

Phylogenetic view of the compensatory mechanisms in motor and sensory systems after neuronal injury

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ABSTRACT

Through phylogeny, novel neural circuits are added on top of ancient circuits. Upon injury of a novel circuit which enabled fine control, the ancient circuits can sometimes take over its function for recovery; however, the recovered function is limited according to the capacity of the ancient circuits. In this review, we discuss two examples of functional recovery after neural injury in nonhuman primate models. The first is the recovery of dexterous hand movements following damage to the corticospinal tract. The second is the recovery of visual function after injury to the primary visual cortex (V1). In the former case, the functions of the direct cortico-motoneuronal pathway, which specifically developed in higher primates for the control of fractionated digit movements, can be partly compensated for by other descending motor pathways mediated by rubrospinal, reticulospinal, and propriospinal neurons. However, the extent of recovery depends on the location of the damage and which motor systems take over its function. In the latter case, after damage to V1, which is highly developed in primates, either the direct pathway from the lateral geniculate nucleus to extrastriate visual cortices or that from the midbrain superior colliculus–pulvinar–extrastriate/parietal cortices partly takes over the function of V1. However, the state of visual awareness is no longer the same as in the intact state, which might reflect the limited capacity of the compensatory pathways in visual recognition. Such information is valuable for determining the targets of neuromodulatory therapies and setting treatment goals after brain and spinal cord injuries.

1. Introduction

The human brain is a product of 500 million years of vertebrate evolution. Subcortical structures such as the basal ganglia, brainstem, and spinal cord are relatively well preserved and homologous across a variety of vertebrate species; however, through evolution, on top of these structures, a huge cerebral cortex was added in higher vertebrates, especially in primates (moreover in humans), a phenomenon called “encephalization” (Jerison, 1977, 1985; de Sousa and Wood, 2007). In parallel, the cerebellum and precerebellar nuclei were also expanded. This evolutionary process led to the generation of multi-layered sensorimotor circuits such as spinal, brainstem, and transcortical circuits in higher vertebrates. It is not yet understood fully how these circuits are coordinated in a variety of behavioral contexts, but it is generally

considered that the low-level circuits are more reflexive with shorter processing times and less flexibility, while the high-level circuits are more cognitive with longer processing times and more flexibility. The function of each circuit is restricted by its innate properties. For instance, in the case of the motor system, cortico-motoneuronal (CM) cells are connected with a smaller number of motoneurons than the interneuronal systems in the brain and spinal cord, which enables the CM pathway to control more dexterous movements than the interneuronal systems (Fetz and Cheney, 1980; Kuypers, 1982; Buys et al., 1986; Takei and Seki, 2010). Thus, transcortical circuits might have developed novel elements to enable more flexible but complex functions in higher primates. Conversely, the existence of multi-layered circuits not only supports high-level functions but also makes the neural systems more redundant, and as a result, more resilient to partial damage. Damage to a

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particular circuit can be compensated for by the remaining circuits. However, it is not easy to demonstrate the precise compensatory mechanisms after neural damage because of technical limitations. However, the recent development of selective circuit manipulation techniques (for review, see Isa, 2022) has enabled us to dissect the post-injury compensatory mechanisms precisely, even in primates. In this review, we introduce two unique examples of studies on nonhuman primate models of post-injury functional recovery. The first example is the recovery of dexterous hand movements after damage to the direct CM pathway, which specifically developed in higher primates. In this case, the function of the CM pathway is compensated for by other descending motor pathways that are phylogenetically older (Isa et al., 2013, 2019; Isa, 2017, 2019). The second example is the recovery of visuomotor and visual cognitive functions after damage to the primary visual cortex (V1). Here, the function of V1 is compensated for by other V1-bypassing visual pathways, some of which are phylogenetically older (Isa and Yoshida, 2021). On the basis of these findings, we propose therapeutic strategies for these neural injuries.

2. Recovery of dexterous hand movements after injury to the corticospinal tract

2.1. Anatomy of the CST in different vertebrate species

Dexterous hand movements developed uniquely in higher primates including humans and their development is critically related to human civilization. At the same time, dexterous hand movements are highly sensitive to injury to the corticospinal tract by stroke or traumatic injury and are difficult to recover, presumably because huge amounts of neural resources are devoted to such fine motor control (Sobinov and Ben-smaia, 2021). Therefore, the recovery of dexterous hand movements should be a major target of rehabilitation therapy (Anderson, 2004).

It is generally considered that the corticospinal tract is the key system for dexterous hand movements (Phillips and Porter, 1977; Heffner and Masterton, 1975, 1983; Porter and Lemon, 1993). In higher primates, approximately 90% of corticospinal tract axons originating from the motor cortex cross the midline at the caudal brainstem (while the remaining 10% does not cross the midline), descend in the dorsolateral funiculus, and terminate mostly in laminae VI, VII, and IX on the contralateral side to the cell bodies, and partly to lamina VIII on the ipsilateral side after crossing the midline again (Kuypers, 1981; Armand

et al., 1997; Rosenzweig et al., 2009; Yoshino-Saito et al., 2010). In lamina IX, they are connected to motoneurons and form direct CM connections (Bernhard and Bohm, 1953; Landgren et al., 1962). These direct CM connections are unique to higher primates (Kuypers, 1981; Phillips and Porter, 1977; Porter and Lemon, 1993; Shapovalov, 1975; Lemon, 2008); this pathway does not exist in rodents (Alstermark et al., 2004), carnivora (Lundberg and Voorhoeve, 1962; Illert et al., 1976), and even some new world monkeys such as common marmosets (Kondo et al., 2015) (Fig. 1). In these species, cortical commands are transmitted by neurons in the red nucleus, which mediates the cortico-rubrospinal pathway, the brainstem reticular formation, which mediates the cortico-reticulospinal pathway (Davidson and Buford, 2006, 2007; Riddle et al., 2009, 2010; Soteropoulos et al., 2012), or spinal cord interneurons such as propriospinal neurons and segmental interneurons (Alstermark and Isa, 2012).

