Reaching beyond the midline: why are human brains cross wired?

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The crossing of nerve tracts from one hemisphere in the brain to the contralateral sense organ or limb is a common pattern throughout the CNS, which occurs at specialised bridging points called decussations or commissures. Evolutionary and teleological arguments suggest that midline crossing emerged in response to distinct physiological and anatomical constraints. Several genetic and developmental disorders involve crossing defects or mirror movements, including Kallmann's and Klippel-Feil syndrome, and further defects can also result from injury. Crossed pathways are also involved in recovery after CNS lesions and may allow for compensation for damaged areas. The development of decussation is under the control of a host of signalling molecules. Growing understanding of the molecular processes underlying the formation of these structures offers hope for new diagnostic and therapeutic interventions.

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For neurologists and most medical professionals, the fact that each half of the body is controlled by the opposite side of the brain informs everyday practice. Even patients and their families readily accept that a left hemiplegia is due to a stroke in the right hemisphere. As trivial as it may seem, this mirror disposition implies that nerve fibres originating on one side have to cross the midline to reach their destination. Both hemispheres are connected through the corpus callosum and anterior and posterior commissures. Fibres cross the midline at many sites in the brainstem and at the anterior and posterior commissures in the spinal cord. Long projecting tracts also cross the midline at some point in their course. Visual fibres cross at the optic chiasm, auditory fibres in the pons, and sensory fibres in the lower medulla or at segmental levels in the spinal cord. Among motor pathways, the crossing of the corticospinal tract (CST) has been extensively studied because of its clinical importance and characteristic anatomical features. In this review we discuss anatomical, clinical, and molecular features of midline fibre crossing in the human brain, with emphasis on the motor system.

Anatomy and functional implications of midline crossing

Hippocrates (460–380 BC) was the first to allude to the crossed nature of motor pathways, stating that "if the wound be situated on the left side [of the head], the convulsion attacks the right side of the body".[1] 500 years later, this view was refined by Aretaeus the Cappadocian, who noted that although the paralysis was contralateral to head lesions, it was ipsilateral to cervical lesions: "the cause of this is the interchange in the origins of the nerves . . . each of them passes over to the other side from that of its origin, decussating each other in the form of the letter X".[1] Many centuries later, in 1710, Pourfour du Petit and Mistichelli[1,2] identified the pyramids in the lower medulla as the site of the motor tract decussation. In 1810, Gall and Spürzheim, best known as the founders of phrenology, did an upward dissection of the

fibres from the pyramidal decussation to the cerebral cortex, showing the continuity between these two structures.[3] In the 19th and 20th centuries, through rapid progress in physiology, anatomy, and histology, as well as the development of molecular biology techniques, the course and function of the corticospinal tract (CST) and other motor tracts became better understood.

In human beings and other primates, the CST is the main pathway mediating voluntary movement.[2,4–6] The tract originates from neurons in layer V of the frontal and parietal cortex (Brodman areas 1–5 and 7). Contrary to popular belief, only 60% of the axons originate in the primary motor cortex.[4,7] The tract runs through the anterior half of the posterior limb of the internal capsule and forms the cerebral peduncles before reaching the brainstem. Throughout this course, several subcortical structures are innervated by collaterals.[2,8] At the lower medulla oblongata, a few millimetres caudal to the fourth ventricle, the tract approaches the midline and crosses to the contralateral side at the pyramidal decussation. A small percentage of fibres (10–25%) remain ipsilateral and form the ventral (or anterior) CST.[4] Fibres that cross form the lateral CST, which runs down the spinal cord to the last sacral segments. These fibres mostly synapse at segmental levels onto motor neurons of the dorsolateral part of the anterior horn, which control fine movements of distal extremities.[2,8]

The ventral CST runs right next to the anterior median fissure of the spinal cord, probably not extending beyond the upper thoracic cord in human beings.[8,9] Unlike the lateral CST, the ventral tract shows extensive distal bilateral axonal arborisation extending across the anterior spinal commissure to innervate interneurons on both ventromedial anterior horns, where motor neurons innervating the axial musculature are located.[10,11] An uncrossed corticospinal bundle running ventral to the lateral CST has also been reported.[12,13]

Evolution of the CST and motor decussations

Although the CST is thought to be the most important motor pathway in human beings, it is a phylogenetically
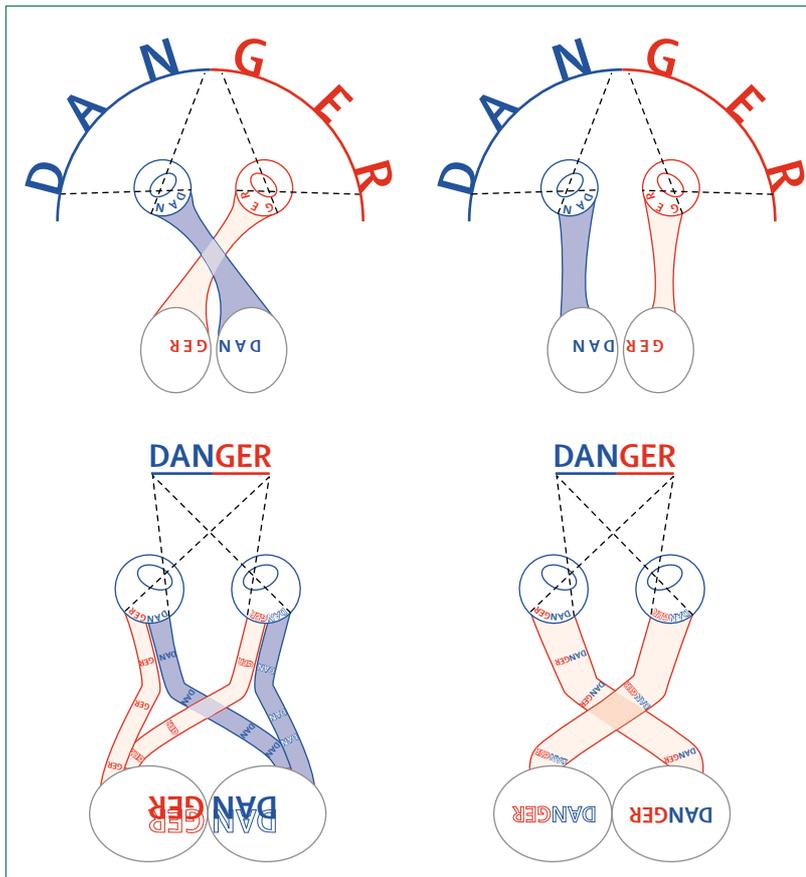
Figure 1: Crossed and uncrossed visual pathways
Images forming on the retina are inverted by the eye lens. Top: in animals without stereoscopic vision (ie, non-overlapping visual fields), lateral eyes allow panoramic view and predator scanning. Complete crossing of efferent retinal fibres at the chiasm is necessary to restore a congruent image of the outside visual word (the word "DANGER" is rebuilt, top left). If no crossing occurred (top right) "DANGER" would not be identified ("GERDAN" is perceived). Bottom: in animals with forward facing eyes, visual fields overlap to allow stereoscopic vision, which improves fine motor skills. Ipsilateral projection of the temporal half of the retinas is necessary to fuse both retinal images homotopically in the brain (bottom left). If complete crossing occurred as in lower vertebrates stereoscopic information would be compromised (bottom right). In human beings, this occurs in albinism and related disorders.[37]

