Primary Visual Cortex: Awareness and Blindsight*

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V1, visual perception, blindsight, cortical lesion, consciousness, cerebral cortex, thalamus

Abstract

The primary visual cortex (V1) is the principal telencephalic recipient of visual input in humans and monkeys. It is unique among cortical areas in that its destruction results in chronic blindness. However, certain patients with V1 damage, though lacking visual awareness, exhibit visually guided behavior: blindsight. This phenomenon, together with evidence from electrophysiological, neuroimaging, and psychophysical experiments, has led to speculation that V1 activity has a special or direct role in generating conscious perception. To explore this issue, this article reviews experiments that have used two powerful paradigms—stimulus-induced perceptual suppression and chronic V1 ablation—each of which disrupts the ability to perceive salient visual stimuli. Focus is placed on recent neurophysiological, behavioral, and functional imaging studies from the nonhuman primate that shed light on V1's role in conscious awareness. In addition, anatomical pathways that relay visual information to the cortex during normal vision and in blindsight are reviewed. Although the critical role of V1 in primate vision follows naturally from its position as a bottleneck of visual signals, little evidence supports its direct contribution to visual awareness.

Contents

INTRODUCTION

Understanding the relationship between neural activity and subjective perception is one of the most fascinating and challenging goals of modern neuroscience. In the domain of vision, damage to the primary visual cortex, or V1, but not to any other cortical region, abolishes visual awareness and leads to chronic blindness. This observation, combined with data from electrophysiological and functional magnetic resonance imaging (fMRI) studies in humans and nonhuman primates, has raised speculation that neural activity in V1 may have a direct and critical role in the generation of a percept.

The present article reviews experiments that shed light on this intriguing topic. We survey experiments pertaining to the visual phenomena of perceptual suppression and blindsight in an attempt to understand the role of V1 in conscious and unconscious vision. In doing so, we refer to diverse features of V1, whose anatomical connections, complex laminar organization, and electrophysiological response profile have been studied extensively in the monkey. Throughout the review, emphasis is placed on discoveries in the past decade. By necessity, several relevant topics are not discussed or are mentioned only in brief. Such topics include neural correlates of perception in V1 pertaining to paradigms other than visual suppression (reviewed in Tong 2003), perceptual correlates outside of V1, and perceptual impairments following cortical lesions in areas other than V1. We do not attempt to provide a comprehensive review of blindsight and refer the reader to recent overviews by pioneers of the field (Cowey 2010, Stoerig 2006, Weiskrantz 2009). A considerable portion of this review is devoted to describing pathways that carry retinal image information to the cortex, the details of which are important for understanding both the determinants of V1 activity during perceptual suppression and the basis for unconscious visual performance during blindsight.

V1, V2, V3, V4, MT, TEO, TE: visual areas in the macaque visual cortex

Perceptual suppression: psychophysical paradigm used to induce the all or none subjective disappearance of a visual stimulus

Blindsight: residual visually capacity in the absence of awareness following damage to V1

EXPERIMENTAL INROADS TO THE UNCONSCIOUS

We begin by briefly describing the two featured paradigms (see **Figure 1**). The next section reviews the modulation of sensory responses in V1 during perceptual suppression, including some strikingly discrepant findings obtained from single-unit and fMRI studies. This is followed by a survey of experiments that give insight into V1-independent vision during blindsight. The final section draws upon these and other findings to evaluate the particular role of V1 in visual awareness.

Perceptual suppression can render a normally salient visual stimulus completely invisible. Stimulus paradigms that induce perceptual suppression are an important component of the psychophysicist's toolbox, as they shed light on unconscious sensory processing. Such paradigms include binocular rivalry (Blake & Logothetis 2002), motion-induced blindness (Bonneh et al. 2001), visual masking (Breitmeyer & Öğmen 2006), and various dichoptic stimulus sequences collectively termed

flash suppression (Tsuchiya & Koch 2005, Wilke et al. 2003, Wolfe 1984). Psychophysical experiments have demonstrated that during perceptual suppression certain stimuli, though completely invisible, can penetrate the first stages of cortical processing. In doing so, they can generate adaptational aftereffects (Blake et al. 2006), guide manual grasping behavior (Roseboom & Arnold 2011), and recruit spatial attention (Lin & He 2009).

An example of a flash suppression stimulus sequence is shown in **Figure 1*a***. In this particular paradigm (Wilke et al. 2003), a salient target stimulus is first presented alone on the screen, often monocularly, for several hundred milliseconds. After this period, a binocular field of randomly moving dots appears in the periphery. This sequence induces the target stimulus to vanish abruptly from perception and remain entirely invisible for several seconds, provided the moving dots remain on the screen. The probability of target suppression is a function of several stimulus parameters, such as the speed at which the dots are moving. In a typical monkey neurophysiological experiment, these parameters are adjusted to induce the target to disappear on approximately 50% of the trials. Then, on the basis of the monkey's perceptual report, neural responses to an identical physical stimulus are compared when the target is subjectively visible or invisible (Leopold et al. 2003, Wilke et al. 2006, 2009). This approach allows one to assess the relationship of a given neural response to the perceptual awareness of a stimulus; the results from the visual cortex are discussed in the next section.

Blindsight refers to the ability of cortically blind patients and experimental animals to use visual information to guide behavior in the absence of visual awareness (Weiskrantz 2009). Human blindsight subjects are able to orient to and answer questions about stimuli presented to the blind part of the visual field. However, when questioned, they report being entirely unaware of the stimuli to which they are responding (Sanders et al. 1974). This situation can be somewhat perplexing for the subject. In their seminal paper, Pöppel and colleagues (Pöppel et al. 1973) asked their subject to direct his eyes to the target, to which he replied, "How can I look at something that I haven't seen?" Nonetheless, the subject was still able to carry out the task. This paradoxical phenomenon of blindsight is not simply due to low-functioning vision, but is instead due to a unique uncoupling between subjective visual perception and visually guided performance (Azzopardi & Cowey 1997). Moreover, it occurs only when damage is restricted to V1 and is generally not present when the damage extends into the extrastriate cortex (Weiskrantz 2009).

