Paradigms for Clinical fMRI

The block design, in which several cycles of two cognitive different states are compared, is the most useful form of cognitive paradigms used clinically (Marquart et al., 2000). The event-related design (Rosen et al., 1998; Richter, 1999), in which many cycles of short duration stimuli (~1 sec) are presented with longer rest periods (~15 sec), can be used if the appropriate synchronization control system and analysis software are available. The single-event design has the advantage of allowing each event to be examined and grouped according to the specific behavioral response to each event; however the transient blood oxygenation level dependent (BOLD) effect for each event is small, thereby requiring extensive image averaging to reach BOLD detection thresholds. Given the need for robust results in the shortest duration testing, the two-condition block design is the simplest to implement on clinical machines.

Given the neurosurgical concern with preservation of eloquent cortex, brain functions of particular interest are primary sensory (e.g., visual, auditory) and motor functions, and high level processing of language comprehension and expression. Compromise of these functions is usually readily apparent clinically and the quality of life of the patient is severely diminished. Functional MRI offers a means to locate these functions, thereby allowing the surgeon to plan on preserving these functions, or prepare the patient appropriately. Only four paradigms will be described as other paradigms can be derived from the same principles (Thulborn, 1999).

PARADIGMS

Basic Clinical Paradigm 1: Language Comprehension

Various modifications of this task have been described elsewhere (Just et al., 1996; Thulborn et al., 1999a). A central fixation condition (30 sec) is compared to a reading condition (30 sec) in which a simple sentence is read, followed by answering a question as TRUE or FALSE by depressing a finger switch. The record of the answers provide a behavioral measure of task performance (response time and accuracy), which is useful to verify that the task is being completed as requested.

Basic Clinical Paradigm 2: Eye Movement (Visually Guided Saccades)

This group of tasks has been described in detail elsewhere (Luna et al., 1998; Luna and Sweeney, 1999). The central fixation condition (30 sec) is compared to a condition (30 sec) in which the patient is asked to make saccadic eye movements to a spot of light randomly appearing at one of five locations spanning about 20° along the horizontal meridian.

Basic Clinical Paradigm 3: Motor Cortex (Finger-Thumb Apposition)

This task compares a finger-thumb apposition condition (30 sec) to a rest condition (30 sec). The pattern of finger thumb apposition can be made unilateral or bilateral and vary from very simple (index finger to thumb) to more complex patterns. This is a robust activation response usually requiring only a couple of cycles in a cooperative patient. Even motivated patients with compromised function and limited movement capability can produce useful maps. The use of other body parts such as arms, legs and feet tend to increase head motion unless restricted in extent.

Basic Clinical Paradigm 4: Visual Cortex

Primary and association visual cortex can be robustly activated by comparing central fixation in a dark field condition (30 sec) with a flashing checkerboard condition (black and white, 8 Hz, 30 sec). The checkerboard stimulus can be presented as whole visual field, alternating left-right hemifields or combinations of upper-lower and left-right quadrant fields. The robustness of this stimulus minimizes the duration of these studies to a few minutes.

COMMENTARY

Background Information

The interpretation of activation maps from single patients in the setting of disease has some uncertainty. Test-retest data is usually not available. The disease process and medications used to treat it may disturb the normal hemodynamic coupling to local neuronal activity. A conservative interpretation of activation maps is applied only to the regions of established normal physiology. These regions can be defined readily