young tract that is found only in mammals and is particularly developed in only primates and a few other animals with precise movements of the extremities.[2,6,14] In these species, CST fibres are numerous (up to a million fibres), large, and extensively myelinated to allow high conduction velocities.[8,15] Most importantly, corticospinal axons generally synapse directly onto spinal motor neurons in primates, whereas in other mammals connections are mostly multisynaptic.[2,16,17] This one-to-one connectivity may enable our exceptional motor capacities. Accordingly, interruption of the CST leads to persistent impairment of fine motor skills in primates whereas the resulting impairment is less pronounced in rats.[6,18]

The broad interspecies[2,15,19] and interindividual[8] anatomical variations of the CST are thought to reflect its recent emergence in evolution. Unlike more primitive and more redundant polysynaptic motor tracts, connections from the cortex to spinal motor neurons are monosynaptic or disynaptic in the CST. This long-range targeting may generate greater topographic variations. The CST develops late during embryogenesis and maturation extends well into postnatal life in human beings, with ongoing connections and myelinisation within the first years of life. This ongoing development is reflected in the progressive appearance of skilled movements and the disappearance of primitive reflexes (spinal walking, Babinski sign) in growing children.[16,20–22] Ipsilateral CST projections regress during childhood.[23,24]

About 75–90% of the CST fibres decussate in human beings, but wide variations exist.[8] Decussation is typically asymmetrical, with fibres originating from the left hemisphere crossing more extensively and more rostrally than those from the right hemisphere. Consequently, the right side of the spinal cord is larger than the left, independent of handedness.[25] A few CST fibres might cross through the corpus callosum, and some fibres recross to the ipsilateral side in the spinal cord.[8,26] Located mostly laterally in the spinal cord of human beings, other primates, and cats, the tract runs down the dorsal cord in rats. In some insectivores, the tract runs in the ventral cord where it can split into several fascicles.[8,14] Caudal extension of the ventral and lateral corticospinal tracts is variable.[2,27] The decussation is absent in hedgehogs and moles while located in the pons rather than in lower medulla in elephants and monotremes.[14,19,28]

In non-mammalian vertebrates, tracts originating in the brainstem, such as the reticulospinal, vestibulospinal, and rubrospinal tracts, control most motor functions. In contrast to the CST, these tracts have striking interspecies similarities.[29] The reticulospinal and vestibulospinal tracts are the most primitive motor pathways, they are present in the embryos of lampreys (primitive vertebrates). These tracts have predominantly ipsilateral projections controlling segmental myotomal contraction, although limb function is also controlled.[17,29] Contact with spinal motor neurons is mostly indirect (ie, via interneurons).[29] In human beings, the vestibulospinal and reticulospinal tracts control muscle tone, body posture, and balance. The rubrospinal tract is intermediate between these "primitive" tracts and the CST. It exists only in species with limbs or pseudolimbs, mediating, for example, fin movements in rays (cartilaginous fish).[29] Like the CST, the rubrospinal tract is mostly crossed, and contains direct projections to motor neurons.[30,31] Whereas the rubrospinal tract is very prominent in lower quadrupedal mammals and still substantial in primates, it regresses in parallel to the emergence of the CST and consists of only a few hundred fibres that project exclusively to the cervical spinal cord in human beings.[32–34] Parallel to the regression of rubrospinal fibres, rubro-olivary projections become more

numerous. Fibres originating from the red nucleus are increasingly incorporated into the cerebrocerebellar circuitry and constitute the dominant source of input to the climbing fibres. Therefore, whereas the rubrospinal tract itself is vestigial in human beings, the red nucleus is still involved in motor control, largely via rubro-olivary projections.[33,34]

Teleology of midline crossing

"One of the most obscure issues in biology is, no doubt, to determine to what extent the organism benefits from the singular phenomenon of the decussation."[35] More than a century ago, the Spanish histologist Santiago Ramón y Cajal questioned the teleology of midline crossing. He provided the most comprehensive explanation to date on this topic in an article published in 1898.[36] On the basis that the eye lens inverts images forming on the retina with respect to the outside world, Cajal suggested that crossing at the chiasm was necessary to restore image continuity in the brain (figure 1).[36,37] Crossing is either complete or partial, depending on the existence of binocular vision, generating a representation of each visual hemiworld in the opposite side of the brain. The geometry of the visual tract being set by optical constraints, crossing of the tactile pathways is necessary to allow these two sensory inputs to gather in the brain, generating a global sensory representation contralateral to the stimulus. Motor decussation follows the crossed sensory representation to allow the correct limb to be activated upon sensory stimulation. Because the exquisite manual skills afforded by the CST are highly dependent on adequate visual and tactile inputs, the structure of this tract is particularly influenced by the anatomy of the visual and sensitive pathways, and extensive midline crossing occurs. The generalised crossing of output and input tracts has allowed the gathering of multiple sensory and motor modalities, culminating in the large associative brain areas that are the hallmark of the human cortex.