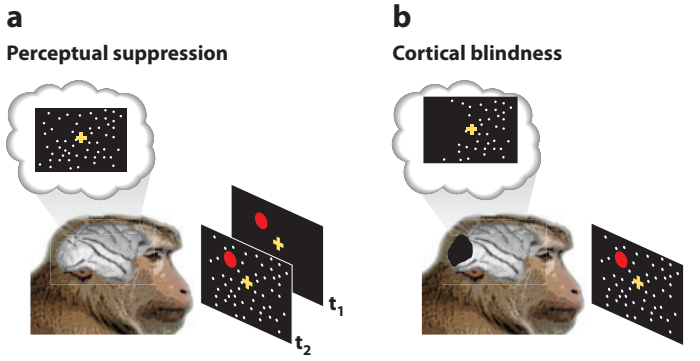

Figure 1

Paradigms to study unconscious vision in monkeys. (*a*) During perceptual suppression, a target stimulus is continuously presented on a video monitor but disappears because of a visual illusion. Depicted here is generalized flash suppression (Wilke et al. 2003), where the presentation of a bright red patch at time t_1 is followed by the appearance of dynamic surrounding white dots at time t_2, causing the red patch to disappear perceptually for up to several seconds. (*b*) Cortical blindness following V1 lesion leads to the inability to perceive stimuli in an entire region of visual space corresponding to the retinotopic position of the lesion. Following such lesions, blindsight allows for some residual behavioral responses to stimuli presented to the scotoma (blind portion of the visual field).

The blindness that follows damage to V1 in humans appears to be common among primates, but not in other mammals, which have more visual relay projections from the thalamus to other cortical areas, thus bypassing the primary visual cortex (Funk & Rosa 1998, Preuss 2007). Despite nominal blindness, the existence of some residual vision following V1 lesions in the macaque has been recognized for more than half a century (Klüver 1941). In the weeks following the surgical removal of V1,

Flash suppression: a visual stimulation paradigm in which a sequence of stimuli induces a target to undergo perceptual suppression

Visual relay: a neural pathway that receives direct or indirect retinal information and then transmits it further

macaques gradually recover the ability to use visual information to guide hand and eye movements to stimuli in the "blind" (lesion-affected) part of the visual field (Feinberg et al. 1978, Humphrey 1974, Isa & Yoshida 2009, Mohler & Wurtz 1977). While motion detection is the most consistent feature of blindsight, V1-lesioned monkeys have also been reported to discriminate simple patterns on the basis of spatial frequency, shape, texture, and color (Dineen & Keating 1981, Miller et al. 1980, Schilder et al. 1972). Some important aspects of their vision are gone forever, such as the capacity to visually recognize food, objects, or faces of familiar individuals (Humphrey 1974). Importantly, the residual vision in macaques indicates a dissociation between awareness and visually guided behavior. When visual perception was tested using both forced choice and detection tasks, macaques responded correctly to a stimulus in the blind field during the forced-choice task but then, under the same visual conditions, indicated in the detection task that no stimulus was presented (Cowey & Stoerig 1995, Moore et al. 1995). Although it is impossible to determine precisely the subjective experience of a cortically blind monkey, or human for that matter, these experiments indicate that macaques exhibit the hallmarks of blindsight and are, therefore, a good primate model for studying V1-independent vision in the human.

PERCEPTUAL SUPPRESSION OF VISUAL RESPONSES IN V1

We now focus on perceptual suppression, asking how the visibility of a stimulus affects neural responses in V1. This approach of correlating neural activity with subjective perception has been used to investigate whether V1 contributes directly to visual awareness (Tononi & Koch 2008). However, before reviewing the effect of perceptual suppression on cortical neurons, we begin with a survey of the basic anatomy and physiology of the ascending pathways carrying sensory information to V1. In humans and monkeys, nearly all visual information reaches the cortex through a primary visual pipeline that passes from the retina to the lateral geniculate nucleus (LGN) to V1. Reviewing this basic circuitry is necessary to understand how V1's basic sensory responses may interact with signals related to conscious perception. The components of this pathway are also relevant to the discussion of blindsight in a subsequent section.

LGN: lateral geniculate nucleus of the thalamus

CAMKII: calcium/calmodulin-dependent protein kinases II

Converging Visual Signals in V1

The input from the LGN to V1 consists of multiple parallel sensory pathways whose characteristic response properties originate in the retina (for a recent review, see Schiller 2010). In the macaque, LGN-projecting retinal ganglion cells have a wide range of morphologies and physiological response profiles, which are often classified into three main groups: Pα, Pβ, and Pγ. The Pβ cells, projecting almost exclusively to the parvocellular LGN layers, compose more than 80% of ganglion cells in the macaque. They have a "midget" dendritic morphology, which gives them small receptive fields for detailed form vision. Electrophysiologically, they exhibit sustained responses and typically show red/green color opponency in trichromats. The Pα neurons compose roughly 10% of the ganglion cells. Their primary target is the magnocellular layers of the LGN, though they also project to several other target structures (described below). Their "parasol" morphology translates to large, integrative receptive fields. Electrophysiologically, they tend to respond transiently and without color selectivity. The remaining ganglion cells are often grouped together as Pγ, although their morphology and physiological properties are quite diverse (Schiller & Malpeli 1977). The Pγ axons terminate in the interlaminar zones of the LGN, ventral to each magno- and parvocellular layer. The interlaminar zones are strongly associated with the koniocellular pathway, whose neurons are immunoreactive to calcium binding proteins calcium/calmodulin-dependent protein kinases II (CAMKII) or calbindin D28K (Casagrande 1994, Hendry & Yoshioka 1994), and carry blue/yellow

