Functional imaging of cerebral arteriovenous malformations with a comment on cortical reorganization

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Functional brain imaging is poised to become a standard diagnostic tool. The authors review their experience using functional positron emission tomography (fPET) in patients with cerebral arteriovenous malformations (AVMs).

Twelve patients, three males and nine females aged 16 to 30 years, 11 with a cerebral AVM and one with a cavernous angioma, of which five were located in the central area and seven in a speech region, underwent fPET and three-dimensional magnetic resonance imaging. These studies were coregistered in stereotactic space and correlated to Brodmann's areas that were identified from the atlas of Talairach and Tournoux. Vibrotactile and/or motor stimulation of the contralateral hand were used to identify the central region in patients whose AVM resided within, or close to, the motor strip, and language tasks specifically designed to activate visual, auditory, expressive, or semantic language were used in patients whose AVM resided within, or close to, Broca's or Wernicke's areas.

Somatosensory and motor activation reliably identified the central region in all cases as validated by identification of Brodmann's areas and by intraoperative cortical mapping, which was performed with the patient under local anesthesia. Similarly, language tasks accurately lateralized major language function to one hemisphere concordantly with neuropsychological assessment, including dichotic listening and intracarotid Amytal tests, and localized language areas appropriately as verified by stereotactic coordinates.

Functional cerebral imaging is feasible in patients with structural brain lesions. It is a reliable method to identify the relationship of a cerebral AVM to the central region. The determination of a similar relationship to language areas is dependent on the development and further validation of language-based tasks designed to activate visual, auditory, expressive, and semantic aspects of language specific to particular sites within the anterior and posterior speech regions.

Key Words * arteriovenous malformation * functional imaging * magnetic resonance imaging * positron emission tomography

Functional imaging of the brain is no longer an arcane and expensive research tool available to only a few academic centers. It is poised to take its place in the routine assessment of patients with a variety of
pathologies in functionally important areas. The time is therefore opportune to review our ongoing experience with functional imaging in patients with cerebral arteriovenous malformations (AVMs) in or around eloquent areas to see what has been learned since we first demonstrated that functional imaging could be useful in a clinical setting.[7,8]

**CLINICAL MATERIAL AND METHODS**

**Patients and Methods**

Twelve right-handed patients, three males and nine females aged 16 to 30 years, had either a cerebral AVM (11 cases) or a cavernous angioma (one case) in, or close to, the pre- and postcentral gyri (five cases) or in an area subserving expressive (one case) or receptive (five cases) language functions. Each patient underwent functional imaging studies using three-dimensionally coregistered magnetic resonance (MR) imaging and positron emission tomography (PET) during the vibrotactile and motor stimulation of the hand contralateral to the AVM or during the performance of visual, auditory, expressive, or semantic language tasks (that is, functional PET (fPET)). One patient with an AVM in what proved to be the nondominant left temporal lobe also underwent language activation fPET scanning. All AVMs were cortical but extended deeply into the white matter. Two patients had a cerebral hemorrhage, eight were epileptic, and two had manifestations of chronic ischemia in the form of memory loss and intermittent hemiplegia. Five lesions were smaller than 3 cm in largest diameter and seven were larger.

The patients gave informed consent prior to undergoing fPET, in accordance with the ethical guidelines of our institution. The oxygen-15 water bolus technique was used to obtain brain maps in baseline and activation states using positron emission tomography (model PC 2048-15B; Scanditronix, Uppsala, Sweden). Magnetic resonance imaging was performed using a 1.5-tesla superconducting magnet (Philips Gyroscan ASC; Best, The Netherlands). The MR imaging and PET volumes were aligned in three-dimensional stereotactic space using a volume of interest atlas. The PET images were normalized for global relative cerebral blood flow; activation minus baseline volumes were obtained and anatomical and functional images were merged into a single data set displayed in superposition. Voxel-by-voxel z-score statistical analysis identified peaks of significant activation as x, y, and z stereotactic coordinates that were correlated to Brodmann's areas using the atlas of Talairach and Tournoux.[2,18,20]

Vibrotactile stimulation was performed by applying a vibrator (Vibrator 91; Daito, Osaka, Japan) to the fingertips contralateral to the AVM, 1 second on, 1 second off, beginning 30 seconds before injection of oxygen-15 water. The motor task consisted of having the patient rapidly squeeze a sphygmomanometer bulb.

