Neuroimaging Weighs In: Humans Meet Macaques in "Primate" Visual Cortex

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Introduction

It has been only a decade since functional magnetic resonance imaging (fMRI) was introduced, but approximately four fMRI papers are now published every working day. Here we review this progress in a well studied system: primate visual cortex.

From pseudocolor to action potentials, and back

One of the most pressing questions now is what does fMRI "activity" indicate, in terms of (electrical) neural activity (Logothetis et al., 2001). Current conclusions about the fMRI–electrophysiology relationship may change as data are acquired from brain areas beyond primary visual cortex, after testing additional stimuli and using different experimental designs and different species (Toth et al., 2001; Devor et al., 2002). Current evidence (Logothetis et al., 2001) suggests that hemodynamic (e.g., fMRI) responses are driven significantly by synaptic activity, rather than only spiking activity. To the extent that this is true, it will be difficult to directly translate fMRI activity into single unit predictions.

This is not a new issue: possible mismatches between single unit and functional mapping results have complicated the interpretation of previous data based on EEG, magneto-encephalography (MEG), deoxyglucose, and optical recording activity. However vexing such issues are, remember that any complete understanding of the brain will explain not only the spiking activity, but also the associated synaptic activity and the hemodynamic (fMRI) responses. Until then, a judicious choice of fMRI timing parameters may minimize spiking-synaptic discrepancies (Logothetis et al., 2001).

How can we interpret current fMRI results in visual cortex?

In some cases this spiking-synaptic distinction is moot, because no discrepancy is predicted. For instance, motion and direction selectivity are found in both single units and metabolic/hemodynamic maps (Zeki et al., 1991; Malonek et al., 1994; Tootell et al., 1995b; Geesaman et al., 1997; Vanduffel et al., 2001) within area MT. In general, any property that is calculated at previous neural levels (here, ascending direction-selective inputs from V1 and elsewhere) should be reflected in both synaptic and spiking measures.

In other cases, the predictions are more complex. For instance, maps of the averaged receptive field center at each sampled cortical location (i.e., cortical retinotopy) should be equivalent to each other, regardless of whether they are based on spiking activity (e.g., single units) or synaptic activity (e.g., hemodynamic maps). However, a related measure, receptive field size, may well differ in the two measures. The (presynaptic) measures of receptive field size could be smaller than the size revealed by (postsynaptic) single units in each area, because receptive field size generally expands at progressively higher-tier areas in the cortical visual hierarchy (Felleman and Van Essen, 1991). Alternatively, the metabolic measures could instead be larger than the single unit measures, because the metabolic maps reflect both excitation and inhibition plus hemodynamic or metabolic spread (Grinvald et al., 1994).

Which "primate" visual cortex?

Ten years ago, visual cortex was already well mapped in macaque monkeys. More than 25 areas had been differentiated, each with its own distinct connections and functional properties (Felleman and Van Essen, 1991). At the same time, human visual cortex was essentially *terra incognita*.

This information gap originated mostly from differing technical constraints. In macaques, visual cortex can be studied using highly informative (but invasive) techniques such as single unit recordings, neural tracers, lesions, microstimulation, histology, deoxyglucose, and optical recording. However, none of these techniques can be used routinely in humans. Instead, human studies relied on noninvasive techniques such as psychophysics, EEG, MEG, positron emission tomography (PET), and transcranial magnetic stimulation (TMS).

Because human results were based on quite different techniques than macaque results, a given mismatch between human and macaque data might arise from either evolutionary or technical differences; such comparisons were ultimately unresolvable. fMRI data has begun to resolve this ambiguity, because fMRI can be acquired from both humans and macaques, using identical experimental procedures. Follow-up experiments in macaque can clarify the single unit activity and the anatomical connections in each fMRI-activated region. Recent studies illustrate this approach (Tsao et al., 2000; Dubowitz et al., 2001; Vanduffel et al., 2001, 2002; Nakahara et al., 2002).

Mapping human visual areas

MRI has now revealed more than a dozen distinct areas in human visual cortex (Fig. 1). Considerable historical "baggage" (controversy) sometimes accompanies these naming and mapping efforts, especially when the data are murky and when the new human data reopen lingering questions in the macaque maps.