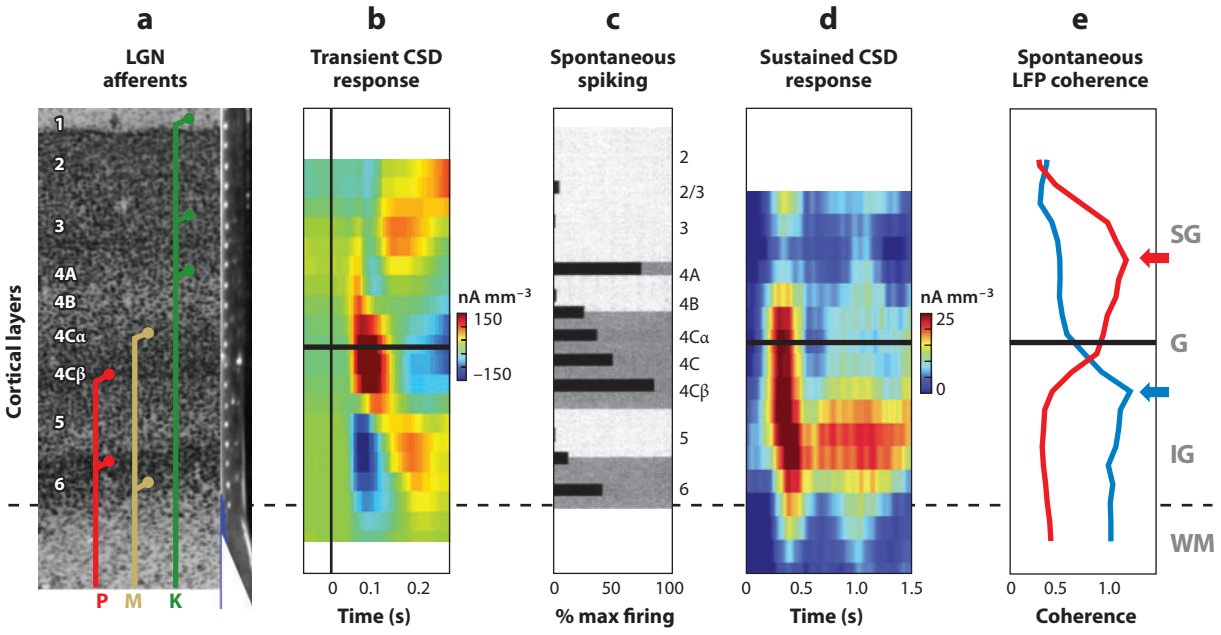

Figure 2

Sensory and spontaneous physiology across V1 layers. (*a*) The basic pathways projecting from the lateral geniculate nucleus (LGN) to the different layers of V1, including the magnocellular (M), parvocellular (P), and koniocellular (K). Adjacent is a photograph of a multicontact linear electrode array. (*b*) Current source density (CSD) response to flashed stimuli in V1. The horizontal line is drawn through the initial current sink in layer 4C (Maier et al. 2011). (*c*) Spontaneous spiking responses in different cortical layers of monkeys sitting in a dark room (Snodderly & Gur 1995). (*d*) Sustained CSD power that persists in the infragranular layers during the presentation of a simple stimulus (Maier et al. 2011). (*e*) Pattern of coherence of spontaneous high-frequency (gamma) local field potential (LFP) activity. Pairwise coherence is computed between each of two different reference positions (*blue and red arrows*) and all other laminar positions (Maier et al. 2010). Abbreviations: SG, supragranular layers; G, granular layers; IG, infragranular layers; WM, white matter.

color-opponent signals (for reviews, see Hendry & Reid 2000, Nassi & Callaway 2009). In the marmoset, injection of retrograde tracers into the koniocellular layers labels the bistratified Pγ cells in the retina (Szmajda et al. 2008).

Each ganglion cell type then relays its signals through unusually strong synapses in the LGN to V1, where the pattern of afferent projections is known in detail (for reviews, see Lund 1988, Nassi & Callaway 2009, Peters et al. 1994). Briefly, neurons from the magno- and parvocellular LGN compartments (carrying Pα and Pβ signals, respectively) project to separate subcompartments of layers 4C and 6. Koniocellular projections (carrying Pγ signals) terminate within and above layer 4A (**Figure 2*a***). The LGN projections to layer 4C are much stronger than those to layer 6. However, the intracortical projection from layer 6 to layer 4C is also prominent and may be an important factor in determining the overall strength of visual responses (Callaway 1998, Douglas & Martin 2004). Layer-6 neurons also transmit channel-specific visual signals back to the LGN in an organized fashion, with upper-tier neurons projecting to the parvocellular layers and lower-tier neurons projecting to the magnocellular layers and possibly also to the koniocellular layers (Briggs & Usrey 2009).

In addition to its LGN input, area V1 also receives afferent input from a large number of extrastriate visual cortical areas, including V2, V3, V4, MT, TEO, and TE (reviewed in Barone et al. 2000, Salin & Bullier 1995), the inferior pulvinar (Benevento & Rezak 1976), the amygdala (Freese & Amaral 2005), and the

Supragranular: laminar position within the thickness of the cerebral cortex above the middle, granular layer

GABA: gamma aminobutyric acid

Infragranular: laminar position within the thickness of the cerebral cortex below the middle, granular layer

claustrum (Baizer et al. 1997). Aside from the claustrum, which sends its densest projections to layer 4, each of these structures projects primarily to the supragranular layers. In fact, ventral stream extrastriate cortical areas V4, TEO, and TE project exclusively to layer 1. This fact is important for understanding perceptual modulation in V1, suggesting that extrastriate modulation of V1 activity affects synaptic activity in the supragranular layers.

