Clinical Decision Making with Advanced Techniques - fMRI

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This lecture will review the clinical applications of functional MRI (fMRI) used to study patients with a broad range of neurological disorders, across a wide spectrum of disease severity.

Mapping the Eloquent cortex

Traditionally mapping of eloquent areas is achieved by methods such as intraoperative cortical stimulation in the awake patient, implantation of a subdural grid with extraoperative stimulation, or intraoperative recording of sensory-evoked potentials (5;6). These methods are accurate, but are invasive. fMRI can obtain these data preoperatively and completely noninvasively. Together with its high sensitivity for visualizing brain lesions, fMRI can define the relation between the margin of a lesion and any adjacent functionally significant brain tissue. fMRI has the potential to predict the possible deficits in cognition or in language; in motor and sensory perceptual functions that would arise from intrinsic lesion expansion, such as bleeding into an arteriovenous malformation; or from therapeutic intervention, such as surgery. This helps the treating physician or the surgeon to explain the relative risk of intervention and nonintervention so that a decision about the treatment option can be made after considering its cost and benefit.

Initially fMRI studies were primarily concerned with the feasibility and the validity of fMRI compared with corticography (2;7;8). Most of the studies revealed good spatial correlation between the two methods. Once a lesion has been localized to the eloquent area, it becomes important to assess the risk that a deficit may follow therapeutic intervention. Yetkin et al. showed that when the distance between the representation of brain function (activated area) exceeded 2 cm, the patients showed no post resection deficit and resection was safe; however, as the distance between the lesion and brain function decreased, the rate of postoperative deficit increased (9). When the lesion margin lay 1 to 2 cm from the zone of activation, 33% of patients showed postoperative deficits. When the lesion margin lay less than 1 cm from the zone of activation, 50% of patients experienced postoperative deficit. Such information can be helpful when consulting the patient and when deciding on the optimal treatment modality.

fMRI, thus, should be able to estimate the risk of surgical treatment which in turn should improve therapy with increased life expectancy and decreased morbidity. However, only very few studies have addressed the effect of fMRI in a neurosurgical context (1;3). In a retrospective study, Lee et al. evaluated the therapeutic efficacy of fMRI and determined how often and in what ways fMRI studies influenced the management of individual patients (3). They evaluated (a) use of fMRI to assess the risk associated with, and thus the feasibility of, proposed surgical resection; (b) the use of fMRI results to guide the placement of the bone flap or of the subdural grids or strips for ictal electroencephalography (EEG) recordings or extraoperative sensorimotor cortical stimulation mapping, and (c) the use of fMRI to help determine whether invasive surgical functional mapping was necessary. In epilepsy patients, fMRI results helped to assess the feasibility of resection in 70% of patients to plan the surgical procedure in 43% and to select the patients for invasive mapping in 52%. In tumour patients, fMRI results helped to assess the feasibility in 55% influenced the planning in 22% and helped to select patients for invasive surgical functional mapping in 78%.

Lateralization of language and memory functions in the surgical treatment of epilepsy

Patients with intractable temporal lobe epilepsy (TLE) show improved seizure control or cure following surgery. An understanding of language lateralisation is needed for presurgical planning. Intracarotid Amobarbital testing (IAT) or the Wada test has been the gold standard for identifying lateralisation of language and memory functions preoperatively, but it is invasive and therefore carries risk. fMRI offers a promising non invasive alternative approach (10). While there is good agreement between conventional invasive Wada testing and fMRI results, fMRI is more sensitive to involvement of the non-dominant hemisphere. fMRI offers the capability of spatially resolving functional activation within each hemisphere, potentially guiding tailored resections to spare eloquent cortex. The reproducibility of distinct patterns of activation in individual subjects is good, potentially allowing clinical decisions to be made on the basis of results. Binder et al. (11) reported a cross validation study comparing language dominance determined by both fMRI and IAT in 22 patients. A semantic decision task was used to activate a distributed network of brain regions in language specialization. Excellent agreement was obtained with both the techniques. There is still some controversy concerning the optimum task for language lateralisation. A majority of the studies opine that a covert verbal fluency tasks yields best correspondence with the Wada test, while others advocate that semantic decision tasks should be used rather than the verbal fluency tasks because the latter tasks may lack the activation of posterior language areas. In our institute we use a paradigm which includes both verbal fluency and semantic decision (see figure 1).

