Positron Emission Tomography Studies of Stuttering: Their Relationship to Our Theoretical and Clinical Understanding of the Disorder

La recherche sur le bégaiement au moyen de la tomographie par émission de positrons : les rapports vis-à-vis de notre compréhension théorique et clinique de ce trouble

by • par

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ABSTRACT

This paper is presented as a tribute to Dr. Einer Boberg who advanced the study of stuttering through both his clinical and research contributions. The focus of the manuscript is related to how our studies of this fluency disorder utilizing functional neuroimaging techniques can shed more light on its neural substrates and the implication that these studies have concerning the clinical application of our therapeutic methods in the treatment of stuttering. The paper offers a review of both our clinical treatment methodology for stuttering as well as a synopsis of our current findings utilizing functional neuroimaging analysis, specifically positron emission tomography (PET), to investigate differences between stuttering and nonstuttering populations during silent and oral reading tasks and in stuttering individuals before and after behavioural treatment. The PET studies reported here form part of an ongoing project aimed at investigating the neural bases of long-term changes in speech fluency in stuttering subjects.

ABRÉGÉ

Ce mémoire est présenté en l'honneur du Dr Einer Boberg qui a assuré l'avancement de la recherche sur le bégaiement grâce à ses contributions en clinique et par la recherche. L'accent du manuscrit est mis sur la manière dont nos recherches sur ce trouble de la fluidité en utilisant les techniques de neuroimagerie fonctionnelle peut jeter de la lumière sur ses substrats nerveux et les incidences qu'ont ces recherches sur l'application clinique de nos méthodes thérapeutiques de traitement du bégaiement. Le mémoire offre à la fois une revue de notre méthodologie de traitement clinique du bégaiement et un synopsis de nos conclusions récentes à partir d'analyse par neuroimagerie fonctionnelle, en particulier par tomographie par émission de positrons (TEP), pour étudier les différences entre les populations bégayantes et non bégayantes au cours de séances de lecture silencieuse ou de lecture orale, ainsi que chez les bègues, avant et après le traitement du comportement. Les études TEP dont il est ici question représentent une partie d'un projet continu visant à étudier les fondements neuraux des changements à long terme de la fluidité de la parole chez les bègues.

KEY WORDS: positron emission tomography • stuttering • functional neuroimaging • treatment • adults

Dr. Einer Boberg, during his illustrious career, was an individual who truly epitomized what our discipline of speech-language pathology is all about. His interest in stuttering led him to develop and refine treatment programs which are empirically based and well accepted by the professional community. Moreover he was a true scientist. His research was directed at uncovering some of the mysteries of stuttering and the changes that come about in individuals who have undergone treatment. It is with this framework in mind that we are honoured to have been asked to submit this synopsis of our work as part of this tribute journal issue to Dr. Boberg.

Dr. Boberg's clinical work involved the development of a behavioural program for fluency enhancement called the Comprehensive Stuttering Program (CSP). Furthermore, the clinical issue of fluency maintenance was always a critical area that was addressed constantly by him through his publications and conferences that he sponsored. His research, among other things, pointed to the neural basis for stuttering and led many of us to continue these lines of investigation.

This paper will attempt to bring the science and clinical treatment of stuttering closer together, in a fashion similar to how Dr. Boberg conducted his work. It will address clinical aspects of stuttering and will outline how we have attempted to treat the problem in our clinical environment. Following this, we will examine the neural basis of the disorder and summarize our own recent attempts at unraveling some of the questions as to the nature of stuttering. Our ultimate objective in writing

this paper is two-fold: First, to pay tribute to a truly remarkable researcher/clinician–Dr. Einer Boberg; and second, to explore the impact that current research in stuttering using functional neuroimaging can have on our work with individuals who stutter.

Some Issues in Clinical Intervention

Various approaches to clinical intervention for stuttering can be roughly characterized along a continuum from stuttering modification to fluency shaping techniques (Peters & Guitar, 1991). We will briefly describe these two approaches as they are relevant to the discussion of our research findings.

Treatment Approaches

The first of these therapy approaches, generally known as stuttering modification, typically deals more directly with the psychological aspects of the problem, in addition to modifying speech behaviour (Breitenfeldt & Lorenz, 1989; Van Riper, 1973). In other words, the attitudes, feelings, and emotions that are displayed by the individual who stutters are addressed very explicitly in therapy and, often, are focused on before an attempt is made to change speech behaviour. Moreover, these treatment procedures employ various techniques directed at self-acceptance, attitude change, and avoidance and anxiety reduction.

The second major therapy approach, generally labeled fluency shaping, primarily involves the modification of the stuttering response to fluent sounding speech by the application of systematic steps and rules of speech mechanics (Webster, 1974; Costello Ingham, 1993). In general, these approaches deal primarily with observable behaviours; attitudinal and cognitive aspects are not dealt with specifically during treatment. In this framework, therapy procedures attempt to reconstruct the respiratory, phonatory, and articulatory gestures used in speech production. We think it's safe to say that, in practice, the approach used by many clinicians falls somewhere between these two extremes.

