EEG source localization of the epileptogenic focus in patients with refractory temporal lobe epilepsy, dipole modelling revisited

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Abstract

EEG source localization of epileptic brain activity is of diagnostic importance in the presurgical evaluation in patients with refractory epilepsy. Localization of the epileptogenic foci by visual inspection of the scalp EEG only is a qualitative and subjective procedure and may be difficult. Techniques such as dipole modelling allow to analyse the characteristics of the generators of the electric activity inside the brain in a quantitative and objective way.

Interictal and ictal dipole modelling reveal different types of spike voltage fields and dipole sources. The published literature shows conflicting evidence in different study populations in terms of results and reliability of localization.

The reliability of dipole models has been questioned, especially in case of deep mesial temporal lobe sources. In order to validate dipole modelling, comparisons between dipole localizations and intracerebral fields, recorded with depth-electrodes, were made. When interpreting results of dipole modelling, the intrinsic limitations of this technique should be taken into account.

Key words : Epilepsy ; electroencephalography (EEG) ; source localization ; dipole modelling ; presurgical evaluation ; epilepsy surgery.

Introduction

The main goal of the presurgical evaluation of patients with medically refractory epilepsy is to determine the location of the epileptogenic zone, defined as the volume of tissue necessary for seizure generation and that has to be resected to stop the seizures. As there are no *direct* measures for determining the extent of the epileptogenic zone, different techniques such as EEG are used to determine the ictal onset zone which is defined as the area from which the earliest EEG changes can be recorded at the time of clinical seizure onset. In temporal lobe epilepsy, it is important to make a differentiation between seizures with an onset in the mesial temporal lobe and seizures originating from the temporal neocortex. Despite the dramatic progress recently made in structural and functional neuroimaging, intracranial EEG recordings remain the gold standard for localizing the ictal onset zone. Since this procedure is invasive and entails several risks for morbidity, the choice for new non-invasive techniques, such as dipole modelling and voltage topography, is relevant.

Source localization consists of analysing interictal spikes and ictal discharges by calculating both forward and inverse problems using different brain compartment models and complicated mathematical algorithms that ultimately produces a voltage field and a dipole source. On the basis of the configuration of this dipole source and the shape of the corresponding voltage field, estimations can be made concerning the localization of the dipole source. In that way irritative and epileptogenic zones can be localized with sublobar accuracy.

The purpose of this paper is to critically review the results of relevant EEG source localization studies in patients with refractory temporal lobe epilepsy published in the past decade, and to assess the reliability and the limitations of this technique.

Dipole modelling

Results of interictal dipole modelling

Table 1 reviews the different types of dipoles described by several authors. Calculated dipoles can be classified either by dipole *orientation* or by dipole *location*.

Dipole orientation

With regard to interictal dipole orientation, a type 1 dipole (tangential dipole) and a type 2 dipole (radial dipole) have been described. They reflect a mesial temporal and a lateral temporal neocortical seizure onset respectively (Baumgartner *et al.*, 1995 ; Boon *et al.*, 1995, 1997, 1999 ; Ebersole, 1994, 2000 ; Mine *et al.*, 2005). Moreover, a third type of cortical source, the anterior temporal tip cortex, that is contributing to temporal spike fields, has been identified by dipole modelling (Ebersole, 2000). A type 1 dipole pattern may evolve into a

Table 1

Survey of different types of diples/voltage fields in relation to area of seizure onset