Localizing spontaneous ictal activity

With the recent advent of methodologies that allow concurrent EEG and fMRI, it has been possible to localize regional metabolic changes accompanying spike-triggered approaches or using retrospective analysis of continuously acquired data (12;13;13). These techniques capitalize on the temporal resolution of EEG and spatial resolution of fMRI. The approach of concurrent EEG and fMRI recording tends to be more efficient and accurate in comparison with the spike-triggered approach (13)). These techniques may be of particular value in presurgical evaluation of neocortical epilepsy where paroxysmal activity on EEG may remain poorly localized. Also these techniques may provide new insights into anatomical and pathophysiological correlates of unifocal and multifocal spike discharges.

fMRI for Understanding Brain Plasticity

Another application of fMRI that has received increasing interest is the study of “brain plasticity” which includes for example the study of recovery of motor function in stroke patients. fMRI could play an important role in determining the prognosis of recovery of function in stroke patients. Most of the studies on functional recovery after stroke on groups of patients have been performed with positron emission tomography. Because fMRI provides increased spatial resolution and has the ability to study these patients individually and repeatedly from stroke onset to full motor recovery, fMRI has now become the technique of choice. Cao et al., studied the consequences of early ischemic stroke and demonstrated that there was an increased recruitment of ipsilateral motor cortex during hand movements in children who had hemiparesis from intrauterine stroke (14). Cramer et al., identified increased activation of a motor network in the unaffected hemisphere to a greater extent than found in controls, an increased degree of supplementary motor area activation, and perilesional activation (15). A study of brain plasticity in patients who have arteriovenous malformations located within the primary motor cortex, revealed three typical patterns of takeover of function: (a) functional displacement within the affected primary motor cortex (b) activation within the ipsilateral unaffected primary motor cortex, and (c) prominent activation in nonprimary motor areas (16). More recently, Carpentier et al., (17) proposed a classification scheme of plasticity with 6 grades based on inter-hemispheric pixel asymmetry and displacement of activation. Grade 1 represents the normal activation pattern, grade 2 appears to reflect a mass effect, grade 3 reflects the impact of the lesion on the activation (interface disorder) with no clear evidence of plasticity, grade 4 represents possible local plasticity, whereas grade 5 represents definite ipsilateral plasticity, and the grade 6 pattern represents definite contralateral plasticity. As designed, the classification categories, ranging from grades 1 to 6, correspond to levels of reorganization ranging from none to highly reorganized patterns of motor function. A case with grade 6 plasticity is presented in figure 2.

Another study has described longitudinal cortical reorganization in the auditory brain areas at several intervals (1 week, 5 weeks, and 1 year) after a right cochlear nerve resection for an acoustic neurinoma (18). Before surgery, the patient had normal bilateral hearing; that is, when auditory stimulation was given to one ear (a) both the ipsilateral and the contra lateral auditory cortices were activated, but (b) the level of activation in the ipsilateral cortex was approximately one fifth of the level on the contralateral side. After surgery, the patient exhibited sudden and complete hearing loss on the right side. As expected, no cortical activation could be visualized when the resected right ear was stimulated; however, on stimulation of the other ear, an increase in the level of neuronal activity was observed in the ipsilateral auditory cortex at 1 and 5 weeks after surgery, increasing to complete symmetric activation of the left and the right auditory cortices 1 year postoperatively.

