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Editorial

'The stone of madness' and the search for the cortical sources of brain diseases with non-invasive EEG techniques

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See Article, pages 1963–1973

1. Introduction

In the masterpiece 'The extraction of the stone of madness' due to the famous Dutch painter Hieronymous Bosch (1450–1516) (see Fig. 1), a foolish man turns to a charlatan surgeon for his own release from illness. This theme is inspired by folk satire and by the hostility against the physicians' guild at that time. In fact, in that age head surgery for the extraction of 'stones' from the brain in psychiatric disorders was relatively widespread. Five hundred years later, the invasive approach to the knowledge of brain diseases has providentially changed thanks to modern brain imaging techniques, such as—for instance—the computerized tomographic scan (CT), the electroencephalography (EEG), the magnetoencephalography (MEG) or the functional magnetic resonance imaging (fMRI). Only the last 3 techniques supply fruitful information on the brain function and can be integrated with CT or MRI methods able to offer a detailed topography of brain structures.

In the following paragraphs, we will briefly recall some technical advances of these last 10 years in the improvement of our capability to extract 'information' about the brain activity in a non-invasive way. Then, we will comment on the article by Zhang et al. (2003) where a cortical imaging technique is used to estimate potential distributions over a simple model of dura mater in 5 epileptic pediatric patients before surgery.

2. The problems of conventional EEG recordings

Among the different non-invasive different brain imaging techniques, EEG and MEG alone directly reflect neuronal firing and exhibit a remarkable temporal resolution (in milliseconds) despite a poor spatial resolution (in the order of few square centimeters). This lack of spatial resolution occurs essentially in the case of EEG because of the spread of brain signals due to the low conductivity of the skull and the rather low signal-to-noise ratio of the data (Nunez, 1995). These potentials originate mainly in the radially oriented cortical pyramidal neurons. The potential distribution arising from these sources is quite wide over the scalp surface because of the different conductivities of cerebrospinal fluid, meninges, skull and scalp. Furthermore, the distortion of the scalp potential distribution is increased by the ear and eyeholes, which represent shunt paths for intra-cranial currents (Nunez, 1981, 1995). As a result, the distribution of the scalp potential shows a low spatial resolution not allowing a reliable localization of the cortical generators of the event-related potentials. Moreover, the variations of electrical reference may enhance or attenuate the spatial components of the potential distribution over the scalp acting as a spatial filter of the cortical generators (Nunez, 1981). For these reasons, the addition of more electrodes is not sufficient per se to improve the spatial information content of an EEG record significantly (Nunez, 1995).

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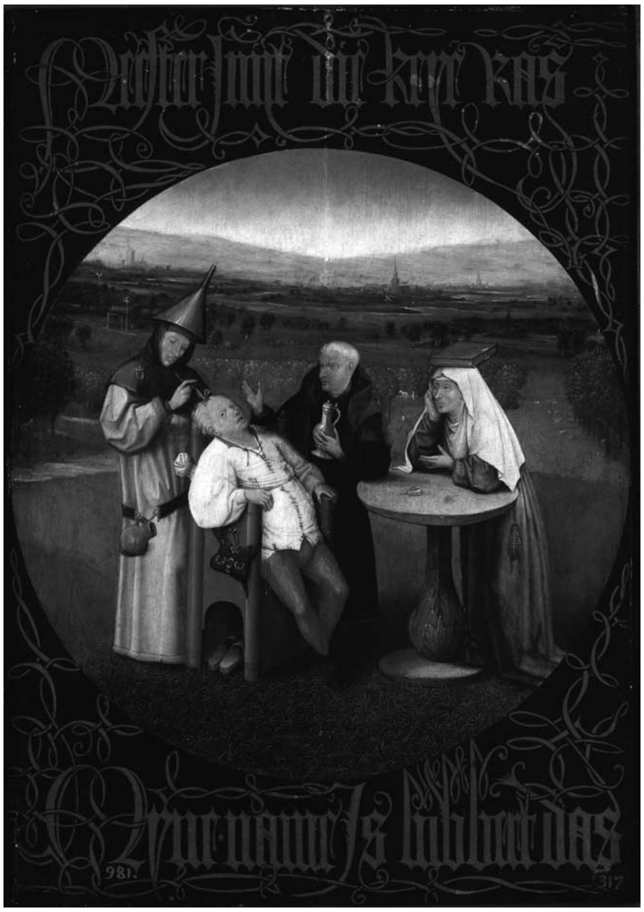

