ERP Source Localization in Neuro-Cognitive Rehabilitation Research

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We provide here a brief overview of methods by which the sources of event-related potentials (ERPs) are located in the brain and the role that such ERP source localization might play in neuro-cognitive rehabilitation research (NCRR). The term *ERP source localization* has at least two meanings distinguished by somewhat different objectives: 1) identification of the electrical generators responsible for all or part of ERPs recorded from the scalp, and 2) measurement of electrical activity from specific brain regions of interest (ROIs) based on scalp-recorded ERPs. Presented below is a discussion of basic concepts related to ERP source localization, followed by an example drawn from our own research involving individuals with aphasia. More general introductions to ERPs and their role in NCRR can be found on this website in [3] and [16] respectively. For a general introduction to ERP source localization, see [4] and [5].

Some Basics

Benefits. To begin, let's consider why ERP source localization might be worth the effort. As with other types of functional brain imaging, ERP source localization can provide NCRR with a tool for evaluating how the functional integrity of specific brain areas is influenced by pathology or remediation. For example, prior knowledge about the anatomical sources of standard ERP "components" enables their interpretation with respect to those sources in patient populations. More generally, one can attempt to localize the sources of any scalp-recorded electrical response produced or influenced by an experimental manipulation, be it a component, steady-state oscillation, or other form of ERP. If, instead of ERPs per se, one's primary interest is in a particular anatomical ROI, its electrical activity can in some cases be monitored moment-by-moment on the basis of scalp-recorded ERPs. Though ERP source localization has poorer spatial resolution than many other forms of functional imaging and is largely limited to cortical sources, it has excellent temporal resolution. This temporal resolution increases its sensitivity to transient responses and is extremely useful for measuring selectively those portions of brain activity that are functionally specific to a cognitive process of interest.

Models. ERP source localization is sometimes referred to as *source modeling*, and for good reason. A basic feature of most methods is the construction and application of various types of models. One such model is the *source model*, which represents the putative sources responsible for electrical measurements on the scalp. Changes on the scalp over time are explained by changing parameters of the source estimates. These parameters consist of the magnitude and direction of current flow at different spatial locations, which may be registered to an MRI in order to determine their corresponding anatomical locations. Besides a source model, ERP source localization often involves a *head model* of electrical volume conduction relating current flow at different spatial locations to measurement on the scalp. It typically comprises representations of different materials (e.g. bone, skin, and gray matter), each characterized by a different electrical resistance. Both types of model may vary in their degree of realism. For example, head models may range from a set of concentric spheres to a set of geometrically realistic compartments based on an MRI. Source models may be constrained to different degrees by anatomical information (e.g. locations of gray matter) obtained from an MRI. The MRI used to inform realistic models may be from a single individual or a composite made by combining spatially normalized MRIs from different individuals. Likewise, source localization may be performed separately for each individual or on composite group data.

Varieties. The overall goal of ERP source localization is to construct a source model based on scalp-recorded ERPs. The source models obtained through different methods can be classified in terms of two orthogonal distinctions. First, some source models (*distributed*) consist of estimates of current originating from each of many tiny volumes throughout the brain, while others (*discrete*) are comprised of a small number of sources situated in a few choice locations. Second, ERP source models can be classified as *global* or *local*. Global models attempt to "explain" the total distribution of ERPs across the scalp in terms of a set of sources within the brain. Here the source estimates all function together, in the sense that the value of each depends on that of all the others. Local models estimate the contribution of individual regions of interest (ROI) to the ERP scalp distribution. What makes these models "local" is that the estimates for a given ROI need not depend on the value or existence of estimates for any other ROI. Moreover, the ROIs need not be major contributors to the scalp measurements, but may be selected instead on the basis of anatomical, hemodynamic, or other considerations.

Taxonomy. The above distinctions lead to the taxonomy shown by Table 1. The distinction between distributed and discrete models is represented by the two rows, the global vs. local distinction is represented by the two columns, and an example of each combination is shown in the four resulting cells. Perhaps, the most widely known methods of ERP source localization involve source models consisting of a small number of current dipoles, in which the location, magnitude, and orientation calculated for each dipole depend on those calculated for all the others. These models are both discrete and global and employed, for example, in the Equivalent Current Dipole approach [6, 12]. Another well-known type of method models ERP sources as a very large number of current dipoles distributed throughout the brain (analogous to voxels in fMRI). Here too, the values calculated for each dipole depend on those calculated for the rest. These models are both distributed and global and are employed, for example, in Low Resolution Tomography (LORETA) [7, 8]. Methods involving local source models are newer and less well known than those involving global models. Regional Activity Estimation [10, 11] and Beam Formers [2, 13] are examples of such methods and can each involve discrete or distributed models. Choosing between these four general approaches depends in part on 1) whether the immediate goal is to identify ERP generators or to monitor specific ROIs and 2) whether the ERPs are believed to arise from a small number of discrete sources.