According to Cajal's model, an inverse relation would exist throughout evolution between the proportion of fibres crossing at the chiasm and the proportion of decussating CST fibres. To our knowledge, this has never been assessed as such, but we believe another evolutionary argument may sustain the theory. In limbless primitive species, a threatening stimulus on the left side of the body perceived in the right hemisphere evokes a flight reaction through contraction of the ipsilateral (right) axial musculature (figure 2), which is mediated by the reticulospinal and vestibulospinal tracts, without the need for midline crossing. A limbed vertebrate, on the other hand, will attempt to escape a similar left-side threat by extending left limbs, pushing on the ground to turn to the right. In this case, the response occurs via the phylogenetically younger rubrospinal and corticospinal tracts, which cross the
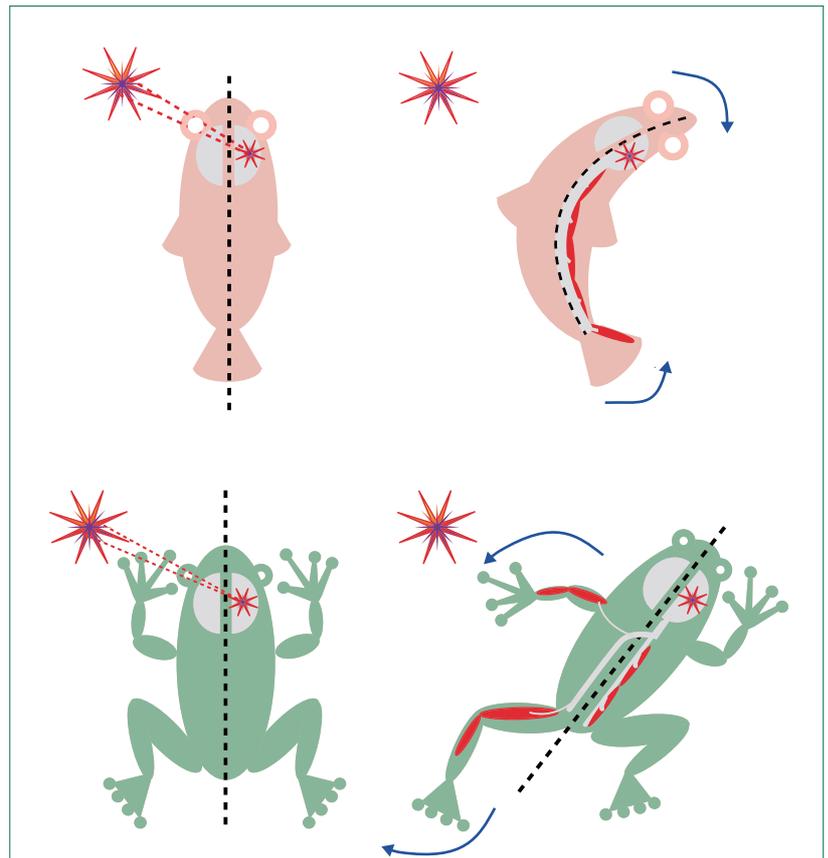

Figure 2: Crossed and uncrossed motor pathways in escape behaviour
Top left: A threatening stimulus (star) seen on the left activates contralateral (right) visual areas. Top right: the limbless vertebrate escapes by contracting the axial musculature on the same side as the activated visual areas, through activation of ipsilateral motor pathways (eg, reticulospinal or vestibulospinal). Bottom: in a limbed vertebrate, escape from an identical threat is accomplished by extension of the limb musculature contralateral to the activated visual areas. This occurs through activation of crossed motor pathways (eg, rubrospinal or corticospinal). Contraction of the right axial musculature occurs as above.

midline (figure 2). Formulated more than 100 years ago, Cajal's hypothesis remains seductive and self-standing, still waiting to be challenged. The use of modern molecular and imaging techniques could allow, as he stated, "more acute observers to dissipate the darkness".[35]

Clinical implications of midline crossing

In addition to comparative neuroanatomy, the non-invasive study of patients with abnormal decussations provides valuable information on brain cross wiring. With transcranial magnetic stimulation, the integrity and anatomy of the CST can be probed by stimulation of the motor cortex with a brief magnetic pulse. This evokes a motor response, the amplitude and latency of which can be measured by surface electrodes placed on target muscles.[38] Diffusion tensor imaging indicates the direction of water diffusion and allows white-matter tracts, including the CST, to be visualised with unprecedented detail (figure 3).[39]
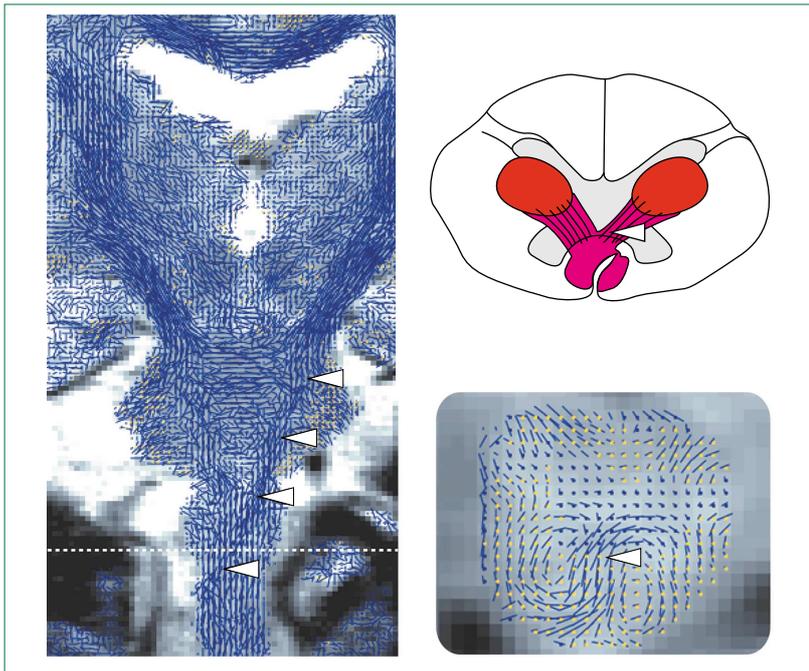
Figure 3: Diffusion tensor imaging of the pyramidal decussation
Left: preferential diffusion of free water along the CST fibres (blue lines) allows this tract to be visualised (white arrowheads=left CST). Bottom right: axial view at the level of the pyramidal decussation (dotted line). Midline crossing occurs at the level of the ventral twirled pattern (white arrowhead). Image courtesy of Dr Hatsuho Mamata.[39] Top right: schematic view at this level (lateral CST in red, decussation in pink).

Congenital diseases associated with anomalous pyramidal decussation

Several syndromic malformations have been associated with an abnormal or absent pyramidal decussation (table).[40–60] Agenesis of the corpus callosum is commonly associated with these malformations, but decussation abnormalities may occur without other pathology. Abnormal fibre crossing is commonly expressed as

mirror movements, which are unintended movements occurring on one side of the body that mirror the contralateral voluntary ones. Mirror movements typically occur in hands and forearms and may hamper activities involving alternate limb movements, such as typing or ladder climbing.[40,45]

Representative examples of diseases involving anomalous decussations are discussed below. Some are associated with other malformations and mirror movements (Klippel-Feil and X-linked Kallmann's syndrome); others are associated with only mirror movements (essential mirror movements). Finally, sensorimotor function is essentially normal in horizontal gaze palsy and progressive scoliosis.

