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Neural Mechanism of Blindsight in a Macaque Model

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Abstract—Some patients with damage to the primary visual cortex (V1) exhibit visuomotor ability, despite loss of visual awareness, a phenomenon termed ''blindsight''. We review a series of studies conducted mainly in our laboratory on macaque monkeys with unilateral V1 lesioning to reveal the neural pathways underlying visuomotor transformation and the cognitive capabilities retained in blindsight. After lesioning, it takes several weeks for the recovery of visually guided saccades toward the lesion-affected visual field. In addition to the lateral geniculate nucleus, the pathway from the superior colliculus to the pulvinar participates in visuomotor processing in blindsight. At the cortical level, bilateral lateral intraparietal regions become critically involved in the saccade control. These results suggest that the visual circuits experience drastic changes while the monkey acquires blindsight. In these animals, analysis based on signal detection theory adapted to behavior in the ''Yes–No'' task indicates reduced sensitivity to visual targets, suggesting that visual awareness is impaired. Saccades become less accurate, decisions become less deliberate, and some forms of bottom-up attention are impaired. However, a variety of cognitive functions are retained such as saliency detection during free viewing, top–down attention, short-term spatial memory, and associative learning. These observations indicate that blindsight is not a low-level sensory-motor response, but the residual visual inputs can access these cognitive capabilities. Based on these results we suggest that the macaque model of blindsight replicates type II blindsight patients who experience some ''feeling'' of objects, which guides cognitive capabilities that we naïvely think are not possible without phenomenal consciousness. © 2021 The Author(s). Published by Elsevier Ltd on behalf of IBRO. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Key words: primary visual cortex lesion, superior colliculus, extrageniculate visual pathway, visual awareness, saccade.

INTRODUCTION

The primary visual cortex (V1) is the entrance point for cortical visual processing, and damage to V1 leads to blindness in the contralateral visual field, namely cortical blindness or hemianopia (Holmes, 1918; Inouye, 2000). However, monkeys with surgical lesioning of V1 retain some level of visuomotor function (Humphrey and Weiskrantz, 1967; Schilder et al., 1967). A human counterpart of this phenomenon was first described in the patients with a gunshot wound (Pöppel et al., 1973). Then, a case report of patient ''D.B.'', who had his V1 surgically removed at the age of 33 years, was published in 1974 (Sanders et al., 1974; Weiskrantz et al., 1974). D. B. showed typical hemianopia, but was able to reach for a target presented in the blind field without visual awareness of the target. Such a dissociation between phenomenal awareness and the ability for goal-directed actions

was termed ''blindsight'' by Weiskrantz and colleagues. Another famous blindsight patient was ''G.Y.,'' who experienced damage to the left V1 and optic radiation at the age of 8 years in a traffic accident (Barbur et al., 1980). Studies of his vision comprise a very important part of blindsight research, some of which are explained below. Since then, blindsight has attracted considerable attention not only from clinicians but also from neuroscientists, psychologists, and philosophers.

A number of patient studies have been published (described in detail in the section ''Historical views on human studies''), but they are on a relatively small number of patients because of the difficulties in finding patients with more or less restricted damage to V1. To complement these human studies, several lines of nonhuman primate studies have been conducted (described in detail in the section ''Historical views on nonhuman primate studies''). The advantage of nonhuman primate models is that the extent of lesioning is controllable and some additional manipulations of circuit function are possible. However, they were mostly

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purely behavioral studies or neuronal recordings in anesthetized preparations when we initiated a series of experiments on a macaque monkey model of blindsight approximately 18 years ago. The aims of our studies were to identify the neural pathways underlying blindsight, to clarify what kind of cognitive functions were retained in blindsight, how they were executed by the neural circuits in the absence of V1, and what functions were impaired by V1 lesioning. In most of these studies, saccadic eye movements were used as a behavioral measure, whose advantage and disadvantage in arguing blindsight will be described later. A variety of analytical methods were combined including kinematic analysis of behavior, cognitive tasks with psychophysical measures, electrophysiological recordings, pharmacological inactivation, pathway-selective perturbations with viral vectors, neuroimaging techniques, and neuroanatomy. In this review, we provide a historical overview of the studies on human subjects and on nonhuman primates. Then, we summarize all of the results from our laboratory and propose our hypothesis on what blindsight is.

HISTORICAL VIEWS ON HUMAN STUDIES

After the first report of residual vision in patients with damage to V1 (Pöppel et al., 1973), extensive studies of patients including D.B (Weiskrantz, 2009) and G.Y. (Barbur et al., 1980) were conducted to understand blindsight. We are not going to cover all of them here, but the essential findings are summarized below.

Visual and visuomotor functions

Concerning low-level visual information processing, the performance of orientation discrimination of moving stimuli is very high in blindsight patients (Weiskrantz et al., 1995). The performance of orientation discrimination of static line segments was reported to remain at the level of chance (Morland et al., 1996), however, there is evidence that, at least in some patients (e.g. D.B., Weiskrantz, 1986) the threshold for orientation discrimination was found to be ~10° as compared to 2–3° at the corresponding location in the intact field. Also, there is demonstration in different patients of shape discrimination and even category discrimination (Trevethan et al., 2007; van den Stock et al., 2015). In a detection task of grating stimuli, the threshold for luminance contrast is increased in blindsight compared to normal vision (Sahraie et al., 2006). In addition, according to a study examining the effect of spatial frequency, sensitivity to components with a high spatial frequency (> 4 cycles/°) is reduced in blindsight (Sahraie et al., 2003). Concerning color, there are reports that color information can be detected and discriminated (Brent et al., 1994; Cowey and Stoerig, 2001). Conversely, some reported that human blindsight patients with V1 damage or hemispheric cortical resection are unable to detect stimuli composed of blue-yellow color opponent channels (koniocellular pathway) (Sumner et al., 2002; Leh et al., 2006; Tamietto et al., 2010).

Shape perception, such as the discrimination of simple shapes and words, was reportedly retained in two blindsight subjects (Marcel, 1998). Concerning facial recognition, blindsight subject G.Y. answered correctly to two choices more often than chance when discriminating facial expressions (De Gelder et al., 1999). This ability is sometimes called "affective blindsight." Interestingly, the same patient performed better than chance when discriminating the identity of faces (De Gelder et al., 1999). A further study based on functional magnetic resonance imaging showed that the processing of emotional faces can be mediated by an extrageniculo-striate neural pathway (Morris et al., 2001).

Regarding attention, blindsight subject G.Y. showed attentional effects such as a shorter response latency to invisible visual stimuli using information either from a foveal or peripheral cue in an attentional task using the Posner cueing paradigm (Kentridge et al., 1999, 2004).

Residual visuomotor activity, such as reaching or saccades in hemianopia, is sometimes called "action blindsight" (Danckert and Rossetti, 2005), and includes accurate localization by pointing (Danckert et al., 2003) and accurate obstacle avoidance without awareness of the obstacle (De Gelder et al., 2008; Striemer et al., 2009). Interestingly, obstacle avoidance can be abolished by introducing a 2-s delay (Striemer et al., 2009). This was considered to be due to sensitivity to looming stimuli (Pelah et al., 2015; Hervais-Adelman et al., 2015). In healthy subjects, transcranial magnetic stimulation of V1 reproduces blindsight. In such a condition, switching of the forearm-reaching trajectory occurs without awareness of the shift in target location (Christensen et al., 2008).

Functional recovery and plasticity

Several reports have suggested that training and plasticity are necessary for regaining function in blindsight. In a study by Sahraie and colleagues (Sahraie et al., 2006), subjects with visual cortical damage were trained in visual discrimination. The subjects answered whether the visual stimuli were presented during trial period 1 or 2. The subjects continued to perform this type of training at home and their performance improved over several months. Huxlin et al. (2009) reported that subjects trained to discriminate between directions of random dot-motion stimuli improved their sensitivity to near normal levels after 9–18 months. The subjects in these two studies were adults and the rehabilitation training started long after the injury. Thus, these studies suggest that, even in the adult brain, functional recovery may occur through large-scale structural changes.

Diffusion tensor imaging has revealed possible sites of pathway plasticity after brain injury in patients with blindsight, for example, strong connectivity from the lateral geniculate nucleus (LGN) to the middle temporal (MT) area in patient G.Y. (Bridge et al., 2008). In the context of affective blindsight, strong connectivity from the superior colliculus (SC) to the amygdala via the pulvinar is implicated (Tamietto et al., 2012). In a hemidecorticated patient with action blindsight, a novel pathway from the SC on the ipsilesional side to the contralateral cortex, which is not seen in normal subjects, was identified by diffusion tensor imaging (Leh, 2006). So far, the types of

connectional changes observed in human blindsight roughly fall within at least in two broad categories: one is the aberrant fiber tracts not otherwise present in the intact brain (Bridge et al., 2008) or strengthening of fibers also detectable in the normal brain (Tamietto et al., 2012). That may include the observation by Rodman and colleagues in monkeys which showed that intact structures like MT continued responding after V1 lesioning.

"Awareness" in blindsight

Blindsight subjects are not entirely without conscious experience of visual stimuli. For example, patient G.Y. reported a kind of "awareness" during motion discrimination that was not always correlated with the performance of discrimination (Weiskrantz et al., 1995). According to G.Y., he often has a "feeling of something" when the intensity of visual stimuli is high (Zeki and Ffytche, 1998). However, this is not the same as a so-called visual experience. For example, G.Y. describes the sensation as "a black shadow moving over a black background" (although he emphasizes that this is a metaphor). Weiskrantz called this type II blindsight, and distinguished it from type I blindsight, which has no such conscious experience. Conversely, Zeki and Ffytche (1998) argued that such sensations were a kind of visual experience, while they also identified a dissociation of G.Y.'s performance and "awareness," which manifests as a dissociation of performance and confidence. For example, G.Y. failed to optimize post-decision wagering, which is proposed as a method to quantify conscious awareness (Persaud et al., 2007). The dissociation between performance and "awareness" was also assessed by signal detection theory, in which confidence judgement is used to quantify sensitivity. In G.Y., the sensitivity of a forced choice task (which reflects performance) was higher than that of a "Yes–No" detection task (which reflects awareness), which was higher than zero, thus objectively confirming type II blindsight in G.Y. (Azzopardi and Cowey, 1997).

HISTORICAL VIEWS ON NONHUMAN PRIMATE STUDIES

As we described earlier, reports of residual vision in monkeys with surgical lesioning of V1 (Humphrey and Weiskrantz, 1967; Schilder et al., 1967) precede the first report of residual vision in patients with damage to V1 (Pöppel et al., 1973). After that, a huge number of studies have been conducted to understand the mechanisms of blindsight. Again, we are not going to cover all of them, but the essential findings are summarized below.

Visual and visuomotor functions

Early studies by Humphrey's group and Pasik's group examined residual visual capacity after bilateral lesioning of V1 and the surrounding cortices. For example, the monkey "Helen" was able to reach for moving stimuli and walk around an open space containing obstacles without any problems, namely showing successful obstacle avoidance (Humphrey,

1974). Pasik's group systematically studied the visual features of residual vision and found that monkeys with bilateral lesions can discriminate targets defined by luminance/brightness (Pasik et al., 1969; Schilder et al., 1971), sinusoidal grating (Miller et al., 1980), and shape or color (Schilder et al., 1972). These animals are also able to discriminate between the presence and absence of visual stimuli (Pasik and Pasik, 1973) and to perform visually guided reaching (Feinberg et al., 1978; Solomon et al., 1981).

Later studies examined residual vision and visuomotor processing in monkeys with unilateral ablation or cooling of V1, thus enabling selective lesioning of V1 and a comparison of residual vision with the normal visual field in the same animal. For example, monkeys with complete or partial ablation of unilateral V1 can make saccades or press a lever to indicate the presence of a target in the visual field corresponding to the injury site (Mohler and Wurtz, 1977). This residual visuomotor processing can be completely abolished by additional lesioning of the SC. In a visually guided reaching task, the participants correctly select the location of a visual stimulus presented on a display in two choices (Cowey and Stoerig, 1995). Another study showed that sensitivity to target luminance in the visually guided saccade task decreases after V1 lesioning (Moore et al., 1995). Hemianopic monkeys are also able to detect and discriminate chromatic targets (Cowey and Stoerig, 2001).

Blindsight in monkeys

Since blindsight is defined as a dissociation between phenomenal awareness and goal-directed action, demonstrating residual vision in monkeys is not sufficient evidence of blindsight. An explicit test for the loss of phenomenal awareness is needed, but this is impossible for monkeys in the absence of language. Instead, evidence for the loss of visual awareness has been examined. For example, the study cited above (the section "Visual and visuomotor functions") showed that successful performance in a visually guided saccade task is possible only when it has a forced choice condition (Moore et al., 1995). When the temporal cue or go signal is not given simultaneously with stimulus presentation, the performance of visually guided saccades decreases.

Another study tackled this problem by introducing a "Yes–No" task paradigm to V1-lesioned macaques (Cowey and Stoerig, 1995). In their study, monkeys with unilateral V1 lesioning were tested in a reaching task in the forced-choice mode and "Yes–No" choice mode. In the case of forced choice, their performance was more than 90% successful in the affected visual field; however, in the "Yes–No" choice mode, in which they have to report whether they have seen the target or not, their success rate dropped to less than 10%. The authors claimed that this was evidence indicating that the visual awareness of the monkeys was impaired in the affected visual field. However, this study was criticized in terms of task design and analysis (Mole and Kelly, 2006; Allen-Hermanson, 2010). To overcome these claims, we introduced a new

task and analysis using signal detection theory (Yoshida and Isa, 2015), which we explain in detail below (the section "Visual awareness").

Functional recovery and plasticity

In contrast to human studies, there was no detailed analysis of functional recovery after lesioning in an animal model when we started our research project. This was later accomplished in our study of the time course of behavioral recovery (Yoshida et al., 2008). Concerning plasticity, the age at which lesioning occurs seems to be key. Studies from Gross's lab showed a better performance in the detection of stimuli in the contralateral hemifield in monkeys with surgical ablation of unilateral V1 at 5–6 weeks of age than in monkeys with ablation in adulthood (Moore et al., 1996). They also showed that the detection of random dot motion (without clues for positional information) is also possible in monkeys with V1 lesioning in infancy (Moore, 2001). In addition, recent studies by Bourne and colleagues have shown that the connection between the pulvinar and the area MT is strengthened in the marmoset with V1 lesioning at the juvenile stage (Warner et al., 2015), suggesting the age as a critical factor for the plasticity. point out to lesion onset as a critical factor.

Neural pathway(s) for residual vision

Superior colliculus. At the very beginning of blindsight studies, Weiskrantz and colleagues were already arguing that the SC, a midbrain visual center, plays a critical role in blindsight. In vertebrate species, such as fishes, amphibians, reptiles, and birds, the majority of retinal ganglion cell axons project to the optic tectum, and in mammals, along with the expansion of the cerebral cortex, a larger portion of retinal ganglion cell axons project to the LGN, and the visual information is then conveyed to the visual cortices. In mice, ~90% of optic fibers are directed to the SC (Linden and Perry, 1983; Hofbauer and Dräger, 1985). In primates, more than 90% of optic fibers are directed to the LGN; however, there are at least 6 other branches that end up in the midbrain and subcortical regions (Weiskrantz, 1972) and one of these contains ~100,000 fibers (Weiskrantz, 2009), which is not trivial. Therefore, it was reasonable to hypothesize that the function of V1 is at least partly taken over by the SC in blindsight.