In macaques, visual cortical areas are distinguished by four main criteria (Felleman and Van Essen, 1991): (1) retinotopy, (2) global functional properties, (3) histology, and (4) intercortical

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connections. In humans, most visual cortical areas have been revealed by functional MRI, using retinotopic and global functional criteria. Recently, anatomical MRI has begun to reveal histological and connection distinctions between areas as well.

Retinotopy

V1 and V2

Lower-tier human areas revealed by the fMRI retinotopy have proven similar to those in macaque, especially V1 and V2 (Fig. 1). These lower-tier areas are evolutionarily conserved in most mammals (Rosa and Krubitzer, 1999; Vanduffel et al., 2002).

V3

An interesting evolutionary divergence occurs in area V3 (also known as V3 + VP). The retinotopy in macaque V3 is essentially equivalent to that in human V3, except for one feature. In human V3, the polar angle magnification matches that in adjacent V2. In macaque V3, however, this dimension is extremely compressed, distorting the area into a uniquely elongated topography (Fig. 1) (Tootell et al., 1997). It has been proposed that new retinotopic areas evolve by "budding" along the vertical or horizontal meridians; the dimensions of macaque V3 could reflect a middle stage in this evolutionary progression.

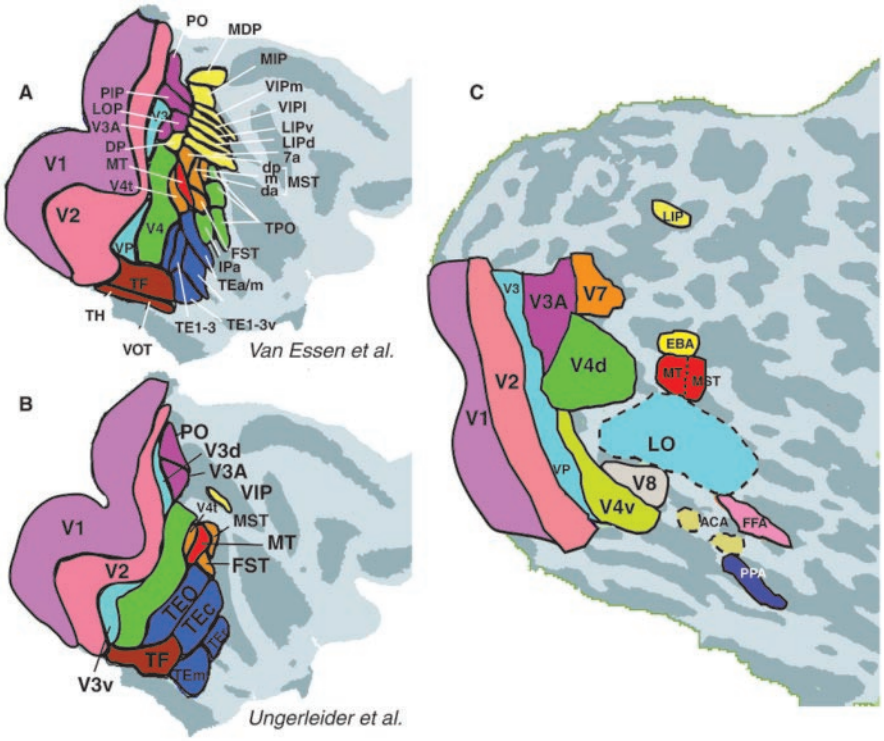

Figure 1. Maps of reported areas in primate visual cortex. Maps are shown on the flattened cortical surface from right hemisphere (light gray, gyri; dark gray, sulci). *A* shows areas in macaque reported by Van Essen and colleagues, and *B* shows the macaque areas reported by Ungerleider and collaborators (adapted from Van Essen et al., 2001). *C* shows areas in human visual cortex, as described in the text. Consensus is highest in lower-tier (generally, left-most) areas; such areas tend to be evolutionarily more conserved, and the retinotopy is more easily resolved.

An old controversy in macaque is whether "V3" and "VP" are independent cortical areas (Burkhalter et al., 1986; Felleman and Van Essen, 1987) or two parts of a common area V3 (Gattass et al., 1988; Lyon and Kaas, 2001). Thus far, these two regions are functionally indistinguishable in the human fMRI, supporting the latter model.