Table 1

Taxonomy of ERP Source Localization Methods

	Global	Local
Discrete	Equivalent Current Dipoles (ECD)	Beamformers or Regional Activity Estimation (REGEA)
Distributed	Low Resolution Tomography (LORETA)	Beamformers or Regional Activity Estimation (REGEA)

Note. Rows and columns designate classes along two orthogonal dimensions and cells contain examples.

Uniqueness problem. A further distinction fundamental to all forms of ERP source localization is that between *forward and inverse solutions*. Both types of solution involve the same three elements: 1) a source model, 2) a head model, and 3) ERPs measured at the scalp. A forward solution starts with a source model and then uses a head model to predict the resulting ERPs. An inverse solution starts with the ERPs and uses a head model to infer a source model comprising the generators. ERP source localization requires finding an inverse solution. To do so, it must take into account an important difference between the two types of solution. Forward solutions consist of a single answer. That is, given a source and a head model, ERPs at the scalp are completely determined. Inverse solutions do not consist of a unique answer. Alternative source models can produce identical ERPs, even with the same head model. The problem is to select between these alternative source models. To limit the possibilities, various constraints are imposed on the location, number, or other features of sources. These constraints are often based on prior information from other methods (e.g. neuropsychological) or measures (e.g. fMRI) about likely sources or on physiological plausibility (e.g. locations of gray matter). Different methods of source localization in combination with different constraints are typically evaluated by obtaining solutions under conditions where the underlying generators are already known, e.g. with simulated data or simultaneous scalp and depth recordings.

Special considerations related to NCRR. ERP source localization must grapple also with problems specific to NCRR. One is the presence of a lesion. As mentioned, most forms of source localization involve a head and a source model. Since the purpose of a head model is to predict how electrical activity of the source model will be conducted to the electrodes on the scalp, it must take into account the size, shape, location, and electrical conductivity of the lesion. The presence of a lesion should also be reflected in the source model. There should be little or no current flow attributed to locations within the lesion and in some cases hyperactivity along its edges. One might either check for these properties to test the correctness of an obtained source model or use them to constrain the set of alternative source models evaluated during source localization. A further consideration concerns the testing of neuropsychological populations. ERP source localization requires a large number of electrodes (typically 20-200+), which can take a long time to apply to the participant's scalp. The recordings must also contain a minimum of electrical noise and artifacts, such as those caused by eye blinks and body movements. These time demands and requirements for physical control may be difficult for patient populations, especially the elderly. Fortunately, they can be reduced considerably through the use of new ERP recording systems that enable fast electrode placement and automated procedures for removing eye-movement artifacts [9].

An Example

To illustrate the concepts described so far, we now turn to a brief description of our own fledgling attempts to employ ERP source localization in NCRR. This work uses LORETA to locate the anatomical sources of ERP responses evoked by speech-like stimuli in aphasic and healthy control participants. The speech-like stimuli were produced by modulating the frequency (FM) of a continuous tone cyclically (high-to-low-to-high pitch) at 4 times a second (4 Hz). Since analogous variations in formant frequencies are essential cues for the perception of speech, such stimuli have proven useful for studying disorders of speech processing, e.g., word deafness and developmental language disorders [14, 15]. LORETA was performed with EMSE® Suite from Source Signal Inc. This method was chosen in order to make as few assumptions as possible about the number or location of ERP sources. These sources were estimated in 8 participants with aphasia and 13 neurologically normal controls. The 8 participants with aphasia had structural lesions in the distribution of the middle cerebral artery (fronto-temporo-parietal). All but one with pure word deafness had anomic or Broca's aphasia. Left Heschls' gyrus was spared in three individuals and involved minimally (<14%) in another two. The immediate goals of this work are 1) to determine how much of the ERP response to FM stimuli comes from primary and secondary auditory

cortex in the left hemisphere and 2) how the response from these areas differs between the aphasic individuals and controls.