Before we turn to how perceptual suppression affects V1 responses, we briefly review some basic features of V1 electrophysiology, including its laminar response profile and the contribution of different inputs. The responses of a given V1 neuron will be shaped to different extents by the LGN afferents, feedback from other cortical areas, input from subcortical areas, and a very large number of synaptic inputs from within V1 (Douglas & Martin 2004). To study the contribution of the feedforward pathway, it is possible to isolate and measure directly spikes arriving into V1 at the LGN terminals, provided V1 neurons are first inactivated [for example, using the gamma aminobutyric acid (GABA) agonist muscimol]. For example, this approach was used in one study to demonstrate the laminar segregation of LGN inputs on the basis of their chromatic selectivity (Chatterjee & Callaway 2003). The primary synaptic influence of these spiking afferents can be determined using current source density analysis, which computes the flow of extracellular ionic currents thought to derive from synchronized postsynaptic potentials (Schroeder et al. 1991). Following an abruptly flashed stimulus, a current sink is induced with a short latency in layer 4C, followed tens of milliseconds later by current sinks in the supragranular and infragranular layers (see **Figure 2*b***). This characteristic spatiotemporal evolution of excitatory synaptic activity from the middle layers toward the laminae above and below is thought to reflect feedforward processing of visual information through the cortical microcircuitry (Mitzdorf 1985), and it is consistent with the laminar distribution of spiking-response latencies (Nowak et al. 1995). In addition to evoked responses, spontaneous activity is also strongly influenced by LGN afferents, even in darkness. Ongoing spiking activity is markedly higher in the LGN-recipient layers compared with other layers (Snodderly & Gur 1995) (**Figure 2*c***), as is high-frequency ("gamma") local field potential (LFP) power (Maier et al. 2010).

Recent work has revealed other basic measures of V1 activity that are not as obviously derived from the pattern of LGN inputs. One study using a variant of current source density analysis found that the sustained response to a stimulus was localized in the infragranular layers, roughly 500 μm below the initial transient sink (Maier et al. 2011) (**Figure 2*d***). Another study revealed two distinct laminar zones of LFP signal coherence, with a boundary between them near the bottom of layer 4C (Maier et al. 2010) (**Figure 2*e***). The extent to which these latter findings can be explained by the LGN input, reverberation within the V1 microcircuit, or corticocortical feedback remains to be determined.

Given the multiple anatomical inputs impinging on V1 and its physiological response profile that appears largely, but not entirely, determined by its LGN afferents, we pose the following question: Does perceptual suppression affect responses to visual stimuli in V1? Obtaining a simple answer to this seemingly straightforward question has proved to be much more difficult than anticipated.

Modulation of Visual Responses During Perceptual Suppression

Using a range of psychophysical tools, including those mentioned above, researchers have investigated the neural basis of perceptual suppression in both macaques and humans. Single-unit and fMRI studies largely agree that perceptual suppression modulates neural responses to stimuli throughout the visual cortex, particularly at the highest stages of the cortical hierarchy (Fisch et al. 2009, Kreiman et al. 2002, Sheinberg & Logothetis 1997, Tong et al. 1998). At intermediate stages, such as areas MT and V4, the correlates of

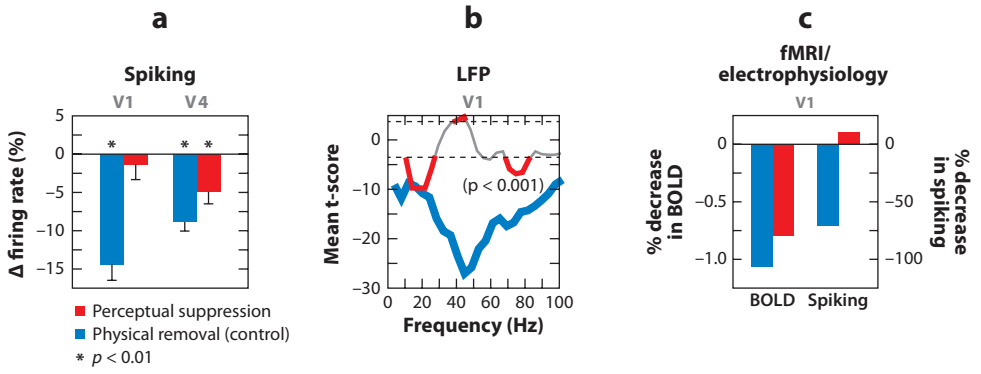

Figure 3

Neural correlates of perceptual suppression in V1. (*a*) Spiking modulation in V1 and V4 associated with perceptual suppression versus physical removal of a stimulus (Wilke et al. 2006). (*b*) Local field potential (LFP) modulation in V1 associated with perceptual suppression versus physical removal of a stimulus (Maier et al. 2008). (*c*) Comparison of the effects of perceptual suppression on the blood oxygenation level–dependent (BOLD) versus spiking signals in V1 (Maier et al. 2008).

perception are mixed throughout the population of neurons (Logothetis & Schall 1989, Wilke et al. 2006), and individual cells change their sensitivity to perceptual suppression in response to the structural details of the inducing stimulus (Maier et al. 2007).

Within V1, monkey electrophysiology and human fMRI studies have found nearly opposite results during perceptual suppression. Single-unit experiments in the macaque have consistently found that the visibility or invisibility of a stimulus has minimal, if any, effect on the firing of V1 neurons (Gail et al. 2004, Keliris et al. 2010, Leopold et al. 2005, Leopold & Logothetis 1996, Libedinsky et al. 2009, Wilke et al. 2006), in agreement with theoretical work suggesting that activity in V1 does not contribute directly to visual awareness (Crick & Koch 1995) (but for a different perspective, see Tong 2003). Compared with single-cell responses, the local LFP signal is more modulated (Gail et al. 2004, Maier et al. 2008, Wilke et al. 2006). However, this change is small relative to control trials in which the same stimulus is physically removed (**Figure 3*b***). At the same time, human fMRI experiments report strongly diminished responses in V1 during perceptual suppression resembling the physical control condition (Haynes & Rees 2005, Lee et al. 2005, Polonsky et al. 2000, Tong & Engel 2001, Wunderlich et al. 2005). As a result, the same paradigms used to argue against the role of V1 in awareness based on monkey electrophysiology have been used to argue for its role in awareness based on human fMRI.