Author	Dipole type	Area or lesion from which seizures originate	Voltage field
Interictal dipole modelling			
Baumgartner *et al.*, 1995	Mesial temporal source	Mesiobasal temporal region	Well circumscribed negativity recorded at the ipsilateral sphenoidal electrode and a widespread positivity over the vertex
	Lateral temporal source	Lateral temporal neocortex	Negativity recorded at the ipsilateral neocortical temporal electrodes and a positivity at the contralateral side of the head
Boon *et al.*, 1995, 1999	Type 1 dipole : Oblique or tangential dipole, with an elevation of more than 15 degrees relative to the axial plane Type 2 dipole : Radial dipole, with an elevation less than 15 degrees relative to the axial plane	Structural lesions in the medial temporal lobe or lateral temporal structural abnormalities, associated with medial temporal lobe lesions	Ipsilateral, well delineated, negative voltage field, occupying less than 50% of the scalp with a contralateral positive voltage field that extends well beyond the midline
		Extratemporal lesions Neocorticale temporale lesion	Less well delineated negativity with a smoother gradient towards a less pronounced positivity
Ebersole, 1994, 1997, 2000	Type 1 spike dipole : Tangential and vertical orientation	Mesial temporal lobe	Infero-lateral negative field, with a maximum often recorded from supplementary subtemporal electrodes Positive maximum at electrodes around the vertex
	Type 2 spike dipole : Radial (horizontal) orientation	Lateral temporal cortex	More lateral negative field Positive maximum on the opposite side of the head
	Prominent horizontal tangential source component	Temporal pole	Inferior frontotemporal negative field maximum and a contralateral posterior positive field maximum
Herrendorf *et al.*, 2000	Radial dipole	Mesiotemporal lobe	
Lantz *et al.*, 1996	Oblique posterior dipole 1 Oblique posterior dipole 2 Straight lateral dipole Oblique anterior dipole	Medial subtemporal lobe Lateral subtemporal lobe Anterior lateral temporal lobe Posterior lateral temporal lobe	
Mine *et al.*, 2005	Vertical dipole	Medial temporal lobe	Steeper well-delineated negative voltage field over the infero-lateral temporal scalp less than half of the head and a positive voltage field over the contralateral parasagittal area that extends beyond the midline
	Horizontal dipole	Lateral temporal lobe	Broad frontotemporal negative field corresponding to a less delineated temporal negative field with a smoother gradient toward the less positive field
Ictal dipole modelling			
Assaf and Ebersole, 1997	Mesiobasal temporal source Lateral temporal source Anterior temporal source Single oblique dipole	Hippocampus Temporal neocortex Entorhinal cortex Entorhinal or lateral temporal neocortex	
Boon *et al.*,1995, 1997	Combined ictal dipole, consisting of a radial and tangential component, in perfect agreement with their interictal findings	Medial temporal lobe lesions and combined medial and lateral temporal lobe lesions	
	Type 2 dipole	Extratemporal en neocortical lesions	

type 2 pattern and vice versa (Ebersole, 2000). However, dipoles of different types were not detected in a single patient in large series of refractory patients (Boon *et al.*, 1996). It is difficult to assess whether the hippocampus or the basal neocortex is responsible for spikes recorded by sphenoidal electrodes or whether a third region such as the entorhinal cortex is involved (Baumgartner *et al.*, 1995).

Lantz *et al.* showed that spikes recorded in the subtemporal regions have an oblique posterior orientation, which agrees with the results of Ebersole, who showed that the oblique dipole is divided into two components, one radial and one tangential, referring to the lateral temporal structures and the mesial temporal areas respectively. The association of the finding of oblique dipoles to mesial temporal EEG activation was clearly demonstrated, and no arguments in favour of lateral temporal EEG activation were found (Lantz *et al.*, 1996).

In contrast to the results of other studies, one group found a radial orientation of the dipole source in patients with temporomesial epilepsy. This could be explained by the fact that the appearance of spikes in the surface EEG probably requires additional involvement of neocortical tissue (Herrendorf *et al.*, 2000), suggesting that these authors have studied propagation, rather than early seizure generation.

Moreover, some authors have observed that spikes originating from deep mesial structures, such as the hippocampus, remain undetectable on the scalp EEG (Alarcon et al, 1994 ; Merlet & Gotman, 1999). In recent literature, there seems to be consensus about the fact that hippocampal sources cannot be *directly* measured from scalp EEG recordings.