An initial step was to construct the models to be employed. These are shown in Figure 1 and included 1) a source model consisting of potential source locations (top row) and 2) a head model for calculating volume conduction between the sources and scalp (bottom row). Both were based on a publicly available standard MRI from a single individual (Colin27) that was "normalized" to average dimensions (MNI Brain) and is used for fMRI source localization in a popular software package (SPM99). The source model contains locations throughout the entire top half of the brain and is represented by a lattice, the vertices of which correspond to current dipoles that can vary in direction and magnitude (including zero when there is no source at that location). The head model contains separate areas corresponding to the scalp, skull, gray matter, white matter, and cerebrospinal fluid. Each area, shown in a different color, was assigned a different electrical conductance obtained from a standard reference [1]. The head and source models were first used to determine a set of algebraic transforms (matrix) that yielded a forward solution for each possible configuration of dipole magnitudes and directions in the source model. These transforms were then converted into a second set of transforms (inverse matrix) for yielding inverse solutions comprised of a configuration in the source model responsible for the observed ERPs.

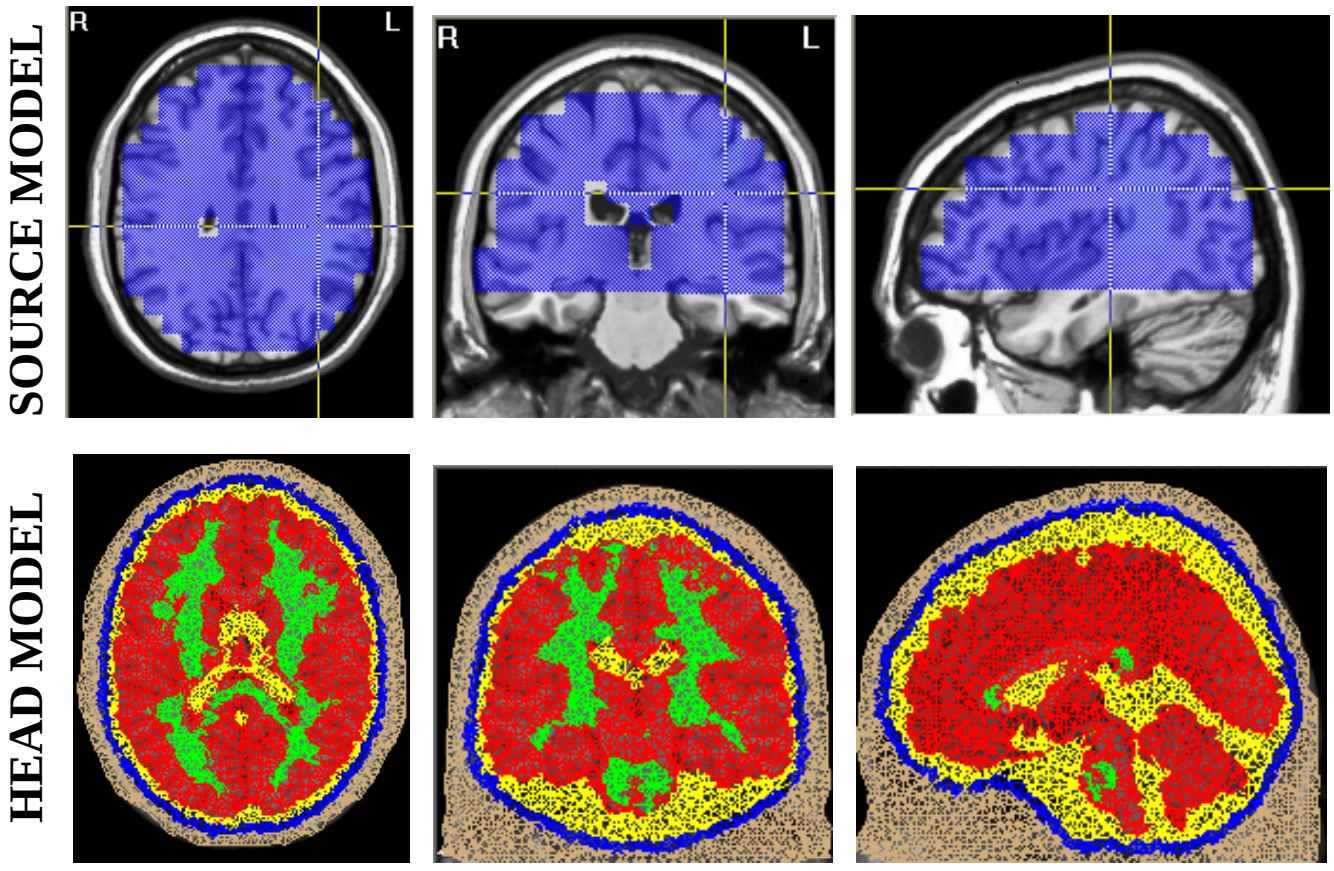

Figure 1. Two models employed in ERP source localization. Top row: Source model. Blue indicates a volume throughout which dipoles are distributed. Bottom row: Head model. Separate volumes corresponding to the scalp (brown), skull (blue), cerebrospinal fluid (yellow), gray matter (red), and white matter (green) were each assigned a different electrical conductance. Both models are shown in axial, coronal, and sagital planes superimposed on the MRI (Colin27) upon which they were based. See text for further details.