V3A

The next most anterior area was given a misleadingly diminutive name ("V3a" for "V3 accessory") because it was discovered between two neighbors (V3 and V4) that were already named (Zeki, 1978; Van Essen and Zeki, 1978). Nevertheless, V3a is an independent cortical area including a complete map of the contralateral hemifield (Gattass et al., 1988; Tootell et al., 1997), the functional importance of which is increasingly recognized.

In both macaque and humans, V3a has large receptive fields (Gattass et al., 1988; Tootell et al., 1997), which are involved in wide-field visual computations. Such calculations include processing of binocular disparity (Tsao et al., 2000; Backus et al., 2001), illusory contours (Mendola et al., 1999), and side-inhibition (Gaska et al., 1987).

In macaque, V3 is moderately motion and direction selective (Felleman and Van Essen, 1987; Vanduffel et al., 2001), but V3A is not (Gaska et al., 1987; Vanduffel et al., 2001). In humans, however, this relationship is reversed: V3A is moderately motion selective, whereas V3 is not (Tootell et al., 1997). Thus the retinotopy defining a region is not absolutely linked to the functional properties of that same region. When such properties differ, do we assume homology based on the retinotopic criteria or the functional criteria? Here the retinotopy appears more fundamental (conserved).

V4

Area "V4" is one of the most controversial areas in primate visual cortex. It was named originally in the macaque, for a paired representation of the contralateral upper and lower visual fields, in ventral and dorsal V4 (V4v and V4d), respectively (Van Essen and Zeki, 1978; Gattass et al., 1988). However, almost all studies of macaque V4 were actually done in V4d, because V4d is easily accessible, whereas V4v is not. Such ventral/dorsal distinctions would normally be moot; however, recent evidence suggests that "V4d" and "V4v" may actually be independent cortical areas, mistakenly considered together (Van Oostende et al., 1997; Nelissen et al., 2000; Tootell and Hadjikhani, 2001).

One investigator reported high color selectivity in single units from V4(d) (Zeki, 1973, 1980, 1983a,b), but more quantitative studies revealed no special color bias (Schein et al., 1982; Van Essen et al., 1981; Schein and Desimone, 1990). Moreover, lesions of macaque V4d do not compromise color vision (Walsh et al., 1992; Schiller, 1993; Walsh et al., 1993). Despite the marginal nature of this evidence, color selectivity was often attributed to V4. It was attractive to think of a color "center," in the way that visual motion is selectively processed in area MT.

Independently, evidence was accumulating for a real color center in human visual cortex. The initial evidence came from clinical reports of color vision loss attributable to damage in ventral occipitotemporal cortex ("achromatopsia") (Pearlman et al., 1979; Damasio et al., 1980; Zeki, 1990). Subsequent neuroimaging studies revealed high color selectivity and retinotopy in the same location, which was named V4 (Lueck et al., 1989; McKee-

fry and Zeki, 1997; Bartels and Zeki, 2000), "V8" (Hadjikhani et al., 1998; Tootell and Hadjikhani, 2001), or VO (Wandell, 1999). Additional satellite areas were activated by attention to color differences (Fig. 1) (Beauchamp et al., 1999; Bartels and Zeki, 2000).

The retinotopy of human "V8/V4/VO" (Hadjikhani et al., 1998; Bartels and Zeki, 2000), however, is completely unlike that reported in macaque V4. Furthermore, the human color areas are not located where V4 should be, on the basis of macaque maps (Fig. 1) (Hadjikhani et al., 1998). Instead, the human color areas correspond to the location of anterior areas TEO/TE in macaque maps (Fig. 1) (Hadjikhani et al., 1998; Tootell and Hadjikhani, 2001). Furthermore, lesions including macaque TEO/TE do produce significant deficits of color vision (macaque achromatopsia) (Heywood and Cowey, 1987; Heywood et al., 1988, 1992, 1995). Neuroimaging (Takechi et al., 1997; Vanduffel et al., 1997; Nelissen et al., 2003) and single unit (Komatsu et al., 1992; Komatsu and Ideura, 1993; Missal et al., 1997) studies also reveal color-related activity in these same macaque regions.