Dipole location

While in general calculated dipole locations correspond more or less with the intracranially recorded spike locations, dipoles tend to be situated deeper in the temporal lobe (Lantz *et al.*, 1996).

RESULTS OF ICTAL DIPOLE MODELLING

Dipole orientation & location

According to a direct comparative study, the orientation and location of ictal dipoles showed a striking correspondence with the orientation and location of interictal dipoles in individual patients (Boon *et al.*, 1995, 1997).

SPIKE VOLTAGE TOPOGRAPHY

Table 1 also shows the results of the spike voltage topography.

The calculated spike voltage fields depend on several properties of the electrical source.

The location, the area and the orientation of the source determine the resultant voltage field (Ebersole, 1997). If the amount of synchronously activated cortex is not large enough, no field will be recorded at the scalp. An area of 6 cm^2 of synchronously activated cortex is necessary to produce a detectable scalp EEG signal (Cooper *et al.*, 1965). Also orientation of the source is important. An electrode directly above a generator does not always record a voltage maximum. This occurs only when the net orientation of the active area is parallel to the skull, because in that case an orthogonal field is produced. As the orientation of a source becomes more tangential, the field maximum is displaced further away (Ebersole, 1997, 2000).

Other factors that influence the voltage field topography are the amplitude, the frequency and the synchrony of the epileptiform discharge. Comparing the negative versus the positive field can reveal information about the location of the source, meaning that the source is closer to the negative maximum, when it is of greater amplitude than the positive maximum. It is also known that superficial sources produce smaller fields with higher voltages, whereas deeper situated sources generate larger fields with lower voltages (Ebersole, 1997).

PROPAGATION OF ELECTRICAL ACTIVITY

Several studies described the propagation of electrical activity from the area of primary activation to other brain regions. The results of these studies are summarized in Table 2.

The presence and direction of electrical propagation can be estimated by analyzing the temporal course of voltage fields. When voltage fields change in terms of amplitude but not in shape or location, this suggests a discrete source with no or limited propagation. On the other hand, changes in shape or amplitude reflect electrical propagation (Ebersole, 1997).

Many authors found evidence for electrical propagation from mesiobasal to lateral temporal areas (Assaf & Ebersole, 1997 ; Boon & D'Havé, 1995 ; Baumgartner *et al.*, 1995 ; Ebersole, 2000 ; Merlet & Gotman, 1999 ; Merlet *et al.*, 1998). When the medial source leads the lateral source, propagation from the mesiobasal to the lateral temporal lobe is likely (Baumgartner *et al.*, 1995). Other authors emphasize the importance of the voltage field topography at the moment of the initial deflection of the spike, because they presume this to be most related to the onset of the spike. Later voltage fields, including the spike peak, may reflect mainly propagated activity (Ebersole, 2000).

A second model of source dynamics describes a sequence of dipole activation from neocortical to mesial. Although the intrinsic excitability of

Table 2

Pathways of propagation

Author	Pathway of propagation	
Assaf and Ebersole, 1997	Hippocampus → basal temporal cortex	mesiobasal ↓ lateral
	Entorhinal cortex → anterior temporal neocortex → temporal tip or inferolateral cortex	
	Lateral temporal cortex → additional areas in the lateral cortex → basal or temporal tip cortex	
Baumgartner *et al.*, 1995	Mesiobasal → lateral temporal cortex	
Boon and D'Havé, 1995	Small time difference between the radial and tangential dipole	
	Tangential component leads : hippocampus → lateral temporal cortex	
	Radial component leads : lateral temporal cortex → hippocampus	
	Simultaneous radial and tangential dipole : single underlying source	
Boon *et al.*, 1997	Type 1 dipole in patients with a medial temporal lesion : hippocampal source	
	Type 1 dipole with lesions extending to the lateral temporal neocortex : hippocampal source	
Ebersole, 2000	Mesiobasal → lateral cortex and lateral cortex → mesiobasal	
Merlet and Gotman, 1999	Mesial → temporal neocortex	
Merlet *et al.*, 1998	Mesiobasal → lateral temporal neocortex	
	Neocortical → mesial temporal cortex	
Mine *et al.*, 2005	Hippocampus → adjacent mesiobasal temporal cortex	

