Chapter 9

Conclusions and Future Directions

We have presented in this thesis the results of our work on the development and assessment of methods for localizing interictal spikes in the context of presurgical evaluation of epileptic patients. Our framework was the combined use of scalp electroencephalography (EEG) and magnetic resonance imaging (MRI).

The first interest of using MRI together with EEG that we have put forward is the possibility to bring anatomical information into the inverse problem of EEG. We have demonstrated the feasibility of studying post-operative patients by modelling brain and skull defects based on T1-weighted MR images. Such patients are not uncommon, and these results show that this population can be included in EEG source localization studies.

The second topic we investigated is the recent possibility of recording EEG within the MR scanner and thereby obtaining functional MR images of the brain areas involved in spike generation. We have developed procedures and assessed their effectiveness for obtaining an EEG of good quality in the scanner, which allows the recovery of the spikes despite the distortions produced by the magnetic field. We have presented measures of the fMRI temporal response to the spikes. We have shown that the responses are similar to those obtained with classical stimulation, and lie within areas that are consistent with EEG findings.

A third avenue that arises from the two previous topics is the integration of results from EEG source localization and fMRI. We have proposed to build statistical maps that reflect the probability of each point in the brain to contain an electrical source, in contrast to the classical methods that consist in displaying a best-fit solution. This permits to assess the level of concordance between the information arising from EEG and fMRI taken separately. This study also allowed us to tackle some of the modelling and decision-making issues that arise when considering the EEG problem as a topic in statistics. This is a first step in the fusion of the two modalities into a common framework, a topic that is currently raising much interest.

I will now present some conclusions, points of discussion and ideas for possible continuation of this work.

EEG Source Localization

Over the years, a plethora of methods has been proposed for solving the inverse problem of EEG, that often revolve however around similar concepts. These methods should not be seen as antagonists, but as different questions asked to the data. It is important to be aware of the temptation to see a given method as representing the "true" distribution of activity in the brain. This danger is an even greater concern with the growing possibilities of representing the results with attractive colours on high-resolution three-dimensional renderings of the cortex.

It is unfortunate that there are only few studies that compare the different localization methods in different source configurations and values of signal-to-noise ratio (SNR). This should be a priority of the field, which would involve large-scale collaboration between research groups. A possibility would be for one or a few laboratories to design simulated signals and real case studies and to send the data to be processed by the different groups that have designed particular methods. One such multi-centre study was proposed by J. Ebersole for epileptic spike data [Ebersole 99].

Generally speaking, one should be aware of the limitations of each method and consider using them in conjunction. For a simple configuration of well-separated sources and in good signal-to noise-ratio conditions, it is likely that most methods will give similar results - at least for indicating the centre of gravity of activated areas. When attempting to retrieve more subtle configurations, for example sources that are close, with time courses highly correlated, or when one is interested in the extent of activated cortex, then one has to be more careful and avoid having expectations that are too high. Warnings have been issued to show the difficulty of resolving too many sources with a limited spatial sampling [Koles 98], to separate very close sources (cf. [Lutkenhoner 98a] for the magnetic case) or to obtain the exact extent of activated cortex [Wagner 02].

In a given application, it is very important to define any solid prior information one has in order to interpret the results, but also to improve the results in difficult situations such as those mentioned above. For example, it is reasonable to assume for most EEG applications that a typical source is a patch of neocortex; anatomical MR images can be used to construct such patches [Lutkenhoner 95].

In temporal lobe epilepsy, there are typical structures involved, such as entorhinal cortex, hippocampus and amygdala. However, these structures are deep, produce little signal on the scalp, and may not possess a simple dipolar field (this particularly true for the amygdala). Nevertheless, there may be hope to disentangle their activity in good SNR conditions [Merlet 98], and methods have been presented to deal with non-dipolar sources [Trontelj 91]. The information arising from functional MRI is of course potentially very interesting, as discussed below.

Some a priori knowledge on plausible values of current densities would be very informative, and would probably be of much help in resolving the size of activated cortex, given of course accurate conductivity values. A few attempts have been made to give typical values for cortical current density (see [Hämäläinen 93, Alarcon 94] and [Baillet 01a] for discussion). These values are possibly dependent on the application, as the subpopulation of neurons involved in a given area or the type of inter- and intra-area connections could play a role.