Early studies using anesthetized macaque monkeys showed that the visual responses of the superficial layer of the SC were retained following ablation or cooling of the ipsilateral V1 (Schiller et al., 1974). In awake monkeys with complete or partial ablation of the unilateral V1, residual visuomotor processing via saccades and reaching are completely abolished by additional lesioning of the SC (Mohler and Wurtz, 1977). The visual responses of macaque MT cortex neurons after V1 damage retain almost the same degree of direction selectivity as in the normal condition, although firing frequency is reduced (Rodman et al., 1989). Conversely, when V1 and the SC are both damaged, the responses in the MT cortex are completely lost (Rodman et al., 1990). This suggests that the response of MT neurons after V1 damage is mediated by the SC and cannot be explained by a direct input pathway from the LGN to MT cortex. More recently, our group revisited this issue and confirmed that the reversible inactivation of the SC impairs visually guided saccades (Kato et al., 2011). Thus, the essential role of the SC in visuomotor processing in blindsight has been confirmed repeatedly in macaque models of blindsight.

Geniculo-extrastriate pathway. In contrast to the established role for the SC in blindsight, there have been arguments on the thalamic relay of visual signals for blindsight. As for the visual pathway to the cortex, earlier studies focused on the role of the SC–pulvinar–extrastriate pathway to bypass V1 (Diamond and Hall, 1969; Bender, 1983, 1988; Warner et al., 2015). Later anatomical studies have shown that some portion of the pulvinar receives direct retinal inputs, which could convey the visual signal to the cerebral cortex (Kaas and Lyon, 2007; Gattass et al., 2014). However, as to the role of the pulvinar, Kaas and colleagues suggested it should be minimal, because the tecto-recipient zone of the pulvinar overlaps minimally with the area containing neurons projecting to the extrastriate cortex (Stepniewska et al., 1999). Conversely, Cowey et al. (2011) showed that there are surviving neurons in the dorsal LGN that project to the extrastriate cortex after V1 lesioning and suggested they would mediate the direct visual inputs to the extrastriate cortex in blindsight monkeys. It was later shown that some koniocellular layer neurons (K-cells) in the dorsal LGN project directly to the MT area (Sincich et al., 2004). In line with this, Schmid et al. (2010) showed that inactivation of the dorsal LGN impairs visual responses in the extrastriate visual areas and the performance of visually guided saccades to targets on an artificial scotoma in monkeys made with V1 lesioning. Their proposal was that that the SC-LGN (K-cells)-MT pathway is critical for blindsight. Yu et al. (2018) showed that in marmosets with V1 lesioning, the remaining dorsal LGN neurons are activated strongly by visual stimuli and might have the potential to convey information for residual vision. More recent patient studies showed further evidence suggesting that human blindsight is mediated by the LGN-MT pathway using diffusion-weighted magnetic resonance imaging and fiber tractography (Ajina et al., 2015b) and functional connectivity analysis in functional magnetic resonance imaging (Ajina and Bridge, 2018). Thus, evidence has been accumulating that the LGN-MT pathway plays a major role in blindsight. We revisited this issue in the section "Thalamic relays: LGN vs. pulvinar" by pharmacological inactivation of the pulvinar in blindsight monkeys (Kinoshita et al., 2019) and pharmacological inactivation of the pulvinar and LGN separately in blindsight monkeys (Takakuwa et al., 2021).

STUDIES FROM OUR LABORATORY: BEHAVIORAL ANALYSIS

Around 2003, we initiated the projects to clarify the neural mechanism of blindsight by using macaque model,
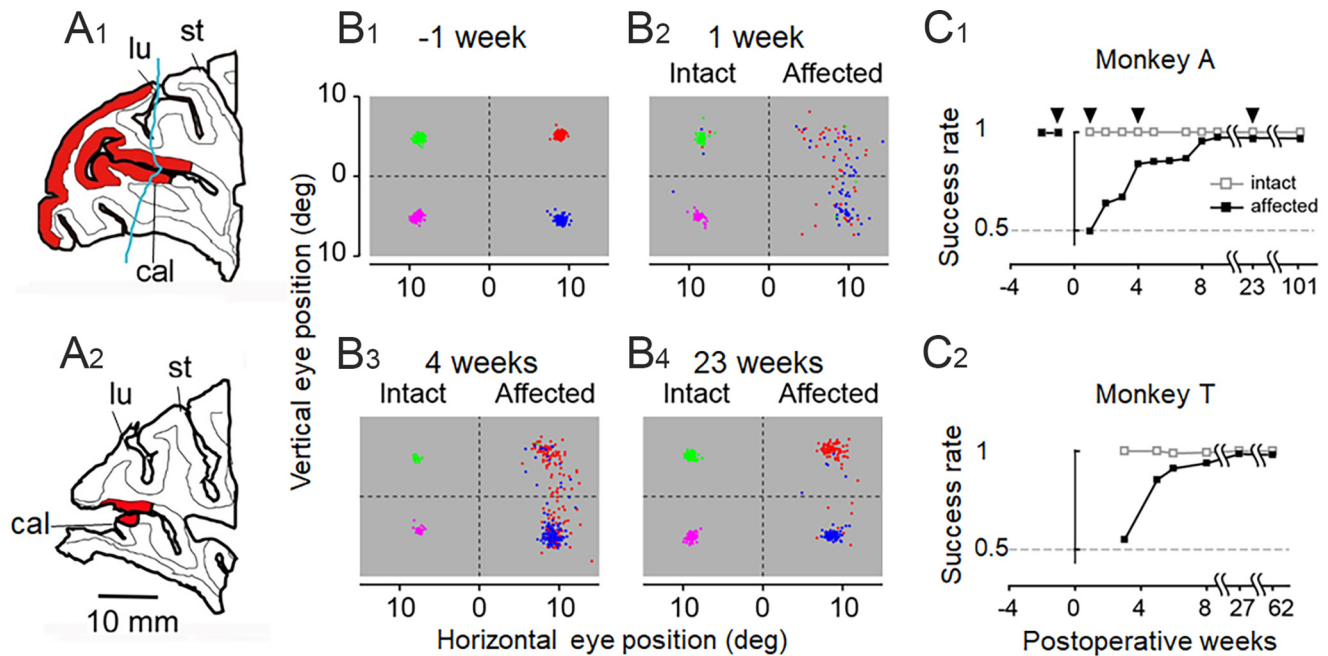
Fig. 1. Lesion extent and recovery of visually guided saccades. **(A)** Parasagittal sections along the calcarine sulcus (cal) on the intact **(A1)** and lesioned **(A2)** side. The extent of V1 is indicated in red. As judged from the lesioned side, the presumed rostral border of the lesion is indicated in **(A1)** with a light blue line. lu, lunate sulcus; st, supratemporal sulcus. Modified from Kato et al. (2021). **(B)** Recovery of visually guided saccades. Endpoints of saccades toward four different target locations indicated by different colors are plotted. **(B1)** At 1 week before V1 lesioning, **(B2)** 1 week after V1 lesioning (the day of the first postoperative experiment), **(B3)** 4 weeks after V1 lesioning, and **(B4)** 23 weeks after V1 lesioning. **(C)** Recovery of visually guided saccades after V1 lesioning in two monkeys, **(C1, C2)**, respectively. Success rate of saccades is plotted against postoperative weeks. Note that the success rate recovered to greater than 90% at 8 weeks postoperatively.

primarily triggered by Cowey and Stoerig study in 1995, in which visual awareness of macaques with V1 lesion was tested in Yes–No task paradigm. Our goal was to clarify the visual circuits underlying blindsight by combining various neuroanatomical and neurophysiological techniques, and visual cognitive functions retained after V1 lesion by applying a variety of contemporary cognitive neuroscience paradigms developed targeting macaques. We used saccadic eye movements as effector. We recognized that the risk of using saccades because the superior colliculus is playing roles in both input and output sides of the possible blindsight circuits. Actually many human blindsight studies have been using button press as the effector. However, because we were used to experiments on saccade motor system in macaques and visuomotor pathways for the saccades were better understood than those for the hand movements. Therefore, we thought that we should first clarify the outline of the system using saccades and then shift to the hand movement systems.

Extent of V1 lesioning

First, in the step visually guided saccade task, macaque monkeys are required to sit on a monkey chair and fixate on a central fixation point for 0.4–1.5 s under the head-fixed condition. Then, the fixation point disappears and another light spot (diameter: 0.45°) is presented in a different location in the peripheral visual field. The monkeys have to make a saccade within 0.7 s, and if

the saccade is correct, they are rewarded with a drop of water or juice. After the monkeys are trained to perform this task, V1 is surgically removed. In our studies, almost the entire V1, except for the region representing the fovea, is aspirated on one side, including the underlying white matter and adjacent V2 area to mimic the situation in blindsight humans (Sanders et al., 1974; Weiskrantz et al., 1974; Barbur et al., 1993) (Fig. 1A). To impair the visual field with at least a 25° eccentricity, we extend the lesion rostrally along the bank of the calcarine sulcus. Conversely, to spare the parafoveal region of the visual field, we leave the most ventral-rostral-lateral part of the surface area of V1. With such a lesion, the monkeys do not show any deficit in their ability to acquire the central fixation point with gaze (Yoshida et al., 2008; Isa and Yoshida, 2009).

Recovery process and properties of visuomotor function

To exclude the possibility that gaze was guided by light scattering on the intact visual field, we tested the effect of placing the target in a blindspot in the intact visual field and confirmed that the light scattering from the target did not guide the saccades of the monkeys.

Recovery of visually guided saccades

Intensive training on the step visually guided saccade task is usually initiated at 1–2 weeks after surgery. The monkeys are trained for several hundred trials each day
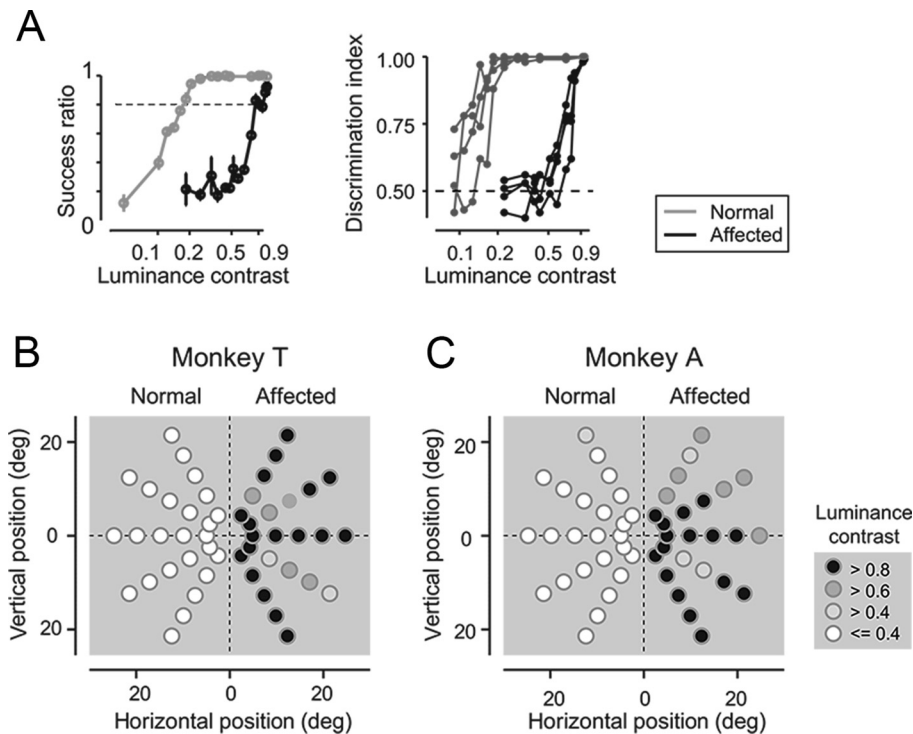
Fig. 2. Sensitivity to luminance contrast. **(A)** Psychometric functions. Left, the success ratio was plotted against luminance contrast. Gray line, trials with targets in the normal hemifield; black line, trials with targets in the affected hemifield. Target eccentricity, 10°. Monkey T. Trials with different directions are merged for each hemifield. The dashed line indicates a success ratio of 0.79, which corresponds to $d' = 2$ in five-alternative forced choices in signal detection theory, used for defining the threshold for luminance contrast. Both plots were fitted with logistic functions with statistical significance ($p < 0.01$). Right, the discrimination index was plotted against luminance contrast for the same data as in the left panel. The discrimination indices of four pairs of neighboring targets are plotted against luminance contrast. Gray lines, normal hemifield; black lines, affected hemifield. The dashed line indicates the chance level. **(B)** The threshold for luminance contrast is displayed as grayscale for each target position. **(C)** Same as in **(B** but for another monkey. Adapted from Yoshida et al. (2008).

in this task on 5 days per week. All nine monkeys used in this series of experiments recovered the ability to perform saccades at several weeks to months (mostly less than 2 months) with a success ratio of greater than 80% and a variety of experiments are initiated after this level of recovery is achieved (Fig. 1B, C).

Sensitivity to luminance contrast. A previous study showed that sensitivity to target luminance in the visually guided saccade task decreases after V1 lesioning (Moore et al., 1995). We also systematically measured sensitivity to luminance contrast in the intact and lesion-affected visual hemifields and constructed the psychometric functions. Compared to the intact field, sensitivity to target luminance decreased considerably in the lesion-affected visual hemifield (Fig. 2A). Thus, by systematically mapping the detection threshold, we could construct a "deficit map" of the visual field and clearly delineate the extent of the impaired and intact parts of the visual field (Fig. 2B). Therefore, we could easily detect if there was some region of V1 that was spared from damage by using this deficit map.

Accuracy of saccades. Although we mentioned that the performance of visually guided saccades recovered to a greater than 80% success rate, the endpoint variability of the initial saccades to the target was larger and never recovered to the pre-lesioning level, even at several years after V1 lesioning (Fig. 3A). That is, the saccades became inaccurate following V1 ablation. Conversely, the ability to fixate precisely on the target location was not impaired, which indicates that the inaccuracy of saccade endpoints is not caused by the inability of the visual system to capture the retinal error, but presumably occurs in the visuomotor transformation process for saccade control, which will be described later in this manuscript (see the section "Kinematics of saccades").

Kinematics of saccades. The positive correlation between saccade amplitude and peak velocity, the main sequence relationship, is maintained. Conversely, the trajectory of saccades becomes straighter after V1 lesioning (Fig. 3B). Usually, the trajectories of saccades are curved, suggesting the existence of online correction of trajectory in the midflight of saccades, which detects the error between the efference copy of saccade command and the internal goal of saccades and makes a quick correction to the trajectory. This mechanism is considered to underlie the accurate control of saccades. However, after V1 lesioning, the saccades are not corrected in midflight and the trajectories are straight, resulting in the inaccuracy of initial saccades. The reason why the online correction mechanism is impaired after V1 lesioning is still unclear (discussed later in the section "Saccade decision making").

STUDIES FROM OUR LABORATORY: NEURAL PATHWAY(S) FOR BLINDSIGHT

Superior colliculus

Previous studies on monkeys with blindsight support the idea that the function of V1 is taken over by the SC after V1 lesioning (see 3.4.1 for details). The role of the SC in blindsight has also been shown by manipulation of visual stimulus parameters in human subjects (Leh et al., 2010; Georgy et al., 2016).