Fig. 1. This figure shows the canvas entitled 'The stone of madness' by the famous Dutch painter Jeroen Van Aken, better known as Hieronymus Bosch (1450–1516). With this painting, Bosch intends to attack the practice of folk medicine that often included the removal of 'stones'—supposed to be responsible for different brain diseases—from the brain. Moreover, this work of art bears the inscription "Master, take away the stone, my name is Lubbert Das". It is worth noticing that Lubbert Das was a comical character who originates in the Dutch literature of that time. The stone is represented as a flower (tulip) on the head of the patient near the surgeon's knife, because of the similarity between the words tulip (tulp) and madness in Dutch. Courtesy of the Museum Nacional Del Prado, Madrid (Spain).

3. The high-resolution EEG

High-resolution EEG technologies have been developed to enhance the spatial information content of EEG activity (Gevins et al., 1990; Nunez, 1995). These technologies consist essentially of high spatial sampling (with 64–128 channels) and surface Laplacian (SL) (Nunez et al., 1994) or spatial de-convolution (SD) estimations (Le and Gevins, 1993). The estimation of the SL of the potential needs the modeling of the scalp surface, while the SD estimation is based on the construction of a multi-compartment head volume conductor for simulating cortex, dura mater, skull and scalp surfaces. Most recently, the developed high-resolution EEG enhancement technologies use realistic MRI-constructed subject's head models (Le and Gevins, 1993; Babiloni et al., 1997). SL is computed by a spline Laplacian estimator, and SD by a linear inverse estimation method based on boundary-element (BEM) mathematics. The key-point of high-resolution EEG technologies is the availability of an accurate model of the head as a volume conductor to be used with advanced computational techniques such as SL or SD. However, appropriate techniques have to be used in order to register the electrode positions on the scalp model. Several authors have shown that it is possible to improve the spatial resolution of EEG by using sophisticated computational algorithms and detailed geometrical models of the head as a volume conductor with the help of the MRI data (Babiloni et al., 1996, 2000a, Gevins, 1989; Gevins et al., 1990, 1991, 1994; Nunez, 1995).

4. The search for the cortical sources

However, the ultimate goal of any EEG or MEG recording is to supply useful information about the brain activity of a subject during a particular task. In order to obtain such information we have to start from these EEG or MEG recordings to arrive at an estimate of cortical activity, by using a body of mathematical techniques known as inverse procedures. Examples of these inverse procedures are the dipole localization, the distributed source and the deblurring or cortical imaging techniques (Schneider and Gerin, 1970; Dale and Sereno, 1993; Scherg et al., 1999; Gevins, 1989; Nunez, 1995). Mathematical models for the head as a volume conductor as well as for neural sources are employed by linear and non-linear minimization procedures to localize putative sources of EEG data. Several studies have indicated the adequacy of the equivalent current dipole as a model for cortical sources (Nunez, 1981, 1995), while the importance of realistic geometry head volume conductor models for the localization of cortical activity was stressed recently (Gevins, 1989; Gevins et al., 1991, 1999; Nunez, 1995). The results of previous intra-cranial EEG studies support the idea that high-resolution EEG techniques (including head/source models and proper regularization inverse procedures) might model with an acceptable approximation the strengths and the extension of cortical sources of surface EEG data, at least in certain conditions (Le and Gevins, 1993; Gevins et al., 1994; Babiloni et al., 1996; He et al., 1999).

5. Discrete source localization

Dipole localization techniques provided estimates of the position and of the moment of one or several equivalent current dipoles localized in a head model from the non-invasive EEG and/or MEG recordings. Inferences about the neural sources in the real brain were, then, derived from the position of the localized current dipoles in the head model. Until now, two approaches to the dipole localization have become popular in neuroscience, and both rely on the solution of non-linear minimization algorithms.