Heffner and Masterton systematically investigated the relationship between the termination area of the corticospinal tract in the spinal cord and the degree of hand dexterity across 69 mammalian species and concluded that termination close to spinal motoneurons is highly correlated with dexterity (Heffner and Masterton, 1975, 1983). Furthermore, Lawrence and Kuypers (1968a) along with several other lines of study (Liu and Chambers, 1964; Tower, 1940), showed that hand dexterity was permanently impaired after bilateral pyramidotomy. Furthermore, Lemon and colleagues demonstrated that some cortico-motoneuronal cells are specific for precision grip; they show vigorous firing when the target muscle is used for precision grip, but not for power grip (Buys et al., 1986). All of these observations suggest that through evolution, higher primates acquired direct CM connections, on top of several indirect pathways. Lawrence and Kuypers (1968a) suggested that the brainstem-mediated indirect pathways (e.g., rubrospinal and reticulospinal pathways) (Belhaj-Saif and Cheney, 2000; Darling et al., 2018; Davidson and Buford, 2006; Zaaimi et al., 2012), which remained largely intact in their preparations, had limitations in controlling dexterous hand movements such as fractionated movements of individual digits. Instead, the corticospinal pathway was considered to enable higher primates to perform dexterous and skilled hand movements.

Conversely, apart from the brainstem relays described above, the existence of indirect CM pathways mediated by spinal cord interneurons such as propriospinal neurons or segmental interneurons is not clear in primates. Propriospinal neurons are categorized as interneurons in the

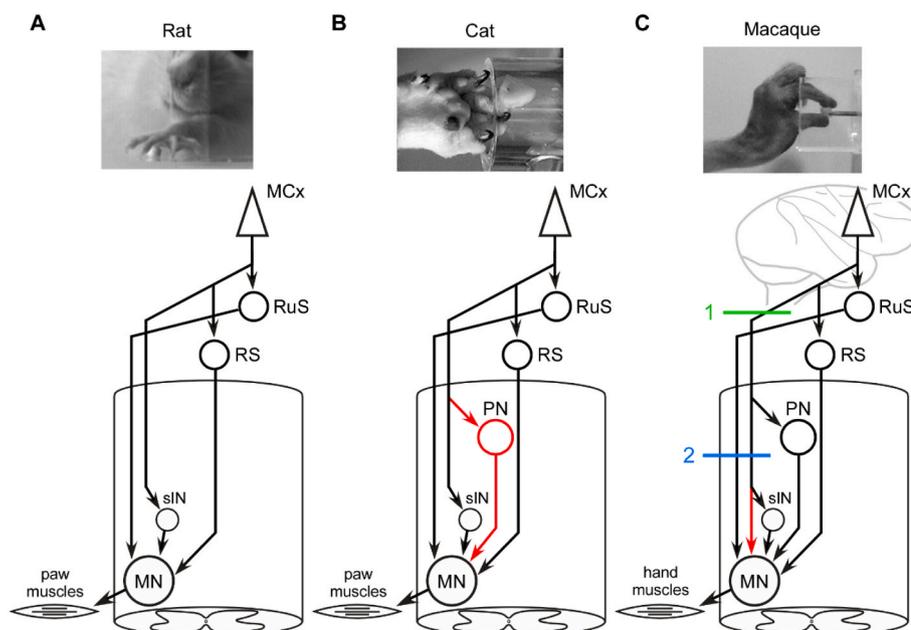


Fig. 1. Interspecies differences in the descending motor pathways from the motor cortex (MCx) to motoneurons (MNs) of the paw or hand. **A.** Rat. **B.** Cat. The propriospinal neurons (PN) are evolved (red). **C.** Macaque. The direct cortico-motoneuronal connections are evolved (red). Line 1 in C indicates the lesion in Lawrence and Kuypers (1968a, b), and line 2 indicates the lesion in Sasaki et al. (2004) and other articles from the authors' laboratory. Modified from Yoshida and Isa (2018). RS: reticulospinal neurons; RuS: rubrospinal neurons; sIN: segmental interneurons. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

spinal cord that connect different spinal segments. In cats, which have no direct corticospinal connections to paw/forelimb motoneurons, Lundberg and colleagues found that the shortest pathway from the corticospinal tract to forelimb motoneurons is disynaptic, and a significant portion of the disynaptic pyramidal excitation of forelimb motoneurons is mediated by propriospinal neurons in the C3–C4 segments (C3–C4 propriospinal neurons) (Illert et al., 1976, 1977). Lesioning of the cortico-/rubrospinal tracts at the C5 segment impairs grasping movements, while reaching is left intact. Lesioning of the cortico-/rubrospinal tracts at the C2 segment impairs both reaching and grasping (Alstermark et al., 1981). These results suggest that C3–C4 propriospinal neurons are involved in the control of reaching in cats, while the segmental interneurons caudal to C6 are involved in grasping.

