Seminars in Cell and Developmental Biology 118 (2021) 50–59

Contents lists available at ScienceDirect

Seminars in Cell and Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

The evolution, formation and connectivity of the anterior commissure

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ARTICLE INFO

Keywords:
Anterior commissure
Brain evolution
Forebrain connectivity
Cortical axon guidance
Corpus callosum agenesis

ABSTRACT

The anterior commissure is the most ancient of the forebrain interhemispheric connections among all vertebrates. Indeed, it is the predominant pallial commissure in all non-eutherian vertebrates, universally subserving basic functions related to olfaction and survival. A key feature of the anterior commissure is its ability to convey connections from diverse brain areas, such as most of the neocortex in non-eutherian mammals, thereby mediating the bilateral integration of diverse functions. Shared developmental mechanisms between the anterior commissure and more evolutionarily recent commissures, such as the corpus callosum in eutherians, have led to the hypothesis that the former may have been a precursor for additional expansion of commissural circuits. However, differences between the formation of the anterior commissure and other telencephalic commissures suggest that independent developmental mechanisms underlie the emergence of these connections in extant species. Here, we review the developmental mechanisms and connectivity of the anterior commissure across evolutionarily distant species, and highlight its potential functional importance in humans, both in the course of normal neurodevelopment, and as a site of plastic axonal rerouting in the absence or damage of other connections.

1. Introduction

Neural circuits between the left and right hemispheres of the human forebrain include connections through the corpus callosum, the hippocampal commissure, and the anterior commissure. In humans, the corpus callosum is the largest of these axon tracts, and connects most areas of the neocortex, predominantly in a mirror-image pattern. The hippocampal commissure, as its name implies, connects hippocampal and associated areas (e.g. entorhinal cortex), and lies immediately ventral to the corpus callosum. The anterior commissure, on the other hand, is the most ventral of the three commissures, and primarily connects olfactory and amygdaloid regions. Despite its small size relative to the human corpus callosum, the anterior commissure is the most evolutionarily ancient of these routes, as it is present in all vertebrates thus far examined, connecting brain areas that are essential for survival. It has also undergone a dramatic expansion, likely playing a key role in the evolution of the neocortex in the common ancestors of all living mammals and the developmental wiring of subsequent brain circuits. The importance of the anterior commissure can be best appreciated when considering its evolutionary origins, the brain areas that project through it, and the functional consequences of disruptions that occur in a range of developmental conditions. In this article, we review key aspects of each of these dimensions to examine the potential roles of the anterior commissure in brain evolution, development and function, as well as identifying gaps in our current knowledge.

2. Comparative anatomy and evolution of the anterior commissure

Connections between the left and right sides of the nervous system are present in all animals with bilateral symmetry, throughout the antero-posterior axis of the central nervous system. The anterior commissure is the only forebrain commissure for which a homologue has been identified in all vertebrate species studied to date [1]. It connects areas involved in olfaction, predominantly olfacto-recipient brain regions, likely allowing animals to locate odour sources by comparing the inputs that reach each nostril. Interestingly, despite the fact that teleost fish have an everted telencephalon (i.e., the medial pallium is

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https://doi.org/10.1016/j.semcdb.2021.04.009
Received 31 January 2021; Received in revised form 8 April 2021; Accepted 10 April 2021
Available online 3 May 2021

located laterally), the anterior commissure of goldfish includes connections between regions homologous to the hippocampus that course through its dorsal aspect (Fig. 1) [2]. In lungfish, however, a basal member of the lineage of limbed vertebrates, commissural connections between medial pallia (e.g. hippocampus homologue) have been reported as the earliest indication of a distinct hippocampal commissure (also known as pallial commissure), running immediately dorsal to the anterior commissure (Fig. 1) [3]. Although new evidence from cartilaginous fish is required to better understand the evolution of telencephalic commissures, it is likely that the hippocampal commissure evolved by detachment of connections originally carried through the anterior commissure.

