Commentary

Brain imaging and stuttering: some reflections on current and future developments

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This special edition is a tribute to the Editor’s foresight in recognizing that this is an opportune time to review the status of the now burgeoning brain imaging studies on stuttering. His idea was to try to bring together some of the current contributors to that research by inviting papers from laboratories that are currently conducting brain imaging investigations of developmental stuttering. Each contributor was given a very wide mandate as to what to present. The invitation simply requested a manuscript that described current research in their particular laboratory and, if possible, share with the Journal of Fluency Disorders readers the direction of their research. There was no expectation that the authors would present completed research, but preliminary findings were certainly encouraged. It’s quite obvious, therefore, that the contributors more than met the terms of that request. The result is a series of papers that constitute an illuminating overview of the different imaging techniques and strategies that are now being used to investigate stuttering — and the implications of the findings for theory and therapy. They contain a number of themes. Included are accounts of studies designed to understand the neural processes associated with the language of persons who stutter, theoretic accounts of the current array of findings and their relevance to other disorders, studies designed to isolate regional activations and deactivations associated with the fluency-inducing procedures and those associated with treatment.

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It was not possible to obtain contributions from researchers using techniques other than functional magnetic resonance imaging (fMRI) or \( \text{H}_2^{15} \text{O} \) positron emission tomography (PET). Consequently readers should be aware that other researchers are conducting studies on stuttering using magnetoencephalography (MEG) (e.g., Salmelin, Schnitzler, Schmitz, & Freund, 2000) or MRI to elucidate the neuroanatomic characteristics of stuttering speakers (e.g., Foundas, Bollich, Corey, Hurley, & Heilman, 2001).

In many ways the studies described in this special edition have only just begun to realize the enormous promise of brain imaging for the investigation of stuttering. For this writer that promise first appeared with the publication of the groundbreaking PET investigations by Petersen, Fox, Posner, and Raichle (1988) and Petersen, Fox, Posner, Mintun, and Raichle (1989). These studies were the first to show the different neural regions throughout the brain that are activated by reading single words, saying those words and generating new words (verb generation). In many respects the findings dramatically verified and enriched earlier theoretic models of the neural system that operates during speech production. They also came at a time when it was becoming increasingly obvious that stuttering must involve abnormal neural processing of speech. Suggestions that this was the case were alluded to in earlier EEG studies (e.g., Boberg, Yeudall, Schopflocher, & Bo-Lassen, 1983; Moore, 1984), but it also became apparent that the source(s) of some of the phenomena that characterize stuttering (e.g., chorus reading) was not going to be understood by focusing solely on peripheral processes (Ingham, 1998). The Petersen et al. studies were a revelation; they suggested that PET could help to isolate the particular neural regions that are functionally associated with stuttering, especially because it could be used in conjunction with fluency-inducing strategies. Later techniques and methods — especially performance correlation analysis (Silbersweig et al., 1995) — added to the promise by suggesting that it might be possible to identify the specific regions that change in conjunction with the frequency of stuttering. Has that goal been achieved? Only partially it seems.

It is clear from the preceding articles that the unusual right hemisphere activations that occur during stuttered speech do recede with treatment or fluency inducing strategies, and there is general agreement that there is a lack of activation in the temporal lobe region. However, there is also marked variability across the findings. In fact, it seems clear that the variety of methodologies used to investigate the neural processes associated with speech may strongly influence the clarity of the findings.

For a while the variability or inconsistency in findings from many imaging studies on speech and language raised concerns about their validity (Poeppel, 1996; but see Démonet, Fiez, Paulesu, Petersen, & Zatorre, 1996). That certainly prompted some vigorous efforts to rectify the inconsistencies (Hickock, 2001) — although recent meta-analyses now suggest that they are much less problematic (Fox et al., 2001; Turkeltaub, Eden, Jones, & Zeffiro, 2002). Nevertheless, there are some unresolved methodological problems that Grabowski and Damasio (2000) contend continue to impact straightforward comparisons among the findings of different imaging studies. They identified at least four such problems:
1. **The problem of paradigm design**: The uncertain stability of a cognitive state across the experimental and control conditions within subtraction designs. This is what Boring (1950) described as the “pure insertion” problem within subtraction designs;

2. **The obstacles to fine-grained anatomical interpretation of results**: The variability between individual anatomy and its transformation into “Talairach space” (Talairach & Tournoux, 1988) anatomy, including variability across studies in mapping Talairach coordinates to regions (see Brett, Johnsrude, & Owen, 2002);

3. **The problem of implicit assumptions about the signal in which one is interested**: Differences among the various smoothing filters that are used to improve the signal-to-noise ratio and which may affect the spatial and temporal shape of responses (see White et al., 2001);

4. **The problem of negative results**: By using conservative statistical thresholds to avoid false positive activations, imaging may demonstrate systems that participate in task performance, but they do not necessarily fully identify the sufficient systems.