In terms of conductivity, the skull is the major factor in determining the conductive properties of the head. It has been discussed recently that the average skull conductivity is probably much higher than that used classically [van Burik 00b, Cuffin 01b]; the anisotropy of the skull (structure in layers) also plays an important role [Marin 98]. A fact that has not been used so far to our knowledge is the different properties of different areas of the skull, in particular at the level of junctions between plates (sutures) [Law 93]. Haueisen has proposed to perform a fine segmentation of the head and use this information in the finite element method ([Haueisen 96], p. 63).

Another avenue comes from tractography arising from diffusion tensor imaging. This has been used as a factor in assessing anisotropy in white matter conductivity [Haueisen 02]. Knowledge of the main tracts could be also be used in constraining links between regions.

In summary, we are in the context of an ill-posed inverse problem, which depends heavily on source and head modelling and on the signal-to-noise ratio. For this reason, it seems sensible to avoid considering only the best solution but rather explore the solution space, as was proposed by Clarke [Clarke 89] and Schmidt et al. [Schmidt 99] in a probabilistic framework, and by Mosher in a subspace processing approach [Mosher 92]. We have followed such an exploratory approach in chapter 8.

Simultaneous EEG-fMRI

The technique of simultaneous EEG-fMRI is an exciting new avenue for studying the sources of epileptic spikes, where measurements are actually made within the volume of the head.

The techniques for recovering the EEG are quite mature now, and have proven efficient for epileptic spikes where the signal is usually quite strong. A recent study has shown that when the time of stimulation is known, it is even possible to recover with averaging evoked potentials performed during the very heavy gradient artefact [Brandeis 03]; this is encouraging for further developments of the technique. Unfortunately, there is no such triggering signal in epilepsy; the recovery of small epileptic discharges on the EEG will have to rely on diminishing the gradient artefact [Anami 03] or on advanced techniques of signal processing. For example, one could build a spatial filter using ICA on EEG away from the artefact, or on large amplitude spikes (if small amplitude spikes are expected to have a similar spatial field). Such a filter could help in concentrating the energy of the spike on a few ICA channels.

In the few series of cases reported so far (see section 4.5), that includes one from our group [Al-Asmi 03], there seems to be a problem of sensitivity as a large proportion of patients presented no activation. This is a surprising fact at first glance because epileptic spikes, as mentioned earlier, are assumed to involve large areas of cortex. However, there are many reasons why there could be a lack of fMRI activation. There could be, among others, a high level of movement during the long session, a BOLD response that is very different from the HRF assumed in the linear model or too small to be detected. For regions in the mesial temporal lobe, there could be signal loss because of susceptibility artefacts, or there could be a more frequent spiking than what is visible on the scalp [Alarcon 94] leading to a constant metabolic demand. Also, the neuro-vascular coupling could be affected in epilepsy, as discussed in [Salek-Haddadi 03b]. These causes should be investigated in order to increase the clinical usefulness of simultaneous EEG-fMRI. Within our group at the MNI, we tested some hypotheses to explain the fact that some patients had no activation

[Bagshaw 04].

The very encouraging point is that when there are results of activated areas, they are usually very consistent with EEG or other clinical findings. More population studies on many types of epilepsies are obviously needed in order to establish EEG-fMRI as a recognized tool for presurgical evaluation, but it is certainly on a good track. Also, some results of correspondence between depth electrodes recordings and EEG- fMRI results have been presented in Lazeyras et al. [Lazeyras 00] and Bagshaw et al. [Bagshaw 04]. This area would deserve more investigation, for assessing the precision of the technique. Such results would also be of interest for the whole fMRI community, as invasive studies in epilepsy give a unique opportunity to obtain electrophysiological recordings within the brain and compare them with fMRI results.

The temporal lobe is the region most often involved in epilepsy. In order to improve the relevance of EEG-fMRI in this form of epilepsy, it will be crucial to obtain good fMRI signal in the mesial regions, which are prone to signal loss. EEG source localization techniques may have important role to play in complementing fMRI when the fMRI signal loss is too severe. Also, techniques that can assess hippocampal signal in fMRI without considering the scalp activity are of interest to assess the side of higher activity, for example ICA [McKeown 98] or temporal clustering analysis [Morgan 04].

