Functional imaging with low resolution brain electromagnetic tomography (LORETA): a review

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Abstract

This paper reviews several recent publications that have successfully used the functional brain imaging method known as LORETA. Emphasis is placed on the electrophysiological and neuroanatomical basis of the method, on the localization properties of the method, and on the validation of the method in real experimental human data. Papers that criticize LORETA are briefly discussed. LORETA publications in the 1994-1997 period based localization inference on images of raw electric neuronal activity. In 1998 a series of papers appeared that based localization inference on the statistical parametric mapping methodology applied to high time resolution LORETA images. Starting in 1999, quantitative neuroanatomy was added to the methodology, based on the digitized Talairach atlas provided by the Brain Imaging Centre, Montreal Neurological Institute. The combination of these methodological developments has placed LORETA at a level that compares favorably to the more classical functional imaging methods, such as PET and fMRI.

Introduction

Currently, the most often used methods for functional imaging of the human brain are positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) (Toga and Mazziotta 1996). These tomographies provide three-dimensional (3D) images comprising information on metabolism. Although the spatial resolution of these images is indeed excellent, the temporal resolution is not high enough to keep up with the speed at which neuronal processes occur. For instance, in a fundamental study by Logothetis et al. (2001), it was shown that the time course of the fMRI haemodynamic response was roughly a low pass filtered (i.e., low time resolution) version of the electric neuronal activity.

More recently, a growing number of studies have been published that make use of functional imaging methods based on the electroencephalogram (EEG) and the magnetoencephalogram (MEG). For a recent extensive review of electromagnetic imaging methods, see Baillet et al. (2001).

It may seem paradoxical that although the human EEG was first reported in 1929 (Berger), the recently developed PET and fMRI methods have preceded the use of electromagnetic tomographies. This is due to a fundamental limitation of extracranial EEG/MEG measurements: they do not contain sufficient information on the three-dimensional (3D) distribution of electric neuronal activity. Over 140 years ago, Helmholtz (1853) reported the general non-uniqueness of the solution to this type of electromagnetic inverse problem. It implies that EEG/MEG measurements (even with an infinite number of sensors) can be explained by many ***different*** distributions of generators. Naturally, one may ask: which solution corresponds to reality? The answer, in general, is that it cannot be determined.

The curse of non-uniqueness (Pascual-Marqui and Biscay-Lirio 1993) may therefore seem to render hopeless the task of developing an electromagnetic tomography. Fortunately, this is not the case. The EEG and the MEG are not due to capricious distributions of electric neuronal generators. Rather, they obey certain electrophysiological and neuroanatomical constraints, that when plugged into the laws of electrodynamics, offer at least an approximate solution to the inverse problem.

It is now widely accepted that extracranial measurements of EEG and MEG are generated by cortical pyramidal neurons undergoing post-synaptic potentials (PSPs). These neurons are oriented perpendicular to the cortical surface. The magnitude of experimentally recorded extracranial signals, at any given time instant, is due to the spatial summation of the impressed current density induced by highly synchronized PSPs occurring in large clusters of neurons. According to calculations reviewed by Hämäläinen et al. (1993), a typical cluster size must cover at least 40 to 200 mm^2 of cortical surface.

All these facts are reviewed in general in (Martin 1991, Dale et al. 2000, Baillet et al. 2001). In addition, independent experimental evidence demonstrating high synchronization of neighboring neurons can be found in (Llinas 1988, Haalman and Vaadia 1997, Sukov and Barth, 1998).

LORETA: neuroanatomy and electrophysiology

Low resolution brain electromagnetic tomography (LORETA) (Pascual-Marqui et al. 1994, Pascual-Marqui 1999) is a functional imaging method based on the electrophysiological and neuroanatomical constraints previously described. For instance, the cortex can be modeled as a collection of volume elements (voxels) in the digitized Talairach atlas provided by the Brain Imaging Center, Montreal Neurological Institute. In this case, the LORETA inverse solution (which is consistent with the EEG/MEG measurements) corresponds to the 3D distribution of electric neuronal activity that has maximum similarity (i.e., maximum synchronization), in terms of orientation and strength, between neighboring neuronal populations (represented by adjacent voxels). In another example, the cortical surface can be modeled as a collection of surface elements with known orientation. LORETA can accommodate this neuroanatomical constraint, and find the inverse solution that maximizes only the synchronization of strength between neighboring neuronal populations.