The ERP data for which we sought sources consisted of power at the 4 Hz cycle time of our FM stimuli measured at each of 29 electrode sites spread across the scalp. The source configurations obtained with LORETA for individuals with aphasia and for healthy control participants are shown in Figure 2. They are color coded with respect to the magnitude of current flow at each location and superimposed on the MRI used to construct the models in Figure 1. These inverse solutions were constrained by anatomical information from the MRI, as well as features specific to LORETA related to physiological plausibility. Results for the control group are shown in Row 1. As can be seen, the sources with greatest magnitude include areas of posterior superior temporal cortex (planum temporale) involved in perceiving speech, with greater activation in the left hemisphere. A similar pattern can be seen in Row 2 for the participants with aphasia. The configurations of source amplitudes for the two groups were compared by performing a LORETA on the difference between their respective ERPs. The result is displayed in Row 3 and can be seen likewise to involve the planum temporale, particularly in the left hemisphere.

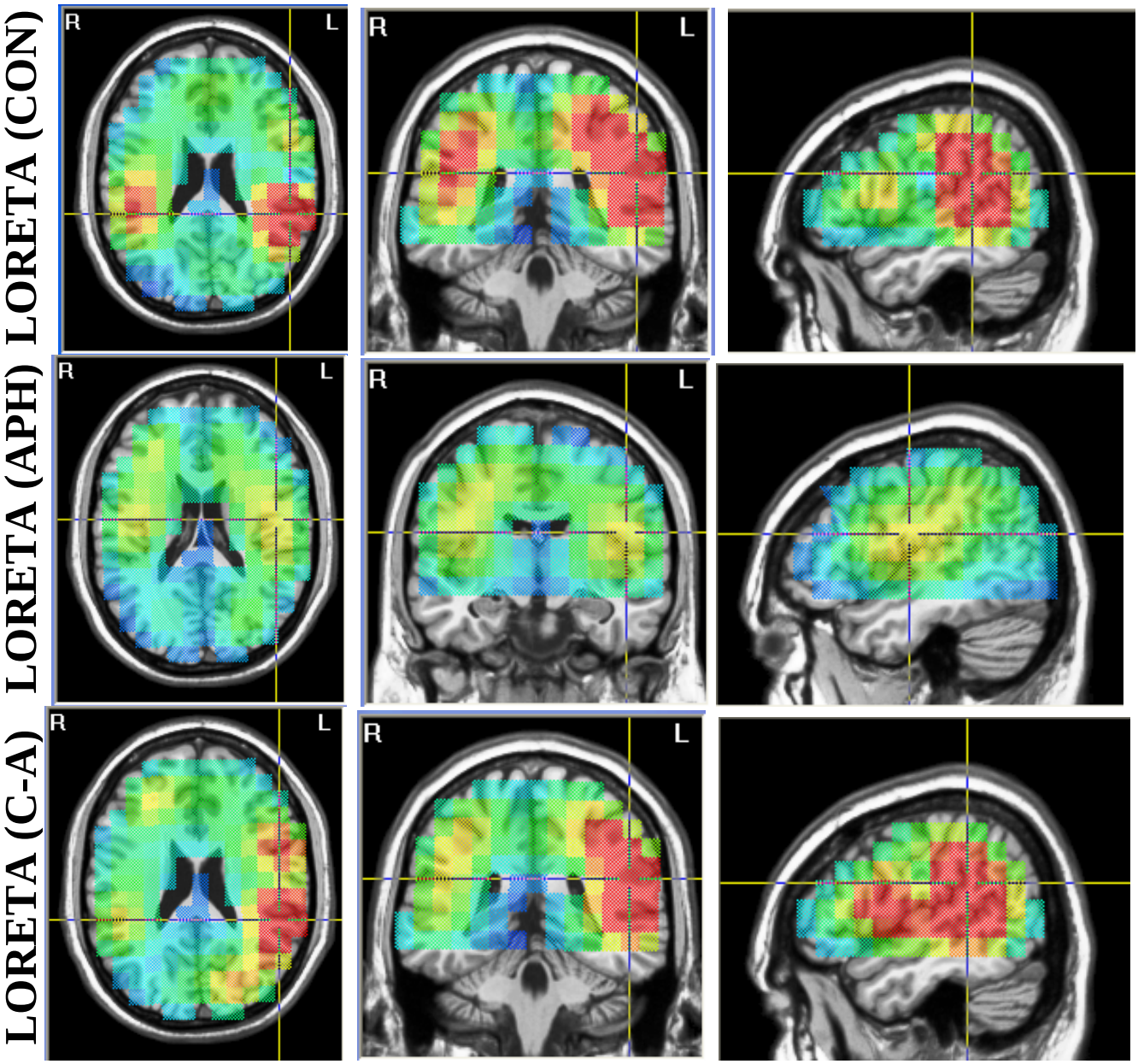

Figure 2. Source model configurations for ERPs to speech-like stimuli in participants with and without aphasia. Each panel displays the source model in Figure 1 with the magnitude of current flow at dipoles throughout the volume color coded (larger to smaller = red-to-yellow-to-green-to-blue). Magnitude estimates were obtained by applying Low Resolution Tomography (LORETA) plus the source and head models in Figure 1 to the group-average ERPs from control participants (top row), group-average ERPs from aphasic participants (middle row), and the difference between the two averages (bottom row). Axial, coronal, and sagital views are shown in different columns and superimposed on the standard MRI (Colin27) on which the models are based. (Note radiological display, i.e. reversed left and right sides.) See text for further details.