Neural correlates of phantom limb symptoms following amputation have been observed, along with an abnormally large region of contralateral motor cortex fMRI activation with stump movement in a patient whose left arm had been amputated at an early age (19). Differential language lateralization has been observed in deaf patients as compared to hearing subjects (20) and activation of visual cortex has been observed with tactile stimulation in a blind individual (21). Thulborn et al., have applied fMRI to language recovery in stroke patients (22). Spontaneous redistribution of function to the right hemisphere was observed within days of the stroke and continued for months afterward.

Clearly, brain plasticity is far from understood. The challenge is to study the physiologic mechanisms behind it. It is unclear why certain stroke patients recover almost completely and why others do not, despite long and intensive rehabilitation. The above-described studies demonstrate, however, that longitudinal fMRI studies in individual patients should allow objective measurement of the recovery function and the effects of rehabilitation or other treatment strategies (eg, neuroprotective drugs) on this recovery.

fMRI in guiding therapeutic development

One of the most exciting prospects of fMRI is to guide therapeutic development, drug development and response monitoring. The greatest impact may be on areas in which sensitive and objective end points were previously difficult to define - for example, neurorehabilitation (23). A similar example is the assessment of outcomes using behavioural therapy, such as for the control of pain. By identifying the biological basis for cognitive and behavioral changes, fMRI offers insights into mechanisms of vulnerability and variability of responses to treatments for neurological and psychiatric diseases.

Finally, an emerging application of fMRI is in brain bionics. Implantable stimulators are currently used in the management of a variety of neurological and psychiatric syndromes including Parkinson’s disease, epilepsy, chronic pain, non-pulsatile tinnitus (see figure 3 and (4)) and obsessive compulsive disorder (see figure 4 and (24)). fMRI can be used to (a) visualize the hemodynamic effects of neurostimulation (25) (Figure 4), (b) to guide the placement of electrodes into brain regions under conscious control (Fig. 3) and (c) to allow paralyzed patients to use motor imagery to control robotics devices (26).

fMRI helps in identifying preclinical expression of neurodegenerative disease

fMRI can be sensitive to early stages of brain pathology. An illustration of this approach was an fMRI based memory study of a group of apparently healthy subjects at risk of developing early onset Alzheimer’s disease (27). One year after fMRI scanning, those who were beginning to develop memory problems in early clinical expression of presumed Alzheimer’s disease were identified. A significant difference in the pattern and volume of activated cortex with the memory task was found in these subjects relative to those who did not develop memory impairment. The alteration in fMRI activation also correlated with APO-E status and subsequent memory decline.