A promising area of application is for non-lesional extratemporal epilepsies, as pointed out by Lazeyras et al. [Lazeyras 00]. Indeed, contrary to the temporal lobe epilepsies, there is little *a priori* knowledge on the structures that may be involved. A “non-lesional” case may be in fact a patient with a lesion that has is difficult to notice on MRI. The results of fMRI could guide the search for such a lesion [Lazeyras 00]. These results could also serve as additional information for implanting intracerebral electrodes.

There is probably more to be gained from EEG than just the timing of the spikes. In our study (chapter 7), we have not found a correlation between the energy of the spike and that of the BOLD response. However, more efforts should be made in this direction. In particular, it is possible that the amplitude of the BOLD response reflects the extent of activated cortex. There has been much interest lately in the correlation between electrophysiology and fMRI signal [Disbrow 00, Logothetis 01], and the simultaneous recording of EEG and fMRI could be an opportunity to study this link non-invasively in humans.

Classically, fMRI is used to find areas where there is a signal increase. However, there is a growing interest in the decrease of signal and its possible relations with decrease of activity in a region ("deactivation"). In epilepsy, several instances of decrease of fMRI signal have been reported, that seem to happen mainly for widespread rhythmic activity such as generalized spike and wave ([Archer 03a, Salek-Haddadi 03b] and in our group [Aghakhani 04]). This could to be put in parallel with similar findings in EEG-fMRI for alpha waves [Goldman 02, Laufs 03]. This could be because widespread rhythmic cortical activity corresponds to an oscillatory state of cortex receiving less input, maybe similarly to what happens during sleep [Steriade 95]. Also, we have observed that the areas of signal decrease tend to be of larger extent than for signal increase [Aghakhani 04]; and that the HRF tends to peak later than for increases [Bagshaw 04]. The reasons for this latter finding are not clear yet.

Integration of EEG and fMRI

The integration of EEG and fMRI measurements should enable to make measurements of time difference between activities in different regions (cf. [Seeck 98]), or to establish patterns of correlation between regions. The traditional view is to consider the spatial information from fMRI and gain temporal information from EEG. However, the localization capacities of EEG should not be overlooked: in good conditions, its precision can be of the order of a centimetre (cf. section 3.4). Also, even though the fMRI response is very slow and may differ from region to region, it has been shown that the time difference between regions could be reflected in the fMRI response [Kruggel 99a], and that fMRI can be used to measure connectivity [Friston 00].

The BOLD signal has been shown to correlate well with local field potentials that, like EEG, are related to EPSPs [Logothetis 01]. This is encouraging for the integration of EEG and fMRI, but there are many reasons for which the exact correspondence may fail. The first remark that comes to mind is the fact that EEG and fMRI measure different phenomena, one vascular, the other neuronal, at different temporal and spatial scales [Nunez 00]. The EEG may not record activity in a region where the neurons are not synchronized, or in a deep region. Approximations in head and source models can lead to reconstructed sources located at a distance from activated cortex. Conversely, fMRI may not be sensitive to a region with frequent activity that requires a continuous metabolic demand (e.g. the hippocampus in epilepsy). An EEG event may only involve a small subpopulation of neurons and be very brief, therefore not requiring a high increase of metabolism. Also, it has been known for a quite long time that fMRI can be sensitive to large veins quite remote from the site of activity, at least at 1.5 T [Lai 93]. For all these reasons, one should approach the fusion of EEG and fMRI with caution.

The simplest manner of combining EEG and fMRI measurements is the establishment of statistical maps independently for the two modalities, and then let human judgement play its part for establishing correspondences between areas found with the two maps. This is what we proposed in chapter 8. Indeed, human judgement is a rather good pattern recognition and decision-making system. It is in fact what the practitioner does when integrating results from clinical examination, structural MRI, SPECT, neuropsychology with her/his knowledge on epilepsy in order to produce a diagnosis.

However, the integration of the two methodologies into a common framework permits potentially more subtle definition of intervals of confidence in localization. This is actually an area of active research [Dale 00, Friston 02, Lahaye 04, Kiebel 04]. The most natural way of combining information from different origins is probably the Bayesian framework, into which most current localization techniques can be described as pointed out in section. Other possibilities exist though. For example, Ahlfors and Simpson proposed a subspace approach that biases the EEG towards nearby fMRI activations [Ahlfors 04].