More recently, our group revisited this issue and confirmed that reversible inactivation of the SC by
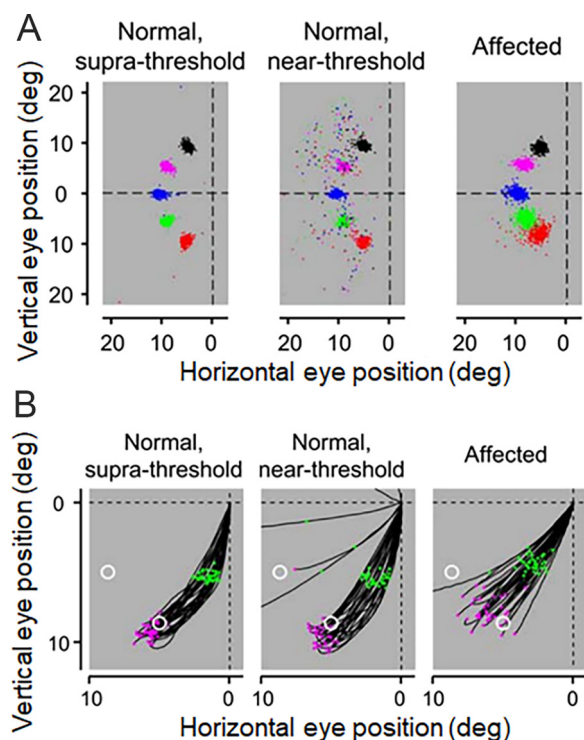
Fig. 3. Accuracy of saccades. **(A)** Scatter in the saccadic end points. The distribution of the saccadic end points in three different task sets: (left) normal (intact) visual field with supra-threshold intensity; (middle) normal (intact) visual field with near-threshold intensity; and (right) affected visual field. Colors of dots indicate the direction of the position of the saccadic targets. For comparison, the figure for the affected hemifield is flipped horizontally. Trials with a target eccentricity of 10° are shown. **(B)** Scatter in the initial direction of saccades. Examples of trajectories of the saccades to a target (10° in eccentricity and lower 60° in direction) in three different task sets (as in **(A)**). For comparison, the figure for the affected hemifield is flipped horizontally. Green dots, the points calculated as the initial direction of the saccades. Magenta dots, the end points of the saccades. White circles, possible target positions. Adapted from Yoshida et al. (2008).

injection of muscimol, a GABA$_A$ receptor agonist, impaired visually guided saccades toward a target presented in the spatial location represented by the injection site on the spatial map in the SC (Fig. 4A), while it did not affect spontaneous saccades with the same vector (Fig. 4B) (Kato et al., 2011). Thus, the essential role of the SC in visuomotor processing in blindsight has been confirmed repeatedly in macaque models of blindsight.

Thalamic relays: LGN vs. pulvinar

Observations with extensive ablation of cortical tissue suggest total subcortical processing for some visuomotor functions (Tomaiuolo et al., 1997; Savina and Guitton, 2018); however, other studies suggest the involvement of cortical visual processing for motion perception or goal-directed movements in blindsight subjects (monkeys: (Schmid et al., 2010; Bridge et al., 2019); humans: (Ffytche et al., 1996; Ajina et al., 2015a; Ajina and Bridge, 2019)). As described above (in the section

"Geniculo-extrastriate pathway"), evidence has accumulated that suggests the LGN-MT pathway plays a major role in blindsight. However, a study using a transsynaptic retrograde tracing technique showed that there is a pathway from the SC to MT or parietal cortex via the pulvinar. Berman and Wurtz (2010) showed that some pulvinar neurons mediate inputs from the SC to the MT area in V1-intact monkeys. Furthermore, Bender (1983, 1988) suggested that V1-recipient pulvinar neurons might become tecto-recipient neurons at more than 3 weeks after V1 lesioning. Thus, the thalamic regions that relay visual signals to the cortex to support blindsight were unclear. To clarify whether the pulvinar mediates the visual signals for blindsight, our laboratory tested the effects of reversible inactivation of the pulvinar with injections of muscimol into the pulvinar, and showed that inactivation of the ipsilesional pulvinar impaired visually guided saccades (Kinoshita et al., 2019).

In this study, furthermore, the involvement of the SC-pulvinar pathway was tested by selectively blocking the synaptic transmission of the pathway from the SC to the pulvinar using a double viral vector infection technique, in which synaptic transmission in the pathway was selectively blocked by the expression of tetanus neurotoxin (TeNT) triggered by the Tet-On driver system through the combined injection of a retrograde gene transfer vector (FuGE-TRE-eGFP.eTeNT) into the pulvinar and an anterograde vector (AAV-CMV-rtTAV16) into the SC, which was developed in our laboratory (Fig. 5A) (Kinoshita et al., 2012). The results showed that the reversible blockade of the SC to the pulvinar pathway impaired the performance of visually guided saccades (Fig. 5B). Thus, among various inputs to the pulvinar, those from the SC plays a critical role in controlling the visually guided saccades. However, at this stage, there are critical problems regarding both lines of study suggesting that the contribution of the LGN vs. pulvinar in subjects with different sized lesions (partial vs. extensive V1 lesioning) and periods of time after lesioning (several months vs. several years) should be investigated. Furthermore, the ability of blindsight was assessed with different measures (visual response measurement vs. saccade performance). In addition, different primate species (macaque vs. marmosets) were used. To solve these issues, we used double dissociation to clarify the roles of the LGN and pulvinar by pharmacological inactivation of each region with muscimol, and investigated the effects in a simple visually guided saccade task using monkeys with an extensive unilateral V1 lesion (Takakuwa et al., 2021). It was clarified that inactivating either the ipsilesional pulvinar or LGN impaired saccades toward a target in the affected field. In contrast, inactivation of the contralesional pulvinar had no clear effect, while inactivation of the contralesional LGN impaired saccades to targets in the intact visual field (Fig. 6). We have also examined what proportion of LGN neurons (K-cells and others) survive after V1 lesioning by staining K-cells with an anti-CaMKII antibody and other cell types with an anti-NeuN antibody. Anti-CaMKII immunohistochemistry showed that the number of K-cells was reduced as the time after V1 lesioning increased (52% at 6 months to 18% at
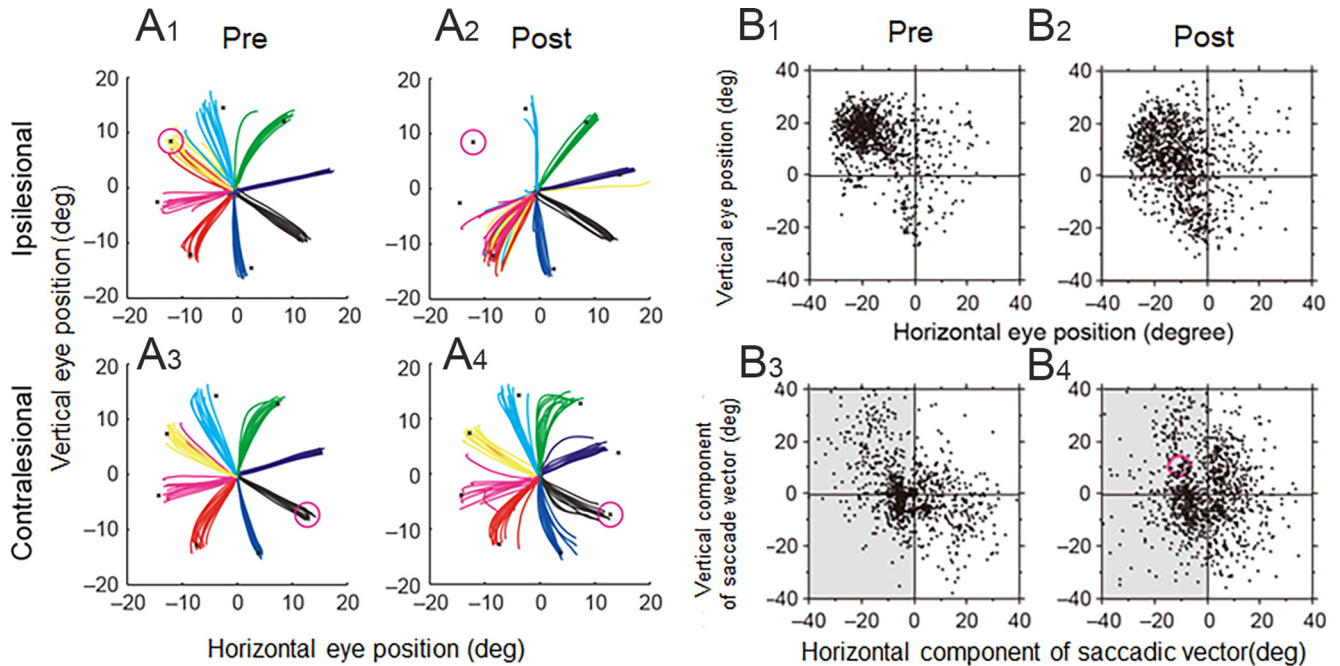
Fig. 4. Effect of superior colliculus (SC) inactivation. **(A)** Trajectories of saccades before and after SC inactivation in the visually guided saccade task. The trajectories to eight possible target positions are distinguished by color codes. Upper row: saccadic trajectories before (**1**: Pre) and after (**2**: Post) inactivation of the ipsilesional SC. Lower row: saccadic trajectories before (**3**: Pre) and after (**4**: Post) inactivation of the contralesional SC. A magenta circle in each panel indicates the visual field represented by the injection site. Small crosses indicate target positions in each experiment. **(B)** Endpoints of spontaneous saccades. (**1, 2**) Distribution of end points in the extrapersonal space before (**1**: Pre) and after (**2**: Post) ipsilesional SC inactivation. (**3, 4**) Distribution of saccadic vectors before (**3**: Pre) and after (**4**: Post) inactivation of the ipsilesional SC. The start points of individual saccades were centered on the zero point of the plot's coordinates and the end points are plotted. Vectorial spaces of the affected sides are shaded gray. The magenta circle in (**4**) indicates the visual field represented by the location of the center of the injection site on the SC map. Adapted from Kato et al. (2011).
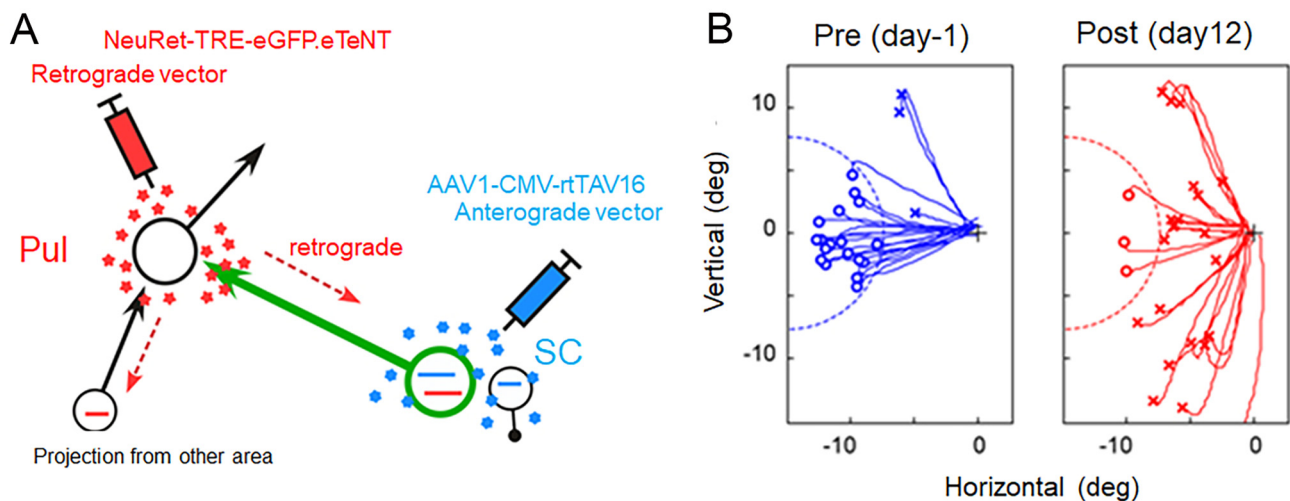
Fig. 5. Selective blockade of the superior colliculus (SC)-pulvinar (Pul) pathway impairs visually guided saccades. **(A)** Double viral vector infection technique. A retrograde gene transfer viral vector (HiRet-TRE-eGFP.eTeNT) was injected into the Pul and an anterograde viral vector (AAV1-CMV-rtTAV16) was injected into the SC. The retrograde vector might be taken up by other areas projecting to the Pul, while the anterograde vector might be taken up by other SC neurons that do not project to the Pul. However, double infection occurs only in neurons whose cell bodies are in the SC and whose axons project to the Pul. Synaptic transmission from SC neurons to the Pul is selectively blocked under the administration of doxycycline (Dox). **(B)** Representative saccade trajectories and saccade endpoints before (Pre) and during (Dox, 12 days after the start of administration) Dox administration. The marks indicate the location of saccade endpoints (o), targets (x), and fixation points (+). The size of saccade error (distance from the target to saccade endpoint) was increased in the Dox period in both monkeys. Adapted from Kinoshita et al. (2019).
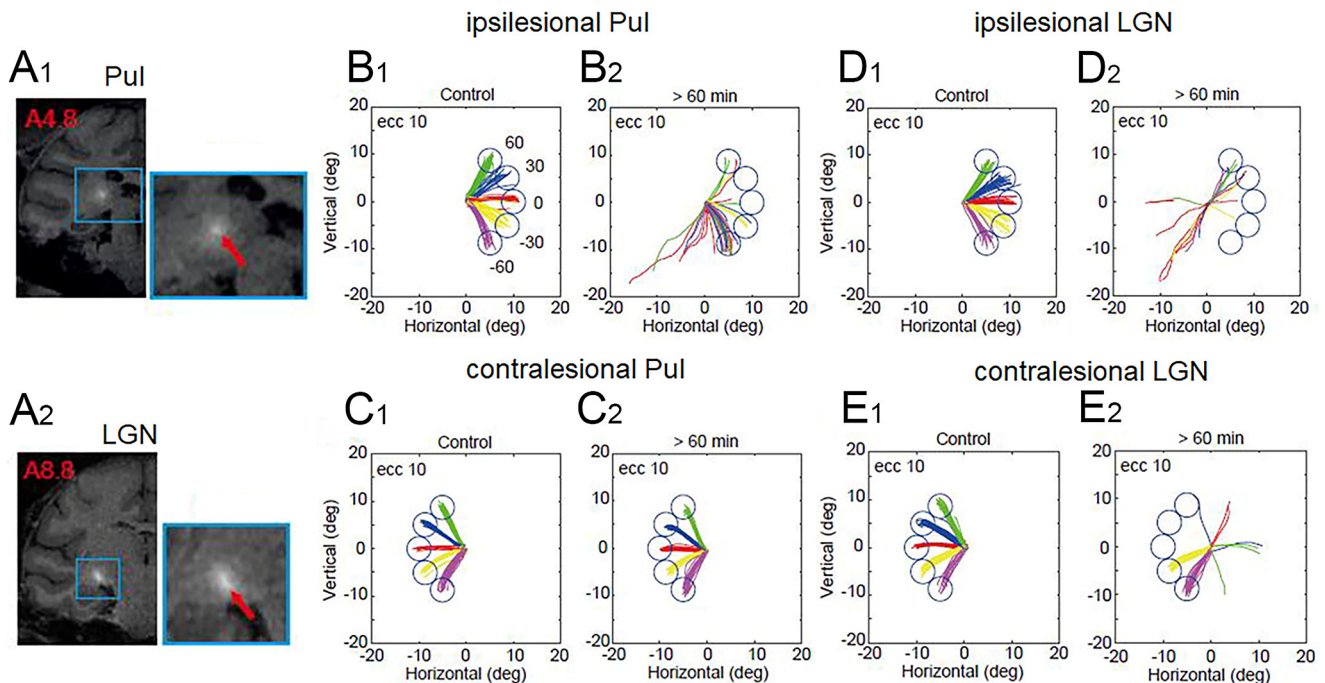
Fig. 6. Effect of inactivation of the pulvinar (Pul) or lateral geniculate nucleus (LGN) on the ipsilesional or contralesional side. **(A)** Muscimol injection sites in the Pul **(A1)** and LGN **(A2)**. The muscimol injection sites are indicated as white shadows of gadolinium in the coronal planes of magnetic resonance images. The anteroposterior levels in stereotaxic coordinates are $+4.8$ mm **(A1)** and $+8.8$ mm **(A2)**, respectively. **(B–E)** Effects of muscimol injections into the ipsilesional Pul **(B)**, contralesional Pul **(C)**, ipsilesional LGN **(D)**, and contralesional LGN **(E)**. Data from before injection (**1**) and at more than 60 min after injection (**2**) are shown. Eccentricity (ecc) of the saccade targets was $10°$. Each number in the left panel indicates target direction. Trajectories of saccades toward individual targets are indicated with different colors. Adapted from Takakuwa et al. (2021).