Klippel-Feil syndrome

Patients with Klippel-Feil syndrome have a short neck and limited head movement, associated with variable fusions of the cervical vertebrae. Mirror movements of the hands occur in up to 75% of patients.[51] Abnormal pyramidal decussation in the medulla has been described in the single autopsy report published.[52] In healthy people, transcranial magnetic stimulation of the motor cortex typically elicits muscle contraction in the opposite side of the body only. In a patient with Klippel-Feil syndrome, however, transcranial magnetic stimulation of either hemisphere elicited bilateral simultaneous responses in hand muscles.[53] The short latency of the contraction (~20 ms) was compatible with corticospinal conduction, suggesting that the ipsilateral response was mediated by an anomalous uncrossed, monosynaptic pathway. In addition, a high degree of synchrony in firing patterns in the left and right muscles suggested the presence of distally branched corticospinal fibres, projecting to homologous motor neuron pools on both sides of the spinal cord (figure 4).[53,61–66] Anatomical and physiological data are sparse, but branching and

Condition	Features	Pyramidal decussation (medulla)	MM	Ref
Arnold Chiari syndrome	Tonsilar herniation and others	?	Yes	40,41
Corpus-callosum agenesis	Variable	Can be abnormal	Common	42
Dandy Walker syndrome	Enlargement of the fourth ventricle, partial or complete absence of the cerebellar vermis, posterior fossa cyst, callosal agenesis (common)	Absent	Yes	43
Encephalocele	Herniation of cranial contents through a cranial defect	Absent	?	44
Essential mirror movements	Isolated, autosomal dominant, rarely recessive, rarely sporadic	?	Yes	40,45,46
Friedreich's ataxia	Progressive gait, speech, and coordination disorder, variable	?	Yes	47
HGPS	Autosomal recessive, horizontal gaze palsy, progressive scoliosis, "butterfly-shaped" medulla on axial MRI, mutation of *Robo3* gene	Absent	No	48,49
Joubert's syndrome	Autosomal recessive, absent cerebellar vermis, "molar tooth sign" in the upper midbrain on axial MRI, gait disorder and ataxia; retinal and renal malformations (occasionally), mutation of the *AHI1* gene	Absent	Yes	50
Klippel-Feil syndrome	Short neck, cervical fusion abnormalities, low-set hairline	Atrophic?	75%	51–53
Lissencephaly	Absent circumvolutions, microcephaly, seizures, mental retardation	Abnormal	?	54
Phenylketonuria	Mental retardation, seizures, variable	?	Yes	55
Usher's syndrome	Pigmentary retinitis, deafness	?	Yes	56
Wildervanck syndrome	As Klippel-Feil with additional sensorineural deafness and eye abduction deficit	?	Yes	57
X-linked Kallmann's syndrome	Anosmia, hypogonadotrophic hypogonadism. Mutation of the *Kal-1* gene.	Atrophic?	85%	58–60

MM=mirror movement; HGPS=horizontal gaze palsy and progressive scoliosis.

Table: Congenital disorders associated with anomalies of pyramidal decussation or mirror movements
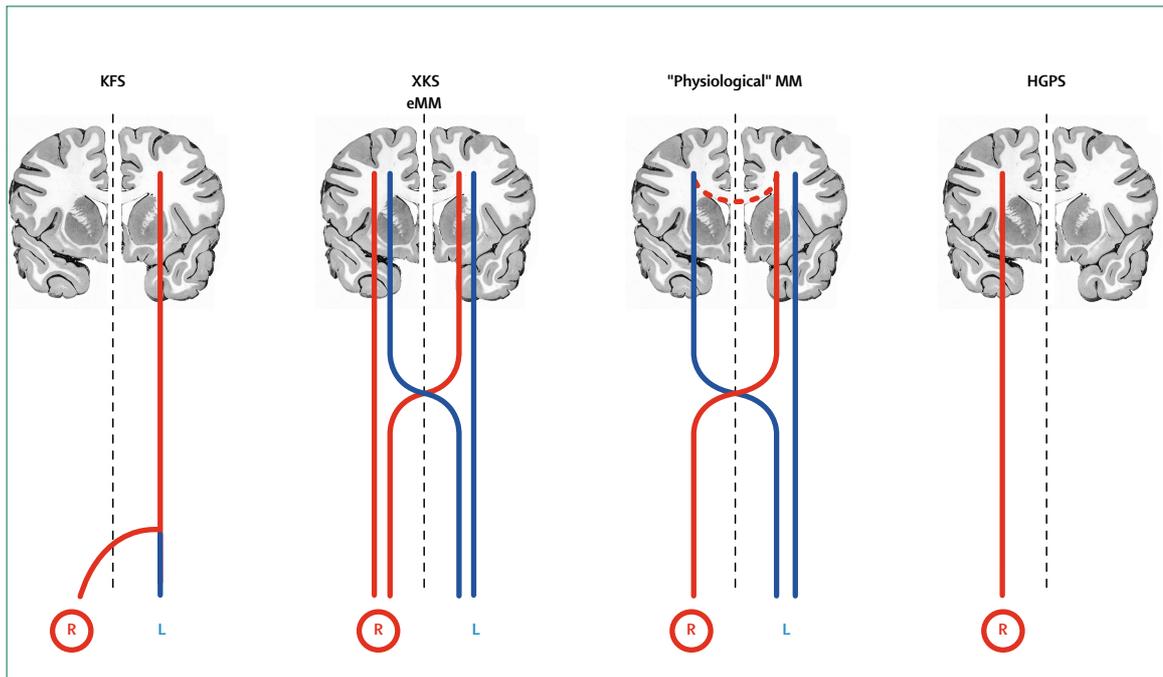
Figure 4: Anomalous decussations in various disorders

Tracts activated upon intended right movement. Red colour indicates tracts mediating voluntary movement; blue colour indicates tracts involved in mirror movements (MM). In Klippel-Feil syndrome (KFS), pyramidal decussation is absent, and axons may branch in the spinal cord.[52,53] In X-linked Kallmann's syndrome (XKS) and essential MM (eMM), neurons in the left motor cortex with ipsilateral and contralateral projections are coactivated,[61,62] and there is activation of the right motor cortex.[63] In physiological MM of childhood, coactivation of both motor cortices occurs due to insufficient transcallosal inhibition of the right motor cortex (dashed red line).[64] The ipsilateral left CST may also be involved.[24,65] In horizontal gaze palsy and progressive scoliosis (HGPS) the right motor cortex controls right-sided muscles.[49,66]

bilateral innervation in the spinal cord could represent a compensatory mechanism for the absence of pyramidal decussation, the price paid being the generation of mirror movements.