The incorporation of *a priori* knowledge into the localization problem must of course be done with caution. By putting too many constraints, for example biasing the inverse problem strongly towards fMRI activations, one may retrieve what has been inputted and little extra information. This is of course the difficult question of the validity of the *a priori*. When in doubt, one should probably avoid using too strong constraints, or use a multi-methods approach and again rely on human judgement to formulate hypotheses.

In my opinion, an ideal combined approach would make use of a model of generation of the BOLD signal from the EEG activity. Such a comprehensive model does not exist yet to our knowledge, but significant work has been accomplished in this direction. For example, the balloon model is a biomechanical model that links brain activation and changes in dHb [Buxton 98]. Turner has proposed an estimate of the maximum distance of BOLD activation from the place of actual neuronal activity [Turner 02]. An EEG model could consist of patches along the neocortex, and a few dipolar sources for medial sources [Merlet 98]. The patches would be attributed a current density following an a priori distribution [Schmidt 99]. The range of plausible current densities is not known, as pointed earlier in this chapter; this topic would deserve further investigation for example with depth electrode and grid recordings. A Bayesian framework could be built using such models and a priori information, using both EEG and fMRI data as proposed in [Trujillo-Barreto 01], and possibly MEG data too [Baillet 99]. Hierarchical models [Penny 04] could be used to encapsulate models at different scales, from cortical column to regions. The columnar level is probably attainable only with fMRI at very high magnet strength and is beyond reach of EEG, but could be interesting to consider in order to establish a theoretical link between EEG and fMRI signals.

Such a comprehensive model would allow for a definition of the range of plausible solutions for inference regarding the number and sizes of activated areas as proposed in [Schmidt 99]. However, with so many parameters, two important problems remains: the exploration of the solution space (e.g. with MCMC methods) that is difficult at high dimensions, and that of the presentation of the results in a condensed manner. For the visualization, it is possible at one extreme to present a representative range of possible solutions with different source location, number and size. At the other extreme, one can integrate at a given point of the head the probabilities of all the solutions containing this point. This last option has the risk of blurring the results, as very different solutions can be combined (for example the classical problem of a “ghost source” in between two close dipolar sources [Baillet 01b]). A possibility is to integrate the results for a given number of sources, as we have done in chapter 8.

The last words

The integration of EEG and functional MRI is very promising for presurgical evaluation of epileptic patients, for clinical diagnostic and for the guidance of depth electrodes implantation. It is also of great interest for localization and timing of brain functions in general. Despite its long standing history, and the advent of other techniques such as magnetoencephalography, it is safe to assume that electroencephalography has still an important role to play.

One has to keep in mind that interictal activity is different from seizures, these latter being usually the main target of EEG investigation. However, as pointed out in chapter 2, the spikes are nevertheless informative on the localization of epileptic regions and in understanding the epileptic process. The exact role of the spike is still under investigation, and it is possible that the technique of EEG-fMRI could shed a new light on this important phenomenon.

The field of non-invasive brain mapping techniques is a very exciting topic in terms of methodology. It involves signal processing, head and signal modelling, elegant statistics (cf. the random field theory). It can resort to advanced methods such as Bayesian models or higher order statistics. It is therefore very tempting to stay at a theoretical level, in the wonderful realm of ideas, where each point is consistent with every other point. It is however from the applied field that will come both the recognition of these methods as useful tools and, maybe even more importantly, the ideas and a priori knowledge that will help improving the methods.

Appendix A

Simultaneous EEG-fMRI Procedure

A.1 EEG Recording in the Scanner

The electrodes we use are topped with a plastic cap (Schwarzer GmbH, Munich, Germany), and we fix them with a classical conducting paste (Ten20, D.O. Weaver & Co., Aurora, Colorado, USA). We place each individual wire as tight as possible on the head, following the shortest path from the electrodes to the vertex, where all wires join to form a bundle. We wrap the head in a tight bandage. We use a wooden ramp from the back of the MR bench to the table on which the amplifier is set, so that wires lie on as flat a surface as possible (figure A.1). This set-up implies that the process of removing the patient from the scanner is slow, a potential concern in epileptic patients: one must be ready to remove rapidly the sand bags and the ramp in case of seizure occurrence.