101 months). Compared to K-cells, magno- and parvocellular LGN neurons experienced greater retrograde degeneration, but a small portion still remained at 101 months after V1 lesioning according to NeuN immunohistochemistry (Fig. 7). These results suggested that the pulvinar and LGN both play key roles in controlling saccades in blindsight monkeys, while in the intact state, the pulvinar is not essential for saccade control. These results further suggest that plastic changes in the visual pathway involving the pulvinar that emerged after V1 lesioning support the ability of blindsight. All said, it should also be mentioned that the function of the direct retina-LGN and retina-pulvinar pathways has not been tested yet.

A review article by Tamietto and Morrone (2016) proposed that blindsight is not a single phenomenon, but should be considered as a constellation of functions of various visual pathways that survive V1 lesioning. The above results from our laboratory clearly showed the roles for the LGN and pulvinar in blindsight. Another recent review article suggested the hypothesis that the LGN route is concerned with basic visual detection, while the pulvinar pathway is more directly linked with visuomotor behavior (Rima and Schmid, 2020). These hypotheses can be tested in our experimental paradigm in future.

Posterior parietal cortex

To understand the cortical areas involved in the control of visually guided saccades in blindsight macaques, we conducted H$_2$O positron emission tomography imaging

in macaques with a unilateral V1 lesion. Saccade-related regions (or saccade-related activity) in blindsight monkeys were detected by systematically changing the number of visually guided saccades in each session and picking up the voxels whose cerebral blood flow was positively correlated with the number of saccades (Kato et al., 2021). By subtracting cerebral blood flow during the pre-V1 lesioning state from that during the post-V1 lesioning state, bilateral lateral intraparietal regions (LIPs) were shown to increase saccade-related activity after V1 lesioning (Fig. 8). To clarify further the role of bilateral LIPs in saccade control in blindsight monkeys, we performed single unit recordings and reversible inactivation of bilateral LIPs. The neuronal responses of LIP neurons were recorded during an overlap visually guided saccade task (300 or 500 ms overlap in the presentation of the fixation point and saccade target) or step visually guided saccade task (no overlap or delay between fixation offset and target onset). As shown in Fig. 9A, a clear visual response to target presentation in the affected field was observed in the ipsilesional LIP. The peak amplitude of the responses was similar to that of the contralesional LIP neurons to the target in the intact visual field (Fig. 9B). The latency of the visual response in the ipsilesional LIP was 141 ms on average, which was significantly longer than that of the contralesional LIP (91 ms on average). To clarify the contributions of the ipsilesional and contralesional LIPs to the control of visually guided saccades, muscimol was injected into the ipsilesional or contralesional LIP for reversible inactivation. Inactivation
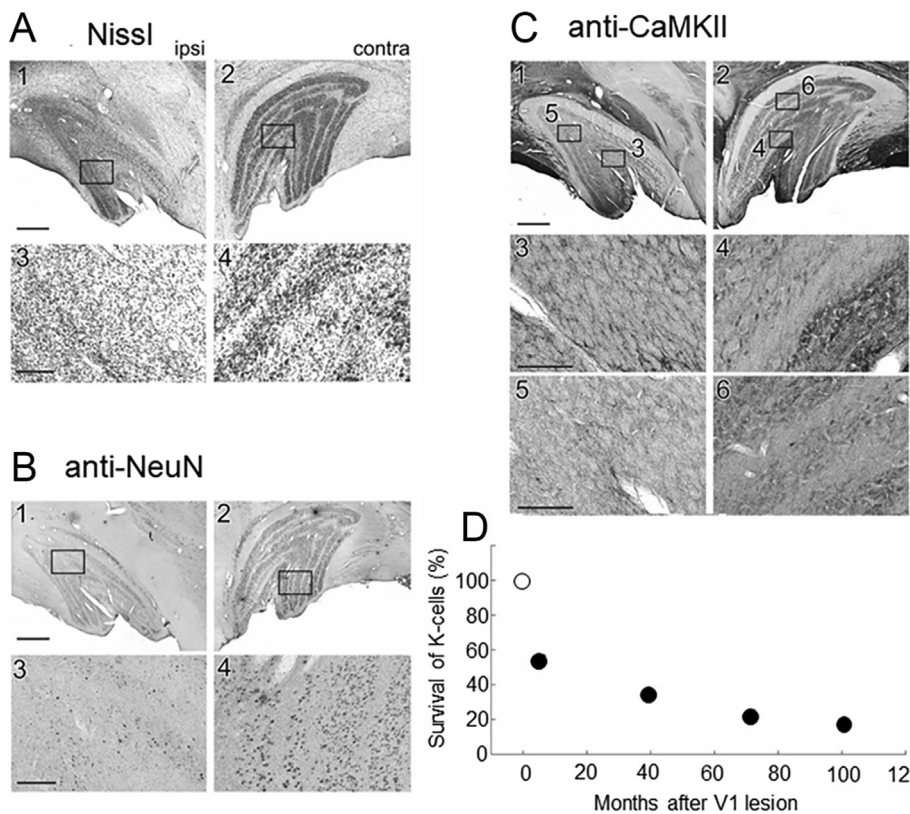
Fig. 7. Retrograde degeneration of lateral geniculate nucleus (LGN) neurons. **(A–C)** Examples of LGN neurons on the ipsilesional and contralesional sides. **(A1–4)** Low (**1, 2**) and high (**3, 4**; the area surrounded by squares in **1** and **2**, respectively) magnification views of Nissl-stained LGN sections on the ipsilesional (**1, 3**) and contralesional (**2, 4**) sides. **(B1–4)** Low (**1, 2**) and high (**3, 4**; the areas surrounded by squares in **1** and **2**, respectively) magnification views of anti-NeuN immunostained sections of the LGN on the ipsilesional (**1, 3**) and contralesional (**2, 4**) sides. **(C1–6)** Low (**1, 2**) and high (**3, 4, 5, 6**) magnification views of anti-CaMKIIα immunostained sections of the LGN on the ipsilesional (**1, 3, 5**) and contralesional (**2, 4, 6**) sides. Panels **3** and **4** are taken from the presumed magnocellular subdivision of koniocellular neurons (K1/K2), and panels **5** and **6** are taken from the presumed parvocellular domain of koniocellular neurons (K3–K6). Scale bars: **1** and **2** = 1 mm; **3**–**6** = 200 μm. **(D)** Relationship between the survival time of the animal (horizontal axis) and survival rate of koniocellular neurons (vertical axis, "K-cells") for five monkeys. Adapted from Takakuwa et al. (2021).

resources for visual information processing have been reduced after V1 lesioning, it is necessary for the LIPs to be more directly involved in the control of lower level visuomotor processing for saccade control. Besides the LIPs, the relationships between the midcingulate cortex, medial superior temporal and MT areas, and caudate nucleus were enhanced after V1 lesioning, the function of which needs to be clarified in future studies.

Drastic changes in the visual circuit organization

All of the above results suggest a drastic change in the visual pathways of blindsight subjects. As summarized in Fig. 10, the LGN still plays a critical role in mediating the visual signals to the extrastriate cortices after V1 lesioning, but it is largely shrunken because of retrograde degeneration. Instead, transmission in the SC-pulvinar pathway is enhanced and partly takes over the role of the LGN and becomes critically involved in the control of saccades. Further, LIPs are not critical for saccade control before V1 lesioning, but become critically involved in mediating the visual signals for saccade control after V1 lesioning. These results suggest that the visual circuits experience drastic changes while the monkey acquires blindsight. What kinds of plastic change occurred in which area of the visual circuits remain to be investigated in future studies?

of the ipsilesional LIP caused a deficit in visually guided saccades toward the affected visual hemifield (Fig. 9C). Moreover, interestingly, inactivation of the contralesional LIP did not impair saccades toward the intact visual field, in which the response field of the neurons is included; however, it caused a deficit in saccades toward the affected visual field (Fig. 9D). Thus, LIPs on both sides play critical roles in controlling visually guided saccades toward the targets in the affected visual field. Involvement of contralesional LIP in blindsight has also been suggested in a human study (Celeghin et al., 2017) and more recent meta-anbalysis of the whole human neuroimaging studies (Celeghin et al., 2019). It is well known that inactivation of LIPs in intact animals does not impair simple visually guided saccades, instead LIPs are presumed to be involved in the control of more complex tasks, such as memory-guided saccades, double-step saccades, and remapping of predicted visual target locations. These results suggested that the LIPs have a role in the visuo-motor transformation process after V1 lesioning. As the

STUDIES FROM OUR LABORATORY: COGNITIVE ABILITIES OF MACAQUES WITH V1-LESIONING

As blindsight subjects are considered to have lost visual consciousness, it could be presumed that they can perform only simple reflexive visuomotor tasks, and may not be able to achieve complex cognitive control of visuomotor behavior. We have examined what kind of cognitive tasks our monkeys with the V1-lesioning can perform and have found that surprisingly various cognitive processes are retained in blindsight subjects, as described below.
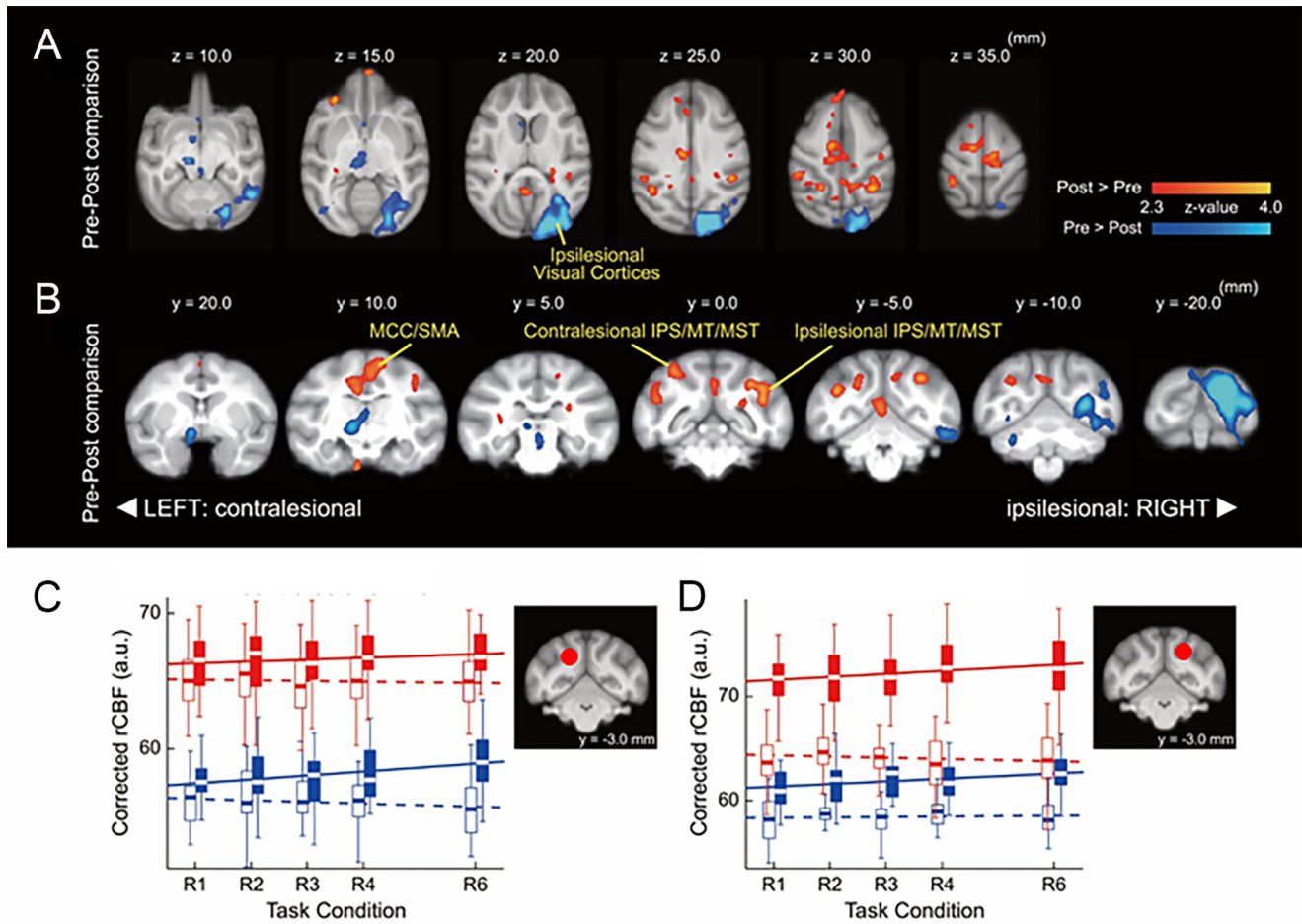
Fig. 8. Interaction effects on regional cerebral blood flow (rCBF) between task and lesion. Interaction effects of task and lesion showing the change in task relationship between the pre- and post-lesion periods in positron emission tomography scanning during the round saccade task. **(A, B)** Brain areas with a significant interaction effect between task condition and lesion. Red-yellow and blue-light blue show a significant increase and decrease, respectively, of task relationship in the post-lesion period compared to the pre-lesion period. **(C, D)** Relationship between rCBF (corrected for global signal) and task condition in the contra- and ipsilesional intraparietal sulcus (IPS), respectively. Box plots and regression lines are shown. Blue and red open boxes with dotted lines indicate the pre-lesion data of individual monkeys. Blue and red filled boxes with continuous lines indicate the post-lesion data of individual monkeys. Adapted from Kato et al. (2021).