To investigate the basis of this apparent discrepancy, a recent study combined fMRI and electrophysiological methods in V1 in monkeys experiencing flash suppression (Maier et al. 2008). During conventional visual stimulation, fMRI blood oxygenation level–dependent (BOLD) and electrophysiological responses, including spiking and LFP, were in good agreement. However, during perceptual suppression, the signals diverged markedly, even though they were measured from the same patch of tissue. When the stimulus was subjectively invisible, fMRI responses dropped to levels near to that of a control condition in which the stimulus was physically removed. By contrast, spiking responses were at the same high levels during visible and invisible periods, again indicating that neural spiking rates in V1 are unaffected by perceptual suppression (**Figure 3*c***). Responses of the LFP showed some significant perceptual modulation but proportionally much less than those of the BOLD signal. Thus, the BOLD and spiking

SC: superior colliculus

signals were fundamentally different in their responses (Logothetis 2002), and the level of the discrepancy was strongly dependent on perceptual visibility. This latter finding may be related to signal discrepancies in V1 associated with other cognitive variables, such as hemodynamic-response modulation observed in the absence of single-unit modulation during spatial attention (Posner & Gilbert 1999, Watanabe et al. 2011) and that associated with the expectation of an impending visual stimulus during a behavioral task that involves predictable stimulus presentation (Sirotin & Das 2009).

Why do BOLD signals show decreased responses in V1 to perceptually suppressed stimuli, whereas spiking responses do not? One possibility is that signals reaching V1 elicit synaptic activity that causes a hemodynamic response but is never translated into changes in the rate of action potentials. Initial results from one study indicate that synaptic activity in the supragranular layers, but not in the deeper layers, drops significantly during perceptual suppression (Leopold et al. 2008). Because cortical areas V4 and TE send their projections exclusively to the supragranular layers of V1, the reported activity changes could reflect feedback from extrastriate areas, where synaptic activity modulates with perceptual suppression. It is tempting to speculate that such synaptic modulation affects V1 BOLD responses, but why such modulation would have virtually no effect on neuronal spiking remains a puzzle. This issue warrants further investigation.

Thus, single-unit modulation during perceptual suppression provides no evidence in support of V1 playing a direct role in visual awareness. In the next section, we explore the same point from a different perspective, reviewing the neural basis of unconscious vision following damage to V1.

BLINDSIGHT: RESIDUAL VISION FOLLOWING V1 DAMAGE

The phenomenology of blindsight has two principal features. The first is blindness, or the loss of visual awareness associated with V1 damage. The second is the capacity of blind individuals to use visual signals to guide behavioral responses. Here, we address the second of these features, leaving the loss of visual awareness as a topic for the final section. Understanding the basis of residual vision during blindsight, including its unconscious nature, requires knowledge of anatomical connections. We begin by describing neural projections to the extrastriate cortex that are thought to underlie blindsight behavior (Weiskrantz 2009).

Anatomical Pathways to the Extrastriate Cortex

All retinal image information reaching the cerebral cortex ascends through synapses in the dorsal thalamus, either in the LGN or the pulvinar (see above for a review of the retinal projections to the LGN). In addition, a very small number of ganglion cells, primarily Pγ and Pα, target the inferior pulvinar (Cowey et al. 1994, O'Brien et al. 2001) as well as several other projection targets located in the forebrain and situated at distinct positions along the neuraxis (see **Figure 4*a***). Approximately one-tenth of all ganglion cells send descending projections to the superior colliculus (SC) in the midbrain. Similar to the pulvinar, the SC receives primarily Pγ and Pα inputs (Perry et al. 1984, Perry & Cowey 1984). Sparser projections terminate in the pregeniculate nucleus and in several nuclei in the hypothalamus and pretectum (Stoerig & Cowey 1997). Some ganglion cells are thought to send collateral projections to multiple targets, such as to both the LGN and the SC (Crook et al. 2008). In addition to their direct retinal input, both the LGN and the pulvinar also receive projections from the SC, suggesting a potential midbrain relay to each of the two structures (Harting et al. 1991, May 2006). There are thus at least four potential pathways by which retinal information can reach the dorsal thalamus (**Figure 4*b***).

In addition, both the LGN and pulvinar project to both V1 and the extrastriate visual cortex. Of particular interest for blindsight are

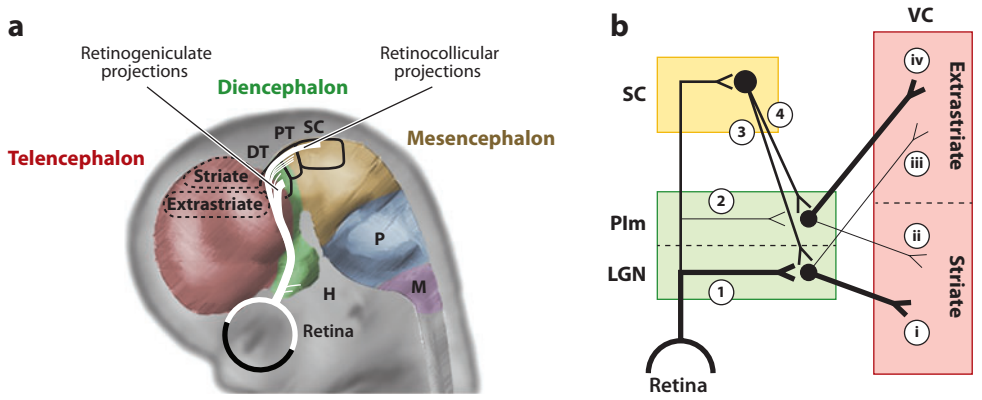

Figure 4

Visual pathways through the dorsal thalamus to the cortex. (*a*) Targets of retinal ganglion cells in the diencephalon and mesencephalon. Projections are depicted on an embryonic brain to emphasize the relative positions of the retinal projection targets with respect to the neuraxis. Note that this depiction is for schematic purposes only, as the neural connections have not been formed at this stage of development. The strongest projections are to the LGN, followed by the superficial layers of the SC. (*b*) Schematic illustration of pathways to the cortex. There are two direct pathways from the retina to the dorsal thalamus, a retinogeniculate pathway (1) and a retinopulvinar pathway (2), as well as two indirect pathways that pass through the midbrain, the retinocolliculogeniculate pathway (3) and the retinocolliculopulvinar pathway (4). Both the LGN and the inferior pulvinar project to both V1 and the extrastriate visual cortex (i–iv), with the LGN projecting predominantly to V1 (i) and the inferior pulvinar projecting predominantly to the extrastriate cortex (iv). Of particular interest for undertanding blindsight are the direct extrastriate projections (iii, iv). Abbreviations: DT, dorsal thalamus; H, hypothalamus; LGN, lateral geniculate nucleus; M, medulla oblongata; P, pons; PIm, medial division of the inferior pulvinar; PT, pretectum; SC, superior colliculus; VC, visual cortex.