It was argued that the presence or absence of a similar propriospinal system in higher primates, which developed direct cortico-motoneuronal connections. Although there have been arguments on the presence of a propriospinal system that mediates cortical commands to hand/arm motoneurons in macaques (Maier et al., 1998; Nakajima et al., 2000), the disynaptic pyramidal excitatory pathway was also shown to be present in macaque monkeys when glycinergic inhibition was reduced by the systemic administration of strychnine (Alstermark et al., 1999). Thus, the existence of the disynaptic pathway mediated by propriospinal neurons is maintained across cats and macaque monkeys. The existence of propriospinal neurons that mediate cortical commands to hand/arm motoneurons in macaques was confirmed (Alstermark et al., 1999; Isa et al., 2006). As described above, the function of propriospinal neurons was assessed by comparing the differences in behavior after lesioning the cortico-/rubrospinal tracts (transection of the dorsolateral funiculus) at C5 and C2 in previous studies (Sasaki et al., 2004; Alstermark et al., 2011). However, this is a very crude method and

more direct evidence is necessary. For this purpose, double viral vector intersectional methodology was developed to selectively and reversibly block synaptic transmissions through propriospinal neurons (Fig. 2A, see 2.3 for details) (Kinoshita et al., 2012). At 1–2 months after double viral vector injections, after blocking the transmission through the propriospinal neurons, leading to impaired precision grip movements and ataxic reaching movements. These results suggest that propriospinal neurons in macaque monkeys are involved in the control of reaching and precision grip movements, which was somewhat different from the observation in cats in which propriospinal neurons are involved primarily in the control of reaching with proximal muscles, but with a minimal role in grasping with distal muscles (Alstermark and Isa, 2012). Thus, even the functions of apparently homologous neural systems can change during evolution, presumably reflecting the importance of dexterous hand movements in primates. Furthermore, single unit recordings from segmental interneurons in the C6–C8 segments showed that the premotor interneurons in these spinal segments are highly activated while monkeys perform precision grip movements (Takei and Seki, 2010, 2013). These results suggest involvement of segmental interneurons in the control of dexterous hand movements.

2.2. Recovery of dexterous hand movements after GST injury

As described above, a bilateral lesion of the brainstem pyramid (Fig. 1C, line 1) results in a permanent impairment of precision grip in macaque monkeys, while the movements of more proximal body parts recover well (Lawrence and Kuypers, 1968a). Additional lesion studies suggested that the recovery of grasping movements is executed by a laterally located brainstem pathway, presumably the rubrospinal tract, while a medially located brainstem pathway, presumably the

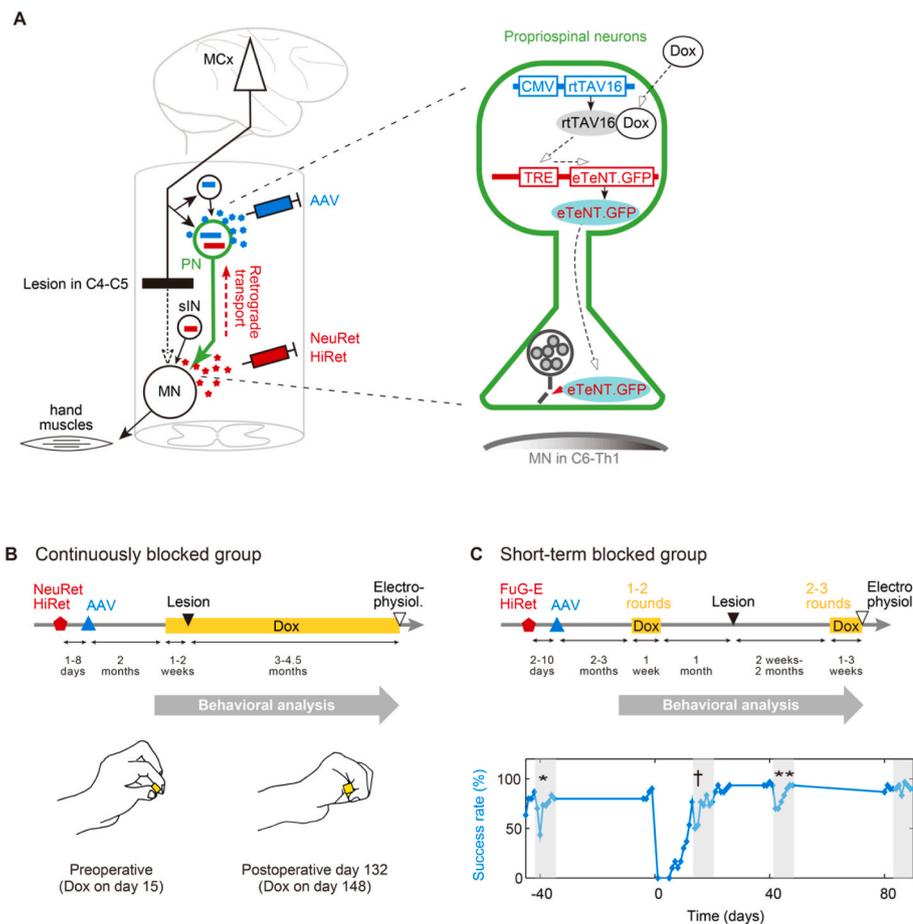


Fig. 2. Effects of the reversible and selective blockade of synaptic transmission through propriospinal neurons on the recovery from partial spinal cord injury. **A.** Double viral vector intersectional technique to selectively block the transmission of propriospinal neurons. Modified from Kinoshita et al. (2012). **B.** Effect of continuous blockade of propriospinal neurons on recovery from dorsolateral funiculus lesioning at C4-C5. **C.** Effect of repeated transient blockade of propriospinal neurons on recovery from dorsolateral funiculus lesioning at C4-C5. Modified from Tohyama et al. (2017) and Isa (2019). Dox: doxycycline.