Visual awareness

As we stated above, not only a test for residual visuomotor processing but also an explicit test for the loss of visual awareness are necessary to provide evidence of blindsight in monkeys. Cowey and Stoerig (1995) tackled this problem by comparing performance in a forced choice task and a "Yes–No" detection task using V1-lesioned macaques. In their study, first, performance in the forced choice task was tested in which the target appeared in all the trials and the monkeys were "forced" to respond. There, the success rate was more than 90% correct. In contrast, in case of the "Yes–No" task condition, the target was presented only in 10% of the trials and they are required to move the hand to the target. In other 90% of the trials, the target was not presented (termed "catch trials) and the monkeys were required to reach to the "blank target" at the corner of the screen. This mimicked the condition for the human patient to verbally "report" the presence of the target, in this case by pointing to it, and verbal report of the absence of the target, in this case by point to the blank target. Then, the success rate of the intact field was nearly 100%, while that in the affected visual field was less than 10% correct. The authors claimed that this was evidence indicating inability of reporting the presence of the target, which suggested that the visual awareness of the monkeys was impaired in the affected visual field. However, there have been claims against this study pointing to the fact that different visual tasks were used in the forced choice and "Yes–No" tasks, and the monkeys displayed a decision bias including an economical bias to obtain some amount of reward in the task (Mole and Kelly, 2006; Allen-Hermanson, 2010). To overcome these claims, we introduced a revised version of the "Yes–No" task in which we used a step or overlap visually guided saccade and compared performance between the forced choice task (in which the target appears in 100% of trials either in the upper or lower part of the visual field) and the "Yes–No" task (catch trials in which the target does not appear were introduced in trials in which the monkeys
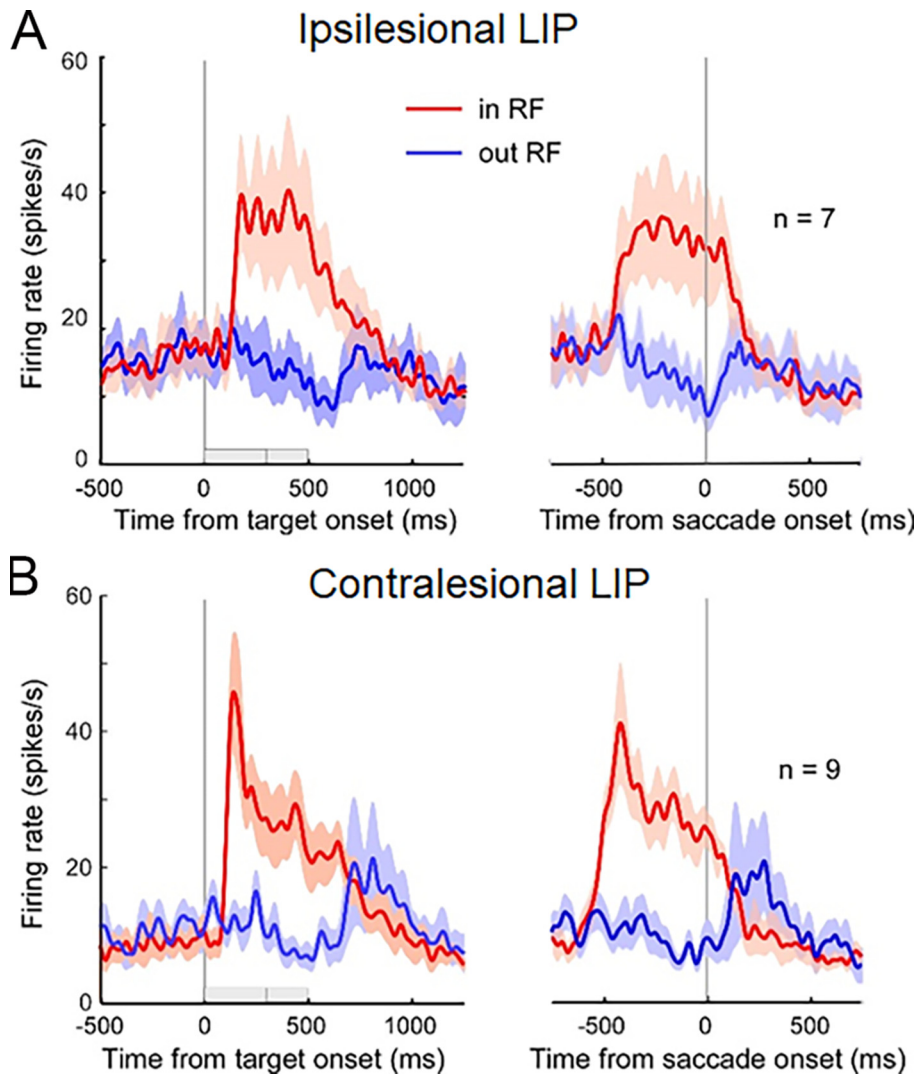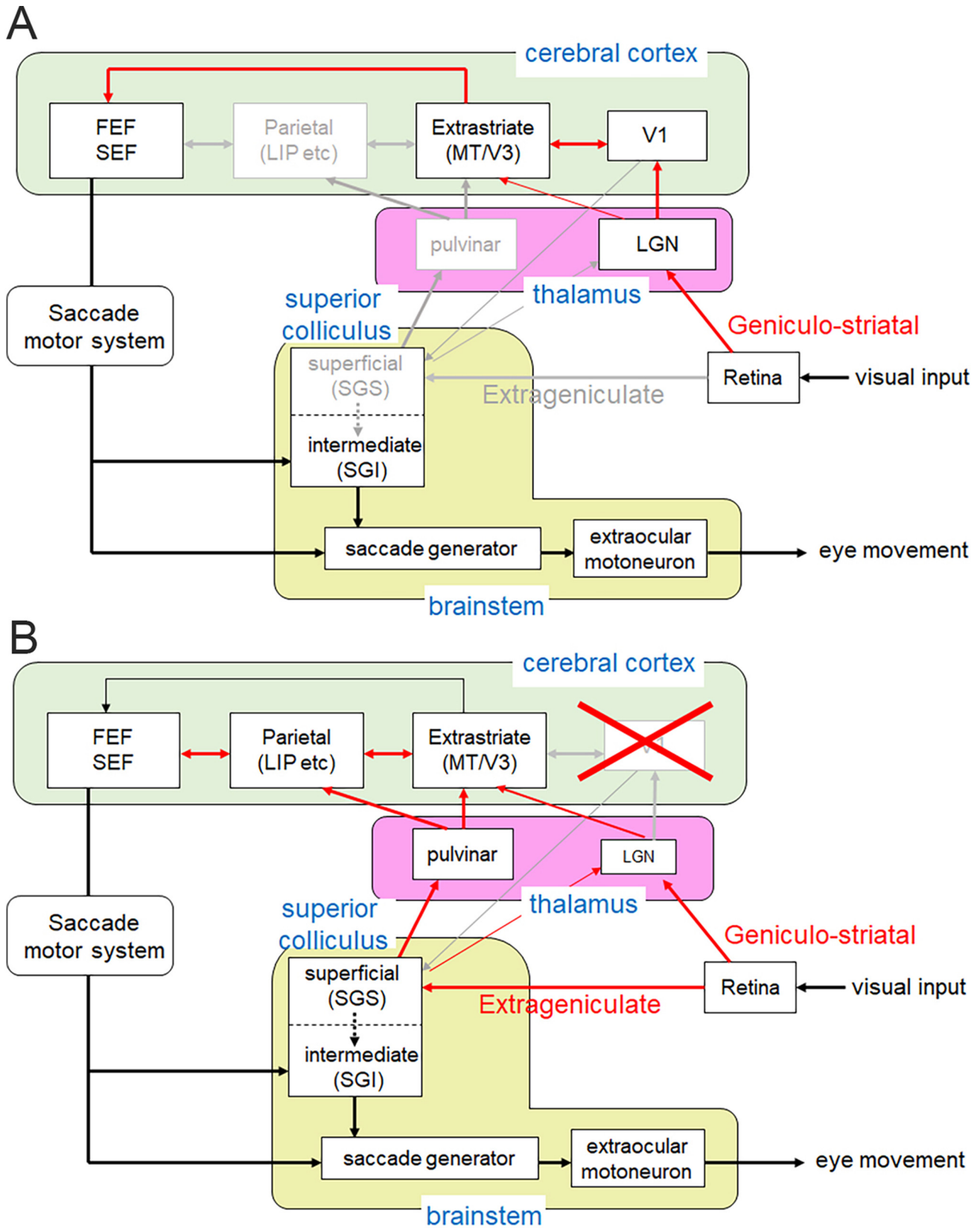
Fig. 9. Activity of lateral intraparietal regions (LIPs) and the effect of LIP inactivation in blindsight monkeys. **(A, B)** Population activity of neurons in the ipsilesional **(A)** and contralesional **(B)** LIP during the overlap visually guided saccade task. The left and right panels are aligned to target onset and saccade onset (vertical gray line), respectively. The red traces indicate the mean firing rate when the target was presented in the response field (RF). Blue traces indicate the mean firing rate when the target was presented outside the RF. Shaded areas indicate standard error of the mean. Gray bars on the horizontal axis of the left panels indicate the overlap periods of the fixation point and target (varying between 300 and 500 ms). **(C, D)** Success rates of visually guided saccades to the target in the affected (left) and intact (right) visual field. Inactivation of the ipsilesional **(C)** and contralesional **(D)** LIP. The data for saccades toward the affected and intact visual hemifield are represented in the left and right panel, respectively. The data points of individual experiments, before injection (Before) and after injection (After), are presented on the left and right side of each panel with connecting lines, respectively. SD, standard deviation. Adapted from Kato et al. (2021).

G.Y. (Azzopardi and Cowey, 1997). In this experiment, performance in the forced choice task was nearly 100% in the intact and affected visual hemifields, while performance in the "Yes–No" task dropped close to the chance level when the target was in the affected visual field, while performance was still > 90% successful when the target was in the intact visual field (Fig. 11B). Furthermore, to estimate sensitivity, we systematically changed the ratio of the catch trials and varied the Hit and False Alarm rates to yield a receiver operating characteristic curve. Then, the sensitivity (Da) dropped significantly when the target was in the affected visual field compared to the intact field (Fig. 11C–F). These results suggest that visual awareness was impaired in the affected visual field. However, the value was still not zero, which suggests the existence of some conscious experience. This observation was similar to that in patient G.Y. (Azzopardi and Cowey, 1997). From these results, we suggested that our macaque model of blindsight was similar to type II blindsight patients who have some "feeling of something happening" toward the targets presented in their lesion-affected visual field (see also the section ""Awareness" in blindsight"). This "feeling" might lead to the ability to perform several cognitive tasks, which are described below.

Saccade decision making

To analyze the decision for saccade initiation, we introduced the diffusion model by Ratcliff and colleagues (Ratcliff, 1978; Ratcliff and Tuerlinckx, 2002; Ratcliff et al., 2003), which is a rise-to-threshold model and applies the random walk model for the accumulation of information. We analyzed the distribution of the SRTs for visually guided saccades toward the intact and affected visual fields. In short, the distribution of the SRTs was narrow for the affected visual field compared to the intact field, and analysis clarified that the decision threshold was lower for saccades toward the affected visual field (Fig. 12). This means that the decision for saccade was less deliberate and saccades were initiated before sufficient information had accumulated after V1 lesioning compared to saccades with normal vision.

had to maintain fixation and to respond with saccades in the remaining trials to report that they had "seen" the target) (Yoshida and Isa, 2015). We also compared behavior using near-threshold stimulus intensity on the psychometric function in the intact and affected visual fields (Fig. 11A). Here, the stimulus condition was the same between the forced choice and "Yes–No" sessions, with the only difference being the presence of catch trials. Furthermore, to remove the influence of decision bias, we introduced signal detection theory and compared the sensitivity (D' or its derivative Da) to estimate awareness, which was the method used for human blindsight patient

Fig. 10. Neural circuit diagrams for the control of visually guided saccades in the intact state and after primary visual cortex (V1) lesioning. **(A)** Circuits in the intact state. The retina-lateral geniculate nucleus (LGN)-V1-extrastriate-frontal eye field (FEF)/supplementary eye field (SEF) pathway plays a major role. **(B)** After V1 lesioning, the LGN is largely degenerated; however, it still controls saccades through the direct pathway to the extrastriate cortex, while the superior colliculus (SC)-pulvinar pathway is upregulated and plays a major role through its direct routes to the extrastriate and/or posterior parietal cortex. LIP, lateral intraparietal region.
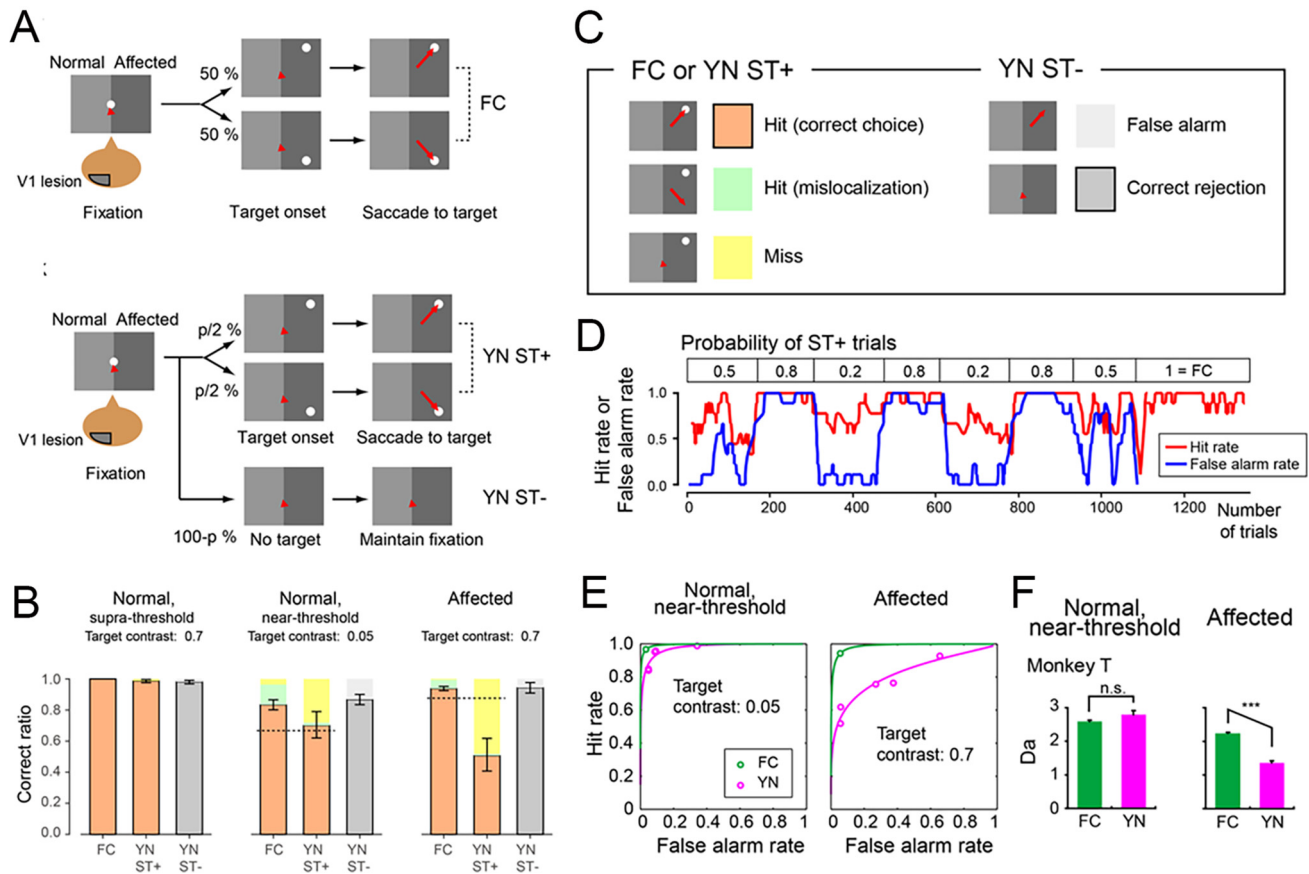
Fig. 11. Performance in the "Yes–No" task and analysis of sensitivity with signal detection theory. **(A)** Behavioral tasks. Top, forced-choice (FC) task. After a fixation period, a saccadic target appeared in one of two positions in one of the hemifields. Trials in which the stimuli were presented in different hemifields were in different blocks. Bottom, "Yes–No" (YN) task. YN trials with a saccadic target (YN ST +) were identical to the FC task. YN trials without a saccadic target (YN ST− condition) were randomly interleaved. The ratio for the ST + condition ($p\%$) was fixed either as 30% in the results for **(B)** or varied across trial blocks in the results for **(C–F)**. **(B, C)** An example of performance in the FC and YN tasks. The bars with black edges indicate the ratio of correct, rewarded trials to total trials. See the text for the classification of trials according to the behavioral responses. Left panel, trial blocks in which supra-threshold stimuli (target contrast 0.7) were presented in the normal hemifield ("Normal, supra-threshold"). Middle panel, trial blocks in which near-threshold stimuli (target contrast 0.05) were presented in the normal hemifield ("Normal, near-threshold"). Right panel, trial blocks in which stimuli (target contrast 0.7) were presented in the affected hemifield ("Affected"). **(C)** Definition of Hit, Miss, False Alarm, and Correct rejection. **(D–F)** Behavior and analysis based on signal detection theory. **(D)** An example of a session in which the probability of ST + trials was varied in different blocks. The value for each point represents a running average of the adjacent nine trials. Red, hit rate. Blue, false alarm rate. "FC = 1" indicates a trial block for the FC task. **(E)** Empirical receiver operating characteristic curves for the normal, near-threshold condition (left) and for the affected condition (right). Magenta, data for the YN task. Green, data for the FC task. A circle indicates a data point for each ST + probability. Lines indicate fitted lines. **(F)** Sensitivity, as expressed by Da, was plotted for the FC and YN tasks and for two trial conditions and for one monkey. ***$p < 0.001$; n.s., not significant. Adapted from Yoshida and Isa (2015).