the direct pathways from the thalamus to the extrastriate cortex (**Figure 4*b***). These projections have been extensively investigated using retrograde tracers injected into the extrastriate cortex, which leads to dense labeling in the pulvinar and much sparser labeling in the LGN. The LGN labeling, though sparse, has been observed in many experiments (reviewed in Rodman et al. 2001, Sincich et al. 2004). Much of the dense labeling in the pulvinar can be attributed to its role as a corticocortical relay (Sherman 2005, Shipp 2003). However, some of the retrogradely labeled pulvinar neurons, and all the labeled LGN neurons, are candidates for relaying visual information from either the SC or the retina to the extrastriate cortex.

A closer examination of these pathways reveals that the extrastriate-projecting neurons in the LGN are most commonly found in the interlaminar zones. Injection of retrograde tracers into the dorsal stream (MT) or ventral stream (V4) portions of the extrastriate cortex reveal that more than half of extrastriate-projecting neurons label positively for CAMKII and calbindin, suggesting that these neurons are part of the koniocellular pathway (Rodman et al. 2001, Sincich et al. 2004). However, unlike the konicellular neurons that project to the superficial layers of V1, neurons sending projections to the extrastriate cortex have large cell bodies with a multipolar morphology, suggesting that the term koniocellular, indicating very small cells, may be inappropriate. Strangely, the LGN projections to the extrastriate cortex terminate neither in layer 4, which is characteristic of feedforward thalamic projections, nor in the supragranular layers, which is characteristic of modulatory thalamic connections (Jones 1998). Instead, the inputs are primarily directed to layer 5, where neurons project to the thalamus, striatum, and midbrain (Benevento & Yoshida 1981). It is interesting to speculate that

this laminar pattern of LGN input to extrastriate cortical areas is related to the unconscious nature of the visual signals used during blindsight.

Establishing that a putative pathway actually relays visual information to the cortex is more challenging. Given the sheer number of retinal projections to the LGN, it seems likely that extrastriate-projecting LGN neurons receive a direct retinal input and send it to the extrastriate cortex. This possibility is supported by the finding, in marmosets, of presynaptic retinal afferents synapsing on MT-projecting neurons in the koniocellular layers (Warner et al. 2010). Retinal afferents were also found to synapse on MT-projecting neurons in the histochemically defined PIm subregion of the inferior pulvinar (Warner et al. 2010).

Establishing visual pathways through the SC is even more difficult, because two synapses must act as relays. As reviewed above, Pα and Pγ ganglion cells project to the superficial layers of the SC. Within the superficial layers, a subset of neurons sends projections to the LGN and a different subset sends to the inferior pulvinar (May 2006). In the latter, initial anatomical findings in the owl monkey did not show sufficient spatial overlap between SC terminals and MT-projecting cell bodies to support such a relay (Stepniewska et al. 1999). However, recent experiments in the macaque using disynaptic tracing with a rabies virus (Lyon et al. 2010) and electrophysiological identification of neural connections with antidromic and orthodromic stimulation (Berman & Wurtz 2010) argue strongly that such a relay does exist. In fact, both recent studies identified two distinct SC relays through the pulvinar to area MT: PIm, which is the same subdivision that receives direct retinal afferents, and another relay localized in the region of the inferior pulvinar immediately adjacent to the LGN. There is also circumstantial anatomical evidence supporting a relay from the SC to the extrastriate cortex through the LGN. The SC terminals are found primarily in the interlaminar zones, which, as discussed above, is similar to the distribution of most of the extrastriate-projecting neurons (Benevento & Yoshida 1981, Stepniewska et al. 1999). This pattern is consistent with the projection pattern observed in a wide range of mammals (Harting et al. 1991). However, one study found that the laminar pattern of disynaptic labeling in the SC following extrastriate injections in areas MT and V3 was more consistent with the pulvinar route than with the LGN route, suggesting that the colliculopulvinar pathway is more prominent than the colliculogeniculate pathway, at least to certain extrastriate areas (Lyon et al. 2010).

On the basis of these neuroanatomical and neurophysiological studies, each of the four potential pathways carrying visual information from the retina to the extrastriate cortex (retina-LGN-extrastriate, retina-pulvinar-extrastriate, retina-SC-LGN-extrastriate, and retina-SC-pulvinar-extrastriate) is a viable candidate to bypass V1. It is important to point out, however, that these results were established in intact animals. Following V1 lesions, a number of significant changes to the visual system occur at many levels. This is addressed in the next section.

Changes to the Visual System Following a V1 Lesion

In the weeks following an ablation restricted to V1, massive retrograde degeneration decimates the portion of the LGN corresponding to the extent of the lesion. The outcome is a nearly complete loss of magnocellular and parvocellular neurons in the affected region of the LGN (Mihailović et al. 1971). Then, over a period of months and years, the degeneration cascades to the retina and kills half of the Pβ ganglion cells (Cowey et al. 1989, Weller & Kaas 1989). Neither the interlaminar regions of the LGN, where some neurons project directly to multiple regions of the extrastriate cortex, nor the retinal projections to the SC (Dineen et al. 1982) degenerate nearly as much (Cowey 2004). Moreover, the extrastriate-projecting neurons that survive within the LGN are much larger than normal (Hendrickson & Dineen 1982) and stain positively for calbindin D28K (Rodman et al.