reticulospinal tract, is responsible for posture control (Lawrence and Kuypers, 1968b). A more recent study by Zaaimi et al. (2012) showed the involvement of the reticulospinal tract in the recovery of hand function after pyramidotomy. These results suggest that the rubrospinal and reticulospinal tracts could control the movements of proximal body parts and gross hand movements after pyramidotomy; however, for the control of fractionated finger movements, the corticospinal tract is essential.

In contrast, when the corticospinal tract is lesioned at the C4-C5 segments (Fig. 1C, line 2), which leaves propriospinal neurons intact, monkeys show a rather slight deficit or fast and prominent recovery of fractionated finger movements to perform precision grip within 1–2 months after injury (Sasaki et al., 2004; Nishimura et al., 2007). This recovery was demonstrated to be training-dependent, because lack of training during the first month after injury resulted in poor recovery (Sugiyama et al., 2013). These results suggest that propriospinal neurons might contribute to recovery after injury to the direct CM pathway at the C4-C5 segments.

2.3. Functional compensation by propriospinal neurons

We hypothesized that the recovery of dexterous hand movements in macaques with a lesion of the corticospinal tract at the C4-C5 segments is mediated by propriospinal neurons. We assessed this hypothesis by using a combination of blockade of propriospinal neurons and lesioning the corticospinal tract at C4-C5 in macaque monkeys. In this method, a highly efficient retrograde gene transfer lentiviral vector (HiRet or NeuRet, red particles in Fig. 2A), carrying enhanced tetanus neurotoxin light chain and the enhanced green fluorescent protein downstream of the tetracycline-responsive element (TRE-eGFP.eTeNT), is injected into the ventral horn of the C6–Th1 segments, where the motoneurons (MN) of the hand and forearm, the targets of propriospinal neurons (PN), are located. The gene TRE-eGFP.eTeNT (red bars in Fig. 2A) would be transported not only into the PN but also neurons, whose axon terminates at injection site, for example the segmental interneurons (sIN). As the second step, another viral vector, the adeno-associated virus (AAV, blue particles in Fig. 2A), carrying the Tet-on sequence (the variant of reverse tetracycline transactivator, rtTAV16) under the control of the cytomegalovirus promoter (CMV-rtTAV16), is injected into the intermediate zone of the C2–C5 segments, where the cell bodies of PN are located. The gene CMV-rtTAV16 (blue bars in Fig. 2A) would be transported not only PN but also other neurons whose cell bodies are located at injection sites. With these two injections, only PN (whose cell bodies are located in the mid-cervical segments and whose axons project to the motoneurons of the hand/arm muscles) are double-infected (that is, having both genes CMV-rtTAV16 and TRE-eGFP.eTeNT). During the doxycycline (Dox) administration, the complex of expressed rtTAV16 and Dox activates the TRE, then the eGFP.eTeNT is expressed (Tet-on system). The expression of eGFP.eTeNT depress synaptic transmission of the PN by cleaving VAMP2, a transmitter releasing machinery. (Fig. 2A right). That is, synaptic transmission of PN can be reversibly blocked upon the administration of Dox (Fig. 2A) (Kinoshita et al., 2012; Tohyama et al., 2017; Isa, 2022). When the spinal cord was injured during the continuous blockade of propriospinal neurons, recovery was stopped at an immature state. Even at more than 4 months after injury, the monkeys retrieved morsels of food by gripping them with the dorsum of the thumb or palm. These results suggest that transmission through propriospinal neurons is necessary for the recovery of precision grip movements after injury (Fig. 2B). However, in contrast, when transmission through propriospinal neurons was transiently blocked for 1 week at different stages before and after injury, the rate of recovery of precision grip was reduced to approximately 50% both before and during the early recovery stage. However, at 3 months after injury when precision grip movements were mostly recovered and the success rate was almost saturated at near 100%, the effect of blockade of propriospinal neurons was negligible (Fig. 2C), although terminal

electrophysiological experiments under anesthesia proved that transmission through propriospinal neurons was almost totally blocked. These results suggest that propriospinal neurons play a critical role in boosting recovery during the early post-injury stage; however, they no longer function as the only system supporting recovery during the later recovery stage. At this stage, other neural systems including propriospinal neurons, which cannot be sufficiently infected by viral vectors to be blocked in the present experimental condition, or regenerated corticospinal pathways either from the contralesional or ipsilesional motor cortices, and brainstem-relayed indirect pathways might have changed their contribution and are recruited to the recovery process (Isa, 2017, 2019; Isa et al., 2021; Nakagawa et al., 2015; Ninomiya et al., 2022).