The first approach is the so-called 'moving dipole' method (Schneider and Gerin, 1970; Cohen et al., 1990). Dipoles are found at a succession of discrete times, without any a priori assumption about the relation among the localized dipoles at different instants. In general, it is difficult to localize more than two dipoles for each potential/magnetic field recorded, due to the numerical instability of the inverse procedure. However, in spite of this limitation, such a procedure is very popular and allows localizing sources mainly in the primary sensory cortical areas. Generally, the position of the localized dipole obtained with simple spherical models was then integrated into a realistic head model built according to the procedures described above.

The second approach to the dipole localization combines both the spatial and temporal properties of scalp potentials/fields, so as to increase the ratio of available data to degrees of freedom for the minimization procedures. This results in an increase of the number of dipoles that may be reliably localized through EEG and MEG recordings. Different constraints are applied to find the best inverse solutions, such as for example setting the position of the dipoles and estimating the time/series of dipole moments, or determining the orientation of the dipoles and setting their positions. This last approach is called multiple source analysis (MSA; Scherg et al., 1999).

6. Distributed sources estimate

Accurate estimates of the cortical current density could be obtained by using adequately detailed geometrical reconstruction of the main compartments lying between the cortical generator sources and the EEG or MEG sensors. The estimate of the cortical current density from non-invasive EEG and/or MEG data can be obtained by solving a linear problem. In this problem, the cortical sources to be estimated are related to the non-invasive measurements by means of a transfer matrix (lead field matrix) that mimics the effects of the volume conductor (Pascual-Marqui, 1995; Grave de Peralta and Gonzalez-Andino, 1998; Fuchs et al., 1998). In mathematical terms the relationship between the modeled sources $\mathbf{x}$, the lead field matrix $\mathbf{A}$, the EEG/MEG measurements $\mathbf{\Phi}$ and the noise $\mathbf{n}$ can be written as

$$\mathbf{Ax} = \mathbf{\Phi} + \mathbf{n} \tag{1}$$

The estimation of the current density $\mathbf{x}$ is commonly obtained by the solution of the linear inverse problem (LIP) (Grave de Peralta and Gonzalez Andino, 1998; Pascual-Marqui, 1995; Babiloni et al., 2001). The solution is obtained by minimization of the following functional

$$\Psi = \left(\|\mathbf{Ax} - \mathbf{\Phi}\|^2_{\mathbf{M}} + \lambda^2 \|\mathbf{x}\|^2_{\mathbf{N}} \right) \tag{2}$$

where $\mathbf{M}$ is the norm of the data space, $\mathbf{N}$ is the norm of the source space, and λ is a regularization parameter. Essentially, the LIP is based on the minimization of the energy of the error on the sensor data, given by the difference between the real ($\mathbf{\Phi}$) and the modeled measurements, the latter being given through the estimated sources ($\mathbf{x}$) and the lead field matrix ($\mathbf{A}$). A second term involving the energy of the sources $\mathbf{x}$ regularizes the ill-posed problem. The energy of errors on the sensors and the energy of sources are measured in two different metric spaces described by the norms $\mathbf{M}$ and $\mathbf{N}$, respectively. Hence, in each metric space a particular norm may be provided, that could be based on the a priori knowledge about the behavior of the data modeling errors (for the data space) and on the cortical source strengths (for the source space).

The solution of the variational problem depends on both the data and source space metrics. Under the hypothesis of $\mathbf{M}$ and $\mathbf{N}$ positive definite, the solution of Eq. (2) (the cortical current density vector ξ) is given by taking the derivatives of the functional ψ and setting it to zero. After few straightforward computations the cortical strengths ξ are given by:

$$\xi = \mathbf{G\Phi} = \mathbf{N}^{-1}\mathbf{A}'(\mathbf{AN}^{-1}\mathbf{A}' + \lambda\mathbf{M}^{-1})^{-1}\mathbf{\Phi} \tag{3}$$