The language-activation tasks were specific to the area associated with the lesion and have been described in detail elsewhere.[7,8,21] Visually based tasks were used to detect lesions in the inferior aspect of the temporal lobe and auditory-based tasks for lesions in the superior parietal lobule, both part of the posterior speech region (Wernicke’s area); expressive language tasks were used for lesions in the posterior aspect of the third frontal convolution (Broca’s area). In a bilingual subject with a midfrontal AVM, we used a language-activation task, translating from one language to another, known to produce cerebral blood flow increase in this region in normal subjects.[3] Patients undergoing language-activation studies also took part in extensive neuropsychological evaluation, including dichotic listening and bilateral intracarotid Amytal tests.
Fig. 1. Multiplanar, curvilinear reformatted gadolinium-enhanced magnetic resonance images in a patient with a left central arteriovenous malformation (AVM). The images are taken at 8 mm (upper) and 12 mm (lower) from the vertex and demonstrate both hemispheres. In the right hemisphere the precentral gyrus is identified by the asterisk. Using the normal, right hemisphere as a reference, the relationship of the AVM to the central region can be surmised. Curvilinear reformatting is currently under development at the Montreal Neurological Institute.

RESULTS

Sensorimotor Activation

In all cases sensorimotor activation established the relationship of the coregistered AVM to the central region (Figs. 1 and 2). In all cases this was confirmed by correlation to Brodmann's areas using the stereotactic atlas of Talairach and Tournoux; allowances were made for individual variations from the idealized atlas brain, usually of the order of ± 5 mm, and for visible distortion, if any, caused by the mass of the lesion seen on MR imaging. In one case, validation was achieved by intraoperative cortical mapping while the patient was under local anesthesia.[7] In each case, locating the AVM precluded resection. Three patients were treated by stereotactically focused radiotherapy, one after partial embolization. The other two patients were not treated, although one had partial embolization that was not extensive enough to permit treatment using stereotactic radiosurgery.
Fig. 2. Positron-emission tomography (PET) activation results (upper) appearing as concentric colored circles in the same patient as in Fig. 1. The functional (fPET) results are superimposed on the coregistered magnetic resonance (MR) images in the coronal and axial planes (the sagittal plane is not illustrated) where white reflects highest activity and purple least activity. The peak of activation is identified in the posterior aspect of the precentral gyrus. The lower illustrations are false-color, three-dimensional reconstructions of the fPET and MR imaging data, with the brain seen from the top and obliquely from the side.

Language Activation

Neuropsychological assessment suggested that all but one AVM and the cavernous angioma were in the language-dominant hemisphere. This was in the left hemisphere in five cases, in the right in one case, and predominantly in the right in another. The results of fPET correlated with those of the neuropsychological evaluation, dichotic listening, and intracarotid Amytal tests in lateralizing language function. Localization of language sites was also achieved in all cases and corroborated with Brodmann’s areas, as determined from Talairach and Tournoux’s atlas, establishing the spatial relationship between the lesion and areas subserving language (Figs. 3 and 4). The intimacy of this relationship permitted safe resection in only one case. The other AVMs remained untreated because their size, despite partial embolization in one case, precluded stereotactic radiosurgery.
Fig. 3. False-color coronal (upper left) and sagittal (lower left) images of coregistered magnetic resonance (MR) imaging and MR angiography in a patient with an arteriovenous malformation in the left mid-frontal region. The functional positron emission tomography images superimposed on the coregistered MR images (upper and lower right) reflect a word generation minus noise activation and demonstrate a region of peak activity (red cross) in the posterior aspect of the left third frontal convolution (Broca's area). The patient had no difficulties with primary language function following resection of the lesion but had temporary difficulties with translation, as illustrated in Fig. 4.

Two patients were right hemisphere dominant for speech; both were right handed. The AVM resided in the right temporal lobe in one case, in proximity to the area of language activation. The AVM was in the left temporal lobe in the other patient: fPET demonstrated language function to reside in the right hemisphere in areas homologous to those of left hemisphere-dominant individuals.[9]

Fig. 4. This functional positron emission tomography image illustrates the results of a translation minus noise activation in the same patient as in Fig. 3. The peak of activity resides in the midfrontal region in proximity to the arteriovenous malformation (AVM). The patient experienced temporary difficulties in translating from her native language to English after resection of the AVM, reflecting damage to the midfrontal region important for lexical search and retrieval.
DISCUSSION

The demonstration that functional states such as eye opening can produce changes in concentrations of venous oxyhemoglobin and deoxyhemoglobin discernible by MR imaging, combined with our initial demonstrations that functional imaging can reliably identify eloquent areas in patients harboring structural brain lesions, set the stage for the current interest in functional imaging outside of the few academic centers with advanced neuroimaging and image reconstruction capabilities to which it was hitherto confined.[1,7,8] Now most centers with reasonably advanced MR imaging technology can accomplish functional imaging.