Bottom-up attention

Bottom-up attention, or stimulus feature-driven attention, was studied in two ways, i.e., with a saccadic cueing task and with a saliency map model during a free viewing task.

Attention capture and inhibition of return. In the saccadic cueing task (Fig. 13A), a visual cue is presented briefly before the target stimulus in the same location as the cue or at the symmetrical point from the fixation point with stimulus onset asynchrony. In the normal condition, short stimulus onset asynchrony (100 ms) facilitates saccade initiation (shortening the SRT), while a longer stimulus onset asynchrony delays saccade onset (prolonging the SRT). The former phenomenon is called attention capture, and the latter

called inhibition of return. In our study, the SRT was shorter with a stimulus onset asynchrony of 100 ms, suggesting that attention capture was retained with the cue presented in the affected visual field. However, the SRT was still shorter with a stimulus onset asynchrony of 300 and 500 ms, suggesting that attention capture remains, but inhibition of return is impaired (Fig. 13B). Thus, some aspect of bottom-up attention (such as attention capture) is maintained after V1 lesioning, while another aspect of bottom-up attention (inhibition of return) is impaired (Ikeda et al., 2011).

Saliency detection during free viewing. Bottom-up attention was also assessed by investigating whether visual saliency can attract the gaze during free viewing (Yoshida et al., 2012). In collaboration with Itti and colleagues, we showed video clips (total of 70 min containing
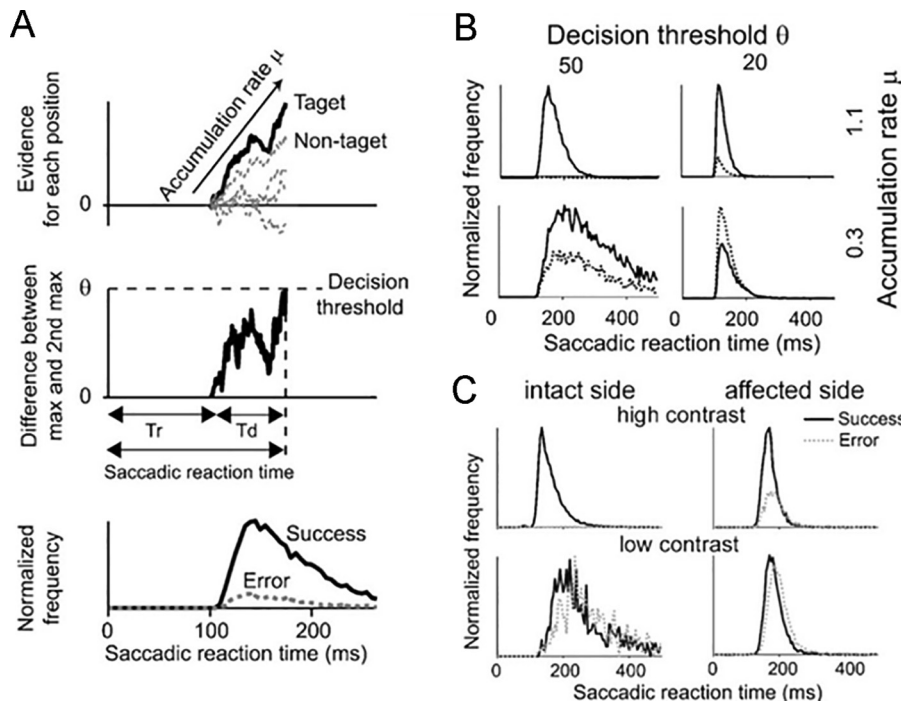
Fig. 12. Decision threshold for visually guided saccades assessed by the modified diffusion model. **(A)** Illustration of the model. Top, the decision signal for the target accumulates with an accumulation rate and Gaussian noise (black line). The decision signals for the non-target accumulate with an accumulation rate 0 and Gaussian noise (gray dotted lines). Middle, when the difference between the maximal signal and the second maximal signal exceeds the decision threshold, a saccade is initiated. Td, time of the decision-related component; Tr, time of the non-decision-related component. Bottom, by repeating this procedure, the distributions of the saccadic reaction times for the success trials and error trials were constructed. **(B)** Sample simulation. The distributions of the simulated saccadic reaction times for the success trials (black line) and error trials (gray, dotted line) are plotted for nine combinations of two parameters: the accumulation rate and decision threshold. Tr is fixed here as 100 ms. Bin size, 5 ms. **(C)** Experimental data for the distributions of the saccadic reaction times. Trials of four trial categories: high luminosity on the normal side (left-up) and low luminosity on the normal side (left-down), and high luminosity on the affected side (right-up) and low luminosity on the affected side (right-down). Black line, success trials; gray dotted line, error trials.

164 natural movie clips) to monkeys with a unilateral V1 lesion (left V1 was removed) and analyzed the saccades toward the intact (leftward saccades) vs. affected visual hemifield (rightward saccades) with the saliency map model (Itti et al., 1998; Itti and Koch, 2001). First, in this model, visual features (color [L-M and S-Lum], luminance, motion, and orientation) in the visual images of each frame of the video clip were processed separately to construct a saliency map (Fig. 14A). We examined whether the saccades were attracted to the points with higher saliency compared to their surroundings by using signal detection theory to compare the distribution of saliency values among the pixels on the screen and the distribution of the landing point of the gaze. It was clarified that the area under the receiver operating characteristic curve value was ~0.62 in the intact visual field and ~0.60 in the affected visual field, indicating that the spontaneous saccades were still attracted by visual saliency in the visual field affected by V1 lesioning (Fig. 14B). Furthermore, we analyzed which visual features attracted the gaze in the intact and affected visual fields by reconstructing the model using the leave-one-out method. Interestingly, motion and luminance saliency were still effective in the affected visual field, somehow as predicted. Conversely, orientation saliency was impaired in the affected visual field, which was striking, but as predicted by the ability of V1 to detect the orientation of the contours of visual objects. Furthermore, surprisingly, L-M color saliency was retained in the affected field (Fig. 14C). Color saliency is often difficult to dissociate from luminance in a natural scene. Therefore, to demonstrate that L-M color saliency was really retained in the lesion-affected visual field, we conducted a color discrimination task by using an iso-luminant stimulus. We varied the luminance contrast with some points around the iso-luminant point and found that the monkeys were able to detect the difference in color along the L-M axis in the affected visual field. These results suggested that the monkeys' gaze can be attracted by visually salient objects during free viewing of a natural scene, especially guided by luminance, motion, and color (L-M) saliency, but the effect of orientation saliency was lost.

Top–down attention

We assessed whether monkeys can exert their top–down attention toward visual objects in the affected visual field by using Posner's cueing paradigm (Yoshida et al., 2017). Here, we tested V1-lesioned monkeys with a visually guided saccade task in which an informative foveal pre-cue with a leftward or rightward arrow (serving as a pre-cue) predicting the upcoming target location was superimposed on the fixation point. After various cue-target onset asynchronies, a saccadic target of variable contrast across trials was presented either in the affected or intact hemifield. In 80% of the trials (valid-cue trials), target location was in the same hemifield that the pre-cue arrow pointed toward, making the cue highly useful for task performance, while in the remaining 20% of the trials (invalid-cue trials), the target was presented in the other hemifield (Fig. 15A). Then, the SRTs were shorter during the valid trials than during the invalid trials. We replicated the trials in the same monkeys using a symbolic color cue and could replicate the effect. These results suggest that V1-lesioned monkeys can use informative cues to localize stimuli in the contralesional hemifield, consistent with reports of a human blindsight subject being able to direct attention in cueing paradigms (Fig. 15B). On the basis of these results, we hypothesized that the SC could be involved in integrating top–down task
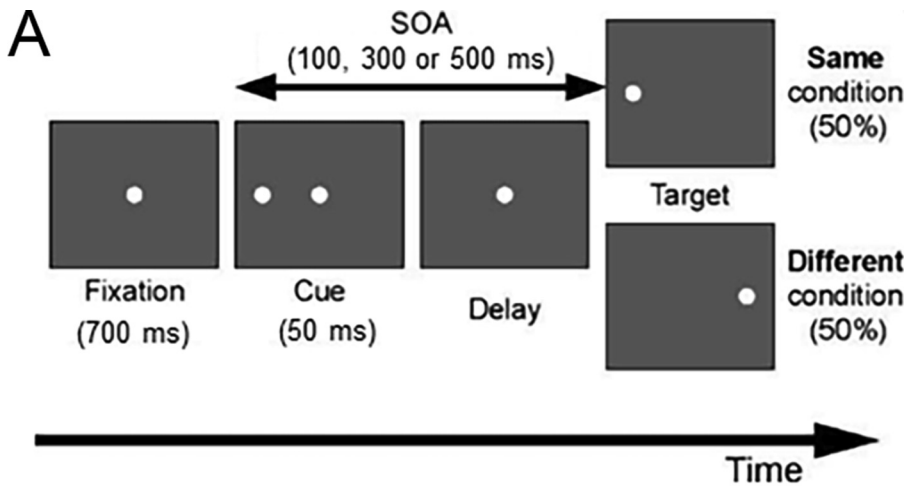
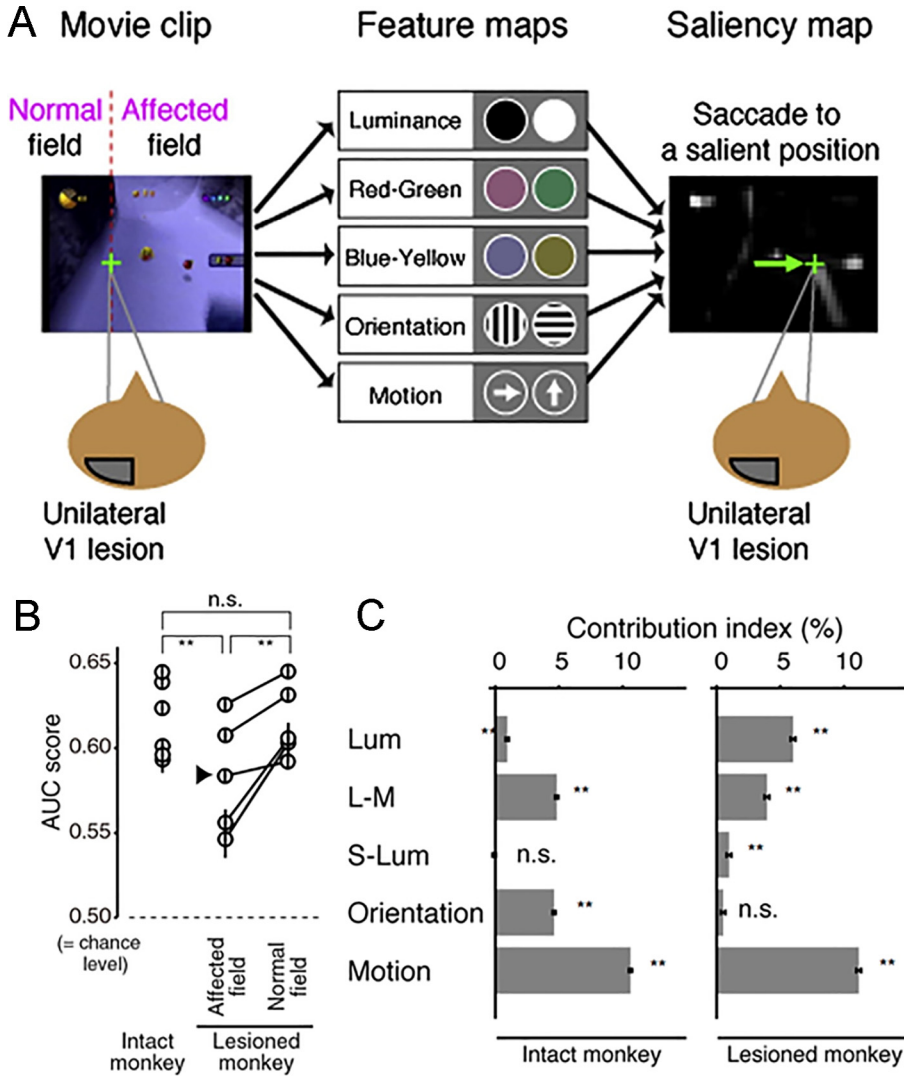knowledge for guiding orienting behavior in the blindsight state.