Therapy formats for adults who stutter have been intensified and several major stuttering treatment programs now offer full day treatment approaches administered in blocks of several weeks. One such model of treatment was first introduced at the Clarke Institute by one of the present authors and is based on the Precision Fluency Shaping Program (Leibovitz & Kroll, 1980). This intensive, three-week treatment is based upon the premise that stuttered speech can be replaced by easier, more fluent speech patterns by systematically altering such behaviours as speech rate, respiration, voice onset, and articulation. Incorporated within the program is a series of procedures that target the establishment of precise fluency skills within the clinical setting. After a period of consolidation, these newly acquired speech skills are then gradually and systematically transferred to everyday, naturalistic settings. Also incorporated within the program are exercises focusing on self-talk or covert thinking as pertaining to effective mental preparation for communication. Program participants are trained in both the application of the fluency skills as well as the proper mental or cognitive set as they set out to transfer their newly acquired speech patterns (Kroll, 1991). Posttreatment and long-term outcome data pertaining to this program of fluency management have been reported elsewhere (De Nil & Kroll, 1995).

It can be noted that this treatment program combines elements of both stuttering modification and fluency shaping approaches. Years of clinical experience have led us and other fluency specialists to understand that effective treatment for stuttering must incorporate procedures that deal with both the problem as a whole as well as the physical manifestations of the disorder. The individual who successfully completes treatment learns to modify both the attitudinal, cognitive, as well as the behavioural components of the speech problem. It is only by offering full and comprehensive programs, including long-term maintenance assistance, that individuals who stutter will be provided with effective forms of relief.

It has been reported that a significant number of individuals will often exhibit either partial regression or even total relapse of stuttering without the continued practice of speech skills following treatment (Boberg, 1981; Hanna & Owen, 1977; Ingham, 1984). Current therapies report success rates ranging from 60 to over 90 percent when the sole dependent variable is perceived fluent sounding speech immediately following treatment. It has been acknowledged however that successful stuttering treatment outcome should be measured using at least the following three elements: (a) the treatment has produced a significant positive change in speech output, (b) the change has generalized across speaking situations, and (c) the change is maintained over time.

For a number of clients, maintenance of fluency skills has proven to be difficult. Indeed, so many published reports addressing treatment outcome invariably point to significant and varying numbers of individuals who experience difficulties with generalization of the learned skills or else who ultimately demonstrate relapse of stuttering after a period of time (Boberg, 1981). Therefore, one of the questions that arises is why we cannot be equally effective for all those who enter our clinics with the goal of complete or near complete establishment of long lasting fluency skills?

In an attempt to find an answer to this question, we are currently engaged in research and clinical efforts directed at optimizing maintenance of fluent speech in the post treatment environment. As part of this effort, using modern functional neuroimaging methods, we have set out to more fully examine some of the neural characteristics of those attending our clinic.

Before summarizing the details of our research, we must necessarily make our case for viewing stuttering from the perspective of its neural basis. Let us go back to the beginning, by examining some of the basic characteristics of stuttering, and by revisiting some of the speculations regarding the neural factors underlying these characteristics.

Characteristics of Stuttering

Stuttering represents a complex multidimensional condition in which the flow of speech or fluency is disrupted by involuntary speech motor events. Stuttering may include a variety of specific disfluency form-types such as audible or silent sound and syllable repetitions, sound prolongations, dysrhythmic phonations, complete blocking, and/or unusual pauses between sounds and syllables of words. Accessory or secondary features frequently accompany instances of stuttering. These secondary behaviours may be observed at the respiratory, phonatory, or articulatory levels of the speech mechanism and may manifest themselves in disordered breathing, glottal fry, or lip pursing and tongue clicking. Additional concomitant behaviours may be observed such as eye blinks, facial grimacing, head jerks, and abnormal body movements prior to or during instances of disrupted speech.

Linguistic and situational avoidance behaviour is often an observable characteristic of confirmed stuttering. Most adults who stutter will report specific sounds or words that result in increased stuttering. Many often will scan the intended utterance in order to predict stuttering and will attempt to avoid such disruption by substituting words, revising phrases, circumlocution, or stopping the entire communicative process. Such reports of frequent scanning behaviour and attempts to predict specific phonemic and lexical loci of stuttering are often encountered in clinical situations. In addition, situational avoidance is often characteristic of chronic stuttering and severity of stuttering often varies with the characteristics of the communicative situation.

Explanatory Models

Researchers and clinicians working in the area of stuttering generally recognize that the cause of stuttering is complex. Over the years, many different explanatory models of stuttering causation have been proposed (Curlee & Siegel, 1997). One of the more persistent themes in several of these models has been that stuttering may be related to atypical brain processes involved in speaking. As early as 1928, Orton and Travis offered a neurophysiological model of stuttering (Orton, 1928; Travis, 1978). It arose from the observation that an unusually high number of individuals who stuttered were either left-handed or ambidextrous. They speculated that stuttering resulted from incomplete development of hemispheric dominance quite often related to a forced shift of handedness in childhood. Although the early model proposed by Orton and Travis was not supported experimentally, the idea that atypical cerebral lateralization for speech somehow plays a role in stuttering has received varying amounts of support over the years. In part due to advances in the development of electrophysiological and neuropsychological techniques and paradigms, the idea of atypical lateralization has been revived in more recent etiological models, such as those proposed by Moore (1984) and Webster (1997).

In a landmark study of the distribution of EEG alpha power in stuttering, Einer Boberg and his colleagues added to the experimental evidence in this area by demonstrating that pre-treatment, most cortical electrical activity was located in the right hemisphere (Boberg, Yeudall, Schopflocher, & Bo Lassen, 1983). Following intensive behavioural treatment, they observed that this activity shifted towards the left posterior frontal cortex in individuals who stutter. The authors offer a theory of shifting inhibitory control over each of the hemispheres to explain differences in cortical and subcortical control before and after treatment.

In our most current research, we have attempted to shed more light on the issue of atypical lateralization in stuttering using recently developed functional neuroimaging techniques. In the following section, we will summarize our main findings to date after reviewing some of the basic principles underlying this technology.