structures in the mesial temporal lobe is essential in maintaining ictal activity in temporal lobe epilepsy, these areas are not necessarily primary seizure triggers, but may act as secondary pacemaker zones for amplification and spread of electrical activity (Ebersole, 2000 ; Merlet *et al.*, 1998).

From the above it is clear that, independent of the source model used, continuous mutual interactions between the mesial temporal lobe and the temporal neocortex exist.

RELIABILITY OF DIPOLE MODELS

The topographical reliability of deep mesio-temporal sources calculated with dipole modelling techniques has been questioned since the first studies were published (Baumgartner *et al.*, 1995 ; Ebersole, 1994 ; Gavaret *et al.*, 2004 ; Lantz *et al.*, 1996 ; Merlet *et al.*, 1998 ; Shindo *et al.*, 1998), mainly because superficial sources seem to be modelled more accurately than deep sources. Moreover, it turns out that epileptic spikes originating in deep mesial structures, and especially the hippocampus, are not detectable on the scalp EEG. These findings question the topographical reliability of dipole modelling.

The best way to validate dipole models is to compare with the actual intracerebral electrical field at the time of the spike or the ictal discharge. Simultaneous scalp and intracerebral recordings make it possible to verify the results of dipole modelling in terms of location and time activation (Gotman, 2003 ; Merlet & Gotman, 1999).

Extent of intracerebral fields

Recent evidence suggests that the extent of brain tissue involved in generating spikes is underestimated. In contrast to previous reports, recently the use of an artificial model and the lack of taking into account the contribution of background activity has met substantial criticism (Cooper *et al.*, 1965 ; Ebersole, 1997 ; Merlet & Gotman, 1999 ; Tao et al, 2005). Subsequent investigations resulted in the identification of larger areas necessary to generate prominent surface spikes. Similar results were found when analyzing ictal EEG changes detectable at the scalp. When no scalp EEG paroxysmal changes could be detected during the intracerebral ictal onset, only a very focal region was activated, no larger than 3 adjacent intracerebral contacts were synchronously activated (Gotman, 2003 ; Merlet and Gotman, 2001).

Associated activity

Since spikes associated with a confined focal intracerebral field are not recorded on the scalp EEG, interictal spikes generated in the hippocampus or the amygdala are never detected on the scalp. Spread to the lateral temporal neocortex is necessary to notice spikes on the scalp EEG. This also suggests that the modelling of a spike by a single dipole source in the mesial temporal lobe is unreliable (Gotman, 2003 ; Merlet and Gotman, 1999). Similar results were found when analysing ictal discharges (Merlet and Gotman, 2001). It is clear that synchronous activation of a large surface

of cortex is necessary to allow recording interictal and ictal EEG activity at the surface.

Concordance between dipole modelling and intracerebral EEG recordings

Concordances between dipole sources and intracerebral fields can only be confirmed when dipoles are found close to an intracerebral electrode contact (Merlet & Gotman, 1999, 2001). Spatial concordance as well as temporal concordance have been described for interictal sources (Boon *et al.*, 1995 ; Merlet & Gotman, 1999 ; Gotman, 2003).

A similar comparison can be made based on the analysis of ictal EEG sources (Boon *et al.*, 1999). When a main source is calculated this is believed to represent the activity of the main generator of the ictal scalp EEG. Secondary sources appear to be a reflection of the spreading of the ictal discharges to regions that may be far away from the primary epileptic zone (Merlet & Gotman, 2001).