This evidence produced a new model in which color is selectively processed not in V4 but instead in or near TEO/TE. This model is topographically consistent across both humans and macaques (Fig. 1), and it matches the existing experimental data quite well.

Candidate retinotopic areas

An additional representation has been reported immediately anterior to V3A, named either "V7" (Tootell et al., 1998a) or "V3B" (Press et al., 2001). Retinotopic details of this area remain unclear, partly because this retinotopic representation is statistically noisy, and it has no certain counterpart in macaque (Fig. 1).

Single unit studies reported a consistent retinotopic organization in area MT in several primate species (Allman et al., 1973; Van Essen et al., 1981); however, it has been difficult to reveal retinotopy in human MT+. Instead, fMRI studies distinguished between presumptive areas MT versus MST in human MT+, on the basis of properties related to the classical contralateral retinotopy (Huk et al., 2002).

To reveal retinotopy in a given area, the stimuli must first activate the cells in that area. For example, Malach's group (Hasson et al., 2002) revealed gross retinotopic activation in lateral occipital (object-selective) cortex by using visual objects arranged as retinotopic stimuli. Earlier retinotopic stimuli (using simple geometrical stimuli) had apparently not activated the cells there. In retrospect, it may be oversimplistic to subdivide cortex into areas that are "retinotopic" versus "nonretinotopic." This distinction now appears to be a continuum, not a dichotomy.

Sometimes, both cognitive and sensory factors need to be considered. After optimizing both the spatial attention and the sensory stimuli, Sereno et al. (2001) unveiled a new retinotopic area in parietal cortex, well beyond conventionally defined "visual" cortex. Conceptually, this is consistent with previous fMRI in occipital (visual) cortex. Typical maps of cortical retinotopy have been produced by manipulating sensory stimuli, without deliberately varying spatial attention (Engel et al., 1994; Sereno et al., 1995; Tootell et al., 1995b, 1997). However such "sensory" stimuli may also include exogenous attention cues. In fact, maps indistinguishable from cortical "retinotopy" were recently demonstrated in the reverse way, by instead manipulating spatial attention, without changing the sensory stimuli (Tootell et al., 1998a; Brefczynski and DeYoe, 1999; Gandhi et al., 1999; Martinez et al., 1999; Somers et al., 1999). Faced with this seeming equivalence in the sensory and spatial attention maps ("attentiontopy"), some investigators deliberately combined both factors to increase the signal strength of the resulting maps (DeYoe et al., 1996).

Global functional maps

MT/MST

Some visual cortical areas have been defined by differences in global functional properties (criteria 2, above). One example is human MT(+), which responds better to moving stimuli compared with stationary stimuli (Zeki et al., 1991; Dupont et al., 1994; Tootell et al., 1995b; Goebel et al., 1998; Sunaert et al., 1999). Several studies since distinguished between presumptive "MT" and "MST" in human "MT+," on the basis of differences in higher-order motion processing (Neri et al., 1998; Dukelow et al., 2001). However, it is difficult to specify the exact size of areas revealed by global functional maps, because this depends on the experimental sensitivity and the threshold chosen, above an accepted minimum. This has been called the "iceberg" problem. Both icebergs and functional activity are visible only above a certain threshold, yet both reflect substantial subthreshold effects.

Lateral occipital complex

"LOc" is a "complex" of multiple areas in "lateral occipital" cortex that share a greater fMRI response to images of objects, compared with non-object controls (Malach et al., 1995; Grill-Spector et al., 2001). Results in LOc are consistent with earlier electrophysiology in comparable regions of the macaque (Vogels, 1999) and human PET studies (Sergent and Signoret, 1992; Kanwisher et al., 1996). Elegant fMRI refinements confirmed that parts of LOc are deeply involved in object recognition (Grill-Spector et al., 2000; James et al., 2000; Bar et al., 2001; Kourtzi and Kanwisher, 2001; Lerner et al., 2002). Such refinements also localized regions that generalize across lower-order visual cues including size, shape, and perhaps viewpoint (Grill-Spector et al., 1999; Vuilleumier et al., 2002) as one might expect in a truly "object-selective" computation. Figure 2 shows the correspondence of LOc in both human cortex and macaque cortex, using equivalent fMRI techniques in both species of awake, behaving primates.