X-linked Kallmann's syndrome

Kallmann's syndrome, first described by Cajal's histology professor, Maestre de San Juan,[67] consists of inherited hypogonadism and anosmia. Mirror movements of the hands and forearms are present in 85% of patients with the X-linked form.[58,59,61] Pyramidal decussation anatomy in this disease is even less well known than for Klippel-Feil syndrome, with no autopsy samples reported. Instead, one morphometric neuroimaging study on nine patients showed large bilateral CST.[60] The physiological basis of mirror movements in X-linked Kallmann's syndrome has, however, been repeatedly addressed.[62,63,68] As in Klippel-Feil syndrome, unilateral transcranial magnetic stimulation elicits bilateral hand movements.[53,61,62] Responses are simultaneous and of short latency, also implying an anomalous fast-conducting uncrossed tract. In contrast to Klippel-Feil syndrome, there is no evidence for terminally branched, bilaterally projecting axons. Instead, in patients with X-linked Kallmann's syndrome there seems to be abnormal simultaneous firing of both ipsilaterally and contralaterally projecting neurons within the same areas

of motor cortex, which generate mirror movements (figure 4).[53,61,62] Ipsilaterally-projecting corticospinal neurons involved in the generation of ipsilateral or bilateral movements have been identified in several animal[11,69,70] and human[71–73] studies. These neurons are present in the premotor cortex and supplementary motor area but are also intermingled with contralaterally projecting neurons in the primary motor cortex.[62] Conspicuous ipsilateral projection pathways in X-linked Kallmann's syndrome may result from a "hypertrophic" or abnormally persistent ipsilateral CST with abnormal distal muscle control.

In healthy people, only left cortical activation is observed upon intended right hand movement. However, in patients with X-linked Kallmann's syndrome an additional ipsilateral activation (ie, right cortical upon intended right movement) has been observed. In part, this reflects sensory feedback from the mirroring left hand.[68] Recent data indicate that ipsilateral activity also actually drives ipsilateral movement, especially in patients in whom the abnormal ipsilateral tract is well developed.[63] Bilateral cortical activation would thus represent a compensatory strategy to achieve sufficient force in the target muscle in the presence of an insufficiently decussating CST (figure 4). Interestingly, phenotypic overlap with Klippel-Feil syndrome exists.[74] *Kal1* is the affected gene in X-linked Kallmann's syndrome.

Essential mirror movements

Mirror movements are a normal occurrence in children (in whom they are called "associated" or "bimanual" movements)[45,75] that progressively diminish until age 10 years,[76,77] coinciding with completion of myelination of the corpus callosum.[78] The rarity of mirror movements after this age is thought to reflect the maturity of inhibitory callosal connections, which repress activation of the contralateral motor cortex during voluntary movement.[64] Regression of the ipsilaterally-projecting CST with age may also be involved (figure 4).[23,24,65] Reappearence of mirror movements can occur during complex movements, fatigue, or extreme efforts in healthy adults.[40,79–81] When occurring persistently after adolescence, however, they are considered abnormal. In this case, mirror movements may be secondary to congenital or acquired CNS diseases or lesions. The term "essential" mirror movements is used here to refer to persistent mirror movements occurring in isolation, independent of any associated disease. "Hereditary", "familial", or "congenital" are also commonly used for this category of mirror movements, but the latter denomination is ambiguous as it also includes mirror movements resulting from other congenital conditions such as Klippel-Feil syndrome or X-linked Kallman's syndrome. Both familial[40,45,47] and sporadic[46] forms of essential mirror movements have been reported; familial forms are typically autosomal dominant with incomplete penetrance.[45]

As in other types of mirror movements, transcranial magnetic stimulation evokes bilateral responses in patients with essential mirror movements. Onset of electromyographic activity is nearly simultaneous in both affected limbs, and generally of normal latency.[45,56,75,82] Evoked contraction in essential mirror movements is largest on the ipsilateral side, and most readily elicited in distal muscles.[75,83] These features contrast with "physiological" mirror movements of children, where evoked responses are not simultaneous, have long latency (due to the time needed for interhemispheric spread of excitation across the corpus callosum), and are larger on the contralateral side.[24,75]

The neural mechanisms of essential and physiological mirror movements seem to be distinct.[45,75,84] Essential mirror movements bear strong similarities with those observed in X-linked Kallman's syndrome: voluntary movement activates separate fast-conducting contralateral and ipsilateral projections from the same hemisphere, controlling the two hands and generating, respectively, the intended and mirror movement.[85] In addition, depending on the relative development of the ipsilateral and contralateral tract, both primary motor areas can be recruited to generate an (intended) unilateral movement (figure 4).[45,83,85–88] Wiring abnormalities are still speculative, but essential mirror movements could result from a failure of withdrawal of the ipsilateral corticospinal pathway, which normally regresses in the first 15–18 months after birth.[23,24]

Horizontal gaze palsy and progressive scoliosis

This rare autosomal-recessive, familial disease is characterised by congenital bilateral horizontal gaze palsy and progressive scoliosis developing in childhood.[48,49,89] MRI shows a deep anterior midline fissure of the medulla, which is "butterfly-shaped" in axial views.[66] Transcranial magnetic stimulation evokes strictly ipsilateral motor responses of normal latency. Likewise, sensory evoked potentials activate the ipsilateral somatosensory cortex, but are otherwise normal.[49,66] These observations suggest that pyramidal and medial lemniscal decussation are lacking in this disorder, and that fine motor activity is mediated by the normally minor uncrossed ventral CST (figure 4). Painful stimuli, mediated by spinothalamic fibres crossing in the spinal cord at segmental levels, elicit the normal pattern of contralateral hemispheric activation. Patients have normal sensorimotor function and do not have mirror movements. However, whereas epicritic touch pathways are uncrossed, visual pathways appear normally crossed; this could affect the development of polymodal sensory cortical areas, as discussed above. Interestingly, the scoliosis could be neurogenic, as descending reticulospinal-fibre tracts and CST are involved in axial muscle tone control.[49] Mutations that cause horizontal gaze palsy and progressive scoliosis have recently been identified on the *Robo3* gene.[49]

Injury to the pyramidal decussation

In 1901, Wallenberg[90] described a patient with an acute paralysis of the ipsilateral arm and contralateral leg, for which he coined the term "hemiplegia cruciata". A lesion was present in the region of the pyramidal decussation. In addition, several reports have described bilateral arm paralysis occurring as the result of pressure to or lesion of the lower medulla.[91–95] This clinical presentation, observed more commonly than Wallenberg's seminal case, is called "cruciate paralysis" and can have other causes, such as watershed cortical infarcts ("man in the barrel" syndrome), cervical-central-cord syndrome, and motor-neuron disease.[93]

Wallenberg[90] suggested that, at the decussation, fibres related to arm movements crossed the midline rostrally to those related to leg movements. A median lesion of the upper decussation would therefore affect arms while sparing the legs, accounting for the clinical picture (figure 5).[96–100] Although this explanation has been repeatedly used,[91,92,94,95] segregated decussation of arm and leg fibres at the pyramidal decussation has never been confirmed in animals or humans.[96–100] Instead, a more recent explanation proposes that cruciate palsy results from a selective involvement of the ventral CST. This motor pathway is located very close to the midline

in the medulla, where a discrete injury would only impair proximal arm mobility because the tract probably mainly controls shoulder muscles in adults (figure 5).[96,99]

Are ipsilateral motor pathways involved in recovery after focal brain injury?