Procedures for Functional Brain Imaging

While noninvasive structural neuroimaging techniques have been around since the beginning of our century, the last decade has witnessed an explosive development of functional brain imaging techniques. In contrast to conventional neuroimaging techniques, such as Computerized Axial Tomography (CAT) and Magnetic Resonance Imaging (MRI), that are used to assess the anatomical integrity of the neural system, functional techniques provide images of the neural activity that take place during task performance. The various tasks that can be investigated using functional neuroimaging are limited only by the researcher's creativity and experimental sophistication; and indeed, this creativity has been virtually limitless. Over the last few years, research has been published on language and speech processing (Bahn et al., 1997; Friberg, 1993), auditory processing (Binder et al., 1994; Fiez et al.,1995), memory (Cabeza et al., 1997; Perani, 1998), motor tasks (Jenkins & Frackowiak, 1993; Rossini et al., 1998), vision (Grady et al., 1997), normal and disordered thought processes (Renshaw et al., 1997; Volz et al., 1997), and phobias (Reiman, 1990) among many other topics. The amount of data that has been generated using these techniques during this period has been truly staggering, to the extent that it has led to the establishment of several new scientific journals dedicated specifically to functional neuroimaging (such as *Human Brain Mapping* and *Neuroimage*). In addition,

many other articles are being published in the more established scientific journals such as *Brain*, *Neuroreport*, *Journal of Cognitive Neuroscience*, and *Neurology*.

Positron Emission Tomography

One of the first functional imaging techniques whose merit in studying the dynamic nature of the human nervous system was quickly recognized by neuroscientists is positron emission tomography (PET). This technique allows researchers to measure biochemical changes in the brain that occur either spontaneously or when subjects are engaged in performing a specific task. The underlying physical and physiological principles for PET scanning are quite complicated and have been described in various other sources (Roland, 1993). However, in order to allow interested readers to understand the strengths and weaknesses of PET for the study of stuttering, we will attempt to provide a brief and nontechnical review of the basic concepts of this technique.

All neural activity that occurs in the human brain is associated to some extent with metabolic changes. Typically, as the activity increases, so does the metabolic rate. Consequently, observing these metabolic changes would provide us with a measure of the extent to which certain parts of the brain are more or less active during a given task. Positron emission tomography will allow us to do that. Studies that are of interest to the understanding of stuttering are typically based on some measure of change in regional cerebral blood flow (rCBF). Such change is used as an indication of increasing or decreasing metabolic need in the brain. In most studies, a small quantity of a radioactively labeled tracer, such as $[^{15}O]H_2O$ (radioactively labeled water), or ^{18}FDG (radioactively labeled fluoro-deoxyglucose), has been injected in the bloodstream of the volunteer subject. By measuring the distribution of these tracers in the brain over time, using cameras that are sensitive to the gamma rays that are emitted by the radioactive tracer, researchers obtain a measure of oxygen or glucose consumption, respectively. Currently, most functional neuroimaging studies of language have been done using $[^{15}O]H_2O$ as tracer. The relatively short half-life (approximately two minutes) of this compound allows researchers the best (although not optimal – see following discussion) temporal resolution for the study of various cognitive and sensorimotor processes during language formulation. Furthermore, the short half-life and the small dose of tracer needed during each injection provide the opportunity to obtain multiple scans during a single experimental session. This allows researchers to investigate and compare variations in neural activity during a number of different experimental tasks, or during several repetitions of the same task, during an experimental scanning session.

Although PET scanning has proven to be an effective and powerful tool for the investigation of neural activation during task performance, it has a number of disadvantages in the study of human behaviour. First of all, the level of localized neural activation that is related to the task under investigation often is only slightly (approximately 3-5%) above the overall background activation that is going on in the brain as a whole. Consequently, for many cognitive tasks, including language processing, it is very difficult, and often impossible, to detect these changes in individual subjects. Therefore, investigators increase the power of their observations by averaging neural activation in a number of different individuals performing the same task(s) (Friston, 1995). If the localization of neural activation across the different subjects is relatively consistent, averaging the signal will magnify this activation while neutralizing the background activation. Unfortunately, averaging does mask any interindividual differences in neural activation during task performance that may be present among the subjects (Steinmetz & Seitz, 1991).

A second disadvantage of PET scanning is the need to inject a radioactive tracer in the blood stream in order to measure metabolic changes in the brain. Although the amount of exposure to radioactive material is well below the maximum level considered to be safe, it does impose limits on its potential for use with young children, or on the number of times subjects can participate in such experiments. The latter limitation is especially important when repeated scans obtained at various intervals may be necessary or desirable, such as in studies of treatment effects on neural activation patterns.

A third limitation of PET studies has to do with the temporal resolution of the data obtained. Although radioactively labeled water has a relatively short half-life of approximately two minutes, the temporal resolution obtained in these studies typically is between 45 seconds and 1 minute. This poses difficulties for the measurements of cognitive processes that often occur in the order of milliseconds rather than seconds. In an attempt to overcome this problem, several researchers are currently exploring the possibilities of combining PET scans, which provide good spatial resolution but weaker temporal resolution, with electrophysiological measurement techniques, that provide good temporal but weaker spatial resolution (Rossini et al., 1998; Stippich et al., 1998).