One refinement exploited in LO studies was "fMR-A" (fMRI adaptation) (Grill-Spector and Malach, 2001). FMR-A assumes that brain regions will adapt (decrease fMRI response) to repeated presentations of stimuli that are neurally indistinguishable. Conversely, the fMRI signal will remain at higher levels when stimuli are neurally differentiable. Contemporary fMR-A approaches are rooted in earlier experiments showing adaptation to stimulus direction (Tootell et al., 1995a; Culham et al., 1999; He and MacLeod, 2001), color (Sakai et al., 1995; Hadjikhani et al., 1998), and orientation (Tootell et al., 1998b). Such adaptation techniques can even furnish quantitative (bandwidth) measurements of orientation selectivity (Tootell et al., 1998b).

Fusiform face area

Neuropsychology, direct electrical recordings (Allison et al., 1999; Bentin et al., 2002), and neuroimaging (Sergent and Signoret, 1992; Haxby et al., 1996; Puce et al., 1996) all suggest that a specific region in the fusiform gyrus responds selectively to images of faces. In a comprehensive study, Kanwisher et al. (1997) confirmed this face selectivity relative to a wide range of controls and named the region fusiform face area (FFA). This basic face/non-face distinction has been replicated consistently in many laboratories (Puce et al., 1996; Allison et al., 1999; Halgren et al., 1999; Haxby et al., 1999; Tong and Nakayama, 1999; Hoffman and Haxby, 2000; Hasson et al., 2001), a significant accomplish-

ment in itself. Control experiments ruled out many competing interpretations of the "face-selective" activation, including attention, animate–inanimate distinctions, lower-level visual features (Kanwisher et al., 1997), and eye gaze (Hoffman and Haxby, 2000).

Recently, FFA has become the focus of a renewed nature–nurture debate (Kanwisher, 2000). Do the FFA responses reflect an innate predisposition to discriminate face stimuli because facial recognition has clear survival value in the social life of primates? This possibility is supported by "preferential looking" experiments in newborns (Johnson et al., 1991), and by neuropsychology (Le Grand et al., 2001).

Alternatively, perhaps the FFA is an "expertise" center, responding better to any overtrained visual stimuli, including (but not limited to) faces (Tarr and Gauthier, 2000). One notable study tested car stimuli versus bird stimuli in car experts versus bird experts: the overlearned stimuli did produce relatively more fMRI activity in FFA in observers of the matched category (Gauthier et al., 1999). This evidence for a learned component led Tarr and Gautier (2000) to reinterpret the name FFA as the "flexible fusiform area."

Face selectivity has been reported in single units from macaque inferotemporal cortex (Gross et al., 1972; Perrett et al., 1982, 1984; Hietanen et al., 1992; Oram and Perrett, 1992; Rolls, 2000). It is tempting to conclude that these neurons were sampled from a hypothetical macaque FFA. In fact, functional imaging studies suggest that concentrated patches of face-selective cells do exist in macaque inferotemporal cortex (Fujita et al., 1992; Logothetis et al., 1999; Tsao et al., 2001). When not guided by functional anatomy, however, face-selective cells are found only rarely and not in a well defined cortical region (Perrett et al., 1982, 1984; Rolls, 2000). Moreover, such studies can be statistically misleading. If one face stimulus and nine control stimuli are tested, then on average, 1 in every 10 responsive cells will respond most to the face stimulus (be a "face-selective" cell), even in the absence of real face selectivity.