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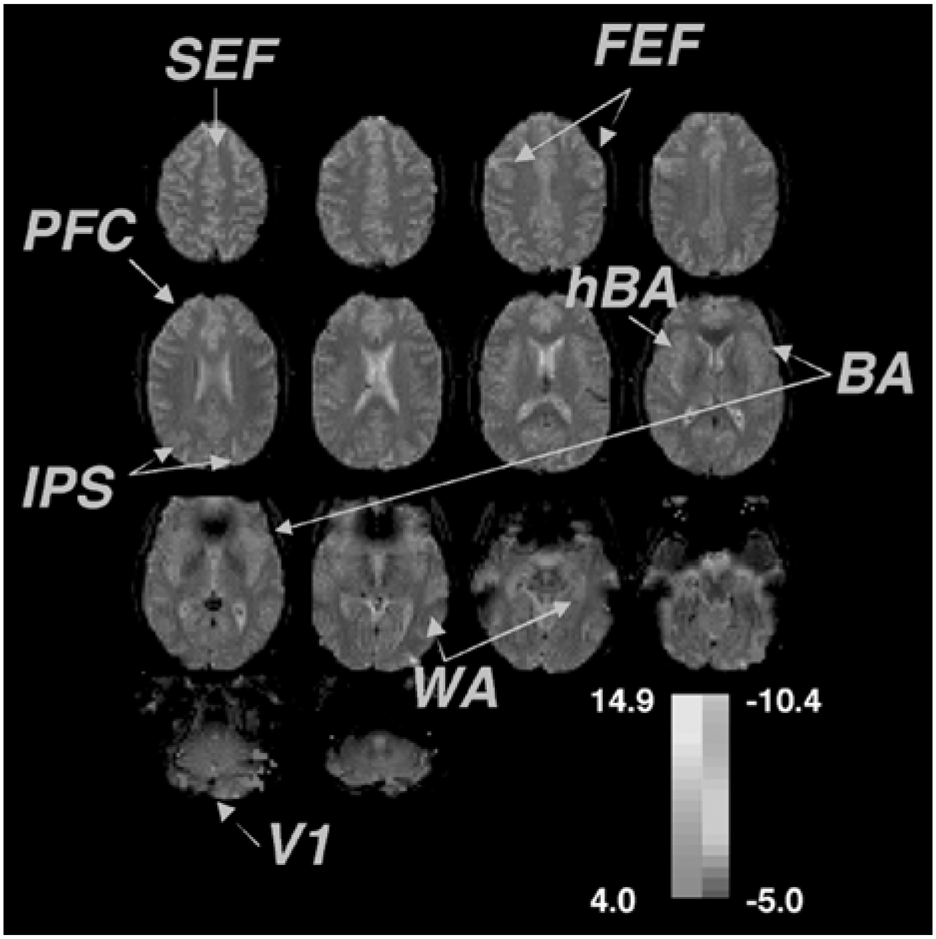

Figure A6.3.1 Representative activation map at 1.5 T for the language paradigm, showing extensive network activation with areas of frontal eye fields (FEF, precentral sulcus), supplementary eye fields (SEF, medial frontal cortex), intraparietal sulcus (IPS), prefrontal cortex (PFC), Broca's area (BA, left inferior frontal cortex), homologous Broca's area (hBA, right inferior frontal cortex), Wernicke's area (WA, left superior temporal gyrus), and visual cortex (V1, calcarine sulcus). This pattern is observed in adults irrespective of gender or handedness. The color scale indicates the *t*-test statistic for activation. The higher *t*-statistic (yellow) has greater statistical significance. **See color plate.**

with perfusion and diffusion MRI studies. A provocative test of hemodynamic reserve could be used such as with vasodilators (i.e., carbon dioxide or acetazolamide). Until there is greater clinical experience, such tests should be used when presurgical mapping is contemplated. Such cases usually require intravenous contrast enhancement to characterize the lesion so that a quantitative perfusion study can be made with the same contrast bolus (Thulborn et al., 1999b).

Having established the regions of the brain in which an interpretation can be rendered, each paradigm requires a pattern of activation in a matched normal population. The activation patterns in normal groups of adults presented in the Figures A6.3.1 to A6.3.4, which are provided to give a basis for such interpretations. No differences across gender or age parameters have been observed by the authors. This does not exclude the possibility that more detailed studies of larger groups may reveal subtle variations in the future.

Critical Parameters and Troubleshooting

When the clinical question relates to mapping language and the expected activation map has not been derived, there is a logical set of steps to take to understand the problem. Head motion is typically the problem, which can easily be checked by viewing the images in an animation loop on a computer screen. Alternatively, head motion can be quantified using software with coregistration algorithms. Head motion will increase in any patient who is

