Organizational Principles of Human Visual Cortex Revealed by Receptor Mapping

This receptorarchitectonic study of the human visual cortex investigated interareal differences in mean receptor concentrations and laminar distribution patterns of 16 neurotransmitter receptors in the dorsal and ventral parts of areas V1, V2, V3 as well as in adjoining areas V4 (ventrally) and V3A (dorsally). Both the functional hierarchy of these areas and a distinction between dorsal and ventral visual cortices were reflected by significant receptorarchitectonic differences. The observation that dorso-ventral differences existed in all extrastriate areas (including V2) is particularly important for the discussion about the relationship between dorsal and ventral V3 as it indicates that a receptorarchitectonic distinction between the ventral and dorsal visual cortices is present in but not specific to V3. This molecular specificity is mirrored by previously reported differences in retinal microstructure and functional differences as revealed in behavioral experiments demonstrating differential advantages for stimulus processing in the upper and lower visual fields. We argue that these anatomical and functional differences may be regarded as the result of an evolutionary optimization adapting to the processing of the most relevant stimuli occurring in the upper and lower visual fields.

Keywords: dorsal, hemifield, hierarchy, retinotopic, stream, ventral

Introduction

The primate visual system comprises numerous cortical areas, which register and process the incoming visual input and forward the computed information to multimodal, cognitive, and motor areas of the cerebral cortex. Within the early visual cortex, the laminar patterns of reciprocal connections (Callaway, 1998; Callaway, 2004; Knierim and Van, 1992) and the increasing computational complexity (Alonso, 2002; Sinich and Horton, 2005) define a hierarchical progression from the primary visual cortex (V1, which receives the vast majority of subcortical input) through adjoining areas V2 and V3 towards higher visual and finally multimodal areas in the posterior parietal and inferior temporal lobes (Kaas and Lyon, 2001; Orban et al., 2004). One of the fundamental organizational principles of at least the early visual cortex is the presence of a retinotopic map within each area containing a representation of the contralateral visual field. Within these maps the lower visual field, i.e., the retinal locations above the horizontal meridian, are represented in the dorsal parts of the visual cortex, whereas the upper visual field is represented ventrally.

It is generally thought that dorsal and ventral parts of V1, that is, containing the representations of the lower and upper hemifields, respectively, form a single homogenous area (Van Essen et al. 2001; Zeki 2003). The same concept is also widely accepted for V2 (Van Essen et al. 2001; Zeki 2003). The relationship between the ventrally located V3v and the dorsally positioned V3d, however, has been a topic of longstanding controversy (Kaas and Lyon 2001; Van Essen et al. 2001; Zeki 2003; Orban et al. 2004). In particular, several authors reported that ventral V3 may be distinct from its dorsal counterpart in terms of its connectivity and functional properties (Burkhalter and Van Essen 1986; Felleman et al. 1997; Tootell et al. 2003). Based on these findings, it has been advocated that V3v should be regarded as a separate area which is distinct from V3d in spite of the complete, single representation of the contralateral hemifield within V3 (Sereno et al. 1995; Shipp et al. 1995). The term VP was hence introduced by some researchers to designate the ventral part of V3. Other groups, however, failed to replicate the findings which have led to the proposition of such a distinct area VP (Lyon and Kaas 2001, 2002, Press et al. 2001; Wade et al. 2002) and conclude the presence of a uniform area V3 with 2 retinotopically defined halves, V3v and V3d. The adjoining areas V4 (located ventrally) and V3A (found dorsally) finally are usually considered distinct and independent of each other (Van Essen et al. 2001; Zeki 2003).

As cortical areas are distinguished by functional and structural criteria (Van Essen et al. 2001; Zeki 2003; Orban et al. 2004), we investigated the molecular correlates of the hierarchical organization as well as the hypothesized distinction between the dorsal and ventral early visual cortex by means of receptor binding site mapping using quantitative in vitro receptor autoradiography.

In particular, this study was aimed at examining the following main questions:

1. Is the hierarchical organization of the human visual cortex reflected by concurrent receptorarchitectonic differences between adjacent areas?
2. Does a neuroanatomical differentiation between upper and lower field representation start at the level of V3 as originally proposed by Burkhalter and Van Essen (1986)? Or does this distinction start no sooner than in the comparison between V3A and V4, supporting the concept of a homogenous area V3 (Zeki 2003)?

