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Looking into the Black Box: New Directions in Neuroimaging

Minireview

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Recent advances in functional magnetic resonance imaging (fMRI) are leading to the emergence of a new kind of neuroimaging study. Traditional positron emission tomography (PET) and fMRI studies localize the cortical areas that are active when people perform a specific mental operation. More recent fMRI studies investigate the computational properties of cortical areas that are already well localized.

Functional Anatomy Using PET and fMRI

Both PET and fMRI measure brain metabolism as a proxy for neural activity (reviewed by Cherry and Phelps, 1996; Cohen, 1996). Local increases in neural activity give rise to local increases in glucose consumption and blood flow. PET can measure changes in either of these quantities by counting emissions from a radioactive tracer. The most popular fMRI method, the blood-oxygenation level–dependent technique (BOLD), measures changes in the relative amounts of oxygenated and deoxygenated hemoglobin that accompany increased blood flow. MRI is sensitive to these changes because the two forms of hemoglobin have different magnetic properties.

Currently, researchers use PET and fMRI mainly to study functional anatomy. The goal of this research is to find the areas in the brain that support a given function. Studies usually compare brain activation under two conditions that are carefully chosen to isolate some mental operation. Selectively activated locations are candidate areas for performing the function in question.

For example, a recent imaging study (Schacter et al., 1996) measured activation with PET while subjects viewed lists of words. Prior to the PET session, subjects heard and studied a list of words. During the PET session, subjects were visually presented with mixed lists that contained words from the studied list and unstudied "distractor" words. The task was to categorize each word as being a studied word or a distractor. Activity was compared between two conditions: one in which subjects correctly categorized most of the studied words and distractors, and one in which subjects falsely identified many distractors as having been heard during the study session. Accurate recognition selectively activated an area in auditory cortex. One interpretation of these results is that accurate memory retrieval involves the recollection of the sensory details that were present at the time of study (e.g., the specific sound of the word), and that no such details exist for falsely recognized nonstudied items.

Studies of functional anatomy have been very successful at identifying cortical areas that are relatively specialized. In the visual system, for example, areas have been uncovered that are more or less selectively responsive to motion (e.g., Tootell et al., 1995, and references therein), faces and objects (reviewed by Kanwisher et al., 1996), and illusory contours (Hirsch et al., 1995; for a recent review of many visual areas, see Tootell et al., 1996). Traditional studies also helped to localize cortical areas that support other senses, motor tasks, and a wide variety of cognitive abilities (reviewed by Roland, 1993; Raichle, 1994; and Ungerleider 1995; for a sampling of current research, see Raichle and Goldman-Rakic, 1996). One problem with experiments on functional anatomy is that most conditions activate many areas. Because of this, it may be difficult (or impossible) to find a pair of conditions that selectively activates only a given area of interest. As a result, many studies report a bewildering number of active areas, and this number is only growing larger as the sensitivity of imaging techniques improves.

Once a functional area is localized, further study is needed to determine more precisely what the area computes and how that computation is performed. For a variety of reasons, including limitations due to poor signal to noise and spatial resolution, such studies have been rare in the human neuroimaging literature.

Measuring Inside Cortical Areas

Recent results, however, indicate that fMRI is capable of looking within individual functional areas to investigate their computational properties. Specifically, these studies demonstrated that fMRI can both measure responses from patches of cortex that are much smaller than entire functional areas and measure parameteric variations in the level of activity of these patches of cortex.

One reason to believe that fMRI can make such measurements comes from comparisons with intrinsic optical imaging, which has measured submillimeter structures in animal cortex, including ocular dominance columns and orientation pinwheels (see the review by Bonhoeffer and Grinvald, 1996). Intrinsic optical imaging measures neural activity by recording local changes in the reflectance of the cortical surface. Two pieces of evidence suggest that this method and BOLD fMRI share a common source of signal. First, the changes in cortical reflectance used by optical imaging arise at wavelengths that are consistent with the spectra of oxy- and deoxy-hemogolobin (Malonek and Grinvald, 1996). The signal measured by BOLD fMRI, as noted above, also depends upon the two kinds of hemoglobin. Second, the contribution of deoxy-hemoglobin in optical imaging has a distinctive time course: a long decrease in deoxy-hemoglobin signal follows an initial 2 s increase. Recently, this same temporal pattern was measured using fMRI, appearing as a short "dip" followed by a longer rise in signal (using the BOLD technique; Menon et al., 1995). If the two techniques share a common source of signal, then fMRI may be able to approach the spatial precision of optical imaging.