After hemispheric stroke, muscles on the contralesional side of the body are not equally affected, and ipsilateral paresis can occur. Although impairment to the distal muscles of the affected arm reflects injury to the crossed CST, ipsilesional shoulder paresis is thought to reflect involvement of the ventral CST, which controls mostly proximal muscles.[11,101] As noted by Cajal,[35] muscles that are always activated bilaterally (eg, muscles of the upper face, of mastication, of the trunk and respiration) are usually spared, thanks to a preserved contralesional motor drive.[101,102] These clinical observations suggest that the contralesional intact cortex may play a part in functional recovery after hemispheric damage, perhaps through ipsilateral corticospinal projections.

Many authors have reported activity of the ipsilateral cortex during motor tasks of the paretic limb after stroke, seemingly confirming this clinical impression.[103–106] However, the results of these neuroimaging studies should be interpreted with caution, as movement-related activation is not necessarily functionally relevant. For example, ipsilateral activation could be associated with mirror movements,[107] with increased task complexity,[108] or with disinhibition of the intact motor cortex through reduced transcallosal input by the injured hemisphere.[64] Studies with transcranial magnetic stimulation are well suited to address these functionality issues. Although ipsilateral motor evoked potentials are absent in most healthy adults[53,102] they can be elicited in ipsilateral paretic muscles after stroke (eg, right transcranial magnetic stimulation after left hemispheric stroke elicits right limb movement).[109–111] The ipsilateral responses are associated with a poor recovery, probably representing the unmasking of a normally minor pathway rather than the sign of a restorative change to compensate for the deficit.[109,110] The latency of the responses is long (~26 ms), which suggests that they are mediated through polysynaptic pathways (eg, the corticoreticulospinal or corticopropriospinal tract; figure 6).[72,109,111] Reorganisation within the affected hemisphere is probably the main recovery mechanism after adult hemispheric lesions, but recent results indicate that activation of the ipsilateral premotor cortex may contribute to motor improvement.[104,112–114]

Recovery after CNS injury depends on the age at which the damage occurs, and processes involved in functional repair differ between young and old brains.[114] Accordingly, transcranial magnetic stimulation-evoked responses after stimulation of the unaffected hemisphere in patients with perinatal brain damage are quite different to those found after acute stroke in
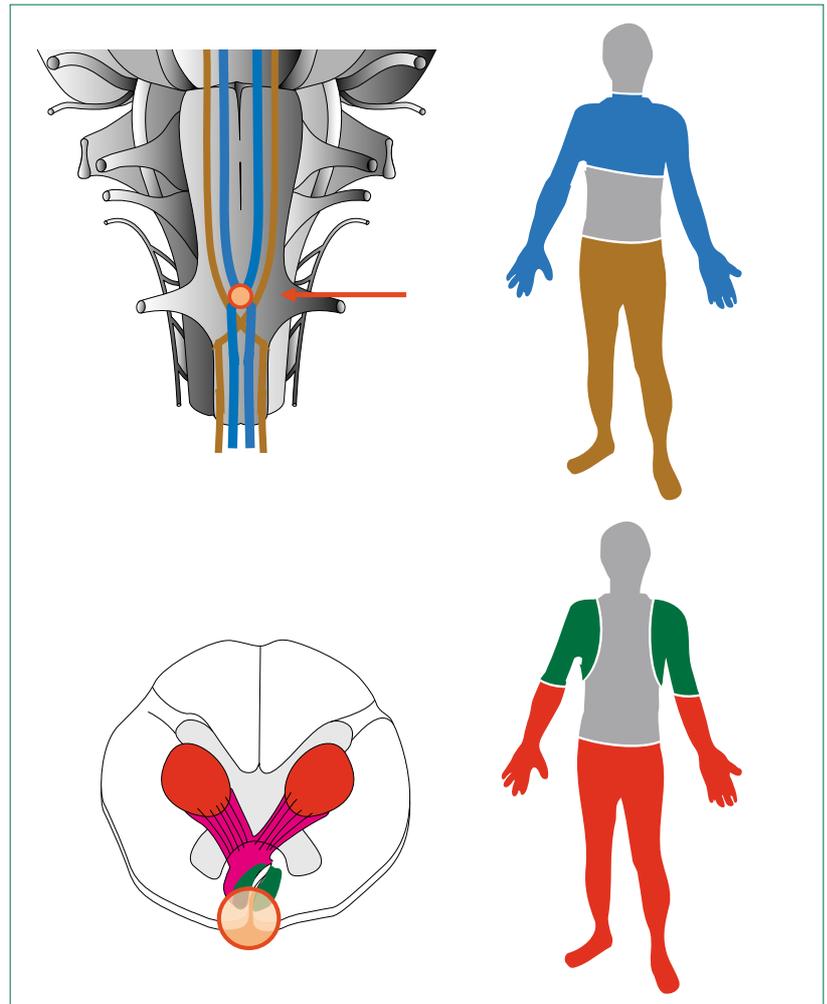

Figure 5: **Cruciate palsy**

Top: Wallenberg's view of the pyramidal decussation in the lower medulla oblongata. Corticospinal fibres involved with arm movements (blue) cross rostrally to those involved with leg movements (brown). A midline lesion at the rostral border of the decussation (orange circle indicated by the arrow) would therefore only affect arm mobility. However, no evidence for segregated crossing exists.[96–100] Bottom: axial view at the level of the pyramidal decussation. Alternative to Wallenberg's model: a midline lesion (orange circle) at the pyramidal decussation would affect mainly the ipsilateral CST (green), which innervates predominantly the proximal arms while sparing the crossed CST (red).