Differential diagnosis of neuropsychiatric disorders

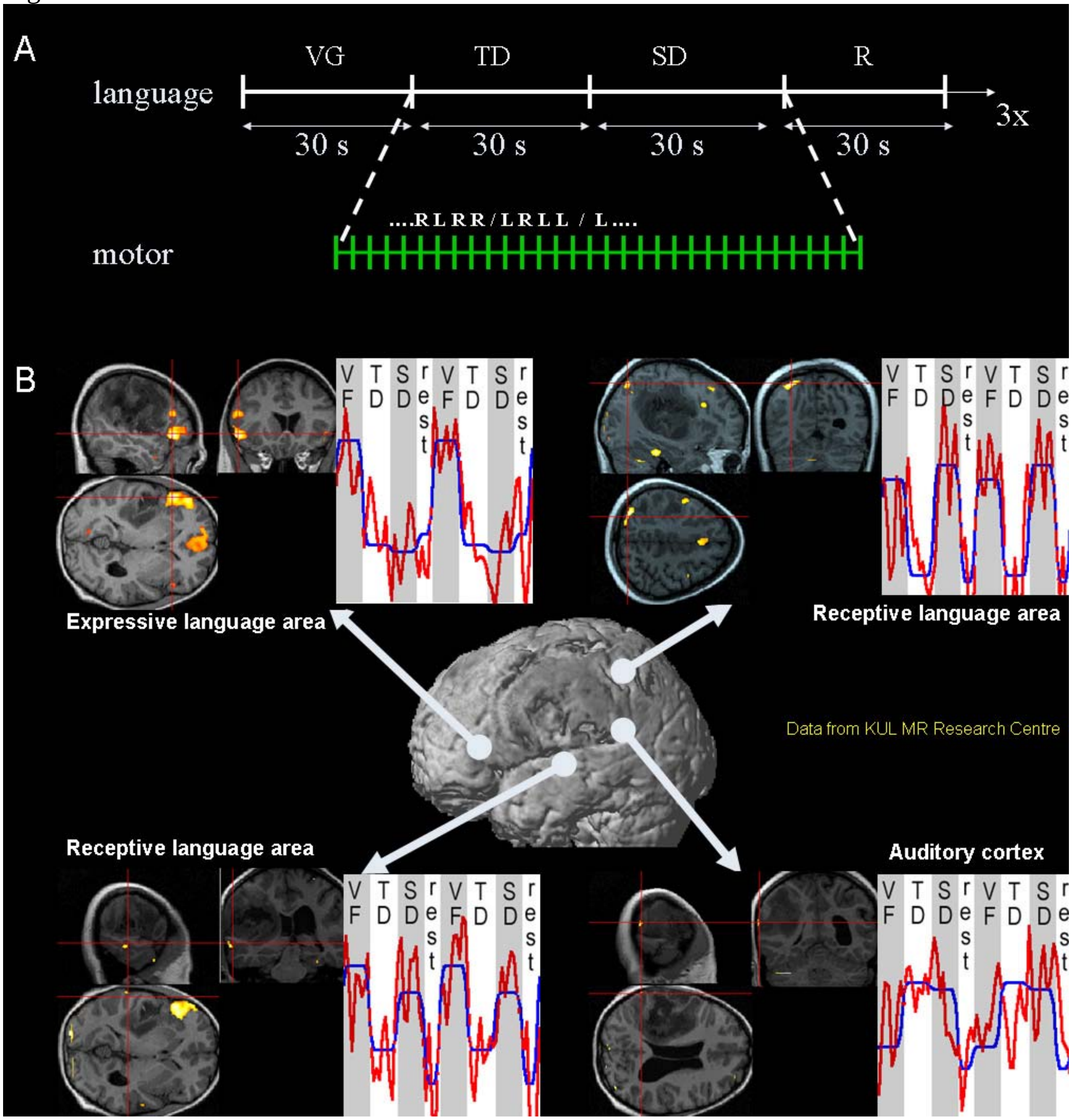
Subjects who have recovered from depression have a substantial risk for recurrence of depression, suggesting that there are persistent abnormalities in brain function associated with vulnerability to depression. Smith et al., applied a pain-conditioning paradigm to study a group of patients who had recovered from depression and who were not on drug treatment, but were at risk of recurrence of depression (28). The recovered depressed patients showed an altered fMRI response in the cerebellum relative to healthy controls. This type of study might be used to distinguish between different types of depression or to identify healthy subjects at risk of depression.

Numerous studies have attempted to demonstrate abnormal responses to task activation in a variety of neuropsychiatric syndromes. Alterations in fMRI response to primary sensorimotor or cognitive tasks have been observed in some psychiatric syndromes, but these have been relatively non-specific (29). For cognitive activation, fMRI studies are further confounded by task performance, since patients typically perform worse than controls. Hence though limited the role of fMRI in psychiatry has to still evolve with better techniques and a better understanding of cognitive functions.