2.4. Limitation of functional compensation

As described above, after lesioning the corticospinal tract at C4-C5, fractionated finger movements recovered considerably; however, were they really the same as hand movements in the intact condition? Zaaimi et al. (2018) compared the involvement of the motor cortex, reticular formation, and spinal cord neurons in muscle activity during reaching and grasping movements by estimating how well the muscle activity of the hand could be reconstructed by combining the effects of single pulse stimulation of each region. They concluded that muscle activity is reconstructed well in the order of the motor cortex, spinal cord, and reticular formation. These observations suggest that even though precision grip recovers, which is apparently similar to the intact state, the detailed movement properties such as muscle synergy or coordination of movements might be different. To examine this hypothesis, we compared the activation pattern of intrinsic hand muscles (extensor digitorum 2,3 and adductor pollicis) in a force-tracking precision grip task in which monkeys have to maintain the required grip force with the index finger and thumb for 3.5 s (Nishimura et al., 2009). In this task, these two muscles are antagonist in the intact state, and they are reciprocally activated in the task. However, they were co-activated after recovery from spinal cord injury. Thus, even though precision grip behavior apparently recovers, muscle synergy changes. The antagonistic muscles become co-activated after injury, presumably because the monkeys have to increase joint stiffness to compensate for the loss of grip force after injury. This is an example of the limitation of compensation by alternative neural systems. The monkeys apparently recover dexterous hand movements; however, muscle synergy during precision grip is different from the intact state.

However, the corticospinal tract was shown to be rewired to hand motoneurons in macaque monkeys at 3–4 months after spinal cord injury and this rewiring is promoted further by the administration of a neutralizing antibody against a repulsive guidance molecule (Nakagawa et al., 2015, 2019). The optimal combination of regenerative/neuromodulation therapy and rehabilitative training promoted remodeling of the corticospinal tract to restore functions of the impaired forelimb in the rodent model of stroke or spinal cord injury (Wahl et al. 2014, 2017; Ganzer et al., 2018). The induction of such rewiring might enable the enhancement of hand dexterity after recovery from corticospinal tract lesions.

Neuroplasticity following spinal cord injury sometimes promotes not only directed rewiring of injured neural fibers but also undirected growth of the fibers. This is a maladaptive change in spared neural circuits, which can cause complications of spinal cord injury, such as neuropathic pain or autonomic dysreflexia (Walker and Detloff, 2021; Michael et al., 2019). Although these complications delay application of rehabilitation to patients with spinal cord injury, early rehabilitative training can help prevent the development of neuropathic pain and the sprouting of c-fibers after spinal cord injury (Detloff et al., 2014).

3. Recovery of visual function after injury to V1

3.1. Anatomy of the visual pathway in different vertebrate species

In primates, the primary pathway for visual image processing is the geniculate pathway, i.e., the retina-lateral geniculate nucleus (LGN)-V1-dorsal/ventral visual stream (Ungerleider and Mishkin, 1982; Felleman and van Essen, 1991) (Fig. 3A). Some lateral geniculate nucleus neurons project directly to the extrastriate visual cortices (Benevento and Yoshida, 1981; Yoshida and Benevento, 1981; Yuki and Iwai, 1981). In addition, less than 10% of optic fibers project to the midbrain superior colliculus (SC) and form the extrageniculate visual pathway (Weiskrantz, 2009). Here, the SC is considered as the prototype center for sensory-motor transformation in vertebrates, whose superficial layer mediates visual input to the pulvinar and whose deeper layer sends motor commands to the brainstem (Fig. 3A) (May, 2006; Basso et al., 2021; Isa et al., 2021). In rodents, 90% of optic fibers project to the SC (Linden and Perry, 1983; Hofbauer and Dräger, 1985), rather than the LGN. The major target of the SC is the lateral posterior nucleus of the thalamus (LP), an area homologous to the primate pulvinar. The LP sends visual signals to the postrhinal cortex (Beltramo and Scanziani, 2019) and amygdala (Evans et al., 2018; Shang et al., 2015; Wei et al., 2015). There is also a geniculate visual pathway through which the LGN mediates visual signals to V1 and other surrounding critical visual areas including areas A, AL, AM, LI, LL, LLA, LM, M, P, PL, PM, and PL (Glickfeld and Olsen, 2017). In primates, huge cortical visual areas have developed on top of the phylogenetically older subcortical visual pathways. The cortical areas are considered to facilitate finely tuned spatial and object vision. However, it has also been reported that the lamprey, a prototypical vertebrate that separated from other vertebrate species approximately 450 million years ago, also possesses a thalamic nucleus that mediates retinal input to the pallidum, which might be the prototype of the geniculate visual pathway (Suryanarayana et al., 2020). Therefore, it might be too early to state that the geniculate visual pathway “emerged” only in higher vertebrate species.

3.2. Recovery of visual function after damage to V1

When V1, the novel visual system that is highly developed in primates, is damaged in humans, patients are considered to become blind in the corresponding location in the contralateral visual field. However, in the early 1970s, case reports on patients with damage to V1 who showed some residual visual capacity despite the loss of visual awareness were made (Pöppel et al., 1973; Sanders et al., 1974), and this phenomenon was termed “blindsight” (Weiskrantz et al., 1974). In parallel to the efforts devoted to understand the properties of visual function in human blindsight patients, the neural mechanisms of blindsight have been explored using nonhuman primate models with a V1 lesion (Fig. 3B) (for review, see Isa and Yoshida, 2021).

