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# Oceans of the brain

**Robert Goldfarb, Ph.D [1*]; Russ E. Davis, Ph.D. [2]**

[1] *Department of Communication Sciences and Disorders, Adelphi University, Garden City, NY*

[2] *University of California, San Diego, USA*

## Abstract

Examination of regional cerebral blood flow is limited by shortcomings inherent in existing neural imaging techniques. In this perspective, we identify problems associated with accurate diagnosis; polytypicality of symptoms, especially in aphasia; and suggest that the brain's responses to acoustic stimuli may provide a fruitful direction for future research. We employ models from oceanography, such as Acoustic Doppler Current Profilers to illustrate techniques which may inform new ways to examine arterial blood flow.

***Keywords***: Cerebral arteries; blood flow; aphasia; ultrasound; oceanography.

## 1. Introduction

Current methods of clinical neuroscience include a variety of techniques to look at brain structure and function. All have various drawbacks which threaten accuracy of interpretation, and impact efficacy of medications. Perhaps we should be listening to the brain, or more properly, observing brain responses to acoustic stimuli, in addition to looking at it. As this paper is written by an aphasiologist, the focus is on assessing effects of stroke on blood flow in the language centers of the brain

The left perisylvian region has been classically described as the zone of language (Wernicke, 1874). Damage following occlusion or narrowing of the left middle cerebral artery (mca) can independently cause language problems (aphasia), speech articulation disorders (apraxia of speech), and many other deficits. Medicinal, mechanical, and surgical techniques have all met with qualified success in resolving thromboembolic occlusions in the distribution of the mca.

In 1996 the U.S. Food and Drug Administration (FDA) approved the use of tissue plasminogen activator (tPA) treatment for managing ischemic stroke within the first three hours of onset. Unfortunately, cerebrovascular accidents often occur during sleep hours, and the three-hour window is missed. In addition, tPA treatment can be contraindicated when the stroke is hemorrhagic, where such intervention can have devastating consequences. Such an outcome received wide attention recently, in the case of Israel's former Prime Minister, Ariel Sharon. Mechanical removal of occlusions with the Merci retriever system was approved for use in patients with stroke in 2004. In one study (Devlin et al., 2007), single-center data focused on 25 consecutive patients where most instances of acute ischemic stroke followed isolated middle cerebral artery lesions. Successful reperfusion was obtained in about half of the Merci trials, although some patients with tandem proximal carotid and intracranial lesions were treated with carotid angioplasty and stenting, and not all patients were treated within the 3-hour window.

At present, decisions regarding areas for reperfusion, whether the intervention is medical, mechanical, or surgical, are based on looking at the brain. The following sections of this report will address some of the limitations associated with visually-based information, and suggest a methodology based on oceanographic research.

## 2.Threats to accurate diagnosis

The advent of neural imaging techniques has presented a challenge to strict localizationists, who posit direct brain-behavior relationships. Evidence of reduced blood flow, narrowing, or obstruction in the left hemisphere mca should correspond with impairments in function associated with the affected portion of the brain. That this is not always the case points to shortcomings both in localizationist theory and in neural imaging, as follows:

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* ***Correspondence should be sent to*:**

Robert Goldfarb, Ph.D., Professor and Program Director, Department of Communication Sciences and Disorders, Adelphi University, Garden City, NY 11530; Fax: 516-877-4783; Tel: 516-877-4785; E-mail:goldfarb2@adelphi.edu; Mailing address: 1160 Third Avenue, #16EF, New York, NY 10065

1) Hypoperfusion: Magnetic resonance perfusion weighted imaging can be useful in identifying hypoperfusion of specific brain regions, which may be associated with disruption of selective language functions. Pharmacological blood pressure elevation may increase regional brain perfusion and language function. Reperfusion of the ischemic and dysfunctional tissue can reveal brain/language relationships before the reorganization which follows a stroke (Hillis, et al., 2001).

   Localizing brain functions has been typically supported by evidence of shared areas of brain damage in individuals with a similar language deficit, and is sometimes called the "lesion overlap" approach. That is, if there is a functional deficit, then the area of the brain damaged in most of these individuals must have been responsible for that function. When the reciprocal association, the probability that the lesion caused the deficit, is evaluated, then the relationship may not be supported. Hypoperfusion does not necessarily specify area of infarct. For example, structural damage or low blood flow in the left posterior inferior frontal gyrus may result in poor drainage into the anterior insula. Reperfusion of the anterior insula will not relieve symptoms of apraxia of speech, a motor programming speech disorder associated with left frontal lobe damage (Hillis, et al., 2004).