**Functional Imaging of Cerebral AVMs**

Patients with cerebral AVMs are well suited for functional imaging because their lesions, if they have not produced an acute intracerebral hematoma, are not associated with cerebral edema and their mass usually does not cause brain distortion, like gliomas and other tumors, factors that could potentially confound the results of functional imaging.[7,8] Furthermore, our current understanding of the natural history of cerebral AVMs is such that resection does not appear warranted if this would put eloquent cortex at risk, especially now that stereotactically focused radiotherapy appears to be a viable therapeutic alternative in selected cases.[13] Thus, the ability to demonstrate that a cortical area intimately related to a cerebral AVM is the site of motor function, language, or vision is of interest to treating physicians. The situation is not quite analogous for cerebral tumors. Benign extraaxial tumors such as meningiomas can usually be removed without neurological deficit, even if they are closely related to eloquent cortex. Malignant intraparenchymal tumors generally require tissue diagnosis regardless of location. If believed to reside in the motor strip, partial resection and diagnosis can be achieved with the guidance of intraoperative cortical mapping, which with current techniques can easily be performed while the patient is receiving a general anesthetic.[5] Thus, the most likely candidates for functional imaging among patients with a presumed malignant brain tumor would be those patients whose lesion might reside in a language or visual area and in whom stereotactic biopsy would be indicated or those patients with a known metastatic lesion in a location at which resection might produce neurological deficits that would not be encountered with radiotherapy.

A potential difficulty in functional imaging of AVMs is the relative ischemia that is produced, in a fashion proportional to its size, by the redistribution of blood away from the normal cortex through the lowered resistance of the arteriovenous fistula.[6,19] Such redistribution of blood flow and the resultant relative ischemia could potentially confound functional imaging studies in patients with AVMs, the activation task having the added burden of activating the adjacent cortex "against the flow," and risk producing false-negative results the closer the area of interest is to the AVM. Thus, the failure of activation of an area adjacent to an AVM, a negative activation study, must be interpreted with due caution as function may still reside within that area but may not be demonstrable because of technical limitations.[10] This may be especially so with more evolved cognitive functions such as language that produce smaller changes in relative blood flow than more primitive ones such as sensory-motor functions. This concern for possible false-negative results may be more pertinent for fMR imaging studies because fMR imaging has a much poorer signal-to-noise ratio than fPET.[4] Functional MR imaging is more subject than fPET to a lack of coincidence between sites of increased blood flow and
areas of increased neuronal activity because fMR imaging reflects phenomena occurring within small veins that drain the activated site but fPET reflects activity within the parenchyma itself.[4,11] This is all the more pertinent in patients with AVMs because the venous drainage may be dramatically altered. Functional MR imaging may thus prove to be too unreliable to be used in therapeutic decision making in patients with AVMs.

**Activation of Eloquent Areas**

The results of functional imaging in AVM patients have been encouraging.[7-9] Sensorimotor activation of the central region appears to be reliable and thus useful in deciding which patients to treat and what therapeutic modalities to use.[7,9]