LORETA: localization error

The consistency of LORETA with physiology is not the only reason for favoring it above so many other published inverse solutions. The most important criterion for choosing a neuroimaging method is that it must be capable of correct localization, since this is the purpose of functional mapping. For instance, consider a method that views the planet earth from afar, and then produces a map that localizes Gaudi's "La Sagrada Familia" in Cuba. Such a method is worthless, as compared to a method that is capable of localizing it to within 100 Km of its actual position.

In a previous review paper that compared all published linear, distributed inverse solutions (Pascual-Marqui 1999), it was shown that only LORETA was capable of correct localization (to within 1 voxel resolution in the average), whereas all other methods were especially incapable of localizing deep sources. Independent validation of the localization properties of LORETA has been replicated by Yao and He (2001) and by Phillips et al. (2002a, 2002b).

LORETA: experimental validation

An additional essential criterion for choosing an inverse solution is its validation with experimental data under conditions where the sources are known *a priori*. For instance, inverse methods can be tested with event related potentials (ERPs) obtained under visual or auditory stimulation.

The empirical validity of LORETA has been established under diverse physiological conditions. Lavric et al. (2001a, 2001b) describe LORETA activation of language areas in an ERP study comparing cognitive mechanisms of regular and irregular past-tense production. Waberski et al. (2001) find LORETA activation of the auditory cortex in a mismatch-negativity (MMN) experiment. In a P300 experiment comparing normal subjects with schizophrenic patients, Winterer et al. (2001) found P300 LORETA activation in most of the areas reported by independent studies that used intracortical recordings. In a visual ERP study under hemifield stimulation,

Steger et al. (2001) found LORETA activation transfer from contra- (P1a) to ipsilateral (P1b) visual cortices.

Other ERP-type studies providing validation for LORETA, and that also report new findings in cognitive processing, are:

1. Using visual stimulation and finding activation of visual cortices: Khateb et al. (2000, 2001), Hirota et al. (2001), Van Leeuwen et al. (1998), Strik et al. (1998), Pegna et al. (1997).
2. Using auditory stimulation and finding activation of auditory cortices: Mulert et al. (2001), Anderer et al. (1998a, 1998b).
3. Using motor and visuo-motor tasks and finding activation of visual and motor cortices: Thut et al. (2000, 1999).
4. Using visual stimulation with faces and finding activation of face processing cortices: Pizzagalli et al. (2000).

LORETA has also been validated in the analysis of epilepsy-related data:

1. Worrell et al. (2000) localized epileptic foci in patients with MRI lesions.
2. Seeck et al. (1998) found the generators of epileptogenic discharges confirmed by fMRI and subdural recordings.
3. Lantz et al. (1997) found activation of interictal epileptiform activity confirmed with intracranial recordings.

LORETA can also be used to find the generators of EEG frequency components. A detailed description of the methods used in this approach can be found in (Frei et al. 2001, Gomez and Thatcher 2001, Pascual-Marqui et al. 1999). Several studies that provide validation for EEG-based LORETA analysis are the following:

1. In agreement with independent PET studies that implicated the rostral anterior cingulate in depression, Pizzagalli et al. (2001) found that the theta frequency band generator in the same region is a predictor for treatment response in depression.
2. Anderer et al. (2000) found that buspirone-induced activation of EEG generators is in agreement with the localization reported in independent PET studies.
3. Dierks et al. (2000) found correlation between the localization of LORETA EEG generators and PET images in Alzheimer's disease.

Other studies that use LORETA and report new findings are:

1. Frei et al. (2001) and Gamma et al. (2000): drug (MDMA) effect study on EEG generators.
2. Connemann et al. (2001): case study of alpha-delta sleep generators in different sleep stages.
3. Jausovec and Jausovec (2001): P300 generators related to IQ.
4. Isotani et al. (2001): EEG generators of hypnotically induced anxiety and relaxation.
5. Prabhu et al. (2001): P300 generators in female alcoholics.
6. Koles et al. (2001): EEG generators during verbal and spatial cognitive tasks.
7. Kounios et al. (2001): evidence demonstrating different neural substrates for the encoding of fusion and juxtaposition concept associations.
8. Anderer et al. 2001: evidence for two distinct sleep spindle generators, one in prefrontal cortex (Brodmann areas 9 and 10) oscillating with a frequency below 13 Hz, and the other in precuneus (Brodmann area 7) oscillating with a frequency above 13 Hz.

9. Pascual-Marqui et al. (1999): comparison of EEG generators of schizophrenic patients with normal subjects.
10. Wang et al. (1999): generators involved in selective attention based on forms defined by motion.
11. Brandeis et al. (1998): evidence showing that "stop" failures in children with attention deficits occur during posterior activation, which may be related to the orienting of attention, preceding and partly determining inhibitory control problems in ADD.
12. Anderer et al. (1998c): drug effect study on P300 generators in age-associated memory impairment.