PhMRI

fMRI techniques are now being increasingly used to investigate regionally specific brain activity associated with the administration of CNS-active drugs, because it is a relatively non-invasive way to perform pharmacological investigations in experimental animals, healthy human volunteers, and individuals with CNS diseases. However, since pharmacological agents themselves can interfere with the mechanisms that give rise to the BOLD signal, careful attention to experimental design and data analysis must be exercised (30). Introduction of a drug into the system could potentially alter the coupling of neural activity along with the regional cerebral blood flow and/or the extraction of oxygen from blood, or may cause local or global cardiovascular changes unrelated to neural activity. Despite all these constraints, fMRI has been successfully used to study acute direct effects of drugs, effects of drugs on task-related activation, chronic effects of drugs, effects of drugs on cerebral metabolism, and variable effects of drugs in different populations (30). Willson et al have shown recently that dextroamphetamine causes measurable decreases in brain activity in a variety of regions during cognitive tasks. The authors proposed that these changes might be linked to behavioral changes observed after dextroamphetamine administration (31). Borras and colleagues, using fMRI techniques have demonstrated that naloxone, even in the absence of psychophysical effects, produces activation in several brain regions that are known to have high levels of mu-opioid receptors and may be involved in endogenous analgesia (32). This use of fMRI, dubbed 'pharmacological MRI' or 'phMRI', holds the promise of providing relatively straightforward pharmacodynamic assays and can be used to establish brain-penetrability parameters, or dose-ranging information for novel therapeutic compounds (33)