Functional Magnetic Resonance Imaging

In addition to positron emission tomography, functional activation in the human brain can be investigated using functional magnetic resonance imaging (fMRI). In recent years, this technique has become the method of choice for the study of many cognitive processes in humans (Binder, 1997; Coull, 1997). One reason for this is that fMRI images are obtained by measuring changes in the magnetic characteristics of hydrogen protons that are naturally and abundantly present within the body. Therefore, there is no need to inject a radioactive tracer

in order to measure metabolic rate. Participants can be scanned for longer periods of time and there is, in principle, no limit to how often participants can be scanned within a given time period. However, the need to introduce strong, rapidly alternating electromagnetic waves during scanning results in a significant noise level in the scanner (up to 90dB) which can be quite uncomfortable for some subjects. Such noise also creates special challenges for tasks involving auditory presentation of experimental stimuli. Another serious problem in fMRI is its sensitivity to movement artifacts. This can pose serious problems, for instance, in tasks that require the subject to speak out loud. Recent developments in signal analysis and event-related paradigms hold the potential to reduce or even eliminate the influence of movement artifacts during tasks which require short verbal responses from participants (Josephs, Turner, & Friston, 1997). However, longer speech utterances, or the presence of external movements during speech (such as tremor-like head movements during stuttering), still pose serious analysis problems, which probably explain why at present no fMRI studies on stuttering have been published. However, because of the advantages offered by fMRI, we are currently using this technique in our laboratory to study cognitive and motor brain processes in people who stutter.

Other Techniques

At present, PET scanning and fMRI are two of the most widely used functional neuroimaging tools used for the study of human language and cognition. A number of other techniques, such as Magnetic Encephalography (MEG), are being used or developed which provide valuable data that compliment PET or fMRI (Stippich et al., 1998). Undoubtedly, deeper and better understanding of the functions of the human brain will come from multi-methodological investigations that combine various techniques in such a way that their individual strengths compliment each other to yield data on neural functions that neither would be able to provide in isolation.

Functional Neuroimaging Studies of Stuttering

To date, a small number of investigators have used functional brain imaging methods in an attempt to test the presence of atypical lateralization in stuttering speakers. The first functional neuroimaging study using measures of changes in regional cerebral bloodflow was reported on by Wood and Stump (1980). Asymmetrical blood flow during stuttering was observed in Broca's (right > left) and Wernicke's area (left > right). Fluent speech, following administration of haloperidol, resulted in a reversal of the blood flow pattern in Broca's area (left > right), but not in Wernicke's area. Although this truly can be considered a pioneering investigation in the study of stuttering, the article may have never received the recognition it deserves. True, the functional neuroimaging techniques were crude compared to today's standards and the methodological paradigm used to study disfluent and fluent speech had a number of serious shortcomings. Nonetheless, considering that that study of language, or any other human cognitive process, really only started 10 years ago with the publication in *Nature* of an article by Petersen and his colleagues (Petersen, Fox, Posner, Mintun, & Raichle, 1988), the fact that Woods and Stump had reported eight years earlier on a study of stuttering using a similar technique at least deserves acknowledgement.

Since the original Wood and Stump study, advances in functional imaging techniques have allowed researchers to refine the search for the neural bases of stuttering (Braun et al., 1997; De Nil, Kroll, Kapur, & Houle, 1996, 1997; Fox et al., 1996; Ingham et al., 1996; Kroll, De Nil, Kapur, & Houle, 1997; Salmelin et al., 1998; Wu et al., 1995; Wu et al., 1997). The imaging tools most frequently used are Single Photon Emission Computerized Tomography (SPECT) and Positron Emission Tomography (PET), using either ^{18}FDG or ^{15}O-H_2O as the radio tracer. Speech tasks have ranged from nonspeech oral movements to oral reading of continuous text. The wide variety of speech tasks, in addition to methodological differences in image acquisition and analysis, often makes it difficult to compare results across studies. Nevertheless, a number of tentative common observations can be crystalized from the data available to date. Most studies have shown some evidence of differences in the activation levels of lateralized language or speech motor processes between stuttering and nonstuttering speakers. These differences range from decreased activation in left hemipshere regions known or thought to be involved in speech and language processing, such as Broca's and Wernicke's cortical areas (Wu et al., 1995) to increased activation of bilateral or right hemisphere regions (Braun et al., 1997; De Nil et al., 1997; Fox et al., 1996). In addition to this atypical lateralized activation of cortical areas well-known to be involved in speech and language processing, most studies also observed differences in activation of other cortical and subcortical areas, such as the anterior cingulate cortex (ACC; De Nil et al., 1997; Pool, Devous, Freeman, Watson, & Finitzo, 1991) and the cerebellum (Fox et al., 1996).

Over the last few years, we have used positron emission tomography to compare neural activation patterns associated with speech and language processing during single word tasks in stuttering and nonstuttering adults (De Nil et al., 1995, 1997; Kroll et al., 1997). In our experiments we have used primarily single word tasks because this way we have better control over task complexity and such tasks allow us to formulate more specific hypotheses about the cognitive processes underlying task performance. Typically, stuttering and nonstuttering subjects were instructed to read single words either silently or orally, or to self-generate a verb following presentation of a noun. These studies resulted in a number of interesting and thought-provoking observations.

Stuttering participants showed relatively greater activation in the anterior cingulate cortex during silent reading. This area, located in the medial wall of the cortex, is part of the limbic system and, actually, serves to bridge the limbic system with the sensorimotor cortex. It is thought to be involved in anticipatory reactions and response preparation, especially when the subject is confronted with complex stimuli requiring a choice between various alternative response selections (Paus, Koski, Caramanos, & Westbury, 1998). As pointed out before, most adult stutterers have a strong tendency to scan the phonetic and orthographic structure of words for signs of potential fluency problems, even during tasks not requiring overt speech. Therefore, we have suggested that the increased ACC activation in the stuttering subjects may reflect their heightened anticipation reactions during the reading task. In addition, and possible related to increased anticipation, the anterior cingulate activation in our stuttering subjects also may point to silent articulatory rehearsal of the words, since this area is thought by some to be part of an inner articulatory loop, which becomes activated especially during less automated tasks (Paus, Petrides, Evans, & Meyer, 1993).