Tetrapods share an overall pattern of areas connected via each of these commissures, with the main areas projecting via the anterior commissure including olfacto-recipient and pallial structures in amphibians and amniotes (Fig. 1). However, a remarkable expansion of the anterior commissure occurred in early mammals, most likely related to the origin of the neocortex and its interhemispheric connections [1,4] (Figs. 1 and 2A). Moreover, the origin of the corpus callosum exclusively in eutherian mammals can be further interpreted as a rerouting of connections originally coursing through the anterior commissure, towards a more dorsal commissural route such as the one provided by the hippocampal commissure. In line with this notion, a striking example of neocortical axon rerouting can also be seen in the fasciculus aberrans, a pathway unique to diprotodon marsupials (e.g., kangaroos, koalas) whereby commissural axons of the dorsal neocortex descend via the internal capsule to join the anterior commissure dorsally (Fig. 1) [5]. Together, the comparative evidence suggests that the anterior commissure, while present in all vertebrates, has undergone substantial evolutionary diversification in terms of both the brain regions that decussate through it, as well as the molecular strategies of axon guidance, including the generation of entirely new axonal tracts. In the following sections, we will focus on the anterior commissure of mammals to better understand the human brain.

3. Connectivity of the anterior commissure in eutherian mammals

Although in eutherians, such as rodents and humans, most portions of the cingulate cortex, neocortex and claustrum project via the corpus callosum, the anterior commissure retains the bulk of olfacto-recipient, amygdaloid and some temporal neocortical components, the latter particularly salient in primates and carnivores (Fig. 2B). These connections reach the anterior commissure via three major routes: the anterior branch, which carries fibres from the anterior olfactory nucleus to the contralateral olfactory bulb (Fig. 3A), the posterior branch, including projections from the piriform cortex, lateral entorhinal cortex, and ectorhinal and temporal association areas (Fig. 3B–D), and the stria terminalis branch, which contains fibres from the cortical amygdala and nucleus of the lateral olfactory tract that join the dorsocaudal aspect of the anterior commissure after circling around the stria terminalis (Fig. 3E–G).

Studies in eutherians such as rats, cats, macaques and humans have further demonstrated that the areas containing neurons that project through the anterior commissure include the anterior olfactory nucleus through its anterior branch, the piriform and entorhinal cortices, as well as lateral/temporal portions of the neocortex cortex through its posterior branch, and amygdaloid areas such as the nucleus of the lateral olfactory tract and cortical amygdala through the stria terminalis branch [6–11]. Commissural projections arising from amygdaloid areas follow the stria terminalis to join the anterior commissure dorsocaudally, and after crossing the midline either continue along the contralateral stria terminalis and/or join the posterior branch before reaching its contralateral targets [8,12,13]. Similarly, the entorhinal cortex sends contralateral projections across the anterior commissure via its posterior branch, but also through the corpus callosum and the hippocampal commissure (Fig. 3C), possibly connecting slightly different circuits (e.g., homotopic, heterotopic neocortical and heterotopic hippocampal, respectively). Finally, although most of the neocortex, the cingulate cortex, and the claustrum of eutherians project exclusively via the corpus callosum, regions of the temporal/lateral neocortex, such as the rodent ectorhinal/temporal association areas, also project via the anterior commissure (Fig. 3D). Such neocortical components of the anterior commissure are more prominent in the highly visual and gyrencephalic carnivores and primates, particularly compared to highly olfactory and lissencephalic rodents and rabbits. For example, neocortical connections include up to 75% of all fibres in cats [14–16], and in primates (including humans) substantial projections from temporal and occipital lobes via the posterior branches constitute the majority of the anterior commissure fibres (Fig. 2B) [7,9,10,17–23], which contrast with a much smaller anterior branch. Although some of these neocortical areas might also project via the corpus callosum and/or hippocampal commissure, it remains unknown whether these arise from separate neuronal populations or instead are distinct branches from