Several studies have measured fine retinotopic structure within early visual areas using fMRI (Engel et al., 1994, 1996; Sereno et al., 1995; DeYoe et al., 1996). In early visual areas, the spatial arrangement of receptive fields maintains the topography of the retina; nearby neurons represent nearby parts of the visual field. The fMRI studies measured this retinotopic organization using a technique that temporally codes receptive field

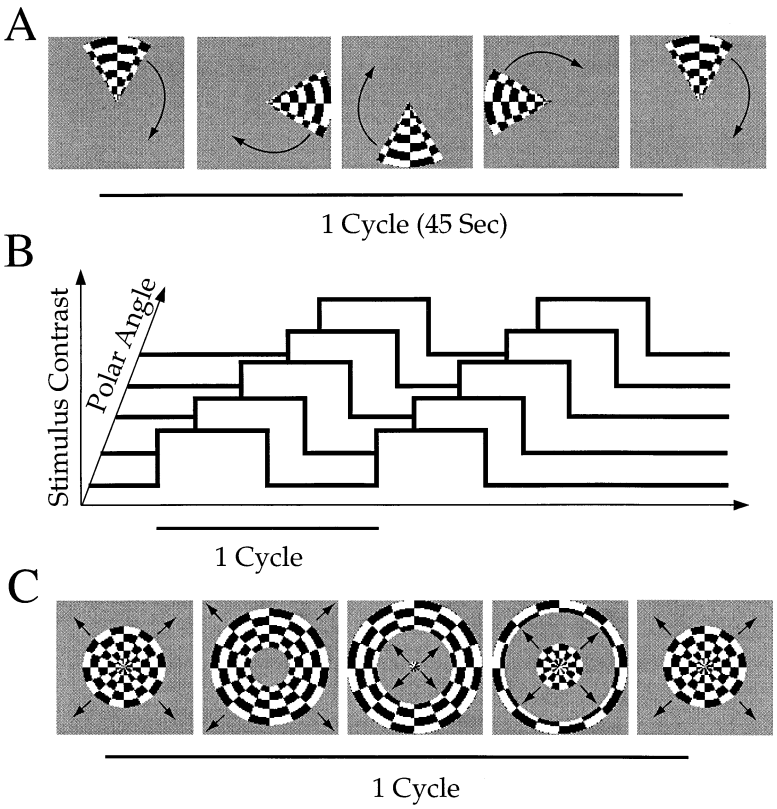

Figure 1. Stimuli Used to Map Retinotopic Organization in Cortex

Stimuli are composed of a contrast-reversing checkerboard pattern flickering at a high temporal rate (e.g., 8 Hz).

(A) A rotating stimulus is shown at five moments in time spanning one stimulus cycle; a typical cycle length is 45 s.

(B) At each location within the visual field, the stimulus alternates with the uniform gray field. Visual field locations further along the direction of rotation receive stimulation later in time. Hence, this stimulus encodes polar angle (Θ in a polar coordinate system) as temporal delay. Two stimulus cycles are shown.