An overview of the papers in this special edition suggests that these unresolved problems might explain much of the variability across their findings. For instance, the subtraction design is a feature of most of the studies. However, Stager, Jeffries, and Braun (2003) have also used performance correlation techniques, which offset much of the pure insertion problem (see also Fox et al., 2000; Ingham et al., in press). With respect to the second problem, some imaging studies use Statistical Parametric Mapping (SPM 99; Wellcome Department of Cognitive Neurology, 1999) to identify activated regions, but others use rather different techniques (e.g., Lancaster et al., 2000). Problems 3 and 4 are especially interesting: There is literally no consistency across these studies with respect to the choice of image smoothing filters and the statistical thresholds that have been selected certainly vary widely. Of course, this list might be augmented because of the use of different imaging technologies. For instance, the three labs reporting on treatment studies (De Nil, Kroll, Lafaille, & Houle, 2003; Ingham, Ingham, Finn, & Fox, 2003; Neumann et al., 2003) have used very different imaging techniques and tasks. The projects reported by Neumann et al. (2003) have used event-related fMRI, while those by De Nil et al. (2003) and the San Antonio group (Ingham et al., 2003) have used H215O PET. In addition, the speaking tasks have ranged from reading single words, reading short sentences, through to continuous oral reading and monologues — with and without the presence of stuttering events. Consequently some differences among the findings should not be too surprising — and especially in light of the history of imaging studies of language function. After reviewing those studies Grabowski and Damasio (2000, p. 445) reached the following sobering conclusion: “When two functional imaging studies attempt to isolate a specific language-processing component using different tasks, the results usually differ.”
Despite a variety of methodologies and techniques, there is an emerging consensus among the contributors’ studies about the brain areas that are implicated in stuttering — or in the neural areas that stuttering speakers employ during speech-related activities. That consensus points to excessive neural activation in the right hemisphere involving the right operculum and especially the regions related to speech motor behavior. In addition there is compelling evidence that this abnormal neural activity is associated with an underactivated auditory system; possibly contributing to what Ludlow and Loucks (2003) described as “a system dysfunction that interferes with rapid and dynamic speech processing for production.” The presence of excessive right hemisphere or bilateral activation appears to be prompted by lexical retrieval tasks that do not involve overt speech production (see Blomgren, Nagarajan, Lee, Li, & Alvord, 2003), which, in turn, may relate to the effect of lexical factors on stuttering (Prins, Main, & Wampler, 1997). The relationship between level of activation in the motor-auditory regions and the production of overt stuttered speech is still unclear. However, the use of different fluency-inducing strategies, such as chorus reading, metronome-trained speech, singing, or prolonged speech, appears to substantially normalize the regional activations in the motor-auditory region. Stager et al. (2003) suggest that this could be due to “a common fluency-evoking mechanism (that) might relate to more effective coupling of auditory and motor systems — that is, more efficient self-monitoring, allowing motor areas to more effectively modify speech.” That observation is certainly consistent with findings emerging from studies conducted by this writer and colleagues. It is also generally consistent with the findings of studies that have evaluated the neural activity associated with the outcome of prolonged speech-related treatments. Complicating matters, however, are the marked differences in the activation patterns obtained from two of these studies at the point of treatment outcome evaluation. De Nil et al. (2003) reported that the “lateralized bias for some areas shifted as subjects first completed intensive therapy and subsequently the maintenance phase.” By contrast, Neumann et al. (2003) found that the overactivations immediately after therapy “were more widespread and more bilaterally distributed than before . . . (but at) . . . follow-up the majority of the overactivations had shifted back to the right hemisphere, but remained still more widespread than before therapy.” Neumann et al.’s finding may also be partially consistent with suggestions that some abnormal activations continue to be evident among individuals who appear to have fully recovered from stuttering (Ingham et al., 2003). Of course the differences between De Nil et al. and Neumann et al.’s findings might simply reduce to the levels of efficacy of two different treatments.