Materials and Methods

Four hemispheres (3 right, 1 left) of subjects with no record of neurological or psychiatric diseases were collected under the body donor program of the Department of Anatomy, University of Düsseldorf. Two of the subjects were males, 2 were females; the mean age was 75 years (age range from 72 to 77 years). The post-mortem delay was between 8 and 13 h, which is well within the published limits of sufficient receptor stability (Kontur et al. 1994). Because fixation...
Table 1

<table>
<thead>
<tr>
<th>System</th>
<th>Receptor</th>
<th>Ligand</th>
<th>Kᵣ (nM)</th>
<th>Pharmacology</th>
<th>Incubation buffer</th>
<th>Penetration</th>
<th>Main incubation exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>S₇-HT₁</td>
<td>5-HT₂</td>
<td>[3H]-ketanserin (0.5)</td>
<td>0.01% ascorbate 30 min, 22°C</td>
<td>Antagonist Mianserin (10⁻⁵)</td>
<td>170 mM Tris·HCl (pH 7.7)</td>
<td>30 min, 22°C</td>
<td>60 min, 22°C</td>
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<tr>
<td>Glutamatergic</td>
<td>AMPA</td>
<td>[3H]-AMPA (10)</td>
<td>50 mM Tris·HCl (pH 7.2)</td>
<td>30 min, 22°C</td>
<td>30 min, 4°C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GABAergic</td>
<td>GABA</td>
<td>[3H]-muscimol (6.0)</td>
<td>50 mM Tris·HCl (pH 7.7)</td>
<td>30 min, 22°C</td>
<td>60 min, 22°C</td>
<td></td>
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</tr>
<tr>
<td>Cholinergic</td>
<td>M1</td>
<td>[3H]-pirenzepine (1.0)</td>
<td>50 mM Tris·HCl (pH 7.4)</td>
<td>30 min, 22°C</td>
<td>60 min, 22°C</td>
<td></td>
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<tr>
<td>Nicotinic</td>
<td>B₂</td>
<td>[3H]-epibatidine (0.5)</td>
<td>15 min, 22°C</td>
<td>15 min, 22°C</td>
<td></td>
<td></td>
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Note: C, concentration; Kᵣ, dissociation constant (population values). DAMP, diphenylacetoxy-N-methylpiperidine methobromide; DPAT, 2-(di-n-propylamino)tertraline; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; PMSF, Phenylmethylsulfonylfluoride.

The dorsal and ventral parts of areas V1, V2, and V3 as well as areas V3A and V4 were delineated based on contrast-enhanced autoradiograms as well as on observer-independent and microscopic cytoarchitectonic analysis using established criteria (Amunts et al. 2000; Rottschy et al. 2007). Regions of interest (ROIs) were defined for each area on each sectioning level at artifact-free locations (Fig. 1). Because for each rostro-caudal level autoradiography for all 16 receptors, myelin- and cell body stainings were performed on neighboring sections, ROI...
delineation could readily be transferred to the individual images (Eickhoff, Schleicher, et al. 2007). From each ROI, a block of 11 adjacent profiles was extracted and averaged to yield a mean receptor density profile for each receptor (Eickhoff, Schleicher, et al. 2007). In total 8–14 ROIs were defined per hemisphere and area, each of which characterized up to 16 (depending on the presence of artifacts and tissue damage) mean receptor density profiles. These profiles were corrected for differences in the relative widths of the cortical layers induced by cortical folding using piecewise linear width normalization (Eickhoff, Rottschy, et al. 2007; Eickhoff, Schleicher, et al. 2007), which linearly matches the widths of the individual layer in a ROI to the widths of the mean lamination pattern of the respective area.

**Statistical Analysis**

Single subject analysis was performed separately for each pair of areas and receptor type by a permutation test (Eickhoff, Schleicher, et al. 2007). First, a mean profile was computed for each area. Dissimilarities in mean receptor concentrations across these profiles were quantified by the asymmetry coefficient (difference between the mean concentrations divided by their sum). Differences in the laminer pattern were quantified by calculating the Euclidean distance between the mean receptor density profiles (consisting of 100 data points each representing the receptor densities at 1–100% cortical depth) after removing effects of absolute concentration (Eickhoff, Rottschy, et al. 2007; Eickhoff, Schleicher, et al. 2007) and the contrast-enhanced, color-coded autoradiographic images in which area borders can be identified based on changes in receptor density or distribution (Fig. 1, cf. Eickhoff Rottschy et al. 2007). Receptor density profiles were subsequently extracted from 8–14 regions of interest (per case) within these areas to quantify the mean concentrations and the laminar distribution pattern (cf. supplementary material, Figures S1–S3) of neurotransmitter receptors within the human early visual cortex. The differences in cortical receptor density and distribution were then analysed between each area and its neighbours as well as between the dorsal and ventral counterparts of a given area (Fig. 2).