2001), suggesting that the koniocellular system may be strengthened following the lesion. One study found that some of the retinal input to the remaining geniculocortical neurons projecting to V4 was mediated by GABA-ergic interneurons and that a portion of the ganglion cells stained positively for GABA (Kisvárday et al. 1991). It was subsequently shown that a small proportion of retinogeniculate neurons are GABA-positive in the normal monkey optic nerve and optic tract (Wilson et al. 1996). These findings suggest that transmission of visual signals through the LGN to the extrastriate cortex is fundamentally altered following V1 damage. As the system recovers, significant changes occur to the types of viable relay neurons, the distribution of retinal and collicular inputs, and, quite possibly, the balance of excitation and inhibition.

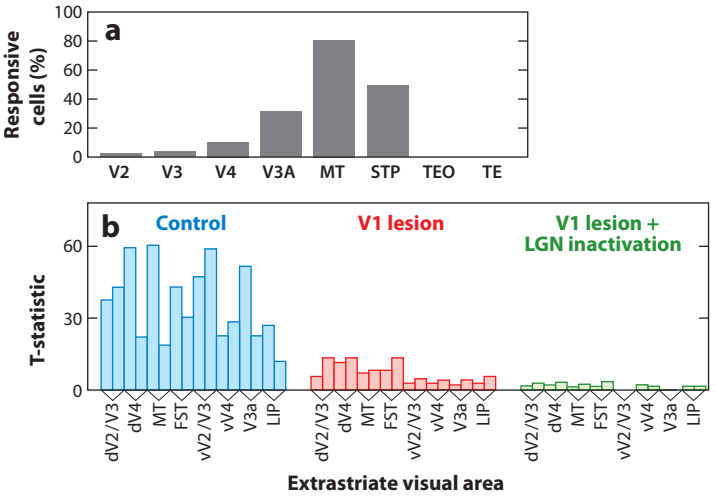

Figure 5

Extrastriate visual activation following V1 lesion and lateral geniculate nucleus (LGN) inactivation. (*a*) Residual responses of single units in multiple extrastriate visual areas following the destruction or cooling of V1 in the macaque (Bullier et al. 1994). (*b*) Functional magnetic resonance imaging (fMRI) responses in a range of extrastriate cortical areas in a normal hemisphere (*blue*), following V1 damage (*red*), and following V1 damage combined with acute inactivation of the LGN (*green*) (Schmid et al. 2010).

Extrastriate Visual Responses Without V1

Electrophysiological experiments in anesthetized macaques first demonstrated that neurons in the superior temporal polysensory area and area MT continue to respond to visual stimuli even after V1 is chronically removed, reversibly cooled, or acutely ablated (Bruce et al. 1986, Girard et al. 1992, Rodman et al. 1989). By contrast, neurons in the inferotemporal cortex are unresponsive to visual stimuli following ablation of V1 (Rocha-Miranda et al. 1975). Subsequent single-unit studies in the macaque showed that the magnitude of residual responses in extrastriate cortical areas differed between dorsal and ventral stream pathways: Dorsal areas showed a higher fraction of neurons with residual stimulus responses (summarized in Bullier et al. 1994) (see **Figure 5*a***). Studies of residual MT responses in other primates have yielded mixed results (Collins et al. 2003, Kaas & Krubitzer 1992, Rosa et al. 2000); the basis of the discrepancy is presently unknown.

Functional imaging has the advantage of simultaneously monitoring neural responses in multiple areas. It also has certain disadvantages, such as poor temporal resolution and the uncertain origin of the blood-based response. Positron emission tomography (Barbur et al. 1993) and fMRI studies (Baseler et al. 1999, Bridge et al. 2010, Goebel et al. 2001) of human blindsight patients have shown responses in the extrastriate visual cortex, particularly in area MT, to stimuli presented to the blind field. Recent fMRI studies in macaques have also shown extrastriate activity in the months following surgical ablation to V1. One study in anesthetized animals used retinotopic mapping to demonstrate preserved responses in regions V2 and V3 corresponding to the blind field (Schmid et al. 2009). Another study in awake animals showed responses in several extrastriate areas to a small stimulus confined entirely to the blind field (Schmid et al. 2010). In that study, V1-independent responses reached on average 20% of the response strength compared with the control condition (**Figure 5*b***). There was a pronounced dorsoventral asymmetry within the early extrastriate cortex: The dorsal

components of areas V2/V3 and V4 showed notably higher residual activity, in agreement with a previous human study (Baseler et al. 1999).

Which Pathways Support Blindsight?

A difficult and sometimes frustrating feature of blindsight is that the experimental evidence fails to converge on a single pathway. There are at least three distinct challenges to this search. The first challenge is the biological complexity of the brain, including its parallel and redundant projections and the imperfect segregation of pathways. The second challenge is the inherent plasticity of the brain, raising the specter that the various candidate pathways change in their relative strengths over time. The third challenge is the imperfect and indirect nature of much of the evidence as it pertains to the pathways that support blindsight.

To take a concrete example, consider an electrophysiological study by Bender (1988) that used lesions to investigate potential sources of visual input into the macaque inferior pulvinar. In that study, visual responses were recorded in the pulvinar of animals that were intact or had experienced unilateral ablation of either the SC or V1. Bender found that, whereas SC ablation had minimal effects, V1 ablation completely abolished visual responses in the pulvinar. This finding suggests that SC inputs alone are unable to drive responses in the pulvinar, which would seem to refute any hypothesis of blindsight based on the colliculopulvinar pathway. However, in reference to the challenges mentioned above, rejecting the pulvinar contribution to blindsight given this finding alone would be unwise. First, regarding the biological complexity of the pathways, Bender's recordings may not have adequately sampled neurons from the two subregions of the pulvinar now suspected to be the critical visual relays (Berman & Wurtz 2010, Lyon et al. 2010). Second, regarding the inherent plasticity of the system, Bender found that, after several weeks, a few neurons in the inferior pulvinar did start to show modest visual responses. Third, regarding the indirect nature of experimental evidence, the demonstration of a physiological pathway in the anesthetized animal may or may not be related to residual visual performance in blindsight.