In some applications, when the actual generator is known to be very well approximated by an active point (i.e., the single dipole), LORETA images might be too blurred, and dipole fitting methods or non-linear tomographies would certainly be preferred (Leder et al. 2001, Fuchs et al. 1999).

LORETA: some criticisms to the method

Other studies have criticized LORETA:

1. In the opinion of Menendez and Andino (2000), the localization property of LORETA, shared by no other linear, distributed inverse solution, is of no value in source localization. In addition, these authors show that for some test sources, LORETA has a localization error of two or three voxels, a fact that was already reported, and not omitted, in (Pascual-Marqui 1995, 1999).
2. In the opinion of Kincses et al. (1999), the electrophysiological and neuroanatomical constraints used by LORETA are arbitrary, and have no physiological meaning.
3. In a simulation experiment that makes use of a capricious source distribution, Michel et al. (1999) apply LORETA with the purpose of demonstrating that it cannot localize correctly.
4. Based on a theoretical lemma, De Peralta-Menendez and Gonzalez-Andino (1998) state that LORETA is incapable of localizing sources on the boundary of the solution space. However, Pascual-Marqui (1999) demonstrated the falsehood of the statement, and demonstrated that those authors had been systematically criticizing LORETA based on an incorrectly programmed algorithm of their own making.

LORETA: more recent papers

Very recently, a number of LORETA publications have appeared that further make use of the method, and in many instances, provide validation:

1. Lehmann et al. (2001) study the LORETA generators of EEG gamma frequency during meditation.
2. Thayer et al. (2001) used LORETA to study the mechanisms of mental rotation of human hands.
3. Berg et al. (2001) use LORETA in a Go/NoGo task to compare patients with writer's cramp and control subjects.
4. Bokura et al. (2001) use LORETA in a Go/NoGo task.

5. Carretié et al. (2001) use ERP LORETA to study emotion and attention interaction.
6. Szelenberger and Niemcewicz (2001) study event-related LORETA in primary insomnia.
7. Schairer et al. (2001) study LORETA images of mismatch negativity.
8. Saletu et al. (2002) study drug effects on EEG and auditory ERPs generators.
9. Pizzagalli et al (2002) compare EEG based generator distributions of control and depressed subjects.
10. Khateb et al. (2002) use ERP LORETA to study the dynamics of brain activation during explicit word and image recognition tasks.
11. Hamm et al (2002) use ERP LORETA to compare the N300 and N400 generators related to picture stimuli in congruent and incongruent contexts.
12. Mulert et al. (2002) correlate LORETA activity with loudness of auditory stimuli for the N1/P2 component, and are able to predict treatment response in major depression.
13. Coatanhay et al. (2002) study EEG frequency domain generators during sleep.
14. Brandeis et al. (2002) study the P3b generators in hyperkinetic children.
15. Vitacco et al. (2002) perform a direct comparison of LORETA and fMRI during a language processing task. Horwitz and Poeppel (2002) write a very encouraging editorial comment on this work.
16. Park et al. (2002) validate LORETA with high density EEG, using single-subject-MRIs, and applying the techniques of statistical parametric mapping.
17. Fallgatter et al. (2002), using LORETA, confirm the implication of the anterior cingulate in conflict monitoring and allocation of attention.
18. Pizzagalli et al. (2002), using LORETA found that in the fusiform gyri, at around 160 ms post-stimulus, liked faces elicited stronger activation than disliked and neutral faces and checkerboard-reversal stimuli.
19. Gallinat et al (2002) found with LORETA frontal and temporal dysfunction of auditory stimulus processing in schizophrenia.
20. Anderer et al. (2002) study the LORETA localization of P300 generators in normal aging and age-associated memory impairment. They obtain with LORETA all P300 generators reported by independent depth electrode studies, except for hippocampal generators which are excluded from the LORETA solution space.

And what about the future?

A new imaging method: s*LORETA* (standardized low resolution brain electromagnetic tomography)

In an accompanying paper in this issue (Pascual-Marqui, 2002), the new imaging method *s*LORETA is fully described. *s*LORETA yields images of standardized current density with zero localization error. The accuracy of these results cannot be improved upon. No other instantaneous, distributed, discrete, imaging method for EEG/MEG has been published (to the best of the authors' knowledge) that achieved perfect localization. All other previously published methods at best produced systematic non-zero localization errors. Experimental validation for *s*LORETA was

demonstrated with visual ERPs to stimulation with pictures of human faces (Pascual-Marqui et al. 2002).

In the very near future, we expect to release a free software package implementing this new method.

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