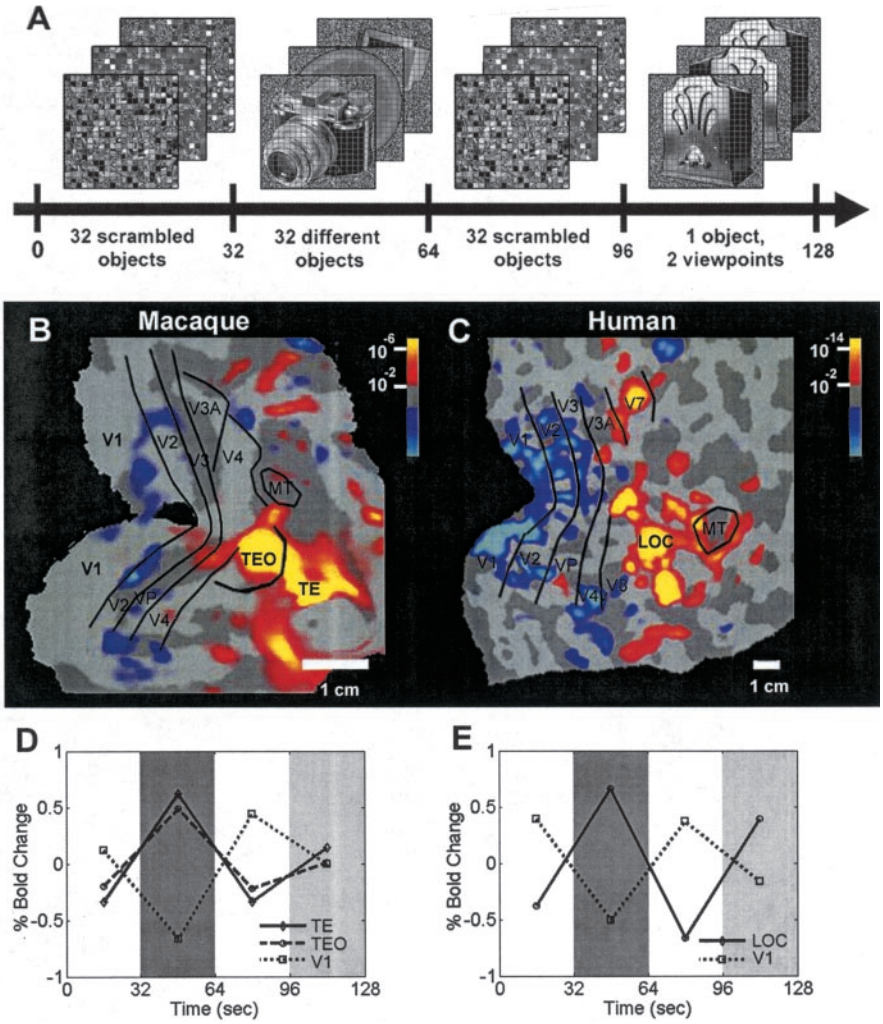

Figure 2. Object-selective (LOc) activation in visual cortex of macaques and humans. In both species, fMRI (BOLD) data were acquired from awake subjects, who fixated the center of a common stimulus set. *A* shows those stimuli, presented in block design in an a– b–a– c sequence (a, 32 grid-scrambled objects; b, 32 different objects; c, one object, presented in two different views). *B* (macaque) and *C* (human) reveal regions activated more by objects than scrambled objects (red-orange) and the reverse (blue-cyan). *D* (macaque) and *E* (human) show corresponding fMRI levels in selected visual areas. The human region activated more by objects (*C*) has been named LOc; it corresponds primarily to higher-tier cortical areas TEO and TE in macaque (*B*). In both species, lower-tier retinotopic areas (e.g., V1, V2, V3) responded better to the control images (scrambled objects), making the reversal in higher-tier areas even more significant. In human LOc and macaque TEO/TE, there was a reduced response to presentations of the single object (condition c, dark gray) compared with the multiple objects (condition b, light gray). Thus macaque shows fMRI-based adaptation in inferotemporal cortex, similar to that in humans. Bold, Blood oxygen level dependent.

Parahippocampal place area

Several fMRI studies described stronger responses to images of places in human parahippocampal cortex (Epstein and Kanwisher, 1998; Maguire et al., 1998; Aguirre et al., 1999). This parahippocampal place area (PPA) activity appears to reflect the encoding of places in memory, not to place-related percepts per se (for review, see Kanwisher, 2000). The evidence for PPA is supported by reports of "place cells" in adjacent hippocampus (O'Keefe, 1979; Georges-Francois et al., 1999) and by neuropsychological patients with "topographic disorientation" associated with damage in parahippocampal cortex (Habib and Sirigu, 1987; Epstein and Kanwisher, 1998; Aguirre et al., 1999).