During oral reading, stuttering and nonstuttering subjects showed clear differences in lateralization of cortical regions thought to be involved in speech production. As expected, the nonstuttering speakers showed a pattern of largely unilateral left hemisphere activation, including Broca's area, and primary sensorimotor and temporal cortex. A similar activation pattern was observed in the stuttering subjects, but this time clearly lateralized to the right hemisphere. The stuttering subjects also showed increased activation in these cortical regions. The widespread activation, involving traditional motor areas, as well as higher order association cortex, suggests that the atypical lateralization in stuttering subjects does not merely reflect the presence of stuttering. Instead it seems to point to a fundamental difference between stuttering and nonstuttering speakers regarding neural systems involved in speech and language.

In all of the studies so far, stuttering subjects were tested prior to receiving any intensive treatment for their fluency difficulties. To date we have completed two studies aimed at investigating how neural activation patterns change as a result of intensive speech treatment. In these experiments, subjects underwent PET scan immediately prior to the start of the treatment program, and again immediately upon completion of the program. In the first of these studies (Kroll et al., 1997), we observed notable changes in neural activation during simple word reading from pre- to posttreatment. Posttreatment, stuttering subjects no longer showed significantly increased activation in the anterior cingulate cortex during silent reading. Possibly this change was related to the fact that the subjects, because of their increased speech fluency and general confidence in their fluency skills, no longer felt the need to scan the words in an anticipatory fashion to look for potential stuttering. Alternatively, it is possible that the reduced activation in the anterior cingulate reflects a decreased tendency to silently rehearse the articulatory movements of the words during reading. When the subjects were asked to read the words out loud, there was a significant increase posttreatment in neural activation of the left primary sensorimotor cortex. It was hypothesized that this change reflected the emphasis placed during treatment on continuous self-monitoring of articulatory speech movements, in addition to the explicit use of fluency skills learned during treatment. These speech skills help the stuttering individual to avoid disfluencies by optimizing the sequencing and timing of articulatory, phonatory, and respiratory movements, a task which seems to tap into strengths specifically attributed to the left hemisphere (Bradshaw & Nettleton, 1981).

The data obtained in our second, and most recent, study on the effects of treatment on neural activation in stuttering individuals seems to confirm some of our earlier findings for the most part. However, it also extends and modifies our earlier observations in a number of important ways. Because, at the time of this writing, the analysis of this complex data set is still underway, we will limit ourselves to a discussion of some of the main trends that seem to emerge out of the results because we believe that they have potential implications for clinical intervention.

A first observation that emerges quite clearly from the data is that differences in neural activation patterns can be observed between stuttering and nonstuttering subjects even when they are reading words silently and no overt or self-reported stuttering is being experienced. Similar to the observations in our first treatment study, differences in activation patterns involve the anterior cingulate cortex. Because of the role of the anterior cingulate in response selection and attention, this observation confirms the difference in cognitive set with which stuttering and nonstuttering speakers approach even a task as simple as single word reading, whether consciously or unconsciously. In contrast to our earlier findings, this increased activation level in the anterior cingulate in the stuttering speakers also can be observed posttreatment, although to a lesser extent. This apparent decrease in activation level posttreatment, together with the fewer subjects (and thus lower statistical power) in the first study, may help explain the discrepancy between our two data sets. In addition to the anterior cingulate, increased activation in the stuttering subjects also is observed in right temporal and frontal cortex, including the area homologous to Broca's area on the left, suggesting that the right hemisphere bias in the stuttering subjects is not directly related to the presence of stuttering, but probably represents an innate or early acquired pattern of neural processing associated with language.

A second clear trend that emerges from the present data confirms our earlier observation of increased left hemisphere activation in the region of the motor cortex post treatment as is

illustrated in Figure 1. As a matter of fact, the present data seem to suggest quite strongly that the increased left hemisphere activation does not replace the existing right hemisphere or bilateral activation bias that can be observed pre-treatment in the stuttering subjects. Instead, the left hemisphere activation appears by-and-large to be in addition to whatever activation was present pre-treatment. This observation, if confirmed, has important implications for our understanding of stuttering and the effects of stuttering treatment. We will attempt to outline some of these implications in the next section.

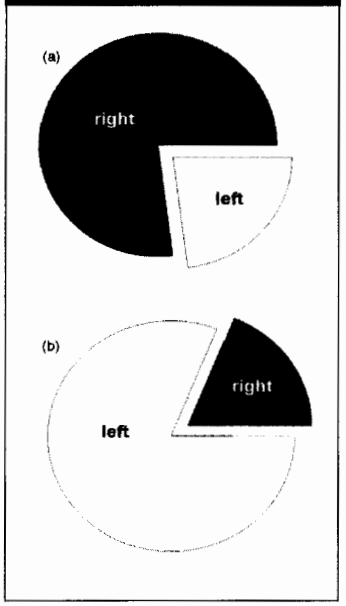

Figure 1: Distribution of activated cortical voxels (expressed as percentage of total activation) in the left and right hemisphere during oral reading. (a) pretreatment and (b) posttreatment.