where $\mathbf{G}$ is called the pseudoinverse matrix, or the inverse operator, that maps the measured data $\mathbf{\Phi}$ onto the source space ξ. Note that the requirements of positive definite matrices for the metric $\mathbf{N}$ and $\mathbf{M}$ allow considering their inverses. The last equation stated that the inverse operator $\mathbf{G}$ depends on the matrices $\mathbf{M}$ and $\mathbf{N}$ describing the norm of the measurements and the source space, respectively. The metric $\mathbf{M}$, characterizing the idea of closeness in the data space, can be particularized by taking into account the sensors noise level by using the Mahalanobis distance (Grave de Peralta and Gonzalez Andino, 1998). Furthermore, the metric $\mathbf{N}$ could include a priori information on the neural sources, so allowing the insertion in LIP of also hemodynamic source constraints from fMRI recordings (Liu et al., 1998; Dale et al., 2000; Babiloni et al., 2000b, in press). However, if any a priori information is available for the solution of the LIP, the matrices $\mathbf{M}$ and $\mathbf{N}$ are set to the identity, and the minimum norm estimation is obtained (Hämäläinen and Ilmoniemi, 1984). In this case the equation for the estimation of cortical current density ξ became

$$\xi = \mathbf{G\Phi} = \mathbf{A}'(\mathbf{AA}' + \lambda I)^{-1}\mathbf{\Phi} \tag{4}$$

7. Cortical imaging

The possibility to model the complex head geometry with the finite element technique allowed Alan Gevins and colleagues to derive a method, they called deblurring, that estimates potential distribution on the dura mater surface by means of non-invasive EEG recordings (Le and Gevins, 1993; Gevins et al., 1999). This method uses non-linear minimization techniques without any explicit model of the neural sources. In fact, just by applying Poisson's equation, Gevins and coworkers—starting from the EEG scalp potential distribution—were able to reconstruct the dura mater potential distribution. This method was also validated by means of subdural recordings, and the deblurred dura mater potential distributions showed a clear improvement with respect to the examination of the raw potential distributions over the scalp. The deblurring method can be viewed as an application of the direct cortical imaging technique, that is a body of methods drawing the dura mater potential distribution from the scalp recorded EEG by using an explicit model of the head as a volume conductor (for a review, see He, 1999). As mentioned before, the particularity of this approach is that no explicit model for the cortical source is necessary (Le and Gevins, 1993; Edlinger et al., 1998; He et al., 1999). Another approach allowing the estimation of the dura mater potential from scalp EEG recordings is the indirect cortical imaging technique. Such technique allows obtaining the dura mater potential distribution through an explicit model for the neural sources. In this approach, a layer of current dipoles simulates the cortical surface and the retrieved dipole strengths are then used to generate potential distributions over a surface of the head model simulating the dura mater (Sidman et al., 1992). It has been proven that even the use of a homogeneous spherical volume conductor for the head and a realistic cortical surface for the dipole layer provided more focused and detailed information than the raw scalp potentials (Srebro et al., 1993; Srebro and Oguz, 1997). However, it must be noted that the conductivity ratio between skull and scalp is far from 1 as assumed for homogeneous models in such papers. The value adopted in these last 30 years by all the researchers in this field for such ratio is 1:80 (Rush and Driscoll, 1968), or even 1:15 as stated more recently (Oostendorp et al., 2000). According to these observations, several researchers (He et al., 1996, 1999; Babiloni et al., 1997; Zhang et al., 2003) developed cortical imaging techniques that took into account the inhomogeneity of the head as a volume conductor by using realistic head models and boundary element mathematics. By regularization, dura mater potentials obtained both from simulation and real EEG recordings presented improved spatial characteristics with respect to the use of raw scalp potentials.

8. An application of the cortical imaging technique

In a paper published by Zhang et al. (2003), an application of the cortical imaging technique to the localization of pathological brain tissue in epilepsy is presented. Zhang et al. (2003) report that the areas of negativity estimated over the dura mater of the reconstructed spherical head model were consistent with the areas of surgical resections in analyzed patients. Hence, it was suggested that this methodology might become a useful alternative to the invasive pre-surgical EEG recordings for the mapping of cortical regions displaying epileptiform activity. The results presented by Zhang et al. (2003) are interesting because of the relatively simple models they used. In fact, the methodology employed involves the estimation of the cortical potential by means of a 3-shell spherical head model, although the results were presented by projection on a realistic head model.

The question at the base of the paper is whether relatively low-demanding computational techniques (i.e. cortical imaging with 24 electrodes and spherical head models) allow reconstructing accurately the dura mater potential by non-invasive EEG recordings. It is worth noting that 24 electrodes and the use of spherical head models represent a technical setting available in almost all the clinical environments. In fact, even if the availability of the MRIs of the patient is now larger than in the past, the complicated technical requirements needed for building up realistic head and cortical models still limit the use of the advanced EEG methods in standard clinical settings.