Extrastriate body area

Quite recently, Downing et al. (2001) described an area activated by images of non-face body parts. Although faces are also body parts, physically connected to adjacent body parts, the face-selective area (FFA) and the body-selective area [extrastriate body area (EBA)] are not adjacent in cortex (Fig. 1). Interestingly, EBA is instead located adjacent to motion-selective MT/MST, in or near region(s) reportedly activated by the perception of biological motion (Grossman et al., 2000).

Alternative perspectives

Presumably further "functional dissection" will clarify these and related issues. In functional mapping, first it is crucial to be able to activate a given area consistently, by any stimulus. After that,

one can easily expand the range of stimuli to more accurately define what the target area "does."

The notion of object- or category-specific areas is appealing but ultimately problematic. For instance, there are far more potential objects and categories than available cortex. Analogous issues have long dogged the interpretation of single unit data from macaque inferotemporal cortex (Barlow, 1972). Recently, Haxby et al. (2001) challenged the entire notion of "category-specific" areas in human object-selective cortex [but see Spiridon and Kanwisher (2002)G. On the basis of correlations, they found that the distributed pattern of response in LOc/FFA was sufficient to distinguish not only between faces and other objects, but between non-face objects as well. This distributed-activity model obviates some problems, but it does not yet unveil the fundamental selectivity of inferotemporal cortical neurons.

On the other hand, the evidence for some sort of object selectivity architecture here is overwhelming, even if we do not yet know what it is. In addition to the above categories, fMRI studies have reported inferotemporal regions selective for images of cars (Halgren et al., 1999), animals (Chao et al., 1999; Maguire et al., 2001), tools (Grill-Spector et al., 1999; Beauchamp et al., 2002), and letter-based stimuli (Puce et al., 1996; Fiez and Petersen, 1998; Hasson et al., 2002).

MRI mapping of cortical connections

To understand brain information processing, it is crucial to know which areas are connected to which. Such maps of anatomical connections can also distinguish between cortical visual areas (criteria 3, above); this is especially important when such areas cannot be functionally distinguished. In macaque, maps of connections are quite detailed (Felleman and Van Essen, 1991; Young, 1992). However, these classical tract-tracing experiments require extensive histology and sampling from many animals.

MR-visible tracer injections

An alternative MR-based approach may reduce these problems. By injecting MR-visualizable compounds, it is possible to trace neural connections without histology (Saleem et al., 2002). Such MR tracing allows multiple deliberate injections, at sites of interesting function or anatomy. This approach can also reveal the route taken by fibers between interconnected areas. Such route information is not furnished by conventional tracers, and it is crucial for interpreting MR diffusion "tracing" data (see below). Unfortunately, this promising approach is no help in human brain, because tracer injections are invasive.

Diffusion tensor imaging

Perhaps human brain connections can be resolved by measuring the diffusion signal in MR images (for review, see Le Bihan et al., 2001). Basically, axons constrain the flow of fluids around and inside them, producing freer diffusion parallel with long axis of the axon. MR imaging can resolve such diffusion anisotropies, but the underlying biophysics is complicated (Norris, 2001).

Diffusion imaging has labeled large and expected connections in human visual cortex (Conturo et al., 1999). Although impressive, such solutions can be unstable: seeding an adjacent voxel can yield very different solutions. It is now crucial to test for unknown neural connections, including error bars or other measures of variability, and to validate diffusion data using classical tracing techniques in the same brains. Moreover, most diffusion approaches (diffusion tensor imaging) cannot disentangle fiber pathways crossing within a voxel (Tuch et al., 2001), and fibers cross often in human brain.

The ultimate question is whether maps of gross diffusion anisotropy can reveal specific (labeled line) connections. Diffusion tracing is like mapping the flow of traffic on major highways: can this ever reveal exactly where a specific car began and ended its trip (J. Culham, personal communication)? Despite these limitations (or because of them), improvements in diffusion mapping have been rapid and significant.