Some Thoughts on Clinical Implications

We can say with increasing confidence that, based on our work and that of others, people who stutter demonstrate atypical brain activation patterns during speaking, thereby strengthening the case for the neural basis of stuttering. One consistent observation has been that people who stutter compared to nonstuttering individuals show a definite bias towards increased right hemisphere activation during speaking. Moreover, the data suggest that areas of increased activation in the right hemisphere include cortical regions homologous to regions in the left hemisphere traditionally considered important for speech production.

Furthermore, our latest data suggest that the right hemisphere biased activation patterns are present not only during oral speech tasks, but also can be found when subjects are asked to read silently, a task in which the presence of disfluencies is virtually eliminated. These observations suggest that the neural patterns are not just reflective of the presence of overt stuttering behaviour, but may represent more fundamental differences in the way people who stutter process speech and language.

The question that arises, of course, is whether the observed activation patterns are innate or developmental in nature. For instance, it has been argued in the past that differences in brain activation patterns between stuttering and nonstuttering speakers may merely reflect the presence of stuttering or some emotional reaction to the disfluencies, rather than pointing to some underlying causal factors for the disorder (Bloodstein, 1987). Others have suggested that atypical activation patterns, indeed, are causally related to stuttering (Moore, 1984). Obviously, data obtained in our laboratory do not provide unequivocal support for either one of these positions. However, we feel that they do suggest some direction to further this discussion.

We believe that both innate and acquired brain processes need to be considered when investigating the neural basis of stuttering. We say this based on our current neuroimaging research of differences in brain activation patterns before and after fluency treatment. As pointed out before, we have found preliminary evidence that the changes in cortical activation that are observed post treatment do not totally replace existing patterns observed prior to treatment, but rather supplement them. Specifically, there appears to be consistent right hemisphere activation in temporal and frontal cortex both before as well as immediately after successful fluency treatment. That is, even though subjects are using their learned fluency targets, resulting in voluntary and deliberate monitoring of articulatory, phonatory and respiratory production, a significant portion of the posttreatment brain activation pattern is strikingly similar to that observed pre-treatment. This suggests that this activation is not immediately affected by changes in overt speech behaviour and fluency. Therefore, we would like to suggest that such activation might point to the presence of neural processes that are relatively stable, and possibly congenital, in people who stutter. If so, it is tempting to speculate about the causal relationship between these activations and stuttering.

On the other hand, certain activation patterns, like the one observed in the anterior cingulate cortex, do indeed seem to change from pre- to posttreatment. Because of the hypothesized role of the anterior cingulate in attention and response selection (Devinsky & Luciano, 1993; Paus et al., 1998; Paus et al., 1993), and our clinical knowledge of how anticipatory and scanning behaviours in stuttering develops over time, we suggest that the changes in the observed activation in the anterior cingulate point to that fact that such activation reflects an acquired rather than an innate characteristic. We interpret our data to suggest that treatment approaches like the one used in our studies, in addition to producing speech motor changes, also result in changes in cognitive strategies that are employed during speech tasks. We further suggest that the initial scanning and anticipatory thought processes are replaced by strategies in which subjects are engaged in fluency inducing self-monitoring behaviour.

We have seen from our data that treatment affects patterns of neural activation. We have also observed that portions of atypical activation appear to be relatively stable even after successful fluency treatment. The question that we are presently pursuing is whether these observations are relevant to the issue of fluency maintenance, as so eloquently addressed by Einer Boberg. We are presently collecting neuroimaging and behav-

ioural data on our subjects who have participated in our treatment while they are in the maintenance phase of the program. Our present hypotheses are that successful and unsuccessful maintenance will be reflected in differential patterns of neural activation. One possible scenario is that successful maintenance is associated with further decreases in atypical activation. Alternatively, it is possible that successful maintenance is associated with a strengthening and further stabilization of compensatory neural processes. We anticipate that our findings will help us to address inter-individual differences in fluency maintenance from a neural perspective. This work may lead to the development or refinement of intervention strategies that facilitate fluency maintenance.

In summary, we believe that current functional neuroimaging techniques such as those that have been used in our studies, will help us to focus more intensely on neural control processes underlying stuttering and in doing so contribute greatly to our understanding of this disorder and its treatment. Importantly, the suggestion that neural activation patterns in stuttering individuals consist both of congenital and acquired elements, reinforces the need to adopt a multidimensional treatment approach focussing on speech motor behaviour as well as cognitive and other thought processes. In many ways, our current treatment program as well as many others, have identified the need for comprehensive programming. Our data corroborate and reinforce this approach and provide a view of its neural underpinnings.

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References

Bahn, M. M., Lin, W., Silbergeld, D. L., Miller, J. W., Kuppusamy, K., Cook, R. J., Hammer, G., Wetzel, R., & Cross, D. (1997). Localization of language cortices by functional MR imaging compared with intracarotid amobarbital hemispheric sedation. *American Journal of Neuroradiology, 2*, 575-579.

Binder, J. R. (1997). Neuroanatomy of language processing studied with functional MRI. *Clinical Neuroscience, 4*, 87-94.

Binder, J. R., Rao, S. M., Hammeke, T. A., Yetkin, F. Z., Jesmanowicz, A., Bandettini, P. A., Wong, E. C., Estkowski, L. D., Goldstein, M. D., Haughton, V. M., & Hyde, J. S. (1994). Functional magnetic resonance imaging of human auditory cortex. *Annals of Neurology, 35*(6), 662-672.

Bloodstein, O. (1987). *A handbook on stuttering.* Chicago: National Easter Seal Society.