Short-term spatial memory

In general, short-term memory is closely linked to consciousness (Baars, 2003; Koch, 2004). To test whether spatial short-term memory is retained or impaired after V1 lesioning, performance in a memory-guided saccade task was tested with a cue in the affected visual field (Takaura et al., 2011). Surprisingly, V1-lesioned monkeys could perform the memory-guided saccade task with a cue in the affected field with a greater than 90% correct ratio (Fig. 16A, B). Furthermore, we conducted single unit recordings from the ipsilesional and contralesional SC while the monkeys performed the memory-guided saccade task, and sustained activity was observed during the delay period in a large fraction of neurons on the ipsilesional side, while sustained activity was much weaker in the contralesional SC (Fig. 16C). The delay period activity of these ipsilesional SC neurons maintained spatial information regardless of whether they exhibited saccadic bursts or not, which was not the case in the contralesional SC. Error analysis revealed that the sustained activity was correlated with the behavioral outcome. These results suggest that the ipsilesional SC might function as a neural substrate for spatial memory in the affected visual field after V1 lesioning. Sustained activity during the delay period of memory-guided saccades has been reported to exist primarily in the prefrontal or parietal cortex in many studies (Gnadt and Andersen, 1988; Funahashi et al., 1989; Chafee and Goldman-Rakic, 1998).
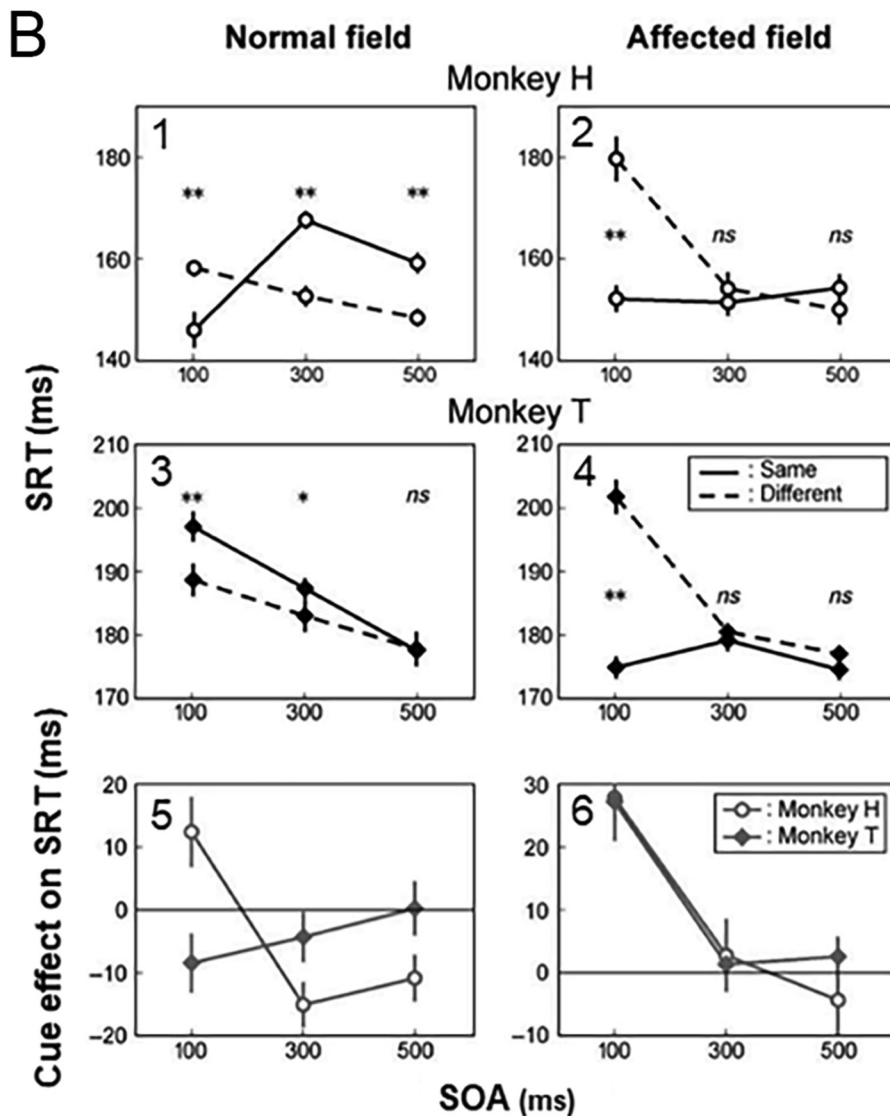
Associative learning

Associative learning is a fundamental aspect of brain function that animals use to modify their behavior in the natural environment. When confronted with stimuli that predict a reward or punishment, or the need to understand action-

outcome relationships, associative learning permits animals to acquire novel adaptive responses. Two forms of associative learning are recognized. (i) Pavlovian or classic conditioning that associates a predictive (conditioned) stimulus (CS) with an (unconditioned) reward or punishment. After training, the CS predictor elicits an anticipatory (conditioned) response (CR). (ii) Instrumental or operant conditioning that associates a behavioral output with a contingent outcome. Instrumental conditioning enables animals to learn novel responses that acquire rewards and avoid punishments. Animal behaviors are frequently modified by associative learning in daily life and some of these might be induced unconsciously. To determine whether subjective "awareness" of visual stimuli is an essential requirement for visual associative learning, we tested the ability of visual stimuli presented to the affected visual field of unilateral V1-lesioned monkeys to act as a CS in Pavlovian conditioning (Takakuwa et al., 2017). While the monkeys fixated on a central fixation point, a cue stimulus was presented in the upper or lower visual field of the intact or affected visual field. In each session, the CS was presented either in the intact or affected visual field only. In some sessions, the cue in the upper visual field led to an immediate large juice reward, while that in the lower visual field predicted a small reward given long after, and this assignment was reversed in other sessions (Fig. 17A). Anticipatory licking to obtain juice drops was elicited in response to the visual CS even if it was presented in the affected visual field (Fig. 17B, C). Subsequent phar-

Fig. 14. Residual saliency-guided eye movements after primary visual cortex (V1) lesioning. **(A)** Saliency model with an example movie frame (left) and its saliency map (right) with the trajectory of an eye movement (green arrow). **(B)** Quantitative analysis of saliency-guided eye movements. Saliency values at each saccade endpoint and for random endpoints were sampled and their distribution histograms were constructed. Receiver operating characteristic analysis was conducted using the histograms to generate area under the curve (AUC) scores for three groups: "intact monkey," data for left and right directions (six hemifields) for the three intact monkeys; "affected field" and "normal field," data for the five lesioned monkeys. Error bars indicate standard error. In all cases, the AUC scores were significantly above chance (0.5) ($p < 0.05$, two-tailed t-test). In group comparisons, ** indicates a significant group mean difference ($p < 10^{-9}$, Wilcoxon signed-rank test after Bonferroni's correction); n.s. indicates not significant ($p > 0.10$, Wilcoxon signed-rank test after Bonferroni's correction). **(C)** Contribution of saliency to each feature. Non-redundant contribution index of each feature (0 indicates that the feature of interest did not contribute to gaze guidance in any unique manner beyond what the other four features could predict). All of the feature contributions, except for those indicated n.s. (not significant), were significantly higher than zero ($p < 0.05$, paired t-test, with Bonferroni's correction for 15 simultaneous tests). Note that the contribution index does not add up to 100% (by definition). Error bars indicate standard error. Modified from Yoshida et al. (2012) with permission.

Fig. 13. Attention capture and inhibition of return in blindsight monkeys. **(A)** Experimental design. Time course of events in the saccadic cueing task. Monkeys had to make correct saccades to the target to obtain a juice reward. The two possible locations for the cue and target were fixed in each block of successful trials. SOA, stimulus onset asynchrony. **(B)** Cueing effects in the bilateral condition, in which the cue and target were presented either to the right or left of the fixation point. **(1–4)** Saccadic reaction times (SRTs) when the target was presented in the normal field (**1, 3**) or in the affected field (**2, 4**) for two monkeys. Solid lines indicate SRTs in the same condition and dashed lines indicate those in different conditions. Error bars indicate the 95% confidence intervals of the mean. Asterisks indicate significant differences between the same and different conditions, as determined by a t-test under Bonferroni's correction for multiple tests (six pairs). *$p < 0.05$, **$p < 0.0001$. **(5, 6)** Cueing effects on SRT, defined as the difference in mean SRTs between the two cue conditions (different condition minus the same condition), in the normal and affected field, respectively. Open circles: Monkey H; filled diamonds: Monkey T. Error bars indicate the 95% confidence intervals of the difference. Adapted from Ikeda et al. (2011).
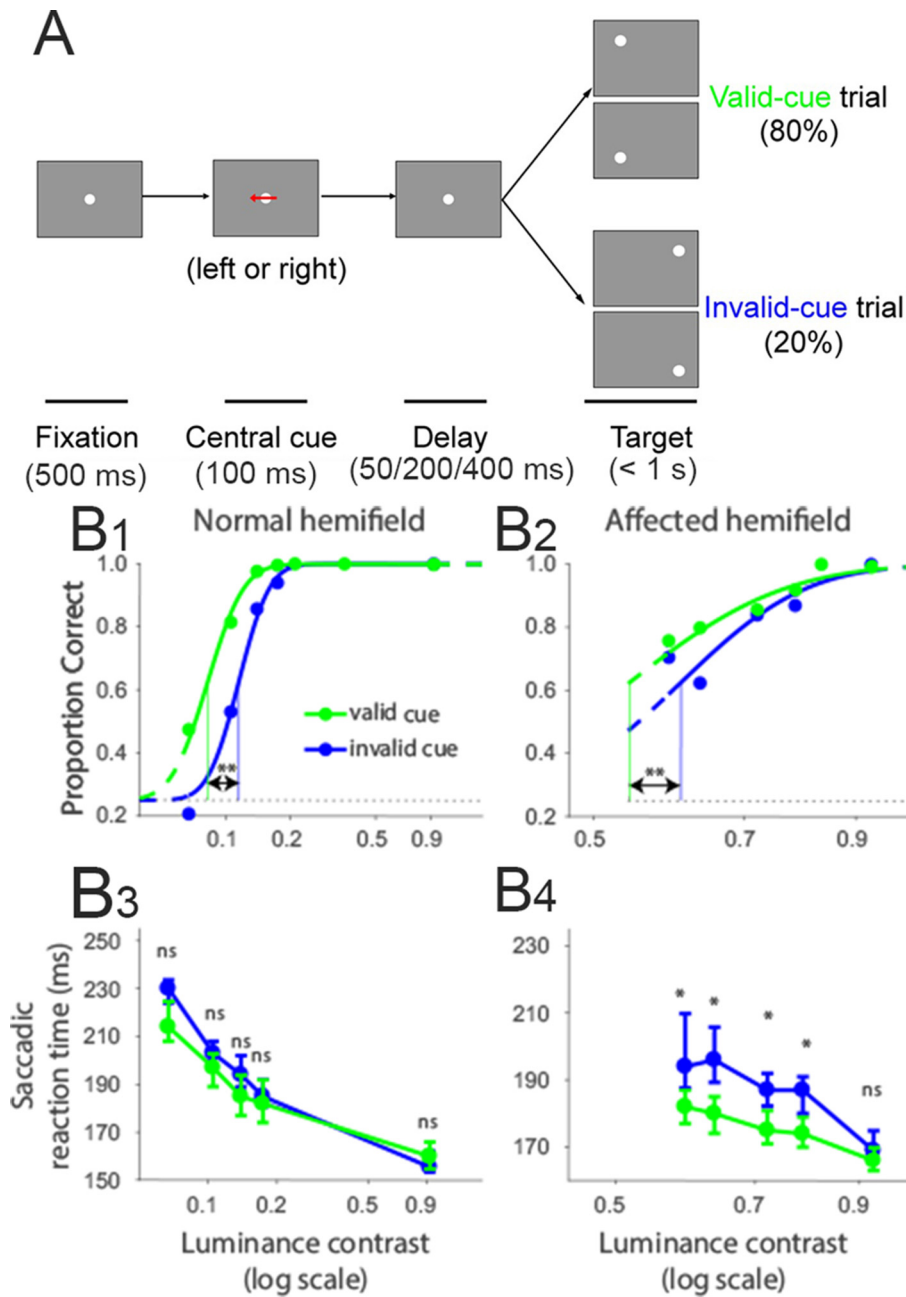
Fig. 15. Top–down attention assessed by Posner's cueing paradigm. **(A)** Schematic rectangular screens illustrating the fixation point, central cues, and saccadic targets for valid and invalid cue trials. The cues were leftward or rightward arrows. The targets were presented at varying intervals (50, 200, or 400 ms) after the briefly flashed cue (100 ms). **(B)** Psychometric curves and saccadic reaction times for the arrow cue task in one example monkey. (**1, 2**) Dots indicate the proportion of correct saccades at various luminance contrasts. Data were fitted by psychometric curves (lines). The dots and lines are shown in green for valid cue trials and in blue for invalid cue trials. Horizontal lines indicate chance level performance (0.25 for four alternative forced choice tasks). Vertical lines indicate the thresholds for each condition. The threshold was defined as the luminance contrast at which a psychometric curve crossed a value of 0.625 (=[1 + 0.25]/2). Significantly different ($p < 0.01$; permutation test). (**3, 4**) Dots indicate median saccadic reaction time at various luminance contrasts. Error bars indicate the 40th and 60th percentiles of the data. Asterisks ($p < 0.05$) and ns (not significant) indicate the results of Wilcoxon's rank sum test with Bonferroni's correction for multiple comparisons. For both rows, the left column shows data for trials with targets presented in the normal (ipsilesional) hemifield (**1, 3**), and the right column shows data for trials with targets presented in the affected (contralesional) hemifield (**2, 4**). Adapted from Yoshida et al. (2017).

macological inactivation of the SC suppressed this anticipatory licking. Concurrent single unit recordings indicated that dopamine neuron responses in the substantia nigra compacta, reflecting reward expectation, could be recorded in the absence of V1, and that these responses were also suppressed by SC inactivation (Fig. 18A, B). These results indicated that the subcortical visual pathway via the SC can relay reward-predicting visual information to dopamine neurons and the SC is necessary for visually elicited classic conditioned responses after V1 lesioning (Fig. 18C). However, in a subsequent study (Takakuwa et al., 2018), we tested the effects of contralesional SC inactivation and found that it was not effective in significantly changing Pavlovian conditioning task performance and dopamine neuron responses to the CS in the intact visual field.

How should we think about the cognition in blindsight?

The most striking difference between macaques with a V1 lesion and human hemianopia patients is the remarkable performance of macaques in visuomotor and cognitive tasks in contrast to the poorer performance of human patients in general. All the above studies from our laboratory on macaque monkeys suggested that blindsight cannot be a low-level sensory-motor response, but the residual visual inputs can access the centers enabling these various cognitive capabilities. This might partly be caused by species difference, as discussed in the preceding section, and also by the amount of training received after lesioning. Macaques with a unilateral V1 lesion were trained intensively on the visually guided saccade task from 1 week postoperatively, which is not the case for the majority of cortical blinded patients. Our studies have suggested an effect of training and plasticity in the visual pathways for the emergence of blindsight. We have the impression that younger
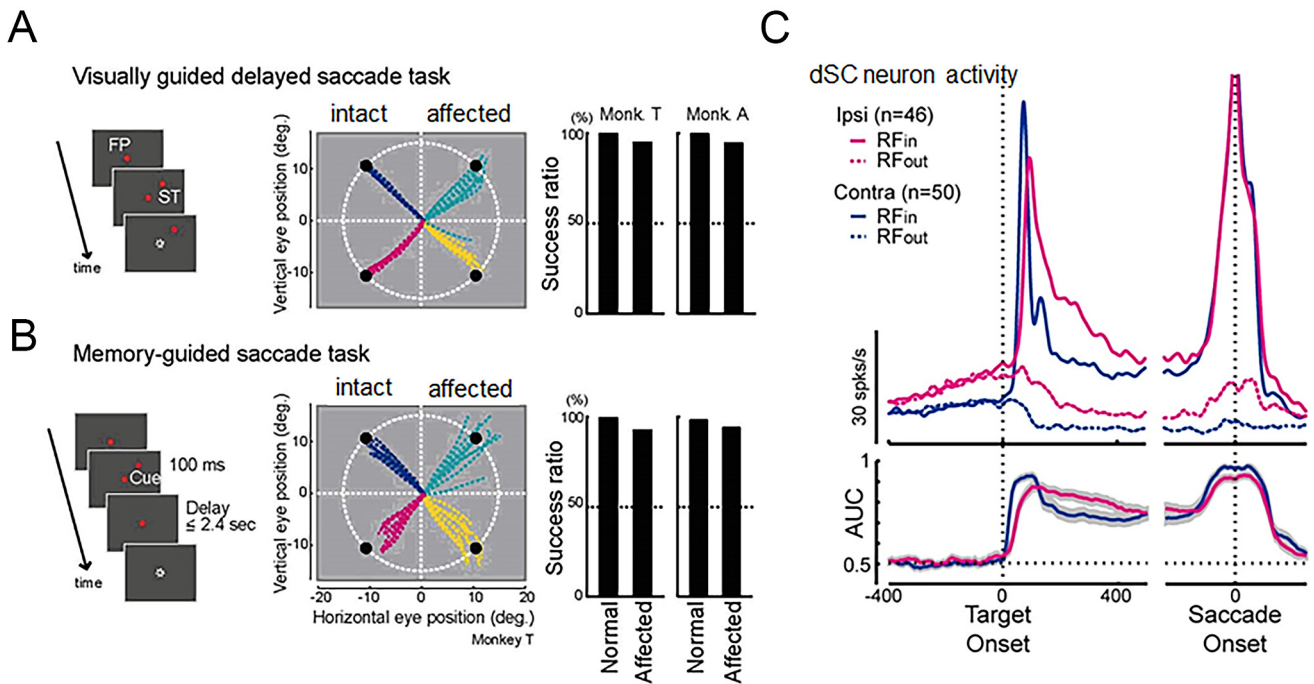
Fig. 16. Performance of memory-guided saccades by blindsight monkeys and neuronal activity in the superior colliculus (SC) during the task. **(A, B)** Behavioral results for the visually guided **(A)** and memory-guided **(B)** saccade tasks. **(A, B)** Left, task schema; middle, trajectories; right, success rates for each visual field in the two monkeys. In the middle panel, the differences in color indicate differences in the position of the target or cue. FP, fixation point; ST, saccade target. **(C)** Population average of the activity of visuomotor neurons in the deeper layer of the SC (dSC) on the ipsilesional side (Ipsi, n = 46, red) and contralesional side (Contra, n = 50, blue) during the memory guided saccade task. The records from the trials with targets in their response field (RF) are indicated with continuous lines (RFin) and those from trials with targets outside their RF are indicated with dotted lines (RFout). Top rows, spike density functions; bottom rows, time course of the AUC (area under the curve) of the receiver operating characteristics curve to discriminate the RFin and RFout trial data. dSC neuron on the ipsilesional side show a sustained increase in activity during the delay period of the memory-guided saccade task with a cue in their response field, while those on the contralesional side show lower level of sustained increase in activity during the delay period of the memory-guided saccade task with a cue in their response field. Modified from Takaura et al. (2011).

monkeys recover the ability to perform visually guided saccades faster than older animals, despite the lack of systematic comparisons among our subject animals. Considering the fact that V1 of type II blindsight patient G.Y. was damaged at the age of 8 years and that of type I blindsight patient D.B. was at the age of 33 years, the retained conscious level might also be influenced by age at the time of damage to V1. The relatively high performance of the macaques in the cognitive tasks might at least partly be due to the effect of such intensive training at a relatively young age. If such an improvement of visuomotor and cognitive functions by intensive training is the case and can be expected, there is a possibility that therapeutic strategies to improve the symptoms of patients with cortical blindness could be developed in the future.