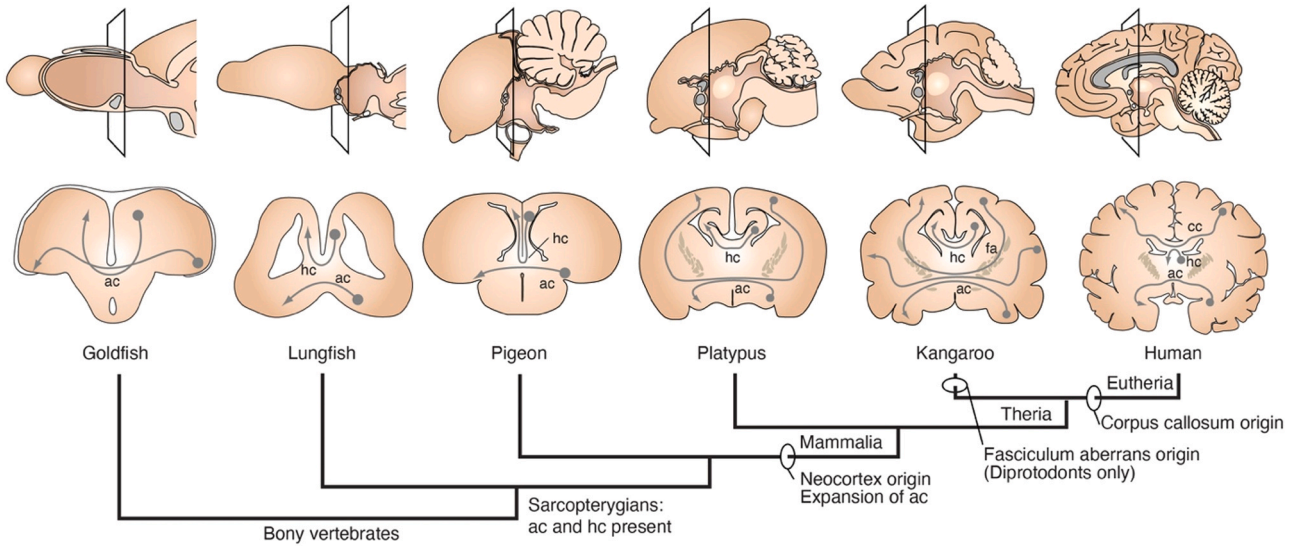

Fig. 1. Schematics through the midsagittal midline of example vertebrate species (top) and coronal views across the telencephalon (bottom) at the levels indicated with boxes. Note the adjacent positions, from ventral to dorsal, of the anterior commissure (ac), hippocampal commissure (hc) and corpus callosum (cc).