Incongruencies between dipole modelling and intracerebral EEG recordings

Spatial incongruence occurs when the intracerebral EEG electrode contact closest to a dipole source is not the contact where the maximal intracerebral field is recorded. This can be found when interictal sources and ictal sources are calculated. Merlet and Gotman state that mesial temporal main sources in the early ictal period are always mislocated in the lateral temporal neocortex (Merlet & Gotman, 1999 ; 2001). Other authors confirm a temporal limbic onset with depth-electrodes (Boon & D'Havé, 1995 ; Boon *et al.*, 1999 ; Homma *et al.*, 2001 ; Merlet *et al.*, 1998). Mislocation can be related to the fact that discharges in the lateral neocortex are the main contributors to the discharge at the scalp. During the later stages of the ictal period mislocations occurred when the maximal field was more superficial, suggesting that, when the seizure continues, the field becomes more complex and less amenable to dipole modelling (Merlet & Gotman, 2001).

In contrast to the main sources, secondary sources were found to be incongruent during the early ictal period when the intracerebral field was neocortical (Merlet & Gotman, 2001).

Confidence limits of dipole modelling

The most common model used in EEG source localization consists of equivalent point-like dipoles, representing the centre of the activated cortical area. The dipole source has a certain probability volume, determined by the position and the orientation of the source and the signal-to-noise ratio. Therefore, reconstructed dipole sources represent the most probable source location. To avoid the perception that the results of dipole modelling describe an exact localization, the standard deviation of the dipole localization is described (Fuchs *et al.*, 2004).

Another way to represent the error range of dipole source localization is by using the residual variance. The dipole with the smallest residual variance guarantees the most acceptable one, because there seem to be no other indications for the best solution (Kobayashi *et al.*, 2003). Further investigations reveal that extension of the source area results in an increase of the residual variance, although very small and nearly negligible. It appears that larger sources can be modeled by a single dipole. A small residual variance does not necessarily reflect a small source area (Kobayashi *et al.*, 2005).

Effect of noise on the accuracy of dipole modelling

Noise influences the accuracy of source modelling. If the signal-to-noise ratio reaches above a certain threshold, localization accuracy decreases and this seems to be the case for superficial and deep sources alike. When the noise level increases further, localization for deep sources becomes even less accurate (Whittingstall *et al.*, 2003).

Limitations of dipole modelling

The clinical interpretation of results obtained by dipole modelling requires a critical consideration of the weaknesses inherent to this technique.

One of the most important limitations is the fact that the dipole can only be calculated by solving the inverse problem. Since the exact number of generators remains unknown and consequently the number of terms in the equations stays unclear, solving the problem leads to different solutions. Usually, the anatomically and physiologically most plausible solution is chosen. There is no such thing as a unique solution for the inverse problem, unless a series of limitations and assumptions are taken into account, such as the use of a three-shell spherical head model and the principles of volume conduction. Spherical head models are far from being physiological. Therefore, anatomical localisation of dipoles is less accurate than orientation. Such inaccuracies can be improved by using a realistic head model. The diagnostic relevance of dipole modelling could be improved by increasing the accuracy in such a way that the calculated source can be precisely related to an anatomical structure. Future research should be pointed at the development of a head model based on neuroimaging images of the individual patient, correlated with the spatial coordinates of the EEG electrode positions (Boon *et al.*, 1997, 1999 ; Vanrumste, 2002).

Even when using a realistic head model, modelling of temporobasal EEG activity is not always possible, due to the fact that scalp electrodes cannot be located basally enough (Herrendorf, 2000) and that the feasibility of calculating dipole modelling depends on the size of the generating area (Merlet

& Gotman, 1999, 2001). To obtain a better spatial resolution when recording spikes originating from deep sources, additional electrodes should be applied (Kobayashi *et al.*, 2000) at the base of the brain, such as sphenoidal electrodes and electrodes at T_1 and T_2 positions. An inferior longitudinal electrode chain should be standard practice in patients with temporal lobe epilepsy (Ebersole, 1997).