Early studies showed predominant visually guided behavior in a monkey (“Helen”) with a bilateral V1 lesion (Humphrey and Weiskrantz, 1967). A variety of visual attributes including luminance/brightness

(Pasik et al., 1969; Schilder et al., 1971), sinusoidal grating (Miller et al., 1980), and shape or color (Schilder et al., 1972) were studied after V1 lesioning by Pasik and colleagues. Even then, there were disagreements over the contributions of the SC and pulvinar (Weiskrantz et al., 1974). Mohler and Wurtz demonstrated that combined V1 and SC lesioning results in the complete impairment of visually guided saccades in macaques (Mohler and Wurtz, 1977). Rodman and colleagues showed that neural responses in the medial temporal area (MT) to moving visual stimulation remain after V1 lesioning in macaques and the residual activity completely disappears after additional lesioning of the SC (Rodman et al., 1989, 1990). However, there were some arguments over the role of the SC-pulvinar pathway in blindsight. Kaas and colleagues studied the SC projections to the pulvinar and found that the pulvinar subareas Plp, Pl_{CM}, and Pl_{CL} mainly receive SC input, but there is a small overlap between these SC-recipient zones and the distribution of neurons projecting to the MT, which mainly originate from subareas PL, Plm, and Pl_{CM} (Stepniwska et al., 2000). Furthermore, Schmid and colleagues showed, by applying functional magnetic resonance imaging to V1-lesioned macaques, that residual visual responses in extrastriate visual areas disappear completely after inactivation of the LGN (Schmid et al., 2010). Visually guided saccades toward medium-contrast targets are also impaired. On the basis of these findings, the authors proposed that blindsight depends on the LGN. This proposal was based on the assumption that neurons in the koniocellular layer of the LGN mainly project to the MT, would survive V1 lesioning, and mediate blindsight. Furthermore, neurons in the lateral geniculate nucleus were shown to be highly responsive to visual stimulation in common marmosets (Yu et al., 2018). Support was also provided by human studies showing that the ability of blindsight is correlated with the thickness of the LGN-MT pathway in diffusion tensor imaging of cortically blind patients (Ajina et al., 2015b; Ajina and Bridge, 2018).

3.3. Functional compensation by the SC to pulvinar pathway

To study sensorimotor and cognitive functions in blindsight macaques and their underlying visual pathways, a series of studies on macaques with a unilateral physical lesion of V1 by aspiration of cortical tissue was initiated (Yoshida et al., 2008). After V1 lesioning, we found that the ability of visually guided saccadic eye movements recovered to a >80% success rate in approximately 2 months. That is, the monkeys needed some time to recover visuomotor behavior after V1 lesioning. Even at the recovered stage, the saccades were less accurate than in the intact state (i.e., saccade trajectories were simply straight and could not be corrected during midflight as in saccades toward a target in the intact visual field), and the luminance contrast threshold for target detection was higher than in the intact state (i.e., targets had to be brighter to be detected). We first confirmed the findings of Mohler and Wurtz (1977) on the critical contribution of the SC to blindsight by reversible inactivation of the SC by microinjection of muscimol (Kato et al., 2011). Further, to test the contribution of the pulvinar, we injected muscimol into the ventrolateral portion of the pulvinar, where we found a number of neurons that were orthodromically activated by electrical stimulation

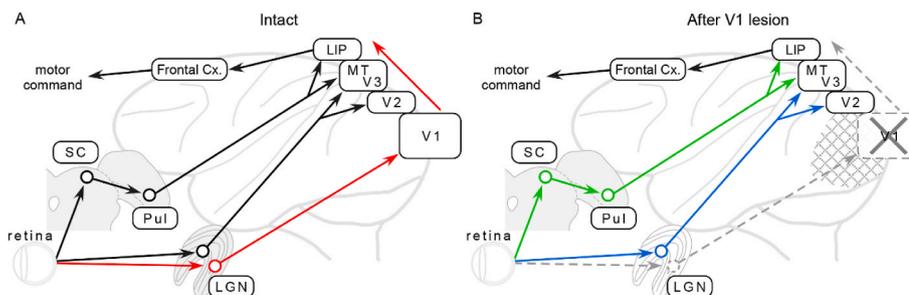


Fig. 3. Visual pathways for motor actions in primates. **A.** Intact state. The primary pathway is the geniculate pathway, which is phylogenetically novel (red). **B.** After lesioning of the primary visual cortex. Although the novel pathway is degenerated (broken line), the ancient pathway (green) and the part of novel pathway (blue) remain. Cx: cortex; LGN: lateral geniculate nucleus; LIP: lateral intraparietal region; MT: medial temporal area; Pul: pulvinar; SC: superior colliculus; V1: primary visual cortex; V2: secondary visual cortex; V3: third visual cortex. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

of the SC (Kinoshita et al., 2019). Then, visually guided saccades toward a target in the contralesional visual field were severely impaired, demonstrating the contribution of the pulvinar to blindsight. In addition, to demonstrate the causal contribution of the SC-pulvinar pathway, we applied the double viral vector intersectional technique (see above). We injected HiRet-TRE-eGFP.eTeNT into the ventrolateral pulvinar and AAV-CMV-rtTAV16 into the SC (Fig. 4A). Then, after Dox administration, saccades toward some of the targets in the contralesional visual field were clearly impaired. These results suggest that the pathway from the SC to pulvinar contributes to the recovery of visually guided saccades (Fig. 4B) (Kinoshita et al., 2019).