Future Developments

At this point, the reader may be left with a number of questions. How do obtained source configurations depend on the specific method, models, and parameters? How can their statistical reliability be appraised? How can lesions be incorporated into a source or head model? We hope to address these and other questions in future versions of this "evolving" review. But, for now, the present version will end with some initial results concerning the third question. The final figure displays an attempt to combine one patient's lesion with a source model. The boundaries of this lesion were drawn by a neurologist on each slice of the standard normalized MRI employed here (Colin27). The combined slices define a volume, which was subtracted from a source model based solely on the gray matter in Colin27 (thus more realistic than that in Figs. 1 and 2). As can be seen, the patient's lesion was in left frontal regions, anterior to classic areas of language comprehension. The resulting source model (and a similarly "lesioned" head model) can be used for more realistic ERP source localization in this particular patient. Since lesions differ between patients, this level of realism will require unique models for each. This raises yet another question: how to combine results across individuals. But such is science.

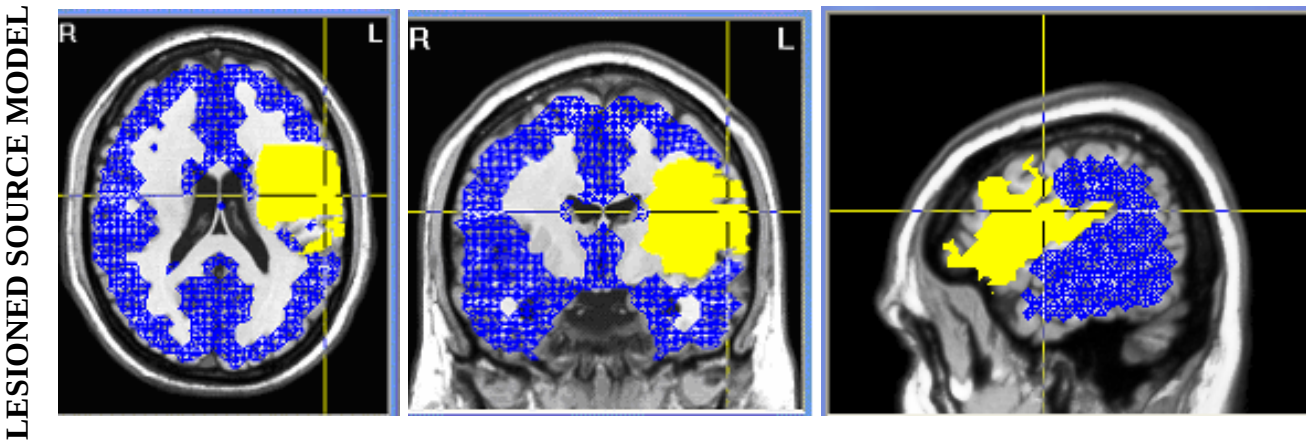

Figure 3. Lesioned source model for an individual with aphasia. The model is shown in blue, which designates a volume throughout which dipoles are distributed and that corresponds to the gray matter in a standard MRI (Colin27) not within the lesion. The lesion is shown in yellow and was manually translated from the individual's MRI to Colin27 by a neurologist. The three panels each show a different view (axial, coronal, and sagital) of the model and lesion superimposed on Colin27. (Note radiological display, i.e. reversed left and right sides.) See text for further details.

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