When electrical brain activity becomes detectable on the scalp EEG, adjacent cortex areas are already recruited. What we analyse as being the source, occupies an area already larger than the actual area of seizure onset, even when applied to early ictal rhythms (Assaf & Ebersole, 1997). Consequently, it can be concluded that source calculations from superficial interictal spikes provide a more reliable localization than from ictal discharges, since usually propagation of the seizure has occurred by the time that the ictal rhythms are recorded at the scalp (Ebersole & Pacia, 1996 ; Foldvary, 2001).

When results from dipole modelling are compared with localization based on intracerebral recordings, selection bias can occur. This is because intracranial electrodes can only be implanted in certain parts of the brain, resulting in only a partial recording of the intracerebral field. When a dipole source is detected in an area that is not covered by electrodes, the results cannot be validated (Gotman, 2003).

Although a dipole source is represented in function of the amplitude of the electrical activity, the strongest activity does not necessarily represent the seizure onset zone. Also background activity and artefacts may have characteristics that contribute to the EEG activity during the seizure. Since no standard method exists to identify electrical activity as being epileptiform, EEG recordings should still be interpreted by an experienced electroencephalographer. Commercial dipole modelling software programs have limitations. In some programs, the spatiotemporal analysis is based on the assumption that, after averaging and filtering the EEG signals, only data related to the seizure remain. This assumption does not hold, since early seizure activity can not always be seen on the scalp EEG. Such programs only analyse electrical activity with a significant amplitude, but not necessarily early seizure activity (Kobayashi *et al.*, 2000).

Another limitation when interpreting results of source analysis is that EEG spikes reflect the irritative zone and not necessarily the epileptogenic or the ictal onset zone (Ebersole, 1994 ; Herrendorf *et al.*, 2000). The latter mostly falls within or near the irritative zone, but the correlation between the two is uncertain (Ebersole, 1994). The epileptogenic zone can be represented by modelling ictal changes on the scalp EEG. But again, certain problems emerge, especially in recording seizures, which is very difficult and may require days of video-EEG monitoring in hospital conditions. Moreover, several ictal recordings may be necessary to check for consistency. Movement and muscle artefacts, propagation of EEG activity and recruitment of additional cortex make recording of seizures often hard. As a result of this, modelling seizures is certainly much more difficult than modelling spikes (Ebersole, 1994).

Different algorithms are used in describing the conductivities representing the brain, cerebrospinal fluid, skull and scalp. Only approximate data are available, because the in vivo conductivity can not be measured exactly. More realistic conductivity data can contribute to a more accurate dipole source analysis in the future (Tseng *et al.*, 1995).

Finally, dipole modelling takes a lot of time, effort and requires the necessary EEG and MRI equipment. It represents a very labour-intensive and time-consuming procedure (Boon *et al.*, 2002).

Conclusion

Dipole modelling of interictal and ictal EEG signals is able to represent cerebral sources in a fairly accurate and non-invasive way. In particular, the orientation of the dipole source is of great importance. Dipole orientation can define cortical areas with sublobar accuracy and source potentials can suggest the presence and direction of propagation of the electric activity.

Some authors state that scalp EEG signals corresponding to focal activity limited to mesio-temporal structures can never be observed, while others claim to have detected scalp EEG signals related to temporal limbic onset.

With regard to clinical interpretation of results of EEG dipole modelling, limitations inherent to the dipole modelling technique should be taken into account.

Despite these limitations, ictal and interictal voltage topography and dipole modelling contribute to a better localisation of the underlying brain source in patients with refractory temporal lobe epilepsy.

These techniques may also be a helpful tool in deciding which patients can have temporal resections without intracranial recordings, thus in limiting the number of (unnecessary) invasive recordings.

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