We use for immobilization a vacuum bag (50 x 70 cm, 10 litre fill), filled with small polystyrene beads (S&S X-Ray Products, Brooklyn, NY). The content of the bag must be sufficient to create a layer thick enough to follow the shape of each electrode and prevent the head from resting directly on a few electrodes, a situation that can become rapidly painful. Too large a bag can be difficult to fit inside the head coil; we feel that 7 to 8 litres should be a good compromise for most scanners.

We use the Schwarzer EMR-32 amplifier, linked with a fibre optic cable to a computer located outside the MR room. The fibre optic is needed to ensure the absence of an electrically conductive bridge between the outside and the inside of the scanner room, a bridge that would deteriorate the quality of MR images. The Schwarzer amplifier has an low-pass analog filter at 300 Hz and a 1 kHz sampling rate. We make use a digital filter

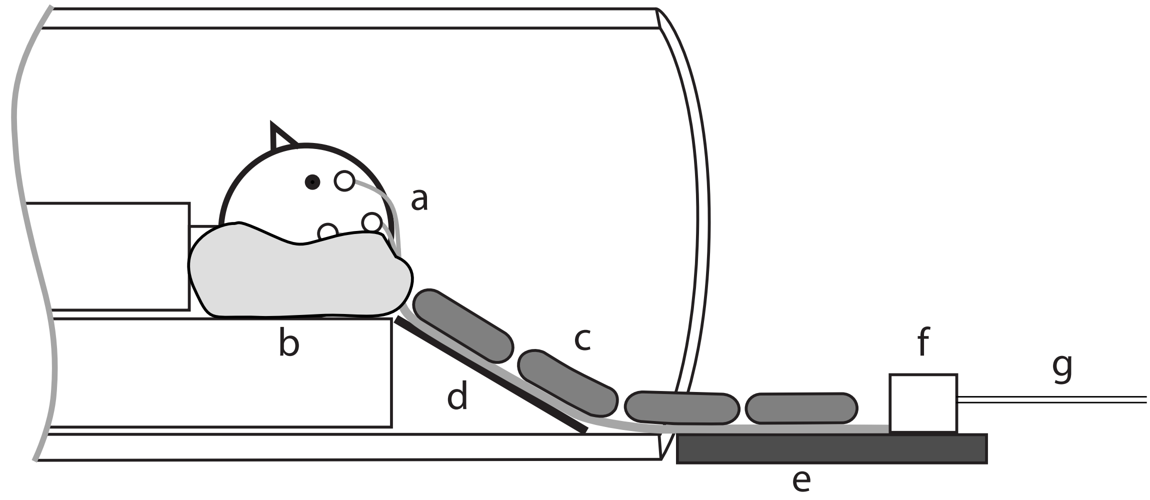

Fig. A.1 Schematic representation of the EEG set-up inside the scanner; **a**: EEG wires joining at the vertex of the head to form a bundle, **b**: vacuum cushion filled with polystyrene beads and wrapped around the head and wires, **c**: sand bags resting on the wires, **d**: ply-wood ramp, **e**: wooden table, **f**: amplifier, **g**: optic cable connecting the amplifier to the computer located outside of the scanner room.

with a high-pass frequency of 0.1 Hz (i.e. a long time constant) to avoid abrupt returns to baseline following each gradient artefact.

A.2 Image Acquisition

In each session, we acquire around 10 runs of 120 frames of BOLD effect-sensitized images, on a Siemens 1.5 T scanner (Siemens, Erlangen, Germany). Each frame is composed of 25 64 x 64 EPI images (TE 50 ms, flip angle 90 deg, $5 \times 5 \times 5$ mm voxel size), lasts 2.5 seconds and is followed by a gap of 0.5 second. The acquisition time for one hundred and twenty frames is therefore 6 minutes. We leave about 2 minutes between runs. The figure of 120 frames and the 2-minute gap were limitations of the fMRI software in our earlier experiments. This limitation is no longer present but we have retained this protocol for consistency. Also, it can be interesting to use the gaps to monitor the state of the EEG and visualize spikes. The gap of 0.5 second could be suppressed to improve Fourier-based filtering, keeping in mind, however, that a continuous scanning noise can be unpleasant for the patient.

The images we obtain (anatomical T1 and BOLD T2*) are of good quality, despite the presence of 21 electrodes and wires in the scanner. On the T1 images, some signal loss is visible around the electrodes, as reported by [Krakow 00]. This is not detrimental, as it does not affect the brain images. It can actually be valuable for locating the electrodes (figure A.2), as required for EEG source localization.