2) Polytypicality: Many adults with communication disorders, such as adults with post-stroke aphasia, display language characteristics that cross diagnostic boundaries. The polytypic nature of aphasia highlights the limitations of classifications which require separate groupings and imply independence of individual language functions (Schwartz, 1984).

   Virtually all aphasias involve reduction of available vocabulary, linguistic rules, and verbal retention span, as well as impaired comprehension and production of messages. It is not unusual for a patient with Broca's aphasia, for example, to have difficulty in auditory comprehension, an impairment listed among the principal diagnostic characteristics of Wernicke's aphasia. Curiously, the patient Broca described in 1861, called "Tan" because that was his stereotypic utterance, did not have Broca's aphasia. The combination of severe oral expressive deficit along with severe auditory comprehension deficit would probably be indicative of a global aphasia (Damasio, 2008).

   While type of language deficit is usually a reliable predictor of site of lesion, the reverse correspondence does not hold as closely. The "exceptions", where lesions as corroborated by computerized tomography did not predict type of aphasia, ran about 16% or about one in six (Basso, et al., 1985).

3) Brains versus veins: The underlying principle of functional magnetic resonance imaging (fMRI) is that magnetic properties of oxygenated blood are different from deoxygenated blood. The scan detects alterations in brain function or physiology associated with cognitive, motor, and sensory task performance. The gold standard of blood oxygenation level dependent (BOLD) technique is better than repeated injections of gadolinium (Gd) at generating images sensitive to the oxygenation level of blood. Arterial spin tagging is an approach similar to Gd, but arterial blood water is "tagged" magnetically using an RF pulse rather than by Gd injection.

   Clinical applications have been limited to attempts to guide neurosurgery or radiation therapy to spare important functional tissue. Applications in neuroscience research include brain mapping studies using BOLD fMRI to assess language lateralization, word generation, and sentence comprehension. BOLD fMRI use in disease states has focused on recovery of language ability after stroke and mapping regional changes in activity during epileptic seizures. Publication of more than 40,000 articles reveal functional brain imaging to localize behavioral and cognitive processes to specific areas in the human brain is often not confirmed by traditional, lesion-based studies (Ross, 2010).

   The "brains vs. veins" issue is related to the part of the functional signal which arises not from the brain capillaries and parenchyma (presumably at the site of activation), but rather from larger draining veins; accordingly, accuracy of localizing neural activity is limited.

**3. Brain responses to acoustic stimuli**

Applications of electroencephalography called evoked potentials or event-related potentials have been demonstrated to be reliable paradigms for learning about language abilities in the human brain. There are specific brain potentials which correspond to auditory stimuli, and which differentiate passive from active listening. In addition, the technique of ultrasound, where pings of sound may be reflected off particles (cells), has been used to measure arterial blood flow, but not yet in human brains.

1) Event-related potentials (ERP): When a neuron fires, an electrical field travels along its axon. By firing simultaneously, neurons in the CNS create a detectable electrical field outside the skull. An electrode net positioned on the surface of the skull, and the resultant waveform shows averaged electrical activity recorded for 1 second after presentation of a word. The ERP response is described in terms of positive (P) and negative (N) peaks and their latencies. Early components indicate intensity of the stimulus; later components indicate attention to the stimulus. The N400 response reveals associative/semantic relationships; the P600 highlights syntactic processing.

   Brain potentials may identify auditory cortical processing, for example, when using P300 event-related potentials to evaluate 12 post-stroke patients, half of whom had amusia (Munte, et al., 1998). The P300 is elicited when a subject detects infrequent stimuli presented in a series of frequent stimuli (P3b), but also when a subject does not detect and only listens passively to infrequent stimuli (P3a). While the P3a has front-central scalp maximum and a short latency, the P3b has parietal scalp maximum and a long latency. The authors reported that patients with amusia had a significant decrement in amplitude for P3a, relative to controls and patients without amusia, an impairment of early stimulus evaluation. The P3b was reduced for both patient groups relative to controls.

   For baseline data on healthy controls (Perkins, et al., 2007), the research group including the first author established fMRI and ERP patterns, prior to a Phase I study of language responses in acute stroke. Group analyses revealed differential fMRI activation patterns for difficult vs. easy contrast for both picture naming and verb generation. In particular, bilateral activation of the inferior frontal gyrus was observed. EEG signal plots were averaged over "easy", "difficult" and "control" trials from -100ms to 900ms. Subtraction maps were generated for the difficult-minus-easy stimuli. ERP results revealed an early parietal (300-400ms) and late temporal-frontal activation (500-600ms) similar to the fMRI activation patterns observed.