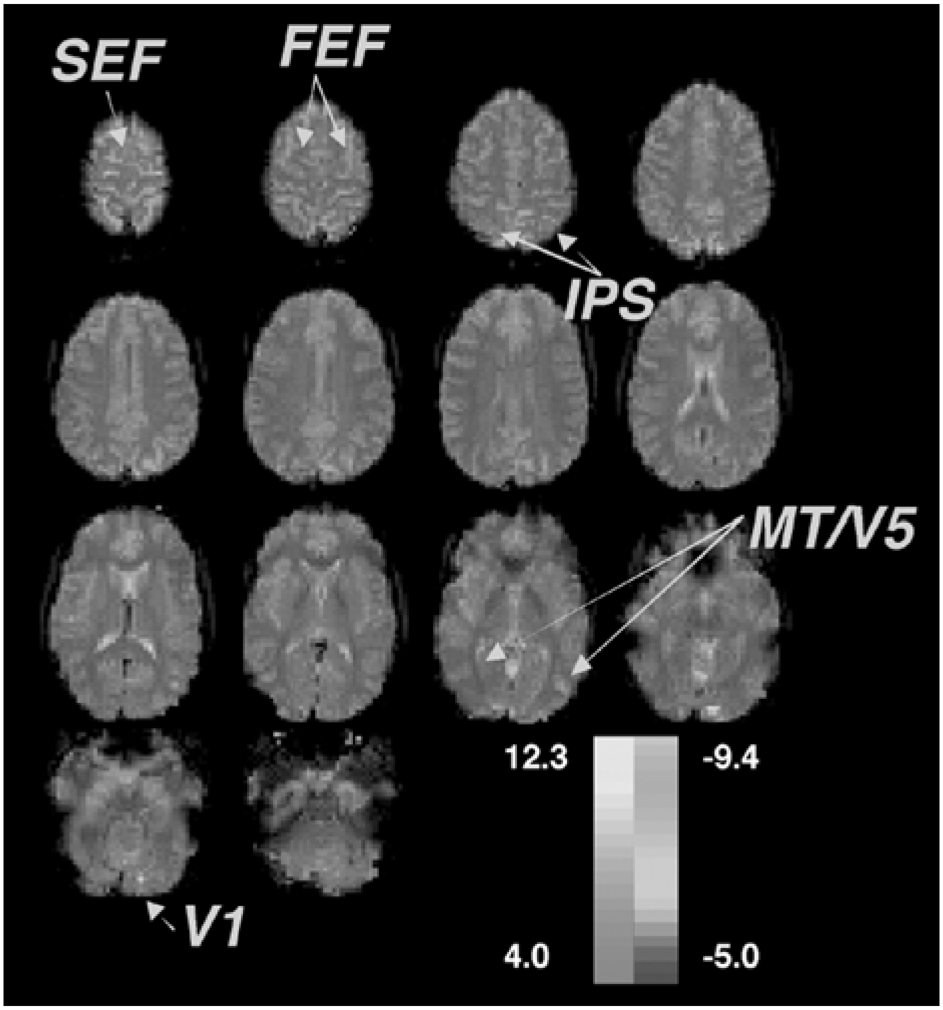

Figure A6.3.2 Representative activation map at 1.5 T for the visually guided saccade paradigm which is used as a control for the language paradigm. The areas of activation (FEF, SEF, IPS, V1, MT/V5) are similar except for the absence of Broca's (BA) and Wernicke's areas (WA), involved in language comprehension. This pattern is observed in both young and elderly adults. **See color plate.**

uncomfortable in the scanner or who does not understand the requirement for immobility during scanning. This can be considered a failure of patient preparation. An active educational process with the staff is important to build skills for performing fMRI on patients. If head motion is not the problem, patient cooperation can be verified by examining the behavioral responses. If there is a poor success rate for answers to questions on the simple sentences to be read, then the patient may have closed their eyes or may have a visual acuity problem that required correction with MR-compatible spectacles. Quality assurance (*UNIT A6.2*) on the scanner can be checked, but if this is the problem the study should not have been performed. Examination of the visually-guided saccade (VGS) paradigm results may indicate that the patient may produce weak BOLD contrast. This may relate to medications or severe cerebrovascular disease with compromised hemodynamic reserve. In some circumstances, a vasodilation perfusion study could be used to verify this possibility, if there is a clear medical indication for this study.