(C) An expanding stimulus is shown at five moments in time spanning one stimulus cycle. This stimulus encodes eccentricity (distance from the fixation point; *r* in a polar coordinate system) as temporal delay.

locations with respect to a polar coordinate system centered on the fovea (Figure 1). To measure the polar angle of receptive fields, subjects view a wedge or several wedges filled with a flickering checkerboard pattern. The wedge rotates slowly in the visual field, much like the second hand of a clock. In these displays, each visual field location alternates between flickering checkerboard and blank background. This alternation is delayed at visual field locations further along the direction of rotation compared with locations closer to the starting point of the stimulus. Hence, the delay in the stimulus at each location in the visual field reflects the polar angle of that location. A similar stimulus, consisting of an expanding ring of flickering checkerboard, maps eccentricity (radius in polar coordinates). In studies using these stimuli, measured fMRI activity rose and fell in response to these stimuli, as the flickering checkerboard moved through the portion of the visual field represented at each cortical location. The delay of the measured fMRI activity varied systematically across cortex and indicated what part of the visual field each cortical location represented.

This technique has been widely used to segregate early visual areas. The rotating stimuli are ideal for this purpose because in primates retinotopic organization with respect to polar angle in V2 is the mirror reversal of the organization in V1 and V3. Studies of monkey cortex, for example, show that as one moves in cortex from V1 toward V2, measured receptive fields move toward the vertical meridian that defines the V1/V2 border (see references in Sereno et al., 1995; DeYoe et al., 1996; Engel et al., 1996). As one enters and continues into V2, receptive field locations move back toward the horizontal meridian that defines the V2/V3 border. As one continues measuring receptive field locations in V3, they move back toward the vertical meridian. fMRI studies uncovered human analogs of V1, V2, and V3/VP by finding these same reversals of retinotopic organization in human cortex (Sereno et al., 1995; DeYoe et al., 1996; Engel et al., 1996; these results are reviewed by Tootell et al., 1996). Figure 2 is an example of measured delay in the fMRI signal in response to a rotating stimulus. The organization of delays (which for this stimulus is the organization with respect to polar angle) shows several clear mirror reversals. These mirror reversals mark the borders of early visual areas.

These results also demonstrate that fMRI can measure structure within individual cortical areas; a clear progression of receptive field locations is evident between the borders. The details of retinotopic maps are perhaps most interesting with respect to eccentricity; they help determine the extent to which the foveal representation is overrepresented, or "magnified" in human cortex. Estimating the amount of cortical magnification in human visual areas is an active area of research (Sereno et al., 1995; Engel et al., 1994, 1996).

fMRI studies of retinotopy also allowed the spatial precision of the technique to be quantified. One way to do this is to determine how well it can localize delays. This reflects how well the technique can localize the response to a stationary stimulus, since a signal of a given delay corresponds to the stimulus at one position

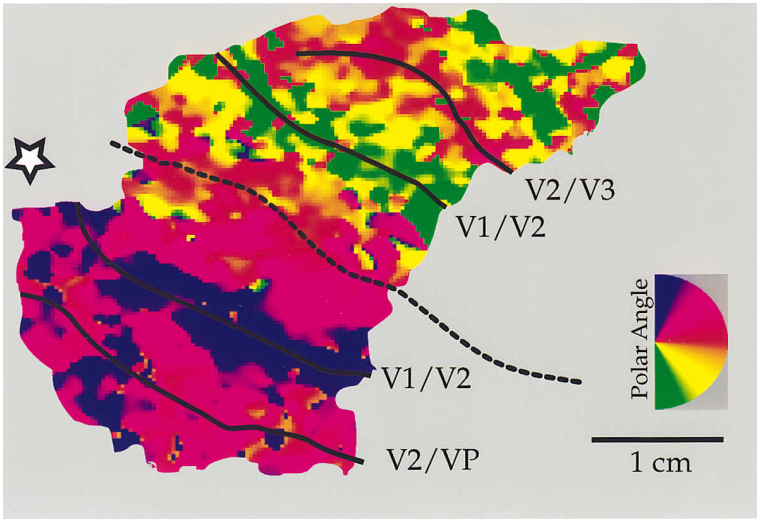

Figure 2. Borders of Early Visual Areas Identified Using Retinotopic Organization Measured with fMRI