TMS/electrocortical stimulation and PET/fMRI

Another approach to mapping human connections is to combine functional mapping with localized neural stimulation. For instance, Paus et al. (1997) stimulated frontal eye fields using TMS, and PET mapping exposed the resultant activation in parietal cortex. Such approaches might clarify connections to and from lateral and superior visual cortex, but several technical problems (localizing stimulated cortex, stimulating deeply buried regions) must first be resolved. It is more difficult to combine electromagnetic stimulation with fMRI [but see Brandt et al. (2001)].

"Functional" connections

Human neural connections might also be inferred from generalized patterns of functional activity (for review, see Buchel et al., 1999; McIntosh, 1999). This approach is appealingly straightforward, but it requires validation in animal models before the human results can be evaluated.

MRI mapping of histological differences

Cortical areas can also be distinguished by histological differences (criteria 4, above), and MR may reveal some of these noninvasively. For example, the obvious laminar differences in myelination in V1 are now imaged almost routinely (Barbier et al., 2002). On the basis of histological studies, myelin-sensitive imaging could eventually distinguish subtler differences in areas V2 (Tootell et al., 1983; Rosa and Krubitzer, 1999), V3 (Burkhalter et al., 1986), V3A (Lewis and Van Essen, 2000), MT (Allman et al., 1973; Van Essen et al., 1981; Tootell et al., 1985), and LIP/VIP (Blatt et al., 1990) and specific parietal areas (Lewis and Van Essen, 2000). Sophisticated analysis of MR images can also reveal quantitative differences in cortical thickness (Fischl et al., 2002); some areas (e.g., V1) are thinner than surrounding areas.

Conclusions

The macaque brain is often described as a "model" for the human brain, but this is somewhat misleading. The macaque belongs to a completely different zoological family (Cercopithecidae) than humans (Hominidae), reflecting independent evolution over several million generations. The macaque model brain is not just a miniaturized version of the human brain, like a toy car or a doll. Thus studying human brain function is not just an exercise in confirming what is already known from animal studies.

Generally, macaque and human brains differ most in higher-order cortical regions and remain more similar in lowest-tier areas. In terms of cortical surface area, higher-order parietal, temporal, and frontal regions are disproportionately expanded in human cortex, compared with corresponding cortical regions in macaque (Eidelberg and Galaburda, 1984; Van Essen et al., 2001; Simon et al., 2002). In lower-tier areas, this relationship is correspondingly reversed: the percentage of demonstrably visual cortex is ~ 55% in macaques (Van Essen et al., 2001) but only ~ 30% in humans.

Within visual cortex, all known mammals have a primary (V1) area, and primates also have a presumptive V2 homolog (Rosa and Krubitzer, 1999). However after that (i.e., in most visual areas), this one-to-one correspondence breaks down. For

instance, third- and fourth-tier cortical visual areas in Aotus and Macaque monkeys are so dissimilar that their relative homology is uncertain (Baker et al., 1981; Kaas and Lyon, 2001). However, this evolutionary divergence is not always related to cortical hierarchical level: the fifth-tier area MT/V5 seems essentially conserved across all known primates, including humans and macaques.

The level of accepted evolutionary similarity between possibly homologous cortical regions is likely to decrease (not increase) as we learn more. It is easy to assume that macaque area X is equivalent to human region Y, if almost nothing is known about region Y. However, further study will (by definition) reveal more detailed features, any of which may differ across species.

When biological regions and mechanisms do correspond in both macaques and humans, it becomes possible to test all of the transitive links to understand the system at a very deep level (i.e., human psychophysics <> human fMRI <> macaque fMRI <> macaque single units/connections). This is a very exciting approach, which should yield real advances in the near future.

But what about those regions that do not correspond in humans and macaques? For example, recent evidence indicates that motion selectivity differs significantly in area V3A of macaques versus humans (Tootell et al., 1997; Vanduffel et al., 2001). Ironically, this makes it more difficult to study motion selectivity in V3A, at least as a common mechanism in primate cortex. This problem becomes even worse (although more widely recognized) in higher-order cortical regions concerned with language and other "uniquely human" functions. When confronted with such frank discrepancies, our best hope is that (1) insights from "basic" lower-tier mechanisms will generalize to higher-tier mechanisms and (2) new noninvasive techniques will be developed to close the gap further.

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