Anticipated Results

A representative activation map for the language paradigm at 1.5 T is shown in Figure A6.3.1. Activation is observed in Wernicke's area (superior temporal gyrus, usually left hemisphere and often bilateral), Broca's area (inferior frontal lobe, usually left hemisphere and often bilateral), frontal eye fields (FEF, precentral sulcus bilaterally), supplementary eye fields (SEF, medial frontal cortex bilaterally), intraparietal sulcus (IPS, bilaterally) and visual cortex (V1) bilaterally. The FEF, SEF,

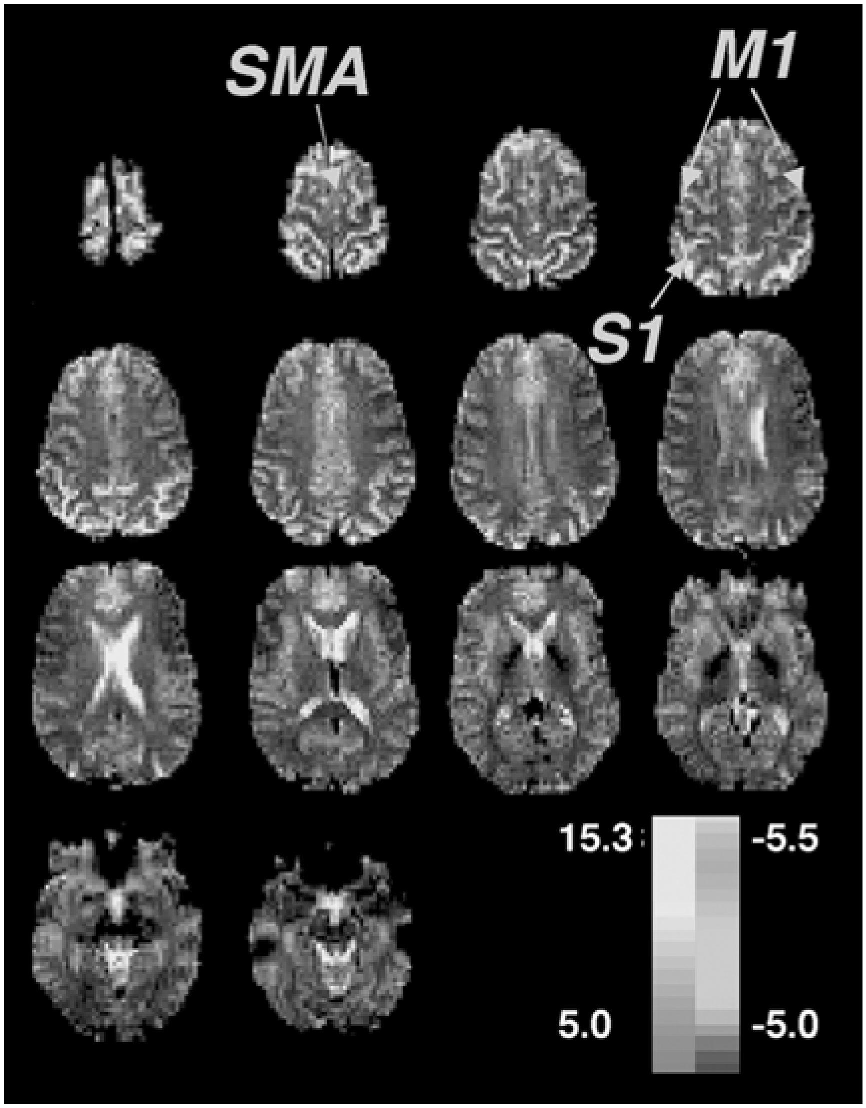

Figure A6.3.3 Representative activation map at 1.5 T for the motor paradigm with bilateral finger-thumb apposition in which motor (M1), supplementary motor area (SMA), and somatosensory (S1) activation are observed. This pattern has been reported in normal adults from multiple laboratories. **See color plate.**

and IPS areas are activated in eye movement paradigms and appear to be related to eye movement during reading. This paradigm is particularly useful as it probes frontal, parietal, temporal, and occipital lobes in a single study. The duration of the paradigm can be less than 10 min. For children or adults in whom reading skills may be deficient, an auditory presentation has been used successfully (Binder et al., 1994; Wessinger et al., 1997; Booth et al., 1999). Because of the loud noise of the scanner, auditory presentation requires careful thought about use of MR-compatible earphones with ear plugs. Ear lobe compression by earmuffs can produce discomfort and increase motion.

A representative activation map for the VGS paradigm at 1.5 T is shown in Figure A6.3.2. This trivial task can be performed by every cooperative patient and even demented patients (Thulborn et al., 2000). It produces robust activation in similar regions to the language paradigm except for Wernicke's (language comprehension) and Broca's (language expression) areas. This paradigm is a useful control study for language mapping to ensure that the BOLD contrast sensitivity is sufficient for the patient of interest.