The work by Zhang and coworkers stated that the reconstruction of dura mater potential distributions made through the described simple computational setup was consistent with the evidences obtained during the successive brain surgery. The long-term goal of this type of study is to remove the need for invasive EEG recordings before surgery in epileptic patients, in order to reduce the degree of complexity and discomfort for the patient subjected to this clinical treatment. In fact, pre-surgical EEG recordings require a period of time long enough (hours, days) to fully describe the behavior of the candidate source(s) responsible for interictal and ictal brain spike discharges. Another interesting aspect of the cortical imaging technique is its supplying the same information (i.e. potential distributions over the dura mater reconstruction) as that of the more invasive subdural EEG recordings. Hence, physicians do not need to change the EEG interpretation patterns they usually applied in the standard reviewing of the subdural EEG recordings.

Naturally, as it provides just images of the potential distributions over the chosen dura mater model, the cortical imaging technique does not supply any information about the depth of the possible neural sources. It may be argued that the state of the art dipole localization techniques using a high number of electrodes and realistic head and cortical models could be used (Silva et al., 1999; Ebersole, 1999; Fuchs et al., 1998), in order to achieve an accurate localization of the epileptic foci. However, dipole localization techniques need the a priori assessment of the number of 'active' brain regions and this could be difficult task in pediatric patients, since the epileptic foci are often found in different parts of neocortex. From this point of view, the use of distributed source models could avoid such a need. In this context, a recent work published in this journal suggested the spatial sampling necessary for a good localization of epileptic foci with distributed source models (Lantz et al., 2003). According to such paper, EEG recordings performed with 64 or even more electrodes are necessary to provide nearly error-free localizations of epileptic sources. Consequently, also distributed source models can be important for an accurate and non-invasive imaging of epileptic foci by using EEG measures.

Despite the success gained by Zhang et al. (2003) in their application of the cortical imaging technique to the epilepsy data, the problem of a wider validation of this type of cortical imaging procedure in the clinical practice is still to be tackled. However, as a starting point, some encouraging figure of merits about the capability of cortical imaging to render the real dura mater potential distribution accurately can be inferred from the available literature. In fact, simulation studies are available to assess the performance of the indirect and direct cortical imaging techniques with realistic head models (Babiloni et al., 1997; He et al., 1999). These simulation studies indicated a good estimation of the dura mater potential distributions for a variety of signal-to-noise ratios and a number of electrodes. Furthermore, other evidences can be obtained from studies estimating the source current density by means of the minimum norm employing spherical and realistic head models (Pascual-Marqui, 1995; Babiloni et al., 2000a, 2001; Lantz, 2003). In fact, when the distributed source current density was estimated with accuracy, the dura mater potential distributions also can be computed reliably just by solving the associate direct problem. In all these studies, the accuracy of the estimation of the cortical current density was remarkable, even when a relative low number of electrodes was adopted.

Another important step towards a clinical use of simple but accurate head models for the localization of brain sources from non-invasive EEG recordings is the use of the so-called ‘standardized’ head models. These models are not directly linked to the actual MRIs of the patient, but rather they are obtained by the average of MRIs from hundreds of normal subjects recorded at the Montreal Neurological Institute (MNI), and freely downloadable from the MNI web site (http://www.mni.mcgill.ca). From the averaged MRIs, accurate ‘standard’ head and cortical models can be derived that can be used in conjunction with the methods sketched above for the localization of cortical sources even in absence of the patient’s MRI. In this case the proper alignment of the employed electrodes with the standardized head surface is crucial. Validation and use of such ‘standardized’ head models has been recently reported in literature (Rossi et al., 2001; Babiloni et al., 2002; Fuchs et al., 2002) and the results seem to be very promising.

In conclusion, it seems that the computational techniques at our disposal allow an accurate estimation of the cortical current density and the associated dura mater potential distributions by means of non-invasive EEG recordings even by using simple spherical or standardized head models. It is out of doubt that—in the near future—the EEG techniques we sketched in this work will be able to make the search for the ‘stone of madness’ less invasive than ever.

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