**Receptorarchitectonic Differences Reflecting Cortical Hierarchy**

Several receptors showed concurrent increases or decreases in mean binding site concentrations in both the dorsal and ventral
Receptorarchitectonic Differences between Dorsal and Ventral Visual Cortex

The ventral (V1v) and dorsal (V1d) parts of the primary visual cortex did not differ significantly from each other with respect to the mean binding site densities (averaged over all cortical layers) or the laminar distribution patterns of any examined receptor (Fig. 2A). In contrast to these findings in the striate cortex, several receptors were identified which showed consistent differences between the ventral and dorsal counterparts of the analyzed extrastriate areas. In particular, differences between the dorsal and ventral parts of V2 and V3, as well as those between V4 and V3A, were characterized by significantly higher densities of M3 receptors and benzodiazepine binding sites in the ventrally located areas (Figs 2A, 3B).

In addition to the M3 receptors and the benzodiazepine binding sites, which showed a dorsoventral asymmetry throughout the entire extrastriate cortex, the ventral parts of V2 and V3 also showed significantly higher GABA_A concentrations than their dorsal counterparts (Figs 2A, 3B). Moreover, GABA_A receptors also showed a nonsignificant trend to higher concentration in V4 as compared with V3A. These 2 areas (V4 and V3A), however, showed a significant difference in mean GABA_B receptor densities, which were both found more frequently in the ventral visual cortex. The only comparison between ventral and dorsal visual areas in which significantly higher receptor concentrations were observed dorsally related to the M1 receptor densities within V2. Notably, however, the same receptor (M1) showed significantly higher concentrations in the ventral part of area V3.

In contrast to the observation that differences in laminar distribution patterns between hierarchically adjacent areas were only sparsely present in the extrastriate cortex (Fig. 2B), we found that 3 of the examined receptors show consistent differences in laminar pattern between ventral and dorsal parts of areas V2 and V3 as well as between V4 and V3A. The 5-HT_1A receptor showed very low relative concentrations in deeper cortical layers (V-VI) of the dorsal visual areas (V2d, V3d, and V3A), which were higher in their ventral counterparts (V2v, V3v, and V4). The GABA_B receptor likewise showed higher concentrations in the lower cortical layers in the ventral visual cortex and in addition also a less pronounced peak in relative receptor concentration at the border between layers I and II ventrally. The third receptor to feature consistent differences was the GABA_A receptor, for which a peaks of high receptor concentrations in layer I were only observed for the dorsal extrastriate cortex. Finally, all 3 analyzed glutamatergic receptors also showed significant dorsoventral differences in laminar pattern. Kainate receptors were found with higher relative concentrations in the infragranular layers of the dorsal part of V2, AMPA binding sites showed a more superficial location of its density peak in V3d as compared with V3v and NMDA receptors lower concentrations in layer II/III in V3v.

Figure 2. Significant (P < 0.05, family-wise error corrected) differences in mean receptor concentration (A) or laminar receptor distribution pattern (B) between visual areas, which are either adjacent or corresponding to each other in the retinotopic organization of early visual cortex.
In this study we analyzed the distribution of 16 neurotransmitter receptors in visual areas V1, V2, V3, and V4/V3A by quantitative in vitro autoradiography (Eickhoff, Rottschy, et al. 2007; Eickhoff, Schleicher, et al. 2007). Importantly, whereas receptorarchitectonic studies on the visual cortex of primates have already been reported (Rakic et al. 1988; Lidow et al. 1989), the present study is the first to investigate the receptorarchitectonic organization of its first 4 hierarchical levels separately for their dorsal respectively components allowing new insights in the relationship between these.