Boberg, E. (1981). *The maintenance of fluency.* New York: Elsevier.

Boberg, E., Yeudall, L. T., Schopflocher, D., & Bo Lassen, P. (1983). The effect of an intensive behavioral program on the distribution of EEG alpha power in stutterers during the processing of verbal and visuospatial information. *Journal of Fluency Disorders, 8*, 245-263.

Bradshaw, J., & Nettleton, N. (1981). The narure of hemispheric specialization in man. *Behavioral and Brain Sciences, 4*, 51-91.

Braun, A. R., Varga, M., Stager, S., Schulz, G., Selbie, S., Maisog, J. M., Carson, R. E., & Ludlow, C. L. (1997). Altered patterns of cerebral activity during speech and language production in developmental srutrering: An $H_2{}^{15}O$ positron emission tomography study. *Brain, 120*, 761-784.

Breitenfeldt, D.H., & Lorenz, D.R. (1989). *Successful stuttering management program (SSMP) for adolescent and adult stutterers.* Cheney, WA: Eastern Washington University.

Cabeza, R., Mangels, J., Nyberg, L., Habib, R., Houle, S., McIntosh, A.R., & Tulving, E. (1997). Brain regions differentially involved in remembering what and when: A PET study. *Neuron, 19*(4), 863-870.

Costello Ingham, J. (1993). Behavioral treatment of stuttering children. In R. F. Curlee (Ed.), *Stuttering and related disorders of fluency.* (pp. 68-100). New York: Thieme.

Coull, J. (1997, May). *Functional neuroimaging: Current developments in PET, fMRI and electrophysiology.* Paper presented at the Third International Conference on Functional Mapping of the Human Brain, Copenhagen, Denmark.

Curlee, R. F., & Siegel, G. M. (1997). *Nature and treatment of stuttering: New directions.* (2nd ed.). Boston: Allyn and Bacon.

De Nil, L.F., & Kroll, R.M. (1995). The relationship between locus of control and long-term treatment outcome in adults who stutter. *Journal of Fluency Disorders, 20*, 345-364.

De Nil, L. F., Kroll, R. M., Kapur, S., & Houle, S. (1995). Silent and oral reading in stuttering and nonstuttering adults: A positron emission tomography study. *ASHA, 32*, 67-68.

De Nil, L. F., Kroll, R. M., Kapur, S., & Houle, S. (1996, March). *An [^{15}O] H_2O PET study of neural processes associated with single word reading in untreated and treated stutterers and nonstutterers.* Paper presentation at the Sixth Annual Rotman Research Institute Conference, Toronto.

De Nil, L. F., Kroll, R. M., Kapur, S., & Houle, S. (1997). *A positron emission tomography study of silent and oral reading of single words in stuttering and nonstuttering adults.* Manuscript submitted for publication.

Devinsky, O., & Luciano, D. (1993). The contributions of cingulate cortex to human behaviour. In B. Vogt & M. Gabriel (Eds.),

Neurobiology of cingulate cortex and limbic thalamus. (pp. 527-556). Boston: Birkhauser.

Fiez, J. A., Raichle, M. E., Miezin, F. M., Petersen, S. E., Tallal, P., & Katz, W. F. (1995). PET studies of auditory and phonological processing: Effects of stimulus characteristics and task demands. *Journal of Cognitive Neuroscience, 7*(3), 357-375.

Fox, P. T., Ingham, R. J., Ingham, J. C., Hirsch, T. B., Downs, J. H., Martin, C., Jerabek, P., Glass, T., Lancaster, J. L., & Glass, T. (1996). A PET study of the neural systems of stuttering. *Nature, 382*, 158-162.

Friberg, L. (1993). Brain mapping in thinking and language function. *Acta Neurochirurgica - Supplementum, 56*, 34-39.

Friston, K. (1995). Commentary and Opinion: II. Statistical Parametric Mapping: Ontology and current issues. *Journal of Cerebral Blood Flow and Metabolism, 15*, 361-370.

Grady, C. L., Horwitz, B., Pietrini, P., Mentis, M. J., Ungerleider, L. G., Rapoport, S. I., & Haxby, J. V. (1997). Effect of task difficulty on cerebral blood flow during perceptual matching of faces. *Human Brain Mapping, 4*(4), 227-239.

Hanna, R., & Owen, N. (1977). Facilitating transfer and maintenance of fluency in stuttering therapy. *Journal of Speech and Hearing Disorders, 42*, 65-76.

Ingham, R. J. (1984). Generalization and maintenance of treatment. In R. F. Curlee & W. H. Perkins (Eds.), *Nature and treatment of stuttering: New directions* (pp. 447-471). San Diego, CA: College-Hill.

Ingham, R. J., Fox, P. T., Ingham, J. C., Zamarripa, F., Martin, C., Jerabek, P., & Cotton, J. (1996). Functional lesion investigation of developmental stuttering with positron emission tomography. *Journal of Speech & Hearing Research, 39*(6), 1208-1227.

Jenkins, I. H., & Frackowiak, R. S. (1993). Functional studies of the human cerebellum with positron emission tomography. *Revue Neurologique, 149*(11), 647-653.

Josephs, O., Turner, R., & Friston, K. (1997). Event-related fMRI. *Human Brain Mapping, 5*, 243-248.

Kroll, R. M. (1991). *Manual of fluency maintenance: A guide for ongoing practice* (2nd ed.). Toronto: Clarke Institute of Psychiatry.