A representative activation map for the motor paradigm at 1.5 T is shown in Figure A6.3.3. The activation patterns show both primary motor and somatosensory cortex activation along

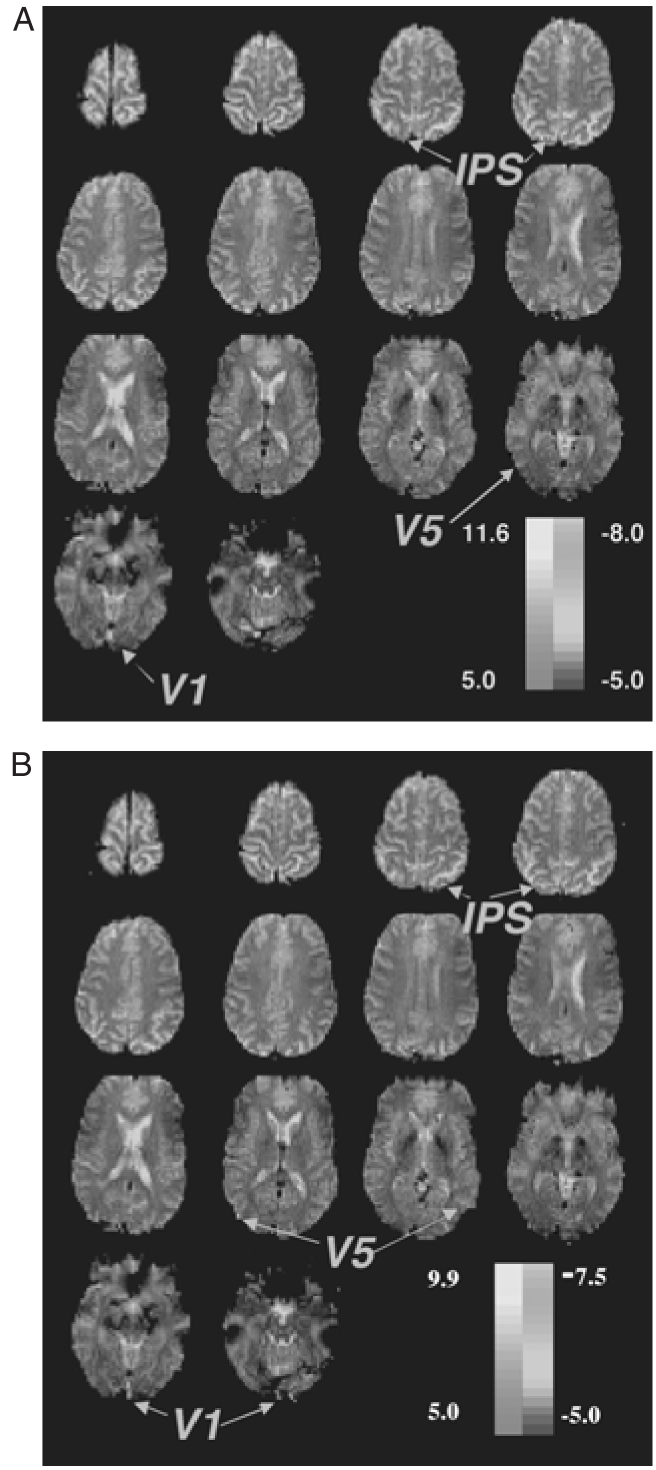

Figure A6.3.4 Representative activation map at 1.5 T for the visual paradigm in which a flashing checkerboard stimulus is shown to the (**A**) left upper quadrant and (**B**) right upper quadrant. The clear contralateral activation in the calcarine fissure indicates that the subject did maintain central fixation for the entire task. Bilateral stimulation indicates lack of central fixation. V5 (also termed MT) is the area of visual association cortex involved in detection of visual motion. IPS and V1 are the intraparietal sulcus and primary visual cortex, respectively. **See color plate.**

the precentral gyrus and postcentral gyrus, respectively. Supplementary motor cortex along the medial frontal cortex is also activated.

Representative activation maps for the visual paradigm at 1.5 T are shown for visual stimulation localized to the left and right upper quadrant fields in Figure A6.3.4A and A6.3.4B, respectively. The activated visual cortex along the inferior bank of calcarine sulcus in the occipital lobe is activated in the contralateral hemisphere. Activation is also present in the intraparietal sulcus and in the visual motion area of MT/V5.

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