EVOLUTIONARY ASPECTS

Blindsight is derived from the existence of two parallel visual systems in the brain. One is the retina-LGN pathway and the other is the retina-SC-thalamus pathway. The former was termed the lemnothalamic pathway and the latter was termed the collothalamic pathway by Butler and Hodos (2005). The existence of these two parallel pathways can be traced back to the lamprey, the oldest vertebrate, in which the existence of both pathways, eventually projecting to the pallium (corresponding to the telencephalon), was confirmed (see details in our recent review on the SC/tectum (Isa et al., 2021)). The relative densities of the two pathways vary from species to species. In lower vertebrates, such as fishes, amphibians, reptiles, and birds, the collothalamic pathway dominates the lemnothalamic pathway. Even among mammals, which have a greater amount of cerebral cortex, ~90% of optic fibers are directed to the SC in the mouse (Linden and Perry, 1983; Hofbauer and Dräger, 1985). In primates, more than 90% of optic fibers are directed to the LGN; however, a considerable number of optic fibers are known to project to the midbrain (Weiskrantz, 2009). Such relative densities of the collothalamic and lemnothalamic pathways might be reflected in the time course of recovery after damage to V1. The observation of general behavior including orienting responses has shown that rodents are little affected by V1 lesioning (Dean and Redgrave, 1984), cats need 1 week to recover innate behavior (Sprague et al., 1977), but 2–3 months if not trained (Wallace et al., 1990), and macaques need 2 months, if trained, for recovery (Yoshida et al., 2008). These results suggest that
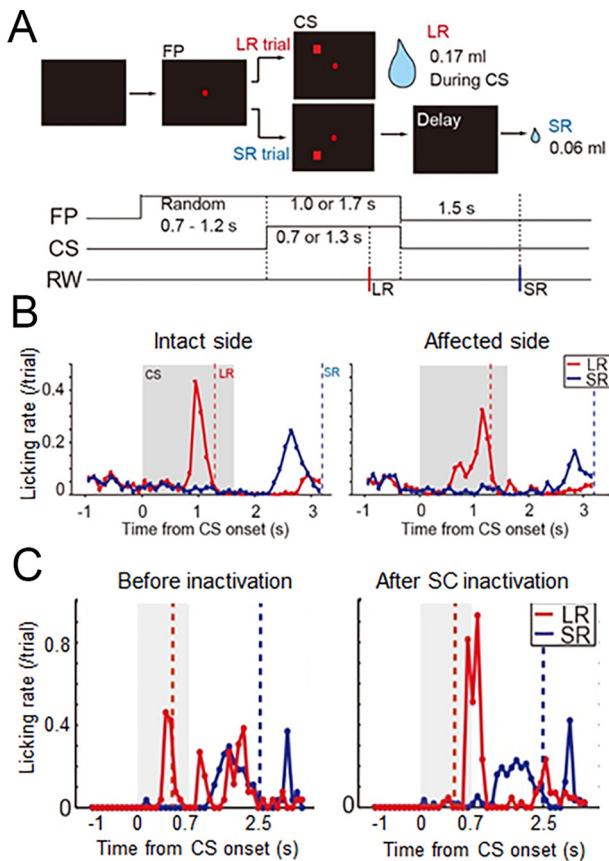
Fig. 17. Performance of blindsight monkeys in a Pavlovian conditioning task. **(A)** Design of the Pavlovian conditioning task. The monkeys were required to fixate on a central fixation point (FP) until conditioned stimulus (CS) offset. Large reward (LR) and small reward (SR) trials were given in a random order. In this task, the LR was delivered during CS presentation, and the SR was delivered at 1.5 s after CS offset. RW, reward. **(B)** Licking rates aligned at CS onset. CSs were presented in the intact (left panel) or lesion-affected (right panel) visual field. Red and blue lines indicate licking rates during the LR and SR trials, respectively. Gray hatched area indicates the CS presentation period. Red and blue vertical dashed lines indicate the time of reward delivery in the LR and SR trials, respectively. **(C)** Licking rates in a daily session before (left panel) and after superior colliculus (SC) inactivation (right panel). The same arrangement as **(B)** Adapted from Takakuwa et al. (2017).

rodents depend more on the collothalamic pathway for general behavioral control, while primates depend more on the lemnothalamic pathway, as has been shown in the comparison of the inactivation of the ipsilesional vs. contralesional SC and/or pulvinar pathways for the control of visually guided saccades (Takakuwa et al., 2021) and visual Pavlovian conditioning (Takakuwa et al., 2017, 2018). Conversely, as discussed above, the collothalamic pathway can support a variety of cognitive processes in the monkeys with a V1-lesioning in which the lemnothalamic pathway is damaged. Even though visual consciousness is impaired, some level of conscious experience (like feeling, but not visual) in type II blindsight patients is retained. If, as described above, our V1-lesioned monkeys have a similar conscious experience as patient G.

Y., their high performance in the cognitive tasks could be explained. Recently, the early visual systems in mice have been studied intensively and a variety of visual cortical areas that receive inputs from the LGN or SC-lateral posterior thalamic nucleus (corresponding to the primate pulvinar) have been identified and their functions assessed using elegant circuit dissection techniques (Beltramo and Scanziani 2019). It is difficult to argue on the phenomenal experiences of animals; however, considering such evolutionary aspects, a comparison of the visual functions of rodents and blindsight primates would be very important because it may lead to a more in-depth understanding of the subcomponents of visual perception and their underlying neural circuits.

REMAINING QUESTIONS

To date, we have investigated the neural circuits involved in blindsight and cognitive functions retained in blindsight subjects using saccadic eye movements as a probe. Here, the LGN and pulvinar are considered to be involved as the thalamic relay of visual signals in blindsight at least for the performance of the simple visually guided saccade task, but this is still an open question for the majority of other visuomotor and cognitive functions. Thus, the visual processing capacity of each region should be defined using a variety of visual stimulus features to dissociate their roles in a variety of visuomotor and cognitive tasks. Furthermore, contribution of the bilateral LIP has been demonstrated, which had been suggested in human neuroimaging studies (Celeghin et al. 2017). However, the mechanisms of how the interplay between the LIPs on ipsilesional and contralesional sides contributes to blindsight is still elusive. As an extension of the current studies, other regions such as the frontal eye field, midcingulate cortex, and caudate nuclei, whose involvement was suggested in a neuroimaging study with positron emission tomography (Kato et al., 2021), remain to be studied.

In addition, other types of eye movement tasks, such as an antisaccade task, countermanding saccade task, double-step saccade task, and smooth pursuit eye movement task, should be used to study different aspects of visuomotor and cognitive functions that can or cannot be triggered by a visual stimulus presented in the affected visual field. Moreover, some human studies have suggested the possibility that blindsight patients can understand facial expressions or biological motions presented in their blind field, which is called "affective blindsight." (De Gelder et al., 1999; Morris et al., 2001) The involvement of the SC-pulvinar-amygdala pathway has been suggested in this phenomenon and some lines of study in intact macaques suggest such possibilities. It might be worthwhile using V1-lesioned monkeys to test these hypotheses.

Conversely, it is well known that goal-directed movements by a hand/arm are also retained in blindsight, and actually in most of human blindsight studies used button press as the effector. The neural pathways involved in hand/arm control in blindsight
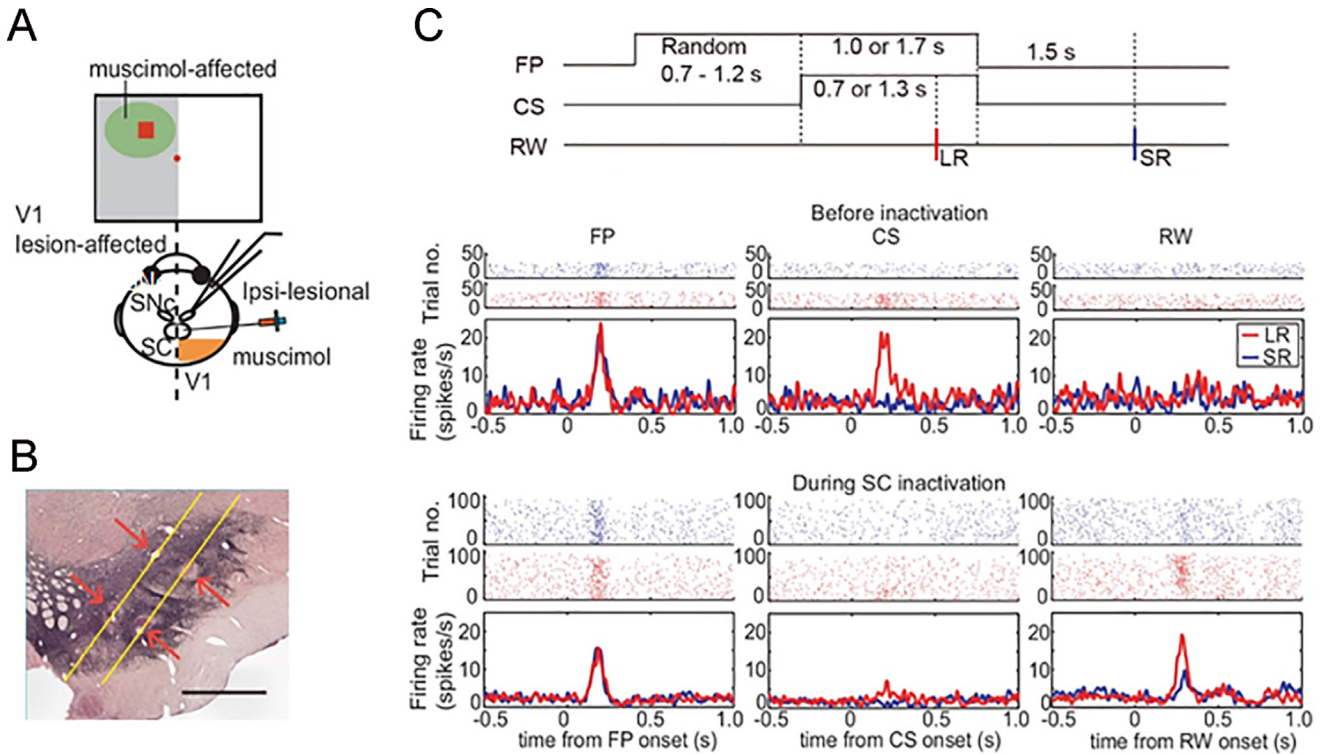
Fig. 18. Activity of an example dopaminergic neuron in the substantia nigra pars compacta during the Pavlovian conditioning task and the effect of superior colliculus (SC) inactivation. **(A)** Schematic drawing of the experimental design for recording dopamine neuron activity in a monkey with a unilateral V1 lesion. **(B)** High magnification view of the substantia nigra compacta and surrounding structures stained with an anti-TH antibody. Red arrows indicate the locations of electrolytic markings. Scale bar, 2.0 mm. **(C)** Effect of SC inactivation on cue-responses in dopamine neurons. Upper, time course of the Pavlovian conditioning task (the same as in Fig. 17). Middle, activity of dopamine neurons before SC inactivation. Raster plots and firing rates. These plots were aligned at fixation point (FP) onset, at conditioned stimulus (CS) onset, and at reward (RW) delivery (left, middle, and right panels, respectively). Lower, activity of dopamine neurons during SC inactivation. After SC inactivation, the responses to the FP were unchanged (left), those to the LR-CS (middle) disappeared, and those to RW (right) increased. Adapted from Takakuwa et al. (2017).

subjects need to be studied and compared with the saccade control system. Furthermore, some cognitive functions need to be explored using the hand motor system as a probe, because the saccade control systems are more innate and less conscious, while the execution of hand movements requires a higher level of conscious control. Therefore, hand/arm motor tasks might be more suitable to assess the conscious/unconscious control of behavior in blindsight.

Finally, how do the blindsight systems function for the unconscious visuomotor and cognitive control systems in intact subjects with normal vision? Our current experimental results have shown that inactivation of the SC or pulvinar does not completely impair visually guided saccades, suggesting that the blindsight system is not fully operative in the presence of an intact V1. However, some studies, such as Christensen et al. (2008), by applying transcranial magnetic stimulation to induce an artificial scotoma, have shown "action blindsight," by which normal subjects can respond to a change in target location for arm reaching presented in the scotoma without awareness of their shift in the ongoing trajectory of reaching movements. Thus, there is a possibility that some aspects of our actions are processed through the blindsight systems without awareness. Experimental studies using reversible inactivation of particular

brain areas or pathways, which have been revealed so far, in intact animals in a variety of cognitive motor tasks would give insights to this question.

There had been a long-standing debate on the neural systems underlying blindsight. On the basis of recent experimental studies using macaque monkeys with a unilateral V1 lesion, some of these questions, such as the thalamic relay of visual signals (the lateral geniculate nucleus or pulvinar?) and contribution of the bilateral posterior parietal cortex, have been demonstrated. These pathways may not be in full operation in the presence of an intact V1. Therefore, it is suggested that plastic changes in the visual systems, particularly those involving the SC, pulvinar, and LIPs underlie the emergence of blindsight. Analysis of sensitivity in visual detection using signal detection theory suggested that visual awareness is largely impaired in V1-lesioned monkeys, but not completely. These findings suggest that V1-lesioned monkeys have retained some level of conscious experience (like "feeling") as in the type II blindsight patient G.Y., which enables the performance of cognitive tasks that are in general believed to require phenomenal consciousness such as short-term memory and associative learning. For emergence of these functions, training effect and the age of the subjects might be key factors. The

studies may open up a new field to promote the visuo-motor and cognitive functions of the cortically blind patients in near future. More studies, especially those on the neural substrate of plastic changes in blindsight subjects, are needed.

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