The case for primate V3

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The visual system in primates is represented by a remarkably large expanse of the cerebral cortex. While more precise investigative studies that can be performed in non-human primates contribute towards understanding the organization of the human brain, there are several issues of visual cortex organization in monkey species that remain unresolved. In all, more than 20 areas comprise the primate visual cortex, yet there is little agreement as to the exact number, size and visual field representation of all but three. A case in point is the third visual area, V3. It is found relatively early in the visual system hierarchy, yet over the last 40 years its organization and even its very existence have been a matter of debate among prominent neuroscientists. In this review, we discuss a large body of recent work that provides straightforward evidence for the existence of V3. In light of this, we then re-examine results from several seminal reports and provide parsimonious re-interpretations in favour of V3. We conclude with analysis of human and monkey functional magnetic resonance imaging literature to make the case that a complete V3 is an organizational feature of all primate species and may play a greater role in the dorsal stream of visual processing.

Keywords: cortical organization; human; primate; vision; visual cortex; visual hierarchy

1. INTRODUCTION

Major technological advances in non-invasive techniques, such as functional magnetic resonance imaging (fMRI), have made it possible to explore cortical organization of the human visual cortex, which occupies a vast breadth of the brain. Many new visual areas as well as homologues to non-human primates have been identified [1–6]. Yet, before lasting conclusions about relative locations and boundaries of human cortical visual areas can be agreed upon, a consensus needs to be reached on the organization of non-human primate visual cortex that can be studied through invasive and more precise methodologies. This is especially important for the organization of the caudal visual cortex, where cortical areas are less specialized across primate species and, as a result, are most likely to resemble those in humans. In non-human primates, while well over 20 visual areas have been proposed, only three visual areas—the primary visual cortex (V1), the secondary visual area (V2) and the middle temporal area (MT or V5)—have been identified using multiple criteria and are considered to be well defined as to their location and extent [7–9].

Just beyond V2, the ‘third tier’ of caudal visual cortex, V3 (in one form or another), is often portrayed as nearly equal in size to V2 in humans [6,10,11], making it the third largest visual area. Yet the location, retinotopic organization, function, size and even the very existence of V3 in non-human primates have been a matter of debate for some time (see [8,9,12]). In the late 1960s, investigators [13,14] using early neuroanatomical tracing methods showed that dorsal V1 (or area 17) was connected to a series of two visual areas within Brodmann’s [15] area 18. These two areas, V2 and V3, were mirror images of each other and approximately equal in size (figure 1a). Connections between the ventral counterparts of V1 and V3 were explored less fully, owing to the problem that these regions were not easily accessible. But the assumption, later confirmed through microelectrode mapping [16], was that ventral V2 and V3 would also be mirror images of each other and would represent the upper visual quadrant (figure 1a). However, other studies failed to find connections between ventral V1 and V3, leading some investigators to downgrade V3 to an incomplete area or to discount the area completely (see [8]). Based partly on the negative anatomical results, some proposed the existence of asymmetric connection patterns, specifically connections existing between lower field representations of V1 and V3 in dorsal cortex (d), but not between upper fields in ventral cortex (v) (figure 1b) [17,22]. This dorsal/ventral asymmetry was further supported by functional evidence for differences in colour and direction selectivity of neurons in V3v (which was renamed the ventral posterior visual area, or VP) and V3d (which was referred to as V3) [23,24]. An alternative to this proposal, developed in part to overcome the unusual V3/VP asymmetry, suggested that several areas, including the dorsomedial visual area (DM), existed in place of V3 (figure 1c; [18,19,25–28]).

Here, we review recent work by Lyon & Kaas [21, 29–32], which provides the missing anatomical support for earlier conclusions about the organization of V3 (figure 1d) and evidence against the two alternative interpretations noted above (figure 1b,c). In an effort

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Figure 1. Comparison of organizational schemes for the ‘third tier’ of visual cortex in the macaque monkey. (a) Early anatomical studies of the connectivity of dorsal V1 by Zeki [14] and Cragg [13], as well as subsequent microelectrode mapping studies of dorsal and ventral cortex by Gattass et al. [16], indicated that two additional visual areas, V2 and V3, were found adjacent to V1 and represented mirror images of each other. (b) Van Essen et al. [17] did not conclusively show that ventral V1 was connected to V3v and, along with functional differences reported between V3d and V3v, treated each region as an independent area, and renamed V3v as VP. (c) Connectional and microelectrode mapping evidence from Kaas and co-workers [18–20] suggested the presence of area DM in place of V3d. (d) More recent work from Lyon & Kaas [21] found anatomical support for both V3d and V3v. See text for more details. This figure was adapted with permission from Lyon & Kaas [21].