Retinotopy with respect to polar angle was measured as delay in the fMRI signal using the rotating stimulus. The data are represented on a computationally flattened medial occipital lobe; up is superior, down is inferior. In humans, V1 is located in the calcarine sulcus, which runs in the medial wall of the occipital lobe; the dashed line traces the deepest part of the calcarine sulcus, and the star indicates the position of the occipital pole. Color represents measured polar angle. Reversals in the change of the polar angle representation can be identified at positions above and below the calcarine sulcus. These are evident as a gradual change toward one color (e.g., from red to green moving dorsally) adjacent to a change in the opposite direction (e.g. from green to red). The reversals near the calcarine identify the boundaries between area V1 and V2. Other reversals identify the V2/V3 boundary and the V2/VP boundary. Data are taken from Engel et al., 1996.

in the visual field. A typical result of these experiments is that on average pixels only 1 or 2 mm apart contain significantly different delays (Engel et al., 1994). Hence, fMRI can localize activity to within 1 or 2 mm. A different way to think about spatial precision is to consider that each pixel in an fMRI image reflects the average neural activity over some patch of cortex. The size of this patch determines the amount of spatial detail visible in the fMRI image and has been measured using the expanding annular stimulus (for details, see Engel et al., 1996). On average, fMRI pixels in V1 reflect activity distributed over cortical patches less than 5 mm in diameter. These numbers represent current upper bounds on the technique that may improve substantially. It remains possible, however, that spatial precision in other cortical areas is worse than these bounds.

Other studies demonstrate that fMRI can measure differential responses to parameterically varying stimuli. In V1, researchers found that fMRI activity increases monotonically with stimulus contrast (Tootell et al., 1995; Boynton et al., 1996). Similar results have been recorded in a human motion area that may be an analog of monkey area MT (Tootell et al., 1996). Finally, in an area selectively activated by objects, activity monotonically decreased as visual noise was added to the stimulus (Malach et al., 1995).

Parameteric studies can provide insight into the representation of information in cortical areas. For example, fMRI contrast response functions measured in area V1 differ from those measured in area MT (Tootell et al., 1995). The MT function resembles contrast response curves measured electrophysiologically from single magnocellular neurons in the macaque, while the V1 function reflects a mixture of parvocellular and magnocellular neurons. This argues that input to the human motion area arises primarily from magnocellular neurons, as is known to be the case in monkey area MT (Tootell et al., 1995).

Parameteric studies also can reveal details of the fMRI imaging process itself. Boynton et al. (1996) measured changes in V1 contrast response as a function of the temporal frequency of the stimulus. The fMRI contrast response functions again resembled the results of V1 single cell recordings, and changing temporal frequency simply scaled the response functions. Because the temporal frequencies used in this study were relatively slow (0.1–0.02 Hz), this scaling was attributed to a temporal blurring of the neural activation by the response of the blood supply. A simple model combining neural activity with a linear vascular response provided a good fit to the data.

Studying Computations within Human Cortical Areas

Collectively, the results reviewed here suggest that fMRI can measure differential levels of activity in relatively small patches of cortex. As a result, investigators can pursue at least two kinds of neuroimaging studies in addition to traditional studies of functional anatomy.

First, fMRI can be used to measure average receptive field properties in small patches of cortex. Examples include parameteric studies of responses to stimulus color, contrast, motion, and spatial pattern measured within identified visual areas. Parameteric studies probe the input/output characteristics of cortical areas more completely than the two condition designs used for functional anatomy. They provide more complete descriptions of how information is represented and processed. Such experiments are typical of electrophysiological research in nonhuman primates, and the results of human studies can be compared to those from other species, providing important tests of model systems (Tootell et al., 1996). Human data will also be uniquely valuable for comparison with behavioral measurements.

Second, fMRI can measure how receptive fields are organized within cortical areas. For example, fMRI should also be able to measure details of cortical maps

in the auditory, somatosensory, and motor systems. It should also be able to reveal large scale computational organization within cortical areas. Examples include regional normalization or suppression of activity, reorganization or plasticity of receptive fields (Karni et al., 1995), and attentional affects.

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