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Diffusion tensor imaging can localize the epileptogenic zone in nonlesional extra-temporal refractory epilepsies when [^{18}F]FDG-PET is not contributive

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Summary Surgical outcome in patients with nonlesional refractory partial epilepsies could be improved by a more precise definition of the epileptogenic zone (EZ). The value of interictal FDG-PET hypometabolism, voxel-based-morphometry (VBM) and diffusion tensor imaging (DTI) is still debated. We compared the sensitivity and specificity of these noninvasive techniques in localizing the EZ with stereo-electroencephalography (SEEG) results. Twenty patients with nonlesional partial epilepsy (13 temporal lobe epilepsy (TLE) and 7 extra-temporal (extra-TLE)) underwent structural MRI, DTI and FDG-PET. FDG-PET was analyzed visually (vPET) blinded and unblinded and by statistical parametric mapping (SPM) (sPET). Individual modifications of grey matter volume and mean diffusivity increase were compared to a control group with SPM.

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The best sensitivity was provided by vPET unblinded (75%) and the best specificity (60%) by DTI. The sensitivity of vPET blinded (55%) was lower and those of sPET (40%) and VBM (35%) were still lower. In TLE, vPET analyzed either blinded or unblinded, performed the best and additional use of the other tools improved slightly the sensitivity. For extra-TLE, combining vPET and DTI results increased the number of pertinent abnormalities detected especially for circumscribed changes in frontal lobe epilepsy (FLE).
Combining vPET and DTI was the more efficient strategy for extra-TLE, allowing the detection of pertinent abnormalities in FLE when FDG-PET alone was not contributive. Combining sPET or VBM with vPET was less useful.

Introduction

Surgery may be an effective therapy for refractory focal epilepsies with a clear delineated focus (Kwan and Brodie, 2000), such as medial temporal lobe epilepsy (MTLE) associated with hippocampus sclerosis (HS) (Dupont et al., 2006). Surgical benefits are less clear for patients with a poorly defined focus such as nonlesional refractory partial epilepsies, often termed ''cryptogenic'' epilepsies. Different studies show that only 37—55% of these patients are seizure free after surgery (Chapman et al., 2005; Lee et al., 2005; Alarcon et al., 2006; McGonigal et al., 2007) and outcomes may be even worse (17% seizure free) in frontal lobe epilepsy (FLE) (Jeha et al., 2007). Pre-surgical evaluation in nonlesional cases is more complex, more expensive and may require invasive and time consuming examinations such as stereo-electroencephalography (SEEG) (Rosenow and Luders, 2001). SEEG is considered the gold standard to localize the epileptogenic zone (EZ) (Spencer, 2002) but the procedure had a limited spatial sampling. The development of noninvasive neuroimaging alternatives, including both structural and functional cerebral imaging, is thus an important goal to improve EZ delineation and optimize SEEG procedures (Lee et al., 2005; Knowlton, 2006).

Several neuroimaging alternatives already exist but there have been few studies on their exact individual and combined contributions. Interictal [^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) hypometabolism (qualitative or quantitative analysis) is an efficient technique in MTLE (Engel et al., 1990) but its sensitivity and specificity are still debated in nonlesional neocortical epilepsy (Henry et al., 1991; Lee et al., 2005; Yun et al., 2006; Knowlton et al., 2008a). Neuroimaging methods derived from magnetic resonance imaging (MRI) are easily available and have been evaluated for accurate definition of the EZ. Within these MRI techniques, voxel-based-morphometry (VBM) of grey matter has a proven accuracy in the detection of subtle dysplastic lesions (Kassubek et al., 2002; Bonilha et al., 2006a). But these findings are controversial (Colliot et al., 2006), highly dependent of post-processing steps and remain unconfirmed in nonlesional epileptic patients. Diffusion tensor imaging (DTI) is another MRI technique in which the exact role and signification in the pre-surgical evaluation of refractory nonlesional epilepsy is under investigation (Yogarajah and Duncan, 2008). DTI may detect signal alterations, possibly reflecting occult dysplastic lesions or gliosis, in regions that appear normal on conventional MRI (Eriksson et al., 2001; Rugg-Gunn et al., 2001, 2002). In patients with extra-temporal epilepsy (extra-TLE), interictal SEEG abnormalities were found to be correlated with an increase in mean diffusivity (MD) (Thivard et al., 2006). However, once again, results for cryptogenic FLE are less clear and the diagnostic yield of DTI in pre-surgical evaluation remains controversial (Guye et al., 2007).

The purpose of this study is to examine the localizing value of these noninvasive techniques in pre-surgical evaluation of refractory nonlesional epilepsy including both temporal lobe epilepsy (TLE) and extra-TLE. The sensitivity and specificity of each imaging strategy were calculated and compared with the EZ localization estimated by SEEG. We wish to address specifically two questions: 1 — what is the localizing value of respectively DTI, VBM and FDG-PET in pre-surgical evaluation of nonlesional epilepsy patients? 2 — which combination of the different noninvasive strategies enhances the ability to localize the epileptic focus?

Methods

Patients

The study population included consecutively 20 patients (10 men and 10 women; age, mean 30.0 ± 8.2 years, range 18—44, duration of epilepsy, mean 17 ± 9.5 years, range 3—38) with nonlesional partial epilepsy who underwent pre-surgical evaluation at the epilepsy unit of the Salpêtrière hospital between January 2003 and January 2006 (see Table 1). They all underwent neurological examination, interictal EEG, video-EEG monitoring, FDG-PET, optimized MRI (Dupont and Baulac, 2004) and SEEG (Adam et al., 1996). MRI data was reviewed by a radiologist (DD) and a neurologist (CA). In patient 11, MRI imaging showed a T2 and FLAIR hypersignal in the right cingulum suggestive of dysplasia. Despite this lesion, we choose to include this patient in our study because the lesion site was clearly not involved in the epileptic network.

The EZ for each patient was defined from SEEG records: 13 TLE patients included 5 MTLE foci, 5 lateral TLE (LTLE) foci and 3 ''temporal plus'' foci, 2 both in the medial temporal lobe and in a region outside the temporal lobe and one in the insula. Seven patients had extra-TLE foci, 3 occipital lobe epilepsy (OLE) foci and 4 FLE foci (see Table 2).

Twelve patients were operated (delay to surgery, mean 55 ± 11 months, range 38—73). Resections were limited in 3 patients due to a potential functional risk (patients 3, 7 and 10). Four patients were not operated because of bifocal EZ and 4 due to a functional risk (see Table 1). Surgical outcome was Class I in 8 patients and Class III in the remaining 4 (see Table 1).

Histopathology, from 10 patients showed no abnormality in 4, astrocytal gliosis in 3, HS in one, focal cortical dysplasia (FCD) in one and oligodendroglioma in one (see Table 1). In the later patient, despite retrospective MRI examination by an experienced