Thus, Schmid et al. (2010) proposed that the LGN is critical for blindsight, while it was proposed that the pulvinar (and SC-pulvinar pathway) is critical. However, the methods for V1 lesioning were different between these studies (lesion limited to the cortical gray matter vs. large lesion including the white matter and adjacent secondary visual cortex) and the functional assessment methods were also different (functional magnetic resonance imaging measurement of visual responses and saccades to targets with medium contrast vs. saccades to targets with maximum luminance). To resolve this issue, it was necessary to make double dissociation experiments for the LGN vs. pulvinar comparison in the same blindsight macaques. Therefore, we compared the effects of muscimol injection into the LGN or pulvinar on the ipsilesional (affected) side and contralesional (intact) side (Takakuwa et al., 2021). We found that inactivation of the pulvinar impaired visually guided saccades toward the affected side, but not toward the intact side. Conversely, inactivation of the LGN impaired visually guided saccades toward targets in the intact and affected visual fields. These results suggest that in the intact state, the LGN is critical for visually guided saccades, whereas to guide saccades toward targets in the lesion-affected blind visual field, the LGN and pulvinar are both necessary. We histologically examined the LGN in the monkeys by immunohistochemistry using antibodies against NeuN and CaMKII. With anti-NeuN staining, we found that magnocellular and parvocellular LGN neurons were largely degenerated, but some remained a couple of years after V1 lesioning. In addition, koniocellular neurons, which could be visualized by CaMKII immunostaining, were also decreased, but 18% of neurons still remained at 101 months after lesioning. Thus, LGN neurons (all of the magno-, parvo-, and koniocellular neurons) are still critical after V1 lesioning, but the predominant decrease in their number has to be compensated for by the pulvinar.

3.4. Visual capacity of the compensatory pathways

However, because the circuit properties and cellular organization are markedly different between the LGN and pulvinar, their capacity for

compensation is not the same. Which aspects of blindsight that the LGN and pulvinar neurons contribute to remains a critical question. To answer this, it is necessary to know the sensorimotor and cognitive capacity of blindsight monkeys. The ability of the blindsight macaques was explored using more demanding tasks than the simple visually guided saccade task and obtained the following results.

Monkeys with a unilateral V1 lesion could perform memory guided saccades with a cue in the blind field (short term memory) (Takakuwa et al., 2017). They could also perform a classic conditioning task with a visual cue in the blind field (Takakuwa et al., 2017), in which the target cue conditions anticipatory licking behavior (conditioning study). A transiently illuminated visual cue in the blind field reinforced searching for a hidden target area on a blank screen with eye movements (“hidden area search task”) (Kato et al., 2021). Here, the visual cue works as a secondary reinforcement of searching behavior (reinforcement study). These results suggest that the monkeys with a unilateral V1 lesion can perform complex cognitive tasks that might require some level of conscious perception of the visual cue.

Then, we evaluated the visual awareness of the monkeys with a unilateral V1 lesion by using a Yes-No task (Cowey and Stoerig, 1995) in which the monkeys were required to answer whether they “saw” a target at near-threshold luminance contrast with saccades and applied signal detection theory to evaluate their ability to detect the visual cue (Yoshida and Isa, 2015). By systematically changing the frequency of “catch trials” in which the monkeys have to report that they did not “see” the target by maintaining fixation, we could systematically vary the Hit and False Alarm rates to construct a receiver operating characteristic curve to estimate sensitivity (d') in the Two-Alternative Forced Choice task and Yes-No task with a visual cue in the intact and blind visual fields. We found that sensitivity did not change in the intact visual field, while it was lower in the blind field, but not zero. These results suggest that visual awareness is impaired in monkeys with a unilateral V1 lesion, but not completely. These results are similar to those of the human blindsight patient G.Y. who said that he “feels something” in the blind field (Azzopardi and Cowey, 1997), and who was categorized as “type II blindsight” (Sahraie et al., 2010).

We also examined the decision to perform visually guided saccades using the diffusion model, a type of rise-to-threshold model of decision making (Ratcliff and Tuerlinckx, 2002). There, the distribution of saccadic reaction times was packed in a narrow range compared to the intact field, which led to the finding that the decision threshold was lower in the blind field, suggesting that the monkeys’ decision to saccade is less deliberate in the blind field (Yoshida et al., 2008).

We tested the ability of saliency detection in the free viewing condition using saliency map computational models (Itti et al., 1998). Here, the gaze movements are superimposed on a saliency map of the visual