Functional imaging of language areas warrants special mention. The anterior speech area (Broca's area) resides within the third frontal convolution in Brodmann's areas 44 and 45.[14,16] The frontal lobe beyond areas 44 and 45 is also the seat of some aspects of language. Thus, the ventrolateral area within Brodmann's area 47 and the contiguous dorsolateral area within Brodmann's areas 9 and 46 are important for lexical search and retrieval processes of single words; translation tasks also appear to activate this region.[3,12,15] This region was the site of an AVM in one of our patients (Fig. 4). She was fluent in Inuktitut, her native tongue, and in English. Immediately following resection of the AVM she had pronounced difficulties in lexical search and retrieval, including translation; however, primary speech function remained intact. She subsequently improved to her baseline status. The posterior speech area (Wernicke's area) is located within the midposterior temporal lobe in the first temporal convolution behind the level of Heschl's gyrus and in the second temporal convolution behind the level of the Rolandic fissure, in Brodmann's areas 20 and 21, and in the inferior parietal lobule, composed of the angular and supramarginal gyri, in Brodmann's areas 39 and 40. The inferior aspect of the temporal lobe corresponding to Brodmann's area 37 may be involved in visual aspects of language processing. All of these areas can be activated with appropriate tasks and one must be certain that a specific task is appropriate for the site in which the lesion resides if reliable data is to be obtained. Such specific tasks are currently in the phase of validation in normal volunteers so that it may be premature to apply some of these tasks to clinical cases outside of those academic settings in which such validation is taking place. A third minor region involved with language function resides within the dominant supplementary motor area.

**Functional Reorganization and Cerebral AVMs**

Functional imaging can also address the question of functional cortical reorganization, a phenomenon sometimes seen, perhaps apocryphically, to occur in patients with cerebral AVMs.

That language function can migrate from one hemisphere to the other, usually from the left to the right, is well known.[17] Such transhemispheric reorganization is seen almost exclusively in patients with early brain injury severe enough to also cause a change in handedness. The investigators who established the occurrence of transhemispheric reorganization using the intracarotid injection of Amytal excluded patients with cerebral AVMs for fear that there would be diversion of the Amytal to the hemisphere containing the AVM with contralateral carotid injection and that ipsilateral injection would result in redirection of the Amytal away from eloquent areas through the arteriovenous fistula, thus confounding their results. Our own data do not suggest that there is an overrepresentation of left handedness in our patients with cerebral AVMs residing in the left hemisphere (our unpublished observation). Thus, the first requirement of functional reorganization, left handedness, is not met. Furthermore, the one patient...
reported here whose AVM was in the language-dominant right temporal lobe remained right handed and the posterior speech area where the AVM resided did not shift to the other side. In another patient the AVM resided within the left temporal lobe and fPET demonstrated language activation in the right hemisphere in areas homologous to those classically seen with left hemisphere language dominance.[9] This patient remained right handed, and both speech areas were in the right hemisphere, not just the posterior one as might be expected had there been reorganization.[16] In the absence of statistical analysis it is impossible to state whether the right hemisphere language dominance in this patient reflects the effect of the AVM occupying the left temporal lobe or is simply a manifestation of the observed incidence of right hemisphere language dominance seen in the population as a whole. The interest of this case, however, is in the demonstration that when language is predominantly in the right hemisphere that it is organized in an identical fashion, involving the same areas, as when it is in its more usual left-side location.[9] Thus, the most that one can say about transhemispheric reorganization of language in patients with AVMs is that if it occurs more frequently than in the general population it does so inconsistently and counterintuitively.

The contention that an AVM can displace language or other function within the same hemisphere is also problematic. Direct evidence of this is lacking and our own operative experience does not support it. Indeed, one of the patients reported here with an AVM in the motor-hand region maintained motor-hand function in the precentral gyrus as documented by intraoperative cortical mapping while the patient was under local anesthesia.[7] Similarly, in the patient whose AVM was in the language-dominant right temporal lobe fPET failed to demonstrate transfer of language to the other side; perhaps the activated region remained intimately associated with the AVM. For the concept of cortical reorganization due to the occupation by an AVM of the area in which a particular function is known to reside to be validated, a specific function must be demonstrated to reside outside of its usual Brodmann area. Such a demonstration can only be achieved with functional scanning if probabilistic maps within standardized stereotactic space are available, allowing precise determination of the location of peaks of activation and of the lesion to specific Brodmann areas.[2,20]

The potential effects of shunting through the arteriovenous fistula and the technical limitations of fMR imaging in this context, producing false-negative results, have already been discussed.[4,11]

CONCLUSIONS

Functional brain imaging has already achieved credibility as an insightful research instrument in normal volunteers. With the availability of appropriate MR imaging technology, functional imaging is now poised to become a useful diagnostic tool. When applied to patients with AVMs we have observed that identification of the pre- and postcentral gyri with fPET is reliable and is thus a useful adjunct to patient management. The potential usefulness of fPET, and presumably fMR imaging, in patients with lesions in putative language areas will depend on the development and validation of language-activation tasks specific to particular sites within the speech regions subserving different aspects of language.

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