With these caveats in mind, a recent study points strongly to the LGN as being a critical relay in blindsight (Schmid et al. 2010). As mentioned above, following V1 ablation in macaques, fMRI responses to small stimuli in the blind field were observed in multiple extrastriate areas. Behaviorally, the monkeys were also able to respond to visual stimuli well above chance. However, following the additional pharmacological inactivation of the LGN, the residual extrastriate fMRI responses (**Figure 5*b***) as well as the monkey's behavioral performance were abolished, indicating that the LGN is critical for V1-independent vision. This result is consistent with two previous findings in macaques, one demonstrating that inactivation of all the LGN layers temporarily blocked visual responses in cortical area MT (Maunsell et al. 1990), and the other, that chemical lesions to all the LGN layers permanently abolished visual detection, with no recovery even after several months (Schiller et al. 1990). The Schmid (2010) findings also challenge explanations of blindsight that do not include the LGN. Whether the sparse direct projections from the LGN to the extrastriate cortex could support this form of residual vision has been addressed by Cowey (2010), who noted that, although the absolute number of such neurons is unknown, they are probably at least as numerous as all the retinal ganglion cells in the rat, a species that is clearly capable of visually guided behavior.

Finally, any reading of the literature makes it difficult to escape the conclusion that the SC must also be involved in blindsight. Ablation of the SC during blindsight abolishes visual performance mediated by eye movements (Kato et al. 2011, Mohler & Wurtz 1977) and visually guided reaching (Solomon et al. 1981), and it obliterates responses in the extrastriate cortex (Bruce et al. 1986, Rodman et al. 1990). The dependence on the SC has generally been interpreted as evidence for the importance

of the colliculopulvinar pathway, although it is also consistent with mediation through the colliculogeniculate pathway (Rodman et al. 1990). These findings, combined with the recent results from Schmid et al. (2010), raise the possibility that retinal information reaches the extrastriate visual cortex following V1 lesions via a colliculogeniculate pathway. Whether this pathway is the ultimate answer to the blindsight puzzle, or whether the challenges outlined above will continue to keep the answer out of reach, remains to be seen.

WHAT IS THE ROLE OF V1 IN CONSCIOUS PERCEPTION?

In closing, let us consider how these and other findings illuminate the specific contribution of V1 to visual awareness. As this line of inquiry runs the danger of becoming too abstract, we formulate our question in terms of a dichotomy, which may, admittedly, also be a false one: Is V1 an essential and inseparable component of the neural processes that generate perceptual awareness, or is V1 primarily a conduit for retinal image information, receiving, processing, and passing it along to higher "perceptual" centers? Within this framework, we conclude that there is insufficient evidence to support the former proposition and that the latter is probably closer to the truth.

First, the neurophysiological results do not provide much support for the view that V1 activity is a direct contributor to visual awareness. Although V1 neural activity correlates with some aspects of perception (reviewed in Tong 2003), firing rates in V1 are only minimally affected when a stimulus is rendered completely invisible. In general, the responses of V1 neurons are much more closely tied to the sensory afferents arriving from the LGN than to perception-sensitive responses characteristic of some extrastriate visual areas.

Second, the blindness produced by V1 damage and unconscious vision supported by V1-bypassing pathways does not imply that V1 has a generative role in perception. Although damage to V1 disrupts many pathways that could contribute to visual awareness, including, for example, feedback to V1 from the extrastriate cortex (Lamme 2001), a more conservative explanation for blindness is the deafferantation of the extrastriate cortex and, possibly, the pulvinar from V1's principal feedforward visual projections. Deprived of all visual information, neither telencephalic nor higher-order thalamic centers can contribute to visual awareness. The fact that vision after V1 damage in blindsight is unconscious is not a compelling argument that V1 activity contributes directly to visual awareness. Residual visual pathways, beyond being sparse in their projections, differ from the geniculostriate pathways in many ways. They are composed mainly of Pγ and Pα channels and may involve a relay in the SC. They may draw on a special category of hypertrophic koniocellular LGN cells that project to layer 5 of the extrastriate cortex, or they may be relayed through the pulvinar exclusively to dorsal stream extrastriate cortical areas. These and many other features may help explain why the visual signals carried to the extrastriate cortex through these residual visual channels fail to reach consciousness. However, none of these explanations points to a special role for V1 in the generation of visual awareness.

Third, it is not strictly correct to say that V1 damage always leads to blindness, as pointed out frequently in the literature on human blindsight (Ffytche & Zeki 2011). In addition to the difficult task of determining what exactly blindsight patients subjectively perceive, at least two findings demonstrate that they can experience vivid visual percepts in the region of visual space corresponding to the V1 lesion. First, blindsight subject D.B. experienced "prime sight": D.B. could consciously see an afterimage generated by a visual stimulus in the blind field but, strangely, not the adapting stimulus that generated it (Weiskrantz et al. 2002). Second, when transcranial magnetic stimulation was applied bilaterally over area MT, blindsight subject G.Y. experienced perceptually visible phosphenes that traveled into his blind field (Silvanto et al. 2008). In both paradigms, the subjects were able to perceive color in the blind

field when chromatic visual stimuli were applied. The bases of these phenomena are unknown, as is their generality. However, they do argue that visual awareness can occur in a region of space corresponding to a V1 lesion. Further evidence for the possibility of V1-independent visual awareness comes from humans, and quite possibly monkeys, whose vision is largely intact if their V1 damage is acquired in infancy (for a recent review, see Silvanto & Rees 2011). Based on studies in marmosets, Bourne and colleagues recently speculated that near-normal vision in the adult following V1 damage in infancy may be due to the abnormal retention of a prominent retinopulvinar pathway to area MT that, under normal conditions, is expressed only transiently in development (Bourne & Rosa 2006, Warner & Bourne 2012). Clearly this topic deserves further investigation.

In summary, the data accumulated from a wide range of anatomical, physiological, and behavioral studies in monkeys and humans paint a picture of V1 as a critical component of primate vision. Its importance, however, stems not from a direct contribution to visual awareness, but rather from its role as a highly adapted cortical lens through which the cerebral hemispheres, including the extrastriate visual cortex and other structures thought to participate directly in perception, receive visual information about the world.

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