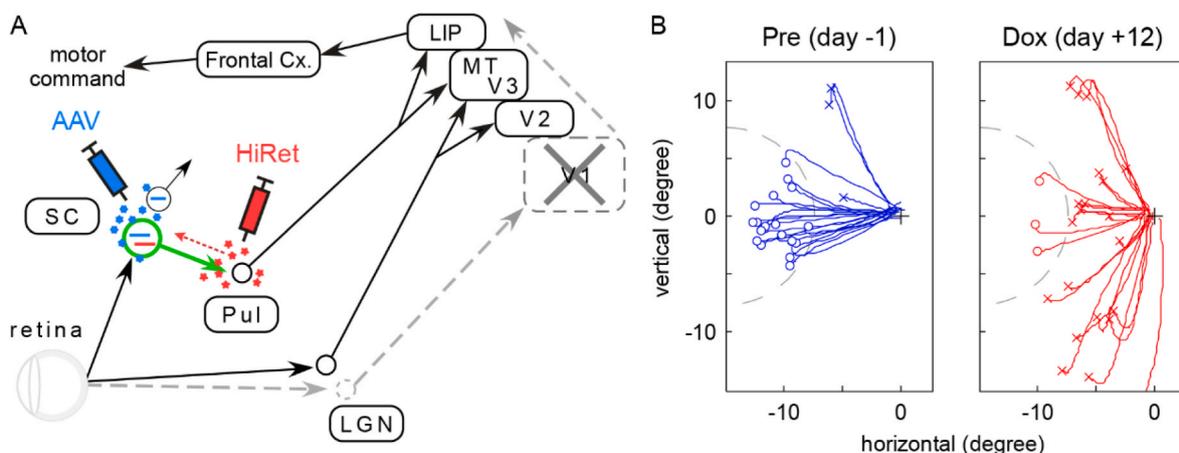


Fig. 4. Effects of selective blockade of the superior colliculus (SC)-pulvinar (Pul) pathway on visually guided saccades. **A.** Experimental design, **B.** Effect of doxycycline (Dox) administration on visually guided saccades. Modified from Kinoshita et al. (2019).

scene that was computed frame-by-frame and how the gaze under the free viewing condition is attracted to the highly salient parts of the visual scene by using signal detection theory (Berg et al., 2009). There, the area under the curve value was higher than the chance level, indicating that gaze is surely attracted to salient objects in the affected field. When we analyzed the contribution of individual visual features, such as luminance, L-M color, s-color, orientation, and motion by the leave-one-out method, the contributions of L-M color, orientation, and motion were high in the intact field. However, in the affected field, the contribution of orientation saliency disappeared, suggesting that orientation saliency is processed exclusively by the geniculate visual pathway, while luminance, L-M color, and motion saliency are at least processed partially by the extrageniculate pathway. Thus, the visual features that attract the monkeys' gaze change after V1 lesioning (Yoshida et al., 2012).

In the hidden area search task described above, when monkeys eye position got into the hidden target area, a visual cue was presented simultaneously. If monkeys hold eye position in the hidden target area for 230 ms, reward juice was delivered. However, there was 2-s delay period between capturing the target area and the reward. During this delay period, no specific task was required for monkeys. When the cue was presented in the intact field, the monkeys stopped searching the target area and looked away. In contrast, when the cue was presented in the blind field, the monkeys continued searching during the 2-s delay period, which suggested that the monkeys were not confident about the presentation of the cue in the blind field (Kato et al., 2021).

These findings indicate that blindsight is not a simple brainstem-mediated reflex, but suggest the presence of a variety of cognitive functions. As long as a relatively simple visual stimulus (a spot of light in this case) is used, monkeys with a unilateral V1 lesion can perform highly cognitive tasks that might require some level of conscious perception of the cue in the affected field, and the state of visual awareness in the affected visual field is no longer the same as in the intact field. To really understand the function of the LGN and pulvinar in blindsight, it is necessary to use a variety of stimulus features and compare the effects of LGN and pulvinar inactivation.

4. Phylogeny vs. compensatory circuits – is there a general scheme?

In this review, we described two examples of functional compensation after neural injury; first, lesioning of the corticospinal tract and second, lesioning of V1.

In both cases, the double viral vector-intersectional manipulation method was used as a very powerful tool to uncover the compensatory circuits. Currently, the transfection efficiency of viral vectors for pathway-selective manipulation techniques is still not very high and needs to be improved. Therefore, if the target pathway includes some fibers which were spared from blockade or if there exist parallel indirect pathways, the effects of such pathway-selective perturbation might be difficult to be interpreted. However, in the case of post-injury compensation, the critical neural elements can be less redundant, and the effects of pathway-selective manipulation might be easier to observe.

These studies show that after damage to phylogenetically novel neural systems, the ancient systems can compensate for their functions through rehabilitative training. These findings look similar to the mechanisms underlying functional recovery following motor cortex lesions in non-human primates and stroke in human patients (Darling et al., 2011; McMorland et al., 2015). Although functions of the damaged neural systems were apparently compensated for, closer investigation of behavioral and physiological parameters revealed that the recovered sensorimotor and cognitive functions are not the same as in the intact state. In the case of injury to the corticospinal tract, fractionated movements apparently recover, but muscle synergy is different from the intact state. In the case of a visual cortex lesion, the monkeys recover the ability to perform visually guided saccades and can complete

cognitively demanding tasks; however, the state of visual awareness is different from the intact state.

These findings may provide us with clues for how to treat patients with damage to sensorimotor and cognitive functions with neuro-modulatory therapies. There are surely cases in which the recovery is difficult, such as severe damages to the peripheral nerves/spinal cords without rehabilitative trainings or a progressive neurological disease, multiple sclerosis. However, otherwise, if the compensatory circuit can be identified, the application of transcranial magnetic stimulation or transcranial direct current stimulation to these compensatory areas to facilitate their activity could be expected to help recovery (Koganemaru et al., 2009; Koch et al., 2013). Conversely, knowing the limitations of the capacity of compensatory circuits may enable us to set the goals of treatment. The studies on the animal models described in this review are expected to promote our in-depth understanding of the physiological recovery process after neuronal injury.

Author's contribution

The authors participated in the core experiments and articles described in this review article. All the authors contributed to writing this manuscript.

Declaration of competing interest

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Data availability

Data will be made available on request.

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