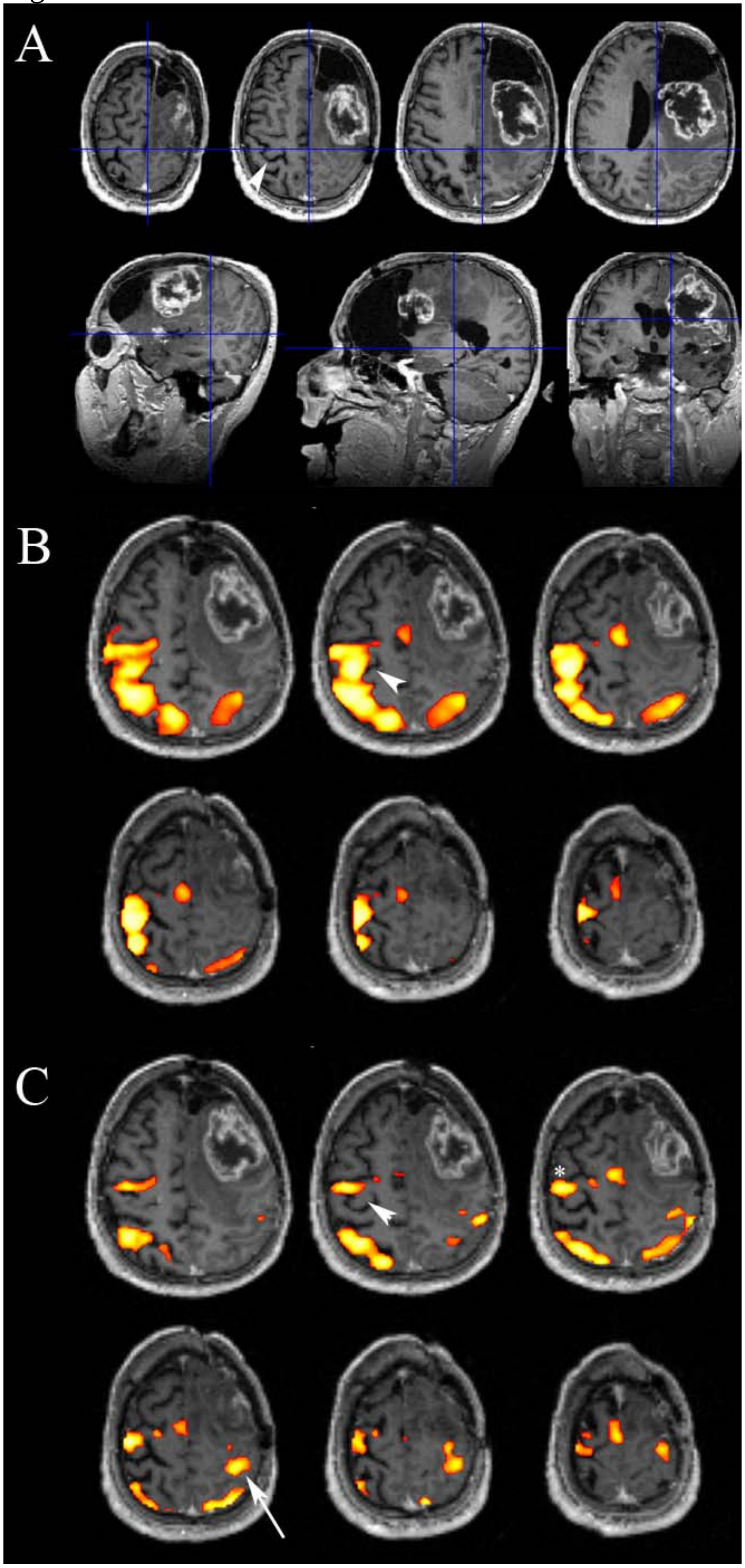
Figure 1



A: Language paradigm consisting of a covert verb-to-noun generation (VG; e.g. auditorily presented noun “car”, and patient covertly responds “drive”), tone discrimination (TD - discrimination of tone pitch), semantic discrimination (SD; e.g. patient makes distinction between objects and animals), and rest (R).

B: Right-handed patient with a very large “fronto-parieto-temporal” tumour in the left hemisphere. The mass-effect of the lesion effaces typical anatomical landmarks. The change in MR signal in response to the different tasks compared to rest is used to identify the nodes of the language network: in the auditory cortex the response is the highest during the execution of the TD task; in the receptive language areas the activity is the highest during the SD-task; in the left inferior frontal region, there’s only increase in MR signal during the execution of the covert verb-to-noun generation task, thus this area corresponds to the classical Broca's expressive language area. Note the lateralisation of Broca's area to the left hemisphere in this right handed patient.