We observed large areas of signal loss in the basal frontal and basal temporal regions on the T2* images, which is a common finding caused by susceptibility artefacts [Ojemann 97]. The hippocampus is obviously a structure of great interest in epilepsy, and we are currently working on solutions for improving the signal in the basal temporal regions. We have documented that this signal loss negatively affects the ability to detect responses in patients with temporal lobe spikes [Bagshaw 04].

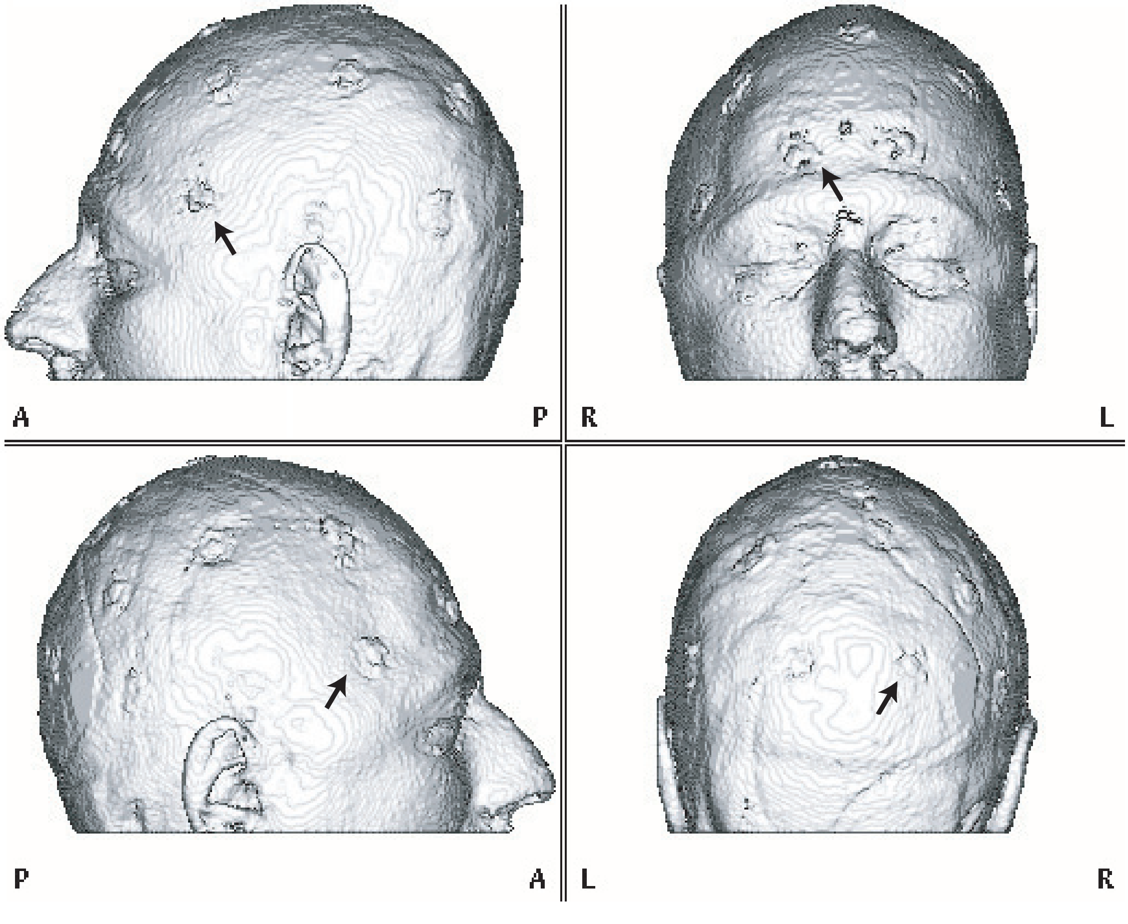

Fig. A.2 Visualization of the electrodes on a 3D reconstruction of the skin surface. The surface was obtained from MRI T1 images recorded with the EEG electrodes in place. Electrodes induce local signal loss on the MRI image (arrows). This information can be useful for EEG processing, such as source localization.

Appendix B

Ethics Certificate

References

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