Kroll, R. M., De Nil, L. F., Kapur, S., & Houle, S. (1997). A positron emission tomography investigation of post-treatment brain activation in stutterers. In H. F. M. Peters, W. Hulstijn, & P. H. H. M. Van Lieshout (Eds.), *Speech production: Motor control, brain research and fluency disorders* (pp. 307-320). Amsterdam: Elsevier Science Publishers.

Leibovitz, S., & Kroll, R. M. (1980). Intensive stuttering therapy: Retrospective data and current maintenance considerations. *ASHA, 21*, 82-82.

Moore, W. H., Jr. (1984). Central nervous system characteristics of stutterers. In R. F. Curlee & W. H. Perkins (Eds.), *Nature and treatment of stuttering: New directions.* (pp. 49-71). San Diego, CA: College-Hill.

Orton, S.T. (1928). A physiological theory of reading disability and stuttering in children. *New England Journal of Medicine, 199*, 1045-1052.

Paus, T., Koski, L., Caramanos, Z., & Westbury, C. (1998). Regional differences in the effects of task difficulty and motor output on blood flow response in the human anterior cingulate cortex: a review of 107 PET activation studies. *Neuroreport, 9*(9), R37-R47

Paus, T., Petrides, M., Evans, A. C., & Meyer, E. (1993). Role of the human anterior cingulate cortex in the control of oculomotor, manual, and speech responses: A positron emission tomography study. *Journal of Neurophysiology, 70(2)*, 453-469.

Perani, D. (1998). Brain imaging and memory systems in humans: the contribution of PET methods. *Comptes Rendus De l'Academie des Sciences Serie Iii-Sciences de la Vie-Life Sciences, 321*(2-3), 199-205.

Peters, T. J., & Guitar, B. E. (1991). *Stuttering. An integrated approach to its nature and treatment.* Baltimore, MD: Williams & Wilkins.

Petersen, S. E., Fox, P. T., Posner, M. I., Mintun, M., & Raichle, M. E. (1988). Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature, 331*, 585-589.

Pool, K. D., Devous, M. D., Freeman, F. J., Watson, B. C., & Finitzo, T. (1991). Regional cerebral blood flow in developmental stutterers. *Archives of Neurology, 48*, 509-512.

Reiman, E. (1990). PET, Panic disorder, and normal anticipatory anxiety. In J. Ballenger (Ed.), *Neurobiology of panic disorders* (pp. 245-270). New York: Wiley-Liss.

Renshaw, P. F., Levin, J. M., Kaufman, M. J., Ross, M. H., Lewis, R. F., & Harris, G. J. (1997). Dynamic susceptibility contrast magnetic resonance imaging in neuropsychiatry: Present utility and future promise. *European Radiology, 7*(5), S216-S221

Roland, P. (1993). *Brain activation.* New York: Wiley-Liss.

Rossini, P. M., Caltagirone, C., Castriota-Scanderbeg, A., Cicinelli, P., Del Gratta, C., Demartin, M., Pizzella, V., Traversa, R., & Romani, G. L. (1998). Hand motor cortical area reorganization in stroke: a study with fMRI, MEG and TCS maps. *Neuroreport, 9*(9), 2141-2146.

Salmelin, R., Schnitzler, A., Schmitz, F., Jancke, L., Witte, O. W., & Freund, H. J. (1998). Functional organization of the auditory cortex is different in stutterers and fluent speakers. *Neuroreport, 9*(10), 2225-2229.

Steinmetz, H., & Seitz, R. J. (1991). Functional anatomy of language processing: Neuroimaging and the problem of individual variability. *Neuropsychologia, 29*(12), 1149-1161.

Stippich, C., Freitag, P., Kassubek, J., Soros, P., Kamada, K., Kober, H., Scheffler, K., Hopfengartner, R., Bilecen, D., Radu, E. W., & Vieth, J.B. (1998). Motor, somatosensory and auditory cortex localization by fMRI and MEG. *Neuroreport, 9*(9), 1953-1957.

Travis, L. E. (1978). The cerebral dominance theory of stuttering: 1931-1978. *Journal of Speech and Hearing Disorders, 43*, 278-281.

Van Riper, C. (1973). *The treatment of stuttering.* Englewood Cliffs: Prentice-Hall.

Volz, H. P., Gaser, C., Hager, F., Rzanny, R., Mentzel, H. J., Kreitschmann Andermahr, I., Kaiser, W. A., & Sauer, H. (1997). Brain activation during cognitive stimulation with the Wisconsin Card Sorting Test - A functional MRI study on healthy volunteers and schizophrenics. *Psychiatry Research Neuroimaging, 75*(3), 145-157.

Webster, R. L. (1974). A behavioral analysis of stuttering: Treatment and theory. In K. S. Calhoun, H. E. Adams, & K. M. Mitchell (Eds.), *Innovative treatment methods in psychopathology.* New York: Wiley.

Webster, W. G. (1997). Principles of human brain organization related to lateralization of language and speech motor functions in normal speakers and stutterers. In W. Hulstijn, H. F. M. Peters, & P. H. H. M. Van Lieshout (Eds.), *Speech motor production: Motor control, brain research and fluency disorders.* (pp. 119-139). Amsterdam: Elsevier.

Wood, F., & Stump, D. (1980). Patterns of regional cerebral blood flow during attempted reading aloud by stutterers both on and off haloperidol medication: Evidence for inadequate left frontal activation during stuttering. *Brain & Language, 9,* 141-144.

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

Wu, J.C., Maguire, G., Riley, G., Lee, A., Keator, D., Tang, C., Fallon, J., & Najafi, A. (1997). Increased dopamine activity associated with stuttering. *Neuroreport, 8*(3), 767-770.