Figure 2

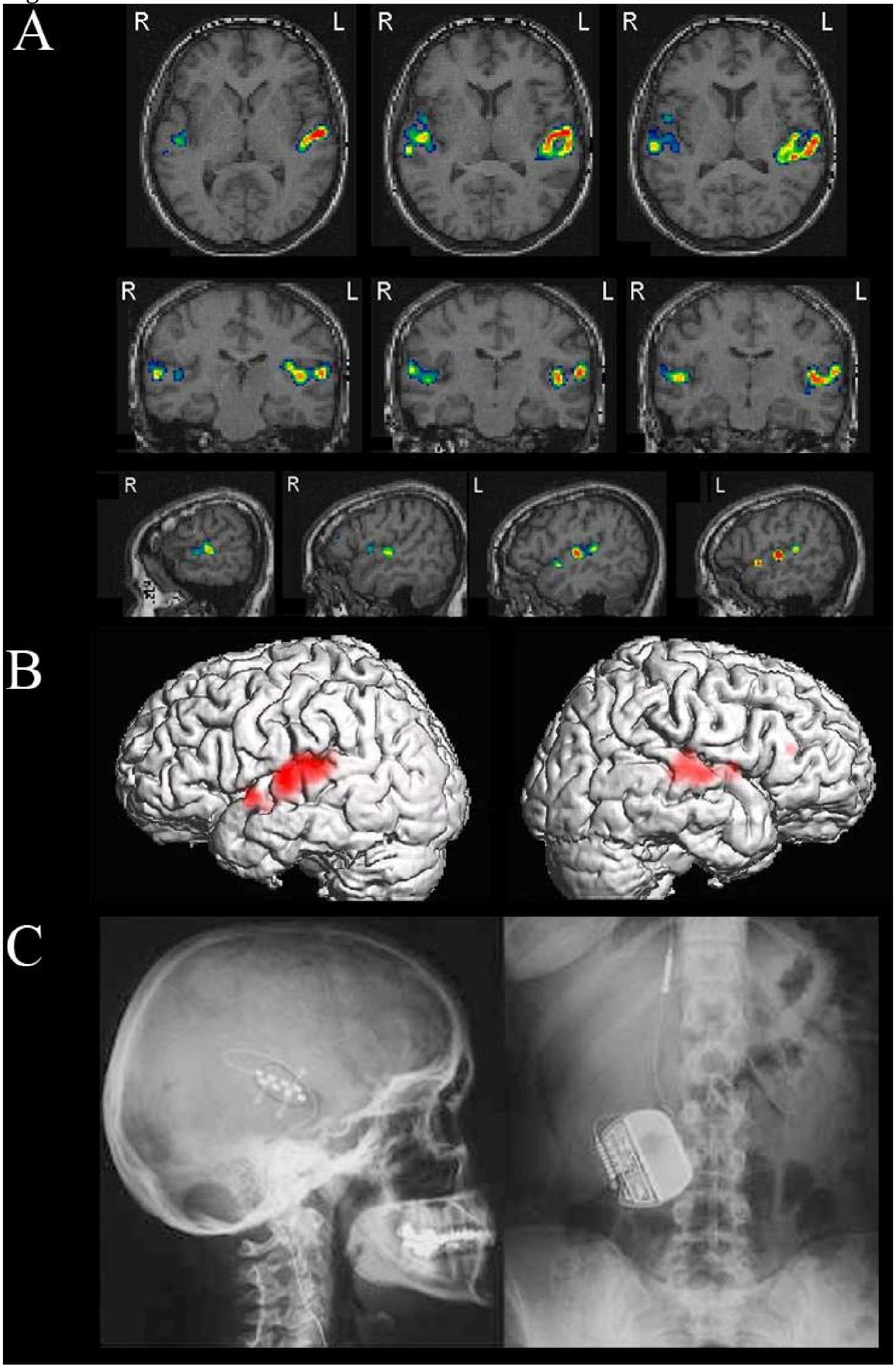


Cortical reorganisation of the motor system in a patiet with a recurrent glioblastoma multiforma three years after resection of a glioma grade 2 in the right frontal lobe. A:

T1w post-contrast anatomical images. B: Activation pattern in response to repetitive left hand clenching versus rest; C: in response to right hand clenching. Arrowheads indicate the position of the right primary motor cortex. The arrow points to the presumed location of the left primary motor cortex