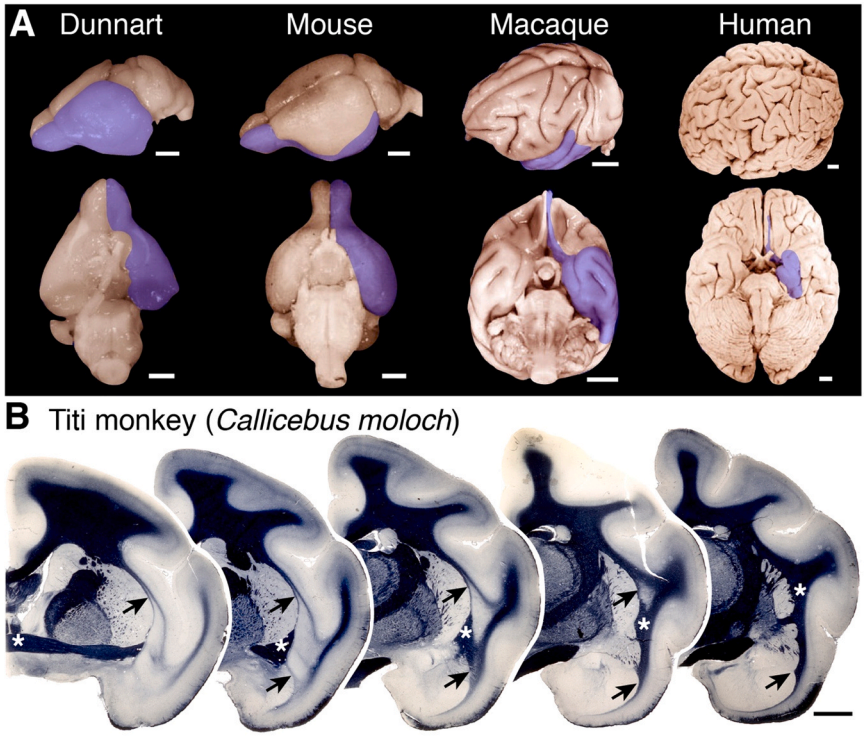

Fig. 2. Brain regions projecting through the anterior commissure in mammals. A, oblique (top) and ventral (bottom) views of a marsupial (dunnart) and three eutherian brains showing broad areas with anterior commissure projections in purple. Note that olfactory-recipient, entorhinal and amygdaloid areas are conserved in all species and most of the neocortex is spared in eutherians, with the exception of temporal regions. B, haematoxylin staining of myelinated fibres in the titi monkey show the anterior commissure and its posterior branch (asterisks), as well as neocortical fibres that join it. Scale bars: 2 mm in dunnart, mouse (A) and titi monkey brains (C); 1 cm in macaque and human brains (A). Specimens used for this publication are from the Defense Health Agency's Neuroanatomical Collections Division of the National Museum of Health and Medicine, the University of Wisconsin and Michigan State Comparative Mammalian Brain Collections supported by the US National Science Foundation.
Images adapted with permission from http://brainmuseum.org.

individual neurons.

4. Development of the anterior commissure

Formation of the anterior commissure precedes that of other telencephalic commissures and occurs after closure of the anterior neuropore, in a region of intense morphogenic patterning [1,24]. This area corresponds to a rostral midline domain, where the septal roof plate joins the pallial alar plate, along the presumptive diagonal band and preoptic area, and within the dorsal extent of the lamina terminalis. Accordingly, the area where the anterior commissure forms is characterised by the confluent expression of cortical transcription factors such as *Nfia* and *Nfib*, septal transcription factors such as *Zic2*, *Six3*, *Dlx1* and *Dlx2*, and preoptic transcription factors such as *Nkx2.1*, *Lhx6* and *Lhx8* [25–29] (Fig. 4).

Before commissural axons reach the midline, and after the anterior neuropore has closed, the lamina terminalis grows dorsally and glial cells accumulate along the midline, from where they help to channel pioneering axons of the anterior commissure [30–35]. Such events are likely conserved throughout vertebrates, as zebrafish also have embryonic glia that help to guide anterior commissure axons [36]. In addition, eutherians, but not marsupial or monotreme mammals, undergo a subsequent event of histogenic fusion of the medial septum, above the level of the anterior commissure, through a specialised population of astrocytes known as 'midline zipper glia' [30], which provide a dorsally extended substrate that is vital for callosal development [37,38]. This midline domain encompassing all three telencephalic commissures has been termed the commissural plate (Fig. 4), and includes distinct dorso-ventral domains of transcription factor expression [26].

By the time axons of the anterior commissure are beginning to cross the midline, a population of glia surround the fibre bundle, forming a tunnel-like structure that is circumscribed by the expression of extracellular matrix molecules, such as chondroitin sulphate proteoglycan, fibronectin, and laminin, as well as the glial marker GFAP [30,35,39]. As in the corpus callosum, an *Nkx2.1*-positive population of guidepost cells are also necessary at the midline for normal anterior commissure development, likely through the expression of midline guidance cues [28].