2. EVIDENCE FOR V3

A number of recent studies by Lyon & Kaas used neuroanatomical tracing in combination with cytochrome and myeloarchitecture to provide evidence for area V3 in several primate species. They showed that by injecting multiple neuronal tracers in known retinotopic locations of V1, both the upper and lower fields are clearly connected to V3. This was first demonstrated in the marmoset monkey [29], in which the regions of the upper visual field far from the horizontal meridian (HM) could be injected with retrograde tracers without the threat of tracer spreading into the lower visual field representation. Furthermore, in the marmoset [29], three additional New World monkey species [31], two species of Old World macaques [21] and one species of prosimian primate [30], their results revealed a mirror-symmetric pattern of connections across three adjacent areas, V1–V2–V3, showing the locations of the visual field meridians (figures 1d and 2a). The vertical meridians (labelled with squares) are found at the V1/V2 and outer V3 borders, while the representation of the HM (circles) is found at the V2/V3 border. The result that V1v is connected to V3v eliminates the need for elaborate explanations of connectional asymmetry between upper and lower visual fields of V3 in the macaque monkey [8,12], whereby V3d had been renamed V3 proper and only represented the upper field, and V3v became VP and only contained the upper visual field representation [17,22,33] (figure 1b; see re-examination of anatomical support for VP below).

In particular, the mirror image progression of connectivity across dorsal V1–V2–V3 indicates that only the lower visual field representation is adjacent to the outer border of V2d. This is more consistent with the presence of V3d at the V2 border (figure 1d) rather than area DM, which would require the presence of the upper field representation immediately adjacent to V2d (figure 1c; see §4). In support of the mirror-image progression reported using anatomical approaches, subsequent intrinsic signal optical imaging experiments by Lyon et al. [32] confirmed them neurophysiologically. These experiments were done in New World owl monkeys because the smooth surface of their cortex made possible the imaging of all three areas (figure 3a). Upon presenting narrow bars of drifting-oriented gratings at the receptive field location of the monkey’s horizontal (red) and vertical (green) meridians, distinct borders between V1, V2 and V3 clearly emerged (figure 3b). It is perhaps important to address an issue raised by Rosa et al. [34] that the vertical meridian and outer border of V3 of Lyon et al. [32] is patchy rather than continuous as might be expected. However,
there are two key points to make with regard to this concern: (i) the activation patches shown in their figures [32] are from single-oriented gratings and therefore these only show discrete clusters of neurons that prefer that particular orientation (known as orientation domains); and (ii) the V1/V2 border that represents the HM is also patchy, but the size and the distance between orientation domains is smaller, consistent with the conclusion presented in Lyon et al. [32] that orientation domains are larger in V3. Thus, this work not only confirms the earlier anatomical findings of Lyon & Kaas, but also provides the first clear neurophysiological/imaging evidence of V3 in New World monkeys.

3. RE-EXAMINATION OF EARLIER ANATOMICAL SUPPORT FOR VENTRAL POSTERIOR OVER V3v

In early publications from the laboratory of David Van Essen [17,22,33], connections between V1 and V3 were found dorsally, but not ventrally. Based, in part, on this dorsal/ventral anatomical asymmetry, and also on reported functional asymmetries [23,24], V3v was considered distinct from V3d and renamed VP (figure 1b). The result was two areas, V3 (formerly V3d) and VP, that represented only one visual quadrant (the upper field in VP and the lower field in V3). However, all ventral V1 injections in their studies were either overlapping with the representation of the HM (see orange injections in figure 2b,c) or placed so near the V1 vertical meridian representation that tracer uptake zones included bordering area V2 (figure 2c). Connectivity from these V1 locations is difficult to interpret because placement at the vertical meridian leads to contamination by tracer uptake in V2 (see red injection in figure 2c), whereas placement along the HM makes it difficult to see two distinct patches (one in ventral V2 and a second in ventral V3), because the V2/V3 border represents the HM. In other words, the two patches are likely to overlap at the border, more closely resembling a single patch. Accordingly, for the most parsimonious interpretation of their ventral cortex connection data, Van Essen and co-workers concluded that two closely spaced patches of labelled cells could be attributed only to ventral V2 and not to both V2 and immediately adjacent V3. Nevertheless, for the dorsal zone, the studies concluded that two closely spaced patches defined dorsal V2 and dorsal V3 (as portrayed in figure 2b,c).