**Receptorarchitectonic Correlates of Hierarchical Organization**

5-HT<sub>1A</sub> and M<sub>2</sub> receptors showed significant changes in mean concentrations when moving from V1 to V2, V3 and V4/V3A, indicative of a monotonic hierarchical progression throughout the early visual cortex (Felleman and Van Essen 1991; Orban et al. 2004; Zeki and Shipp 1988). Others receptorarchitectonic changes, however, were specific to a particular hierarchical level (AMPA increasing from V2 to V3, GABA<sub>α</sub> decreasing beyond V3) indicating discontinuous changes. These may be regarded as potential anatomical correlates of the functional differences between the analysed areas, although the contribution of different aspects of cortical circuitry (connectivity, CO patterns, cyto- and receptorarchitecture) to the functional specialisation of cortical areas, e.g., the local integration of line elements in V1 and V2 (Kourtzi et al. 2003) or the involvement of V2 and V3 in the extraction of 3D-structure from motion (Vanduffel et al. 2002), is yet unclear. Considerable potential for the further investigation of these issues may lie in the combination of functional imaging data with probabilistic cytoarchitectonic maps (Eickhoff, Stephan, et al. 2005; Eickhoff, Paus, et al. 2007) of those visual areas (Amunts et al. 2000; Rottschy et al. 2007) for which receptorarchitectonic data is now reported. Differences in laminar distribution pattern, however, were only observed between coniocortical area V1 and isocortical V2, reflecting the specialized architecture of the striate cortex (Horton and Hocking 1997; Amunts et al. 2000; Eickhoff, Walters, et al. 2005).

**Discussion**

In this study we analyzed the distribution of 16 neurotransmitter receptors in visual areas V1, V2, V3, and V4/V3A by quantitative in vitro autoradiography (Eickhoff, Rottschy, et al. 2007; Eickhoff, Schleicher, et al. 2007). Importantly, whereas receptorarchitectonic studies on the visual cortex of primates have already been reported (Rakic et al. 1988; Lidow et al. 1989), the present study is the first to investigate the receptorarchitectonic organization of its first 4 hierarchical levels separately for their dorsal respectively components allowing new insights in the relationship between these.
Relation of Measurement Sites to Retinotopic Representations

Measurements within V1v - V3v should correspond to regions processing the upper hemifield, while V1d - V3d reflect areas involved in lower field processing (Hansen et al. 2007). The organisation of the cortex lateral to V3v, the “V4 region” certainly shows a complex organisation for which various concepts have been presented (Hadjikhani et al. 1998; Hansen et al. 2007; Larsson and Heeger, 2006; Press et al. 2001; Wandell et al. 2005). In spite of the differences in the proposed organisation of more anterior, lateral or dorsal parts of this region, all authors, however, agree on the fact that the cortex immediately adjacent to V3v contains a representation of the lower visual field. It thus seems likely that the receptor-architectonic measurements within “V4” as anatomically defined in the present study, which were located close to the border with area V3v sample cortex involved in upper visual field processing similar to V2v and V3v. The cortex immediately adjacent to area V3d (anatomical area “V3A”) was shown to contain a lower field representation, which is subsequently followed by representation of the upper visual field (Hansen et al. 2007; Larsson and Heeger 2006; Press et al. 2001; Wandell et al. 2005). Consequently, we may assume that the receptor-architectonic measurements designated as “V3A” should most likely correspond to portions of the cortex devoted to lower visual field processing in a similar fashion to the measurements within areas V3d and V2d.

Relationship between Dorsal and Ventral Parts of the Early Visual Cortex

Our results shed a new light on the controversy about the relationship between dorsal and ventral V3 (Kaas and Lyon 2001; Van Essen et al. 2001; Zeki 2003; Orban et al. 2004). Based on studies in nonhuman primates, it has been suggested that the ventral part of V3 distinct from its dorsal counterpart in terms of function and connectivity and should accordingly be considered a separate area, VP (Burkhalter and Van Essen 1986; Felleman et al. 1997; Van Essen et al. 2001; Orban et al.)

Figure 4. Laminar distribution patterns in ventral/dorsal V2 and V3 as well as V4/V3A for those receptors, showing consistent laminar differences between both visual streams (cf. Fig. 2). All displayed profiles are grand mean profiles obtained from averaging the mean (across ROIs) profiles of the 4 individual cases analyzed in this study.
inferior retina (Chijiiwa et al. 1990; Ollivier et al. 2004). Other groups did not replicate these differences (Rosa et al. 2000; Lyon and Kaas 2002; Wade et al. 2002) and argued that a distinction into V3 and VP would contrast to the single complete visual field representation shared by V3v/V3d (Kaas and Lyon 2001; Zeki 2003) which is comparable to V2 or V1, where dorsal and ventral parts are considered to constitute a single area (Van Essen et al. 2001; Zeki 2003).