One of the recurring issues surrounding brain imaging research on different disorders is the extent to which the findings can contribute to treatment — one of the important themes in this collection of papers. In the case of stuttering, for instance, the present findings give no indication as to how the regional activations (and deactivations) that support stuttered speech might be changed. It is certainly interesting to know that treatment might help to normalize the neurophysiological processes associated with speech production in normally fluent speakers, but is
that of much value if there is continuing uncertainty about the durability of the benefits of the treatments under investigation? For that reason there seems to be some merit in the careful investigation of persons who have fully recovered from stuttering — especially those who have fully recovered by self-managed strategies. It seems reasonable to speculate that these individuals might demonstrate the extent of neural system change that is possible through behavior change and perhaps the specific changes that are necessary to support normal fluency.

It is obvious that brain imaging researchers have focused much of their attention on treatment — but only treatment for adults. That focus, of course, is largely due to restrictions that apply to the use of invasive imaging techniques with children. But it also applies to noninvasive techniques, which, in the case of fMRI, require a young child to be confined for lengthy periods within an MR scanning tunnel. Until this problem is fully solved then questions concerning the age when unusual or abnormal activations appear cannot be addressed.

The initial attempts to identify the neural processes associated with adult therapy have also brought forth other issues. For instance, the only stuttering treatments that have been investigated using brain imaging are those utilizing some variant of prolonged speech (Ingham, 1984). But even those variants involve much more than prolonged speech training. De Nil et al. (2003) used subjects treated by the Precision Fluency Shaping (PFS) program (Webster, 1974), which trains speakers to use syllable prolongation, soft voice onset, and reduced articulatory gestures. Neumann and colleagues have conducted their research in conjunction with a therapy program known as the Kassel Stuttering Therapy or KST (Euler & Wolff von Gudenberg, 2000). KST is a modified version of the PFS utilizing computer-aided training and a structured 1- to 2-year maintenance program. Ingham et al. (2003) used the Modified Phonation Interval (MPI) program (Ingham et al., 2001) which uses computer-aided training to reduce the frequency of short phonation intervals in conjunction with self-managed performance-contingent transfer and maintenance schedules. There is also an obvious difference between the speech tasks used during scanning and the speech tasks required to evaluate therapy effects. The speaking tasks used during scanning conditions may have external or ecological validity, but that has yet to be demonstrated. Nonetheless, even if this was demonstrated to be the case, then imaging data derived from therapy might ultimately constitute little more than a surrogate outcome measure necessarily supplemented by measures of speech performance.

An alternative way in which imaging research on stuttering might advance is through the investigation of strategies for directly modifying the neural system. Exploratory studies on the use of transcranial magnetic stimulation (TMS) (see Hallett, 2000, for a review) may offer that promise, but in ways that are not yet fully understood. Earlier TMS studies by our group were directed towards stimulating neural sites that PET imaging had shown might be implicated in stuttering (see Ingham, Fox, Ingham, Collins, & Pridgen, 2000). An initial attempt at the modification of supplementary motor area activity (based on Fox et al., 1996) did not produce beneficial effects. However, a concurrent investigation (Fox et al., 1997)
that used TMS to explore neural connectivity in healthy subjects did highlight
the technique’s immense diagnostic potential. Indeed, this has since become an
established strategy for identifying neural connectivity (see Sieber & Rothwell,
2003). TMS can also used to determine if the perturbation of an aberrant circuit has
short-term clinical effects. An interesting application of this strategy was recently
reported by Topper, Foltys, Meister, Sparing, and Boroojerdi (2003) with respect
to phantom limb pain. The use of this technique to identify aberrant neural circuits
in adult stuttering speakers and then assess the modifiability of those circuits is
now being explored by our group. That research is also benefiting from the de-
velopment of vastly improved methods for aiming the TMS stimulator at specific
regions. The perturbation strategy might also serve to fully explore the circuitry
within models of the speech production system, such as that proposed by Jürgens
(2002 — also see Ingham et al., 2003). That same strategy might also be useful for
exploring the full implications of Salmelin et al.’s (2000) intriguing MEG finding;
that is, that the order of neural regions are activated in speech production typically
follows a Wernicke’s area → Broca’s area → M1-mouth path in normal speakers,
but among stuttering speakers the path (for producing nonstuttered words) was
found to be Wernicke’s area → M1-mouth → Broca’s area. This study clearly
highlights the importance of neural pathways. It is worth pointing out, however,
that MEG shares with TMS an important limitation — currently both techniques
are unsuitable for investigating subcortical regions of the brain. The perturbation
strategy will therefore require other techniques to elucidate the system that ulti-
mately produces stuttered speech.