adulthood; responses are of short latency and often bilateral, in contrast to the delayed and usually unilateral ipsilateral response observed after lesions in adults.[83,115–118] Analysis of the electromyographic firing pattern indicates that these bilateral responses are due to the branching of corticospinal fibres to homologous motor-neuron pools on both sides of the spinal cord, reminiscent of what is reported for Klippel-Feil syndrome (figure 4).[116,117] The location and process of axonal branching is unknown, but a large body of experimental work indicates that segmental arborisation of descending motor fibres is increased after lesion in young (but not old) animals.[119–121] A drawback of bilateral branching is the generation of mirror movements which, unlike what is observed in
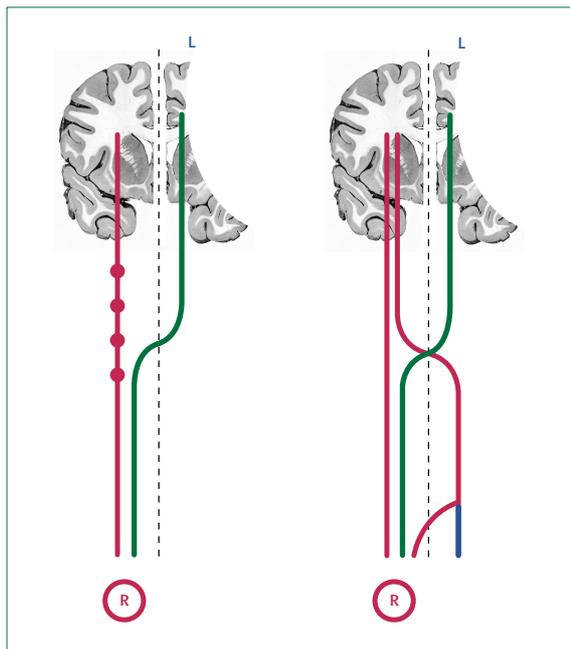
Figure 6: **Crossed and uncrossed motor pathways after hemispheric lesions**
Pathways activated on attempted right movement in patients with left hemispheric lesion. Left: in adults, reorganisation within the affected hemisphere probably accounts for most of the motor recovery (green line). Slow polysynaptic ipsilateral pathways exist (beaded red line), whose functional significance is unclear. Right: in children, branching of contralesional axons occurs in the spinal cord (red line crossing midline), mirror movements are a side-effect (blue line). Ipsilaterally projecting fibres may play a more important part in children than in adults (straight red line).

adults after stroke, are quite common and associated with a good functional recovery.[114,122,123] As an additional adaptive process, the ipsilateral CST, which is present at birth and normally regresses throughout childhood,[24] could be preserved in an activity-dependent manner in children with early hemispheric damage (figure 6).[23]

Molecular gating of axonal midline crossing

During embryogenesis, an axon must be informed whether its fate lies left or right of the midline. If it crosses to the other side, there is no return, and if crossing does not occur when scheduled, the growing axon may never find its target. Neurons are guided by various cues that are sensed by a receptor-laden area at the tip of the axon called the growth cone. These signalling molecules belong to four categories: attractive or repulsive cues, acting either at long-range (ie, diffusible) or at short-range (ie, needing cell contact). Chemorepellants "push" the growth cone from behind, chemoattractants "pull" it from afar, and attractive and repulsive local cues can "funnel" its path.[124,125]

Whether a given molecule is attractive or repulsive will depend on a number of factors including the type of neuron, expressed membrane receptors, concentrations of cyclic nucleotides, and whether or

not midline crossing has already occurred.[126] Initial screening for mutations that perturb axon guidance have been made in invertebrates. The strong evolutionary conservation of the genes coding for these signalling proteins and their receptors have allowed for quick identification of their vertebrate homologues. Consequently, numerous transgenic mice lacking one or another of these molecules have been generated over the past decade. Some of these mutants have contributed to the understanding of human diseases involving commissural abnormalities, including abnormal CST.

Long range midline guidance: netrins and Robo

Axons that will cross the midline are initially attracted to this region by diffusible molecules, such as netrins. Mice deficient in netrin-1 or its receptor have impaired pyramidal decussation and impaired commissural projections.[127,128] Ipsilaterally-projecting neurons are repelled from the midline by a protein called Slit, which acts via receptors of the Roundabout family (Robo).[129] In contralaterally-projecting neurons, which must overcome midline repulsion, sensitivity to Slit is actively repressed, and netrin-mediated midline attraction predominates (figure 7). In vertebrates, the prevention of crossing through activation of Robo receptors is inhibited by another receptor called Robo3 or Rig1.[130] In contrast to other Robo receptors, binding of Slit to Robo3 has no repulsive effect. Because Robo3 is expressed in large amounts on the cell surface before crossing, it competes with other Robo receptors for Slit binding (figure 7). Acting as a "Slit buffer" on commissural axons, Robo3 therefore prevents Slit from activating operative Robo subtypes before midline crossing. After midline crossing, Robo3 is downregulated, which unmasks midline repulsion and prevents recrossing.

In *Drosophila*, absence of the protein that has the same role as Robo3, though acting through a different mechanism, repels axons from the midline before crossing, and no commissures are formed. This phenotype is called "commissureless".[131] Deletion of Robo3 in mice also results in failure of commissural axons to cross.[130] In human beings, Robo3 has recently been identified as the culprit molecule in horizontal gaze palsy and progressive scoliosis. In this disorder pyramidal and lemniscal decussations are absent, and movements and tactile inputs are processed by the ipsilateral hemisphere.[49] This disease can therefore be seen as the human counterpart of the commissureless drosophila and Robo3 mutant mouse.