Based on these 2 concepts we hypothesized a receptorarchitectonic distinction between dorsal and ventral areas to emerge either at the level of V3, in line with the distinction into V3d and V3v/VP proposed by Burkhalter and Van Essen (1986) or no sooner than in the comparison of V4/V3A, reflecting a homogenous area V3 (Lyon and Kaas 2002; Zeki 2003). The results of our statistical analysis, however, do not support either view. Corresponding to the proposed distinction between V3d and VP, we observed differences in receptor distribution between dorsal and ventral V3. However, the same anatomical differences were also evident between the dorsal and ventral parts of V2. That is, contradicting the “VP concept”, our data does not indicate a fundamental distinction between a homogenous area V2 on one side, and 2 separate areas V3 and VP on the other. At the same time, though, the clear architectonic differences within V2 and V3 also disagree with the view that both are homogenous areas within which dorsal and ventral parts only differ by retinotopic preference.

Based on the regional distribution of neurotransmitter receptors we would therefore propose a revised model for the organization of the early extrastriate cortex, in which the undisputed hierarchical difference between V2 and V3 is augmented by a distinction between the dorsal and ventral parts of these areas, that is, their upper and lower field representations. This doroventral asymmetry is then continued within the presumed upper and lower field representations of the subsequent areas V3A and V4.

**Dorsoventral Asymmetries within the Visual System**

Although being unaccounted for in the current concepts of visual cortex organization, the observed differences between upper and lower field representation within the entire early extrastriate cortex concur with previous reports on differences in the neural substrates for processing information from either hemifield. This divergence starts already in the retina, where histological studies have reported reliable dorsoventral asymmetries. In particular the retinas of both humans and non-human primates show an inhomogeneous distribution of regional cone and rod densities (Packer et al. 1989; Curcio et al. 1990; Wikler et al. 1990; Andrade da Costa and Hokoc 2000). At equivalent eccentricities cones are found in higher densities in the superior part of the retina, which receives the input from the lower part of the visual field, as compared with its inferior portion covering the upper visual field. In contrast, the density of rods, in particular in the “rod ring” at the eccentricity of the optic disk is considerably higher in the inferior part of the retina. Moreover, it has been shown (Curcio and Allen 1990), that the ganglion cell densities is up to 60% higher within the superior part of the human retina. Finally, in many species featuring a tapetum lucidum (a reflecting layer immediately behind the retina reflecting light back to the photoreceptors) this structure is either less developed or even absent in the inferior retina (Chijiiwa et al. 1990; Ollivier et al. 2004).

Although differences between upper and lower visual field representations within the superior colliculus or the lateral geniculate nucleus have, to our knowledge, not yet been reported, a diverging architecture of the stripe-subsystem defined by histochemical staining for cytochrome oxidase between the dorsal and ventral aspect of V2 has already been reported (Olavarria and Van Essen 1997). Unfortunately, a further investigation on the receptorarchitectonic correlates of these stripes and the blob-interblob subsystems within V1, which are considered to form parallel streams of V1 to V2 connectivity mediating different aspects of visual perception (Sincich and Horton 2005), was not possible in the current study. Both systems are reliably identifiable only in physically unfolded and flattened specimen, the present study, however, was performed—as part of a whole-brain mapping project—on thin coronal sections through the occipital lobe.

Importantly, these anatomical differences seem to impact the efficiency with which different aspects of visual input is analyzed, as there is a considerable amount of behavioral studies showing differential advantages for visual processing between the lower and upper hemifield. For example, the lower visual field was reported to have advantages in tasks such as visuomotor feedback processing (Khan and Lawrence 2005), visually guided pointing (Danckert and Goodale 2001) and spatial relocation memory (Genzano et al. 2001). In contrast, the upper hemifield seems to be advantageous, for example, for stimuli discrimination (Levine and McAnany 2005) and change detection (Rutkowski et al. 2002).

**Conclusions**

Apart from identifying the receptorarchitectonic correlates of the hierarchical organization within the early visual cortex, this study demonstrated consistent dorsoventral asymmetries within V2 and V3, which contrast with both contemporary concepts about the organization of the early extrastriate cortex (Van Essen et al. 2001; Zeki 2003). Rather, in combination with previously reported functional and anatomical asymmetries they point to a generalized distinction between the neuronal substrates for upper versus lower visual field representation, possibly representing an evolutionary adaptation for processing the most relevant stimuli in each hemifield: Due to the caudal location of the hands, eye-hand coordination will mainly take place in the lower visual field represented in the dorsal visual cortex, whereas visual exploration of larger scenes will predominantly be occurring in the upper visual field, that is, the ventral visual cortex.

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References


