, the inclusion of speech/language processing tasks that do not involve speaking, the administration of more stuttering severity instruments to PWS participants to potentially group them on the basis of behavior outside of the scanner, and continuous measures of task performance while in the scanner to correlate a continuous measure with network organization. Replication or elaboration of this study in fMRI would also allow for activity modeling based on DIVA (Tourville et al. 2010), to allow for stronger quantitative confirmation of our hypotheses. Further modeling work may also allow for a more fine-grained understanding of the dynamics of different forms of dysfluency in stuttering, which were not addressed in the current study.

Conclusions and Future Directions

I have argued that both FAS and PDS, disorders whose primary symptoms are related to the production of speech, are actually better viewed as disorders of feedback. In the case of FAS, I have argued that the cause is excessive auditory error signals that emerge in the absence of appropriate modulation by other parts of the speech motor control network. Since FAS has such a varied and inconsistent etiology, with cases documented following small lesions to many neural areas, it can only be understood in

the context of a network. When any particular region of the network is removed, the network does not fail catastrophically, but its performance degrades sufficiently to produce the relatively subtle symptoms of foreign accent syndrome. The neural network identified in the FAS study was a network that was more active when RV made more errors, and this is why I argued that this represented excessive feedback that is no longer modulated by appropriate inhibitory connections with whichever network area has been damaged for a particular patient.

While it is not possible to say that PDS is entirely a disorder of sensory feedback, it is a crucial part of the compensation strategy that PWS appear to use when they successfully avoid dysfluency. The compensation "network" that emerged from our study differed from the "network" associated with dysfluency in PWS in many ways, but the integration of the STG with the basal ganglia-thalamic-cortical loops when PWS were fluent was strikingly different. Those circuits, and more specifically, better integration between those circuits and other cortical regions involved in speech, also separated the two groups. Most strikingly, however, the compensation "network" utilized by PWS who successfully avoided dysfluency was not at all similar to the "network" utilized by non-stuttering controls. This tends to support the unstable internal model hypothesis proposed by Max et al. (2004), as it suggests that PWS rely more heavily on feedback control of speech due to a weakness of feedforward signals. On this account, the difference between fluency and dysfluency in PWS is simply the degree to which they are able to successfully integrate feedback with input from the flawed feedforward control system.

The basal ganglia emerge as critical participants in neural networks in both FAS

and PDS, which by itself is unsurprising for speech disorders. The (GO)DIVA model posits a specific role for these structures and the BGTC loops that contain them, namely the selection and release from inhibition of competing speech motor plans that have fulfilled certain criteria (Bohland et al. 2010). These criteria are not specified in cognitive terms in current versions of the (GO)DIVA model, I propose that these criteria are primarily phonological in nature. This draws support from the demonstrated sensitivity of the M100 response to distinctive feature information (Riley et al. 2009) and from the role played by classic phonological processing/ auditory feedback generation areas like STG (Hickok and Poeppel 2007; Tourville et al. 2010) in the above studies. Thus, two different neurological disorders shed light on a neural network active in normal speech production.

The importance of inhibitory or modulatory communication between neural regions involved in speech was also in evidence in the case of persistent developmental stuttering. While the network associated with dysfluency in PWS had overwhelmingly positive correlations between active regions, the most important regions associated with fluency had a significant number of negative correlations, especially from STG and the BGTC loops to motor-outflow regions. I argued that these negative correlations disrupted the link between BA 45 and the insula that was associated with dysfluency and likely represented an excessive communication of pre-planned motor movements to the neural area responsible for articulator coordination. In other words, negative correlations with auditory and BGTC loop regions were critical in suppressing unhelpful feedforward control signals in PWS. Although functional connectivity analyses were not used in the FAS study, I predict that strong positive correlations would exist between the

basal ganglia and cortical motor outflow regions, but not between BA 44/45 and the insula. In other words, in FAS, one would expect to find excessive feedback signaling that degraded otherwise robust feedforward commands.

The extent to which the patterns evident in these studies apply to normal, non-disordered speech is the primary question of interest going forward from these studies. Functional connectivity studies of normal speakers producing sentence-length or longer utterances, ideally in fMRI with appropriate noise reduction techniques, and under conditions of normal and deleteriously altered feedback, are needed to fully generalize these results. Certain predictions are made about each disorder as well. Other FAS patients should reveal a similar pattern of activity associated with error in cued narrative tasks, and should show excessive compensation to altered auditory feedback paradigms of the sort employed by Villacorta et al. (2009). PWS should show evidence of a “compensation” network in other tasks besides sentence-generation, and the extent to which individual networks match this compensation network should correlate with the degree or severity of stuttering while completing the task.

Once speech is conceived of as attempting to produce sounds that match auditory targets of some variety, sensory feedback becomes a necessary component for achieving successful motor control. Two disorders with motoric symptoms have been demonstrated to implicate neural feedback networks in interesting ways, and those results mesh well with current computational models. The basal ganglia are central in the results of both studies, and likely play a more linguistic role in the system than previously thought. The next step is to apply similar analyses to normal speech under conditions where feedback control becomes unreliable. It will then be possible to say

with confidence that neuroimaging studies have conclusively demonstrated the neural basis of sensory feedback in speech.

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