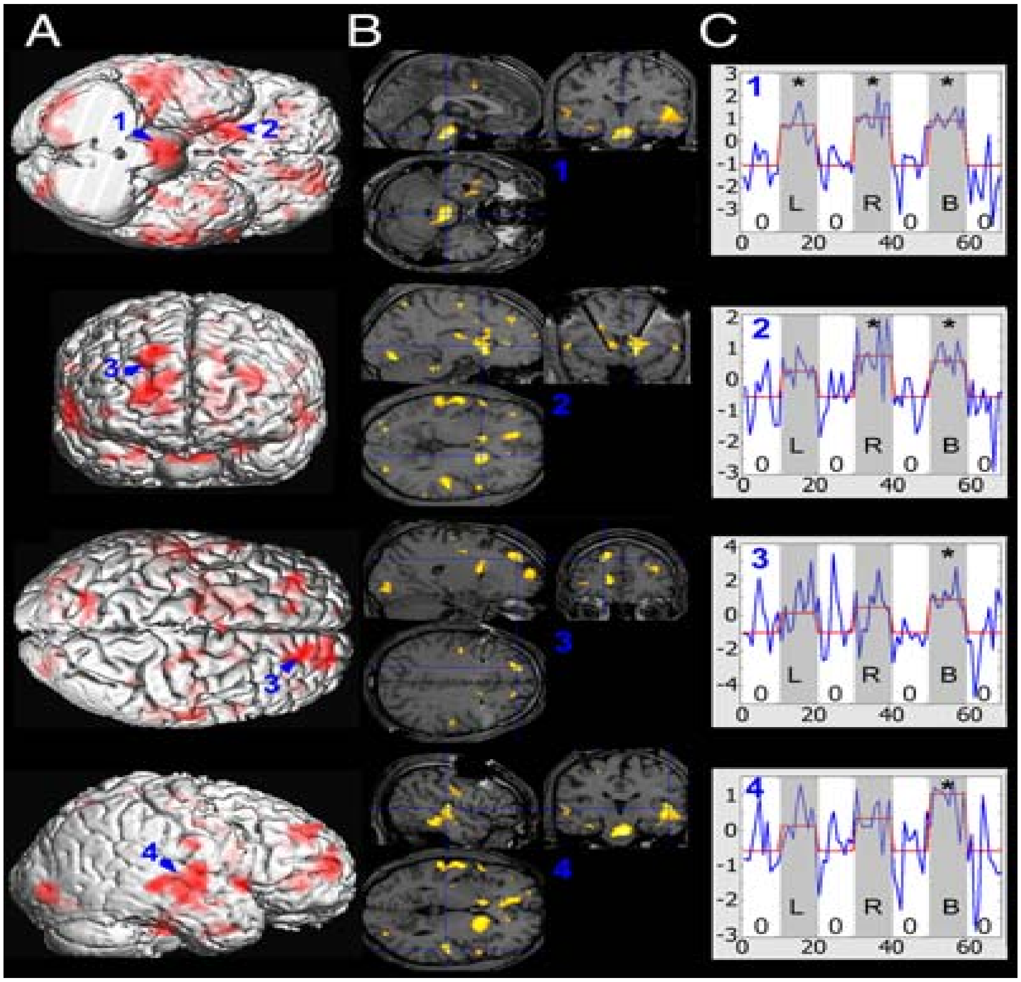
Note the normal pattern of brain activity in B, with contralateral activation of the right M1, PM, and bilateral activation pattern of the SMA and parietal proprioceptive regions. The activation pattern in C should be the symmetric of B, but this is not the case. There is some residual activity in the left M1 (arrow), but ipsilateral activation in the right primary motor and premotor cortices is clearly present.

Figure 3



Functional neuronavigation for the guided implantation of an epidural electrode in a patient with left unilateral tinnitus. A: Auditory cortical activation in response to binaural musical stimulation; the right primary auditory cortex has less differential activity, due to the spontaneous high level of electrical activity in the right auditory cortex, which causes the (phantom) percept of unilateral left tinnitus. B: Same activation represented on 3D surface reconstruction of the brain of the patient. C: post-operative X-ray showing the location of the epidural electrode projected on the skull (left panel) and of the location of the pacemaker (right panel). Adapted from De Ridder et al., 2004.

Figure 4



FMRI study showing cortical and subcortical activation in a patient suffering from obsessive compulsive disorder, treated with deep brain stimulation, when brain activity is subtracted during the stimulation-off condition from brain activity shown during the stimulation-on condition, superimposed onto surface reconstructions (A) and sections (B) of the patient's brain.Regions are labeled as follows: the midline focus in the pons (1), the striatum (2), the focus in the right frontal cortex (3), and the left superior temporal gyrus (4). In the brain sections, the left hemisphere is shown on the right or at the bottom. C, percentage fMRI signal change (blue line) and statistically modeled signal change (red line) during left (L), right (R), simultaneous (B) and no stimulation (0) in the four labeled regions. Conditions for which stimulation versus no stimulation was significant ($P < 0.05$ corrected for multiple comparisons) are indicated by asterisks. Adapted from Nuttin et al., 2003 (24)

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