2) Ultrasound: Deep Brain Stimulation (DBS) is a reversible therapeutic surgical procedure that involves the implantation of a brain pacemaker. The DBS system consists of three components: the implanted pulse generator, the lead, and the extension. Surgeons may use sound waves for locating the lead to the globus pallidus or the subthalamic nucleus. Doppler imaging ultrasound has been used in measurement of superior mesenteric artery blood flow in humans (Qamar, et al., 1986). Regional blood flows of the left common carotid artery, terminal aorta, common iliac artery, external iliac artery, or common femoral artery in humans were measured by Doppler method and electromagnetic flowmeter (Shimamoto¸et al., 1992). Doppler imaging ultrasound also offers the possibility of non-invasive measurements of volumetric ophthalmic artery blood flow in humans (Orge, et al., 2002). In a recent application in mice, ultrasound was used alone to stimulate action potentials directly and drive intact brain activity without surgery (Tufail, et al., 2010).

## 4. Oceanographic research

There are some fundamental similarities between arterial blood flow and ocean currents. In addition, occlusions in arteries may share some features with undersea dune troughs, at least in terms of perturbation of movement of fluids. The methodologies used in gliders which measure climate change based on ocean currents may have applications for measurements of efficacy of drug treatments on blood flow. The mathematical models should apply to all types of currents.

1) The "Spray" and other undersea gliders: Underwater gliders are autonomous vehicles that profile vertically by changing buoyancy and move horizontally on wings (Davis et al., 2003; Rudnick et al., 2004). The Spray glider (Sherman et al., 2001) was developed at Scripps Institution of Oceanography, and has been used at many locations around the world. Measurements have included pressure, temperature, velocity, and acoustic backscatter. Spray gliders have completed over 57,000 dives, covering over 153,000 km in more than 7,200 glider-days (Davis et al., 2008).

   It is possible to reduce the noise contribution to mean turbulence parameters obtained by 3D acoustic Doppler velocity profiler measurements (Hurther & Lemmin, 2001). The corrected profiles of turbulence intensities, turbulent kinetic energy, shear stress, and turbulent energy balance equation terms, such as production, transport, and dissipation, are in better agreement with other measurements from the literature than those from the uncorrected data. Measurement errors persist concerning turbulence quantities over a rough bed, specifically the large sampling diameter close to the bed that does not adequately measure velocity in dune troughs (Kostaschuck, et al., 2004).

2) Mathematical models from Euler and Lagrange: The mathematic models of interest are those of Lagrange (for variable measurements of currents) and Euler (fixed-point measurements). Oceanographers measure currents with moorings anchored to the bottom (clearly Eulerian), from ships (Eulerian in the sense that the coordinates are chosen by the observer), and with floating devices that are carried by the currents (purely Lagrangian). Most numerical models of oceans and atmospheres are in Eulerian coordinates, because the Lagrangian coordinates themselves are so much more difficult to keep uniformly spaced. The resultant statistics with data in both coordinates are averaged in the two frames that are fundamentally different. Measurements relating the two for various ocean phenomena are the current standard (Davis, 2007).

## 5. Future directions

The hypothesis suggested in this paper is that blood moving through the left middle cerebral artery is fundamentally similar to water moving in ocean currents in its potential for Doppler profiling. In both cases, there may be obstructions to the flow, dune troughs in oceans and cerebrovascular disease in brains, which affect turbulent intensity and energy. There may be only two methods for measuring velocity non-invasively: (1) Find something in the moving fluid (blood) whose position can be detected remotely (via radioactive, fluorescing material), and put in bubbles of that material and track them; or (2) Use Doppler reflection of light or sound off particles (cells) in the fluid. The standard Doppler approach measures ocean currents with an Acoustic Doppler Current Profiler that pings and uses return time to infer range, and Doppler shift off multiple beams to measure velocity in at least two directions. Ultrasound scans using Doppler processing for blood flow have been used successfully in some parts of the body, so this works in some circumstances. Why not in brains? Recent rodent stroke model guidelines for preclinical stroke trials (Fisher, et al., 2009; Liu, et al., 2009) can inform the initial aspects of the work. Improved examination of regional blood flow in the left middle cerebral artery should lead to refinements in localizationist theory, with particular reference to differential diagnosis of the aphasias. Advances in nanotechnology may yield an injectable form of Spray or other arterial glider, and permit exploration of the oceans of the brain in humans.

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## Conflict of Interest

None

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