Based on the viewpoint provided by the anatomical work of Lyon & Kaas, the better explanation would be that for both dorsal and ventral locations, the two closely spaced patches of labelled cells represent V2d/V3d and V2v/V3v, respectively (figure 2a). The ambiguity of the Van Essen and co-workers’ data is not helped by the lack of clear architectural delineation of the outer V2 border, which is particularly difficult to determine from reconstructions of parasagittal or coronal brain slices,
and most especially when not stained for myelin or cytochrome oxidase as in these earlier studies. It should be noted that these studies sought to rectify the problem of border delineation through callosal connections. This procedure results in degeneration of neurons driven by callosal inputs. Critically, some reports indicate that these cells are situated along the shared borders between the different visual areas [35]. However, it is not clear that callosal connections, which most probably represent the shared vertical meridian between the two visual hemifields, will have any bearing on the V2/V3 border, which represents the HM. Therefore, the outer V2 border is only a very rough estimate, leaving their data open to many other interpretations. Based on the width of ventral V2 published later by this same group (approx. 1.5–2 cm [36]), the more rostral patch of ventral label could fall beyond the outer V2v border and into the Lyon & Kaas proposed location of V3v (figure 2b,c), consistent with the interpretation of their data (figure 2a).

To be fair, many subsequent anatomical experiments upheld the original interpretation of Van Essen and coworkers that there were no connections between ventral V1 and V3v [19,25,26], further illustrating the elusiveness of V3v. However, as described in the next section, in these and related experiments, the primary focus was on the dorsal part of V3, where evidence was mounting for an alternative to V3d: area DM.

4. V3 VERSUS DORSOMEDIAL

Area DM was originally described in the New World owl monkey by Allman & Kaas [18] as an MT-sized area comprising both the upper and lower visual fields. Retinotopic maps of the region placed DM along the rostral edge of dorsal V2, situated on the dorsal–lateral surface of owl monkey cortex just lateral to the midline. A key and novel result of this upper/lower field map was that the lateral portion of DM contained an upper field representation that was found immediately adjacent to the lower field representation of dorsal V2. Receptive field mapping across a caudal–rostral progression of the electrode track showed the representation of the vertical meridian at the V1/V2 border, as expected from previous reports [37]. However, these reports were challenged by others in the smaller New World marmoset monkey [27,28,34]. Furthermore, some anatomical experiments in marmoset monkeys also found an upper field representation near the outer border of dorsal V2 [34].

In contrast to marmoset and owl monkeys, retinotopic maps in Old World macaque monkeys do not show evidence for an upper field representation adjacent to dorsal V2 [16] (figure 1a). There is therefore a large discrepancy from a neurophysiological standpoint with regard to the interpretation of the region immediately rostral to dorsal V2 in primates. Possible explanations for the V3/DM discrepancies are that New World monkeys have a different organization of caudal visual cortex than their Old World cousins. However, this does not explain why some connectional results in macaques also support the concept of an area DM near the dorsal border of V2 [19,20,26,38]. Additionally, larger New World cebus monkeys show retinotopic maps with organization more similar to those reported for macaques than for the smaller New World monkeys [39].

The recent retinotopic results stemming from connection patterns [21,29,31] and intrinsic signal optical imaging [32] discount the idea of a DM immediately adjacent to the dorsal V2 border. A mirror image of the lower field representation of V2 is found immediately rostral in a somewhat condensed area V3 (figure 1d), consistent with retinotopic maps of V3 in Old World macaques [16] and New World cebus monkeys [39]. DM in turn is displaced by V3, which is approximately half the width of V2. In this way, the modified location of DM places it in a similar location to area V3a, which

Figure 3. Intrinsic signal optical imaging of the HM and VM representations reveal V3d on the dorsal surface of the New World owl monkey cortex. (a) The region of visual cortex imaged is shown on a representative owl monkey brain. (b) The imaged region is rotated so that right is medial (m) and up is rostral (r). Clusters of cells activated by HM stimuli are coloured red and represent the V3/V3d border. Additional activation rostral to V3d may represent the HM of area DM. VM activation is coloured green and identifies the V1/V2 and outer V3d borders. As described in Lyon et al. [32], V1/V2 borders were confirmed histologically. Importantly, only VM stimuli presented to the lower visual field (−) resulted in activation, confirming that the V3d region adjacent to dorsal V2 was not responsive to upper field stimuli further evidence against an upper field region of DM being located immediately adjacent to dorsal V2. Data shown are summarized from Lyon et al. [32].
was originally defined in macaques as containing both the upper and lower field representations immediately adjacent to V3, not V2 (figure 1a).