The broad formation of the anterior commissure in mice sits within a timeline of other major axon bundles, beginning with the posterior commissure (dorsal midbrain; around E13), followed by the optic chiasm, stria terminalis, habenular commissure, columns of the fornix, and subsequently the anterior commissure (between E14 and E15), and then the hippocampal commissure, followed finally by the corpus callosum (between E15 and E16) [40]. The anterior branch of the anterior commissure forms and matures faster than the posterior branch. More recent and detailed studies have found that the first axon bundles that form the anterior branch of the anterior commissure are visible ipsilaterally at around E13-E13.5, with the first axons reaching the midline around E14 [41,42] (Fig. 5).

In the corpus callosum, a pioneering axonal population arises from the cingulate cortex and crosses the midline prior to all neocortical axons [43]. However, the existence and cell-of-origin identity of pioneering fibres in the anterior commissure is less clear. Tracer experiments in hamsters have revealed that the earliest-crossing axons of the anterior commissure arise from cells broadly located in the olfactory peduncle or the superficial layers of the olfactory (piriform) cortex, seemingly irrespective of anterior-posterior location [44,45], or the posterior-to-anterior gradient of neurogenesis in many cortical olfactory structures [46]. Despite the addition of neocortical axons to the anterior commissure in marsupials compared to eutherians, olfactory and perirhinal areas also appear to pioneer the anterior commissure of wallabies [47].

A characteristic feature of callosal development is axonal exuberance and pruning [48–55], which has long been hypothesised to participate in the guidance and ultimate connectivity of the corpus callosum (see for review [56]). However, Lent and Guimarães [57] have reported that this is not the case in the anterior commissure of hamsters, with retrograde labelling revealing a steady linear increase in commissural cells after birth. Similarly, in rats a steady increase in the number of axons within the anterior commissure has been observed throughout development using electron microscopy [58]. In contrast, in the rhesus monkey, anterior commissure axons have been found to be added at an average rate of 115,000 per day during the last two-thirds of gestation, peaking