Very recently, the gene affected in another human disorder involving mirror movements and abnormal pyramidal decussation, Joubert's syndrome, has been identified (*AHI1*, see table).[50] Although the function of the gene product is unknown, the mutation might affect downstream effectors of short-ranging or long-range guidance molecules.
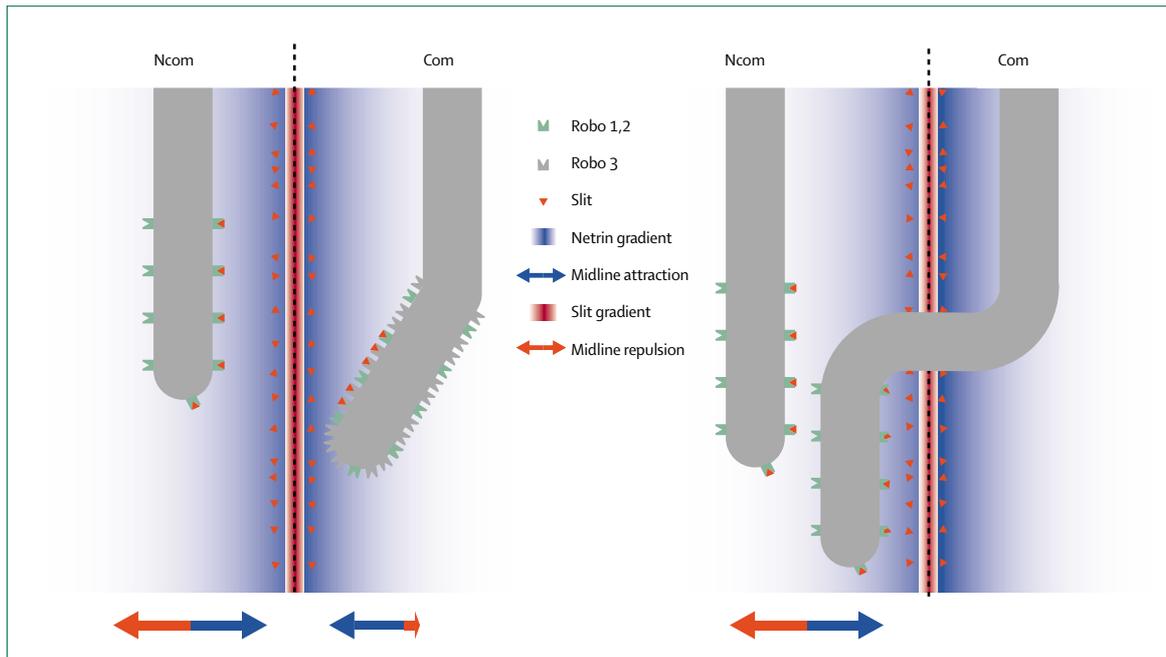
***Figure 7:* Midline repulsion by Slit and its receptor Robo in vertebrates**
Left: all fibres are initially drawn towards the midline (dotted black line) by a netrin gradient (blue). In neurons projecting ipsilaterally (non-commissural, Ncom), this attraction is balanced by the repulsive action of Slit (red triangles), also clustered at the midline, acting through Robo1 and Robo2 receptors (green) on the cell surface. In neurons projecting contralaterally (commissural, Com), Slit is buffered on Robo3 receptors (grey), which have no repulsive action. Netrin action therefore predominates and crossing occurs. Right: after crossing, Robo3 is downregulated and midline repulsion is unmasked, which prevents recrossing.

Short-range guidance: L1, NCAM, anosmin-1 and ephrins
L1, NCAM

L1 belongs to a family of neural cell-adhesion molecules that act as short-range cues. The protein is expressed at high concentrations along major axonal pathways, including the CST, and belongs to a membrane receptor which binds Sema3A, a short-range repelling molecule.[132–134] Targeted disruption of L1 in mice causes CST atrophy and incomplete pyramidal decussation.[133] In these animals, lack of L1 prevents corticospinal fibres from sensing ventrally expressed Sema3A, leading to a failure of a significant proportion of the axons to project dorsally to cross the midline. In addition, the glycoprotein CD24 that is expressed at the point of decussation and that binds L1 to promote adhesion, may not be sensed in mutant animals.[133,135] Disruption of NCAM, another member of the neural cell-adhesion-molecule family, also causes abnormal pyramidal decussation.[136]

Mutations in the *L1* gene have been described in human beings in association with a syndrome called MASA (mental retardation, aphasia, shuffling gate and adducted thumbs), CRASH (corpus-callosum agenesis, adducted thumbs, spasticity, and hydrocephalus), and X-linked hydrocephalus.[137] CNS anomalies resemble those observed in mutant rodents: there are no major malformations outside of the CST and corpus callosum, which are reduced in size. In contrast to mice, however, there is no physiological or anatomical evidence for abnormal pyramidal decussation.[133,137,138] The cause of this phenotypic difference is unknown, but could result from differences in the timing of CST development in human beings versus that in rodents.[137]

Anosmin-1

In X-linked Kallman's syndrome, the affected gene is *Kal1*, which encodes a surface protein called anosmin-1 which shares homologies with neural cell-adhesion molecules such as L1. This protein induces axonal branching and outgrowth in the lateral olfactory tract, and is instrumental in guiding axons from the olfactory bulb towards the pyriform cortex.[139–141] Atrophy of the olfactory bulb, which is a hallmark of the disease, would thus be secondary to inadequate cortical afferentation. Hypogonadism, however, results from impaired migration of neurons synthesising gonadotropin releasing hormones from the olfactory placode to the hypothalamus, leading to failed release of luteinising hormone and follicle-stimulating hormone from the pituitary. Anosmin-1 is also involved in midline fusion during embryogenesis, which explains the common co-occurrence of associated malformations, such as hare lip and cleft palate.[141] Anosmin-1 mRNA can be found in the spinal cord during development.[142] Because embryonic formation of the olfactory and pyramidal tracts is nearly simultaneous (between postovulatory days 52 and 57), axonal misguidance at the medullar pyramid could likewise generate anomalous ipsilateral corticospinal projection and mirror movements.[60]

Search strategy and selection criteria
References for this review were identified by searches of MEDLINE between 1969 and 2004 and references from relevant articles; numerous articles were also identified through searches of the extensive files of the authors. The search terms "decussation", "midline crossing", "mirror movement", "chiasm", "ipsilateral corticospinal", "ipsilateral projection", "ipsilateral pyramidal" were used. The final reference list was generated based on originality and relevance to the topics covered in the review.

Ephrins, ligands, and receptors

Ephrins are short-range repulsive molecules that are clustered at the midline along the CNS. In the lower medulla, however, ephrin-B3 is almost absent, which offers a permissive gate for axonal crossing and pyramidal decussation.[143] In the spinal cord, ephrins prevent contralateral CST axons from recrossing the midline; mice lacking the ephrin-B3 gene have tangled spinal-cord projections which cross the midline several times.[143] Mutant animals move around in a kangaroo-like hopping gait involving front and hind limbs, and are unable to make asymmetric movements.[143] These motor defects have been considered as mirror movements. A similar phenotype can be found in animals lacking the EphA4 receptor, which binds ephrin-B3. In these mice, however, mirror movements are present only in forelimbs since caudal corticospinal fibres are lacking.[144–146] Although no neurological disease has yet been linked to ephrin-B3, the phenotype of mutant animals suggests that dysfunction of this molecule may underlie some types of mirror movements.

Conclusion

Decussations in the human brain, fashioned throughout evolution, allow sensory and motor modalities to gather in modular polymodal cortical areas. Guidance of growing axons across the midline during development is tightly regulated and increasingly understood. Molecules controlling midline crossing are relevant in the understanding of several congenital diseases and could be involved in recovery of function after CNS injury.

Authors' contributions
SV and DJ wrote the manuscript. DJ produced the figures. OR reviewed and edited the text.

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