The retinotopic maps of Gattass et al. [16] are most consistent with the anatomical and optical imaging results from Lyon and co-workers, implying that other maps placing the upper field region of DM immediately adjacent to the outer border of dorsal V2 are either incorrect or have been misinterpreted. A rough comparison of the DM maps put forth in three separate studies shows marked incongruity with regard to the location of the HM and, subsequently, the exact location of the upper and lower visual field representations [18,19,27]. These studies illustrate the difficulty in obtaining clear retinotopic maps in this region. In addition, there is a difference between published reports as to the extent of the visual field covered by the dorsal versus upper visual field representations [18,19,27,34]. Moreover, upon closer examination, there exist several odd, or irregular, details in the most recent interpretations of DM retinotopy [27,28,34]. DM is portrayed as having a discontinuous representation of the HM such that it contains two entirely separate representations of the upper visual field and two representations of central, or foveal, vision (figure 4a). This organizational scheme seems unlikely for a visual area [8,12] and, as we argue below, our re-interpretation of the raw data from Rosa & Schmid [27] includes a V3d interposed between the outer border of dorsal V2 and DM, which helps do away with the irregularities (figure 4b,c).

(a) Re-interpreting a V3d in the retinotopic maps of the dorsomedial area

We show here that a re-interpretation of the Rosa & Schmid [27] retinotopic maps of the DM region from a V3 point of view is consistent with their own raw published data (figure 4c), and, akin to the intrinsic signal optical imaging and connectivity results of Lyon & Kaas, these data allow for a DM that is displaced laterally (figure 4b).

Figure 4. A re-interpretation of the dorsomedial area (DM) map from Rosa & Schmid [27]. (a) Summary diagram of the retinotopic map of DM and surrounding areas. In this original interpretation, DM has a split upper field (+) representation, two foveal representations (star) and two bisecting HMs (grey filled circles). (b) Inclusion of a V3d (which represents only the lower visual field, −) displaces DM rostrally, but now DM only has one upper field and foveal representation, as well as only a single HM (see text for more details). (c) A re-interpretation of the data shown in Rosa & Schmid [27] supports our insertion of V3d between the outer border of dorsal V2 and DM. In particular, penetrations 1–4 (+), which were originally characterized as upper field, are more accurately at the HM and therefore could just as easily represent the V2/V3 border instead of the upper field of DM (see text for more details). Squiggly lines represent microelectrode penetrations in the dorsal intermediate area (DI), which can be split so that the upper half becomes part of the new, displaced DM.
5. HUMAN FUNCTIONAL MAGNETIC RESONANCE IMAGING EVIDENCE FOR A COMPLETE V3

As we will show in this section, there is now considerable evidence from fMRI that a third tier of visual cortex exists in humans, and, unlike non-human primate studies described previously, there is little disagreement regarding its organization other than the occasional use of the term VP in place of V3v [3,11,41].

First, a primary and highly replicable observation is that visual topographic reversals immediately after V2, which represents the border of a subsequent visual area, are seen on both the dorsal and ventral surfaces of the human [6,10,41–50] and monkey cortex [51,52]. The border of this reversal has thus been argued to represent the onset of V3. In contrast to the evidence from monkeys, V3 is not compromised or reduced in size in humans, and it is reasonably clear from these fMRI experiments that both the dorsal and ventral halves of V3 are fully represented in this species (figure 5a). Moreover, monkey fMRI studies have also revealed a comparable extent for V3d and V3v (figure 5b) [51,52]. In the latter study [52], the authors explicitly comment that they could not find any evidence for an asymmetric retinotopic organization between V3d and V3v, and suggest that V3d and V3v/VP belong to the same area.

In a more recent study of the organization of the foveal confluence, using high-resolution fMRI, Schira et al. [53] found that V3 extends through the central visual field representation such that the dorsal and ventral halves are not separated (figure 5a, right). This is in contrast to most depictions of V3 for monkeys (figures 1 and 5b). Also in contrast to the monkey literature, in their study, V2 and V3 are similar in width. Moreover, their maps of V2 and V3 retain more width in the foveal region compared with maps in macaques [16], which implies that human V2 and V3 devote a larger area of cortex to the representation of the retina for eccentricities below approximately 1°. Thus, there may be species differences in the organization of V2 and V3.