As mentioned earlier, neuroanatomic investigations of stuttering are not repre-
sented among the special edition papers. Recent neuroanatomic investigations have
reported that stuttering speakers (adults) display structural abnormalities (Foundas
et al., 2001) or lesions (Sommer, Koch, Paulus, Weiller, & Büchel, 2002). But
the findings portray a complex picture. Sommer et al. reported focal abnormali-
ties in the white matter of the left frontal operculum in stuttering speakers using
diffusion-weighted MRI. They interpreted their findings as evidence of atrophy
of myelinated fibers connecting speech-related regions of the superior tempo-
ral lobe with those of the frontal lobe. Although the abnormality reported by
Sommer et al. is in the same general region (left inferior frontal lobe) as that re-
ported by Foundas et al., the findings from both studies are difficult to reconcile.
Foundas et al. reported larger structures and more gyri; Sommer et al. reported
atrophy. Further, although T1-weighted MRI images were acquired in Sommer
et al.’s subjects (the image type used by Foundas et al.), no abnormalities of T1
images were reported, suggesting a failure to confirm Foundas et al.’s findings.
On the other hand, both studies found abnormalities in approximately the same
brain region, a region strongly implicated in speech production. One possible ex-
planation for these somewhat conflicting reports is that no single type of brain
anomaly underlies all cases of developmental stuttering. Lesion type may vary
based on genetics (or other factors), with lesion location being the more critical
variable.
Much recent imaging research has been aimed at finding powerful methods for influencing neural plasticity — both functional and anatomical plasticity — and this may have immense implications for stuttering research (Taub, Uswatte, & Elbert, 2002). Kochunov et al. (2003) recently observed that these may be inherent properties of the human brain. “Functional plasticity,” as they note (p. 961), “refers to the dynamic changes in functional organization of a system that are driven by an adaptation to a novel stimulation or acquisition of a new motor skill.” For the most part the focus of attention in this area has been on understanding the factors that may influence change in the somatosensory, auditory, visual and motor systems — such changes do appear to have occurred among recovered stutterers (see Ingham et al., 2003). However, as Kochunov et al. also point out, there is now convincing evidence that cortical anatomical plasticity may also occur as a result of a variety of experiences, usually of extensive duration. Amunts et al. (1997), for instance, showed that the normal left–right asymmetry in the size of the precentral gyrus was substantially more symmetrical in professional pianists, especially in the hand area and Kochunov et al. identified intriguing anatomical differences in Asian and Western speakers. Thus it is interesting to consider the possibility that a lifetime of chronic stuttering may impact anatomic structure and thereby impact the possibilities of behavior change and the neural systems that are functionally associated with stuttering. Nevertheless, recent studies showing the success of Constraint-induced Therapy (Liepert et al., 2000; Taub & Morris, 2001) with stroke patients — many of whom suffered their stroke at least a decade earlier — suggest that the limits of neural plasticity in adults are far from established (Taub et al., 2002). In short, the age-dependent limits on recovery may be more speculative than real — and may depend on finding similar techniques for inducing neural plasticity in adult stuttering speakers.

Predicting the future is always hazardous and often of little value, but it can help to etch out goals and expectations. And, in the case of imaging research, these can be reasonably derived from a history that has been largely driven by technological development and discovery. Cerebral blood flow has undoubtedly provided neural researchers with a powerful tool for investigating neural processes. And the search for methods to measure and track that flow will continue to improve the use of that tool. But neural systems can also be monitored and measured by other means, including electroencephalography and neural transmitters. Of far more interest, however, has been the development of tools for modifying neural system activity. Drug research continues to provide the dominant source of interest for producing a therapeutic interaction between the neural system and behavior change — but the benefits from drug research for stuttering are still uncertain (see Ludlow & Loucks, 2003). Meanwhile, research on methods for changing behavior without drug intervention will undoubtedly benefit from further refinements to MRI, PET and TMS. And there is also little doubt that radically different approaches will emerge from within the exciting advances in nanotechnology, stem cell research and genetics.

There are numerous exciting possibilities for assisting research on the theory and treatment of stuttering. At the forefront, however, must be the development of
a neural systems model of stuttering, based on carefully derived empirical studies of speech production tasks that characterize stuttering and its variability — rather than one based on preconceived theoretic constructs. This is the route proposed in Peter Fox’s (2003) provocative paper and it seems to offer the most promise for a dramatic breakthrough in this area of research. Another is the need to conduct imaging studies on children who are at risk for stuttering and those who recover or do not recover from stuttering within the first few years after onset. This is certainly possible with creative studies using fMRI that might also help to identify the formation of the aberrant system that supports chronic stuttering. The need for investigations of stuttering treatment has already been discussed. But there is also a need to investigate the interaction between neural systems (including structure) and treatment responsiveness. Studies in these areas are urgently needed if imaging research on stuttering is going to fully realize its early promise.

References