There are additional reasons to believe that V3d and V3v are present, and represent similar and complete representations of lower and upper visual field quadrants in humans. For example, visual field eccentricity calculations are the same for V3d and V3v [51,54]. Thus, it can be argued that V3d and V3v are likely to be similar in function, since these distinct quarter-field representations do not have different dedications for the fovea versus peripheral vision. Furthermore, both V3d and V3v contain a complete representation of the central 5° literature.
of the visual field, identical to what has been reported for areas V1 and V2. This is in stark contrast to relatively downstream visual areas such as V3A and V3B, which have a large gap in their central visual field representation [55]. These authors also showed that, whereas attention effects were negligible in V1, V2 and V3, they began to emerge only at the level of V4, and became highly prominent in nearby downstream areas such as V3B. These data thus provide further support that V3 should be functionally aligned along with the more ‘basic’ areas in the caudal visual cortex, V1 and V2.

Human V3d and V3v have also been shown to have similar receptive field sizes [45,47]. This point emphasizes that the dorsal and ventral halves of V3 are probably performing analogous computations for the juxtaposed quadrant of visual space. Indeed, it has become quite clear that, in humans at least, a relatively wide expanse of cortex representing an entire hemifield (V3d + V3v) exists, and that both the dorsal and ventral halves share similar functional characteristics. In one of these experiments, Smith et al. [47] reported an increase in mean receptive field size in humans using fMRI from V1 through to V3v/V3d, similar to what has been found in cat and monkey. However, these authors pooled their data across V3d and V3v (VP in their study), and it can only be assumed that this was done because there were no quantitative differences between the dorsal and ventral portions of V3.

Finally, an event-related fMRI study reported attentional facilitation and attention-mediated inhibition (in the unattended quadrant of the attended hemifield) across each of V1, V2 and V3 [56]. In contrast, beyond V3 in subsequent ‘downstream’ visual areas this qualitatively changed. It can thus be argued that the neural attentional mechanisms are also likely to be similarly organized across V3d and V3v.

6. FUNCTIONAL ROLE OF V3

Thus far we have made little reference to the specific functional properties of V3, as the main emphasis has been on establishing its very existence. The limited evidence suggests that V3 plays a role similar to V2, in that it projects to higher-order visual areas of both the dorsal and ventral streams [29,57], and these projections arise from bands or stripes [29] that may segregate projections into parallel processing streams. Consistent with this, single unit recordings in macaque V3d have revealed a fair number of cells selective for colour (20–26%; more associated with the ventral stream) and/or direction (40%; more associated with the dorsal stream) [24,58], although earlier V3d studies [59,60] found a much smaller percentage of direction-selective cells (15%) and no colour selective neurons, and a single study recording from V3v [23] found a higher percentage of colour-selective (60%) and a smaller proportion of direction-selective (13%) cells. While the latter of these studies may suggest a functional difference between V3d and V3v (VP), there is quite a bit of variability among the reported functional properties for V3d alone, therefore this functional asymmetry should be interpreted with caution.

Whereas single unit recordings in macaque V3v are difficult to target and verify histologically, confirmation of the location of V3d and V3v through fMRI is more easily achieved with the retinotopic mapping procedures described above. As such, Smith et al. [41] showed that V3d (V3) and V3v (VP) were equally activated by second-order motion stimuli, compared with nearby areas V1, V2 and V4. This not only suggests a feature more consistent with higher-level dorsal stream function, but also provides evidence for functional homology of V3d and V3v. More recent functional data obtained through fMRI in macaques by Wade et al. [61] show that V3 (both the dorsal and ventral divisions) is far less responsive to chromatic contrast than V2 and ventral stream area V4, further supporting the idea that V3d and V3v are similar functionally, and suggestive of V3 playing a lesser role in the ventral stream.

The overall higher proportion of direction versus colour-selective cells in macaque V3 of most single unit recording studies (see above), the lack of response to chromatic contrast [61] and the greater response to pattern motion [41] for V3 compared with areas V2 and V4 suggest that V3 is more affiliated with the dorsal stream of visual processing. While there is also probably some contribution to ventral stream areas as well [29,57,62], there are anatomical data to support a greater alignment to the dorsal stream. Feed-forward input to V3 comes from layer 4B of V1 [22,57] (or layer 3C, using the terminology of Hassler; see [63,64]), the same layer that provides direct projections to dorsal stream area MT, and to the thick stripes of V2, which in turn provide projections to MT [65]. In addition, as for MT, there is a di-synaptic relay from the superior colliculus through the inferior pulvinar to V3, probably critical for the early detection of motion, but this relay is not found for V2 or V4 [66].

In conclusion, a considerable amount of new fMRI data support the existence of a complete V3 in both human and macaques. This evidence, along with a re-interpretation of earlier neuroanatomical and neurophysiological data in light of newer findings of Lyon & Kaas across several non-human primate species, makes a strong case for the existence of a complete V3 in all primates.

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