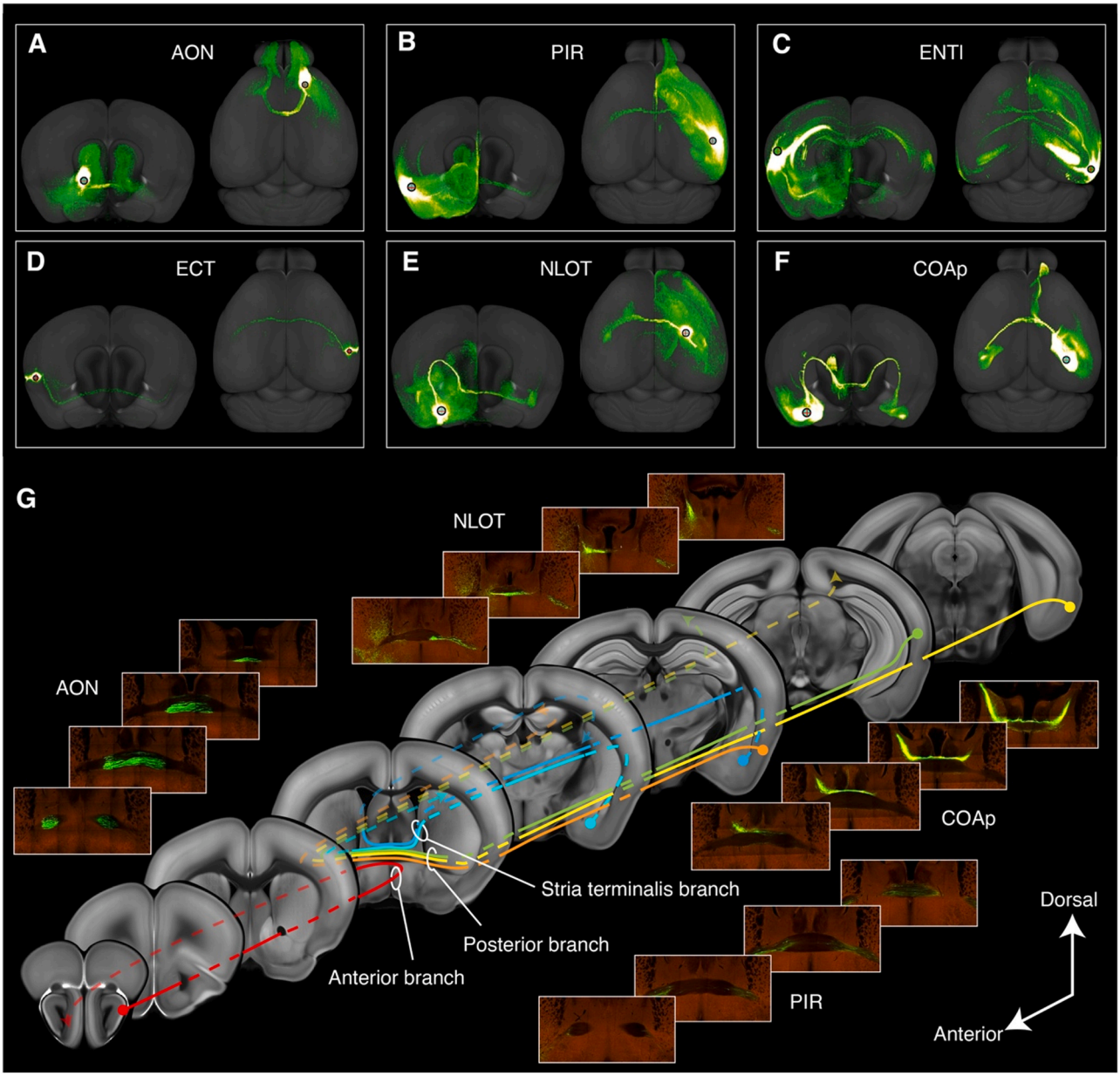

Fig. 3. The anterior commissure of eutherian mammals consists of three main branches. As shown in mice, these are the anterior branch (A), the posterior branch (B–D), and the stria terminalis branch (E–G). A–F, whole-brain 3D projection density reconstructions of representative tracer injections (adeno-associated virus expressing enhanced green fluorescent protein, AAV-EGFP) in the regions indicated (small circles). Views are in coronal (left, seen from anterior) and horizontal (right, seen from above) planes. G, schematic serial representation of the main projections through each branch of the mouse anterior commissure, and insets of coronal series showing axons crossing the midline through distinct subdomains. AON, anterior olfactory nucleus; COAp, cortical amygdala area, posterior part; ECT, ectorhinal area; ENTl, entorhinal area, lateral part; NLOT, nucleus of the lateral olfactory tract; PIR; piriform area.
Modified from mouse connectivity projections data from the Allen Institute (experiments ids: AON, 113443572; COAp, 114249084; ECT, 180403712; ENTl, 180297139; NLOT, 187269162; PIR, 146984209).

at around 11 million axons at birth, after which they are reduced to around 3.3 million axons during the first three postnatal months [59]. However, this phenomena has not been studied in other species, and it remains unclear whether and to what extent exuberance and pruning of the anterior commissure might vary between mammalian lineages. One explanation for inter-species differences is that the pattern of exuberance and retraction observed in the monkey may be particular to axons arising from the neocortex, given that primates have a much greater neocortical component of the anterior commissure than other eutherian species.

Work done by Lent and Guimarães [57] using DiI injections in hamsters determined that axons comprising the anterior commissure show steady axonal growth. However, a recent study using *in utero* electroporation to label anterior commissure axons in mice reported waiting periods, i.e., stopping and starting over the course of axonal growth [42] (Fig. 5B). These observations may be significant because pauses or waiting periods in axonal growth have been hypothesised to represent crucial moments in pathfinding decisions. Moreover, after pioneering anterior commissure axons arrive at the midline (E14), there is a pause in development prior to the invasion of the contralateral hemisphere [42]. By E16, axons once more engage in a "progressive" strategy, growing consistently until E17, at which time they have invaded initial contralateral targets, such as the olfactory cortex. Axon bundles then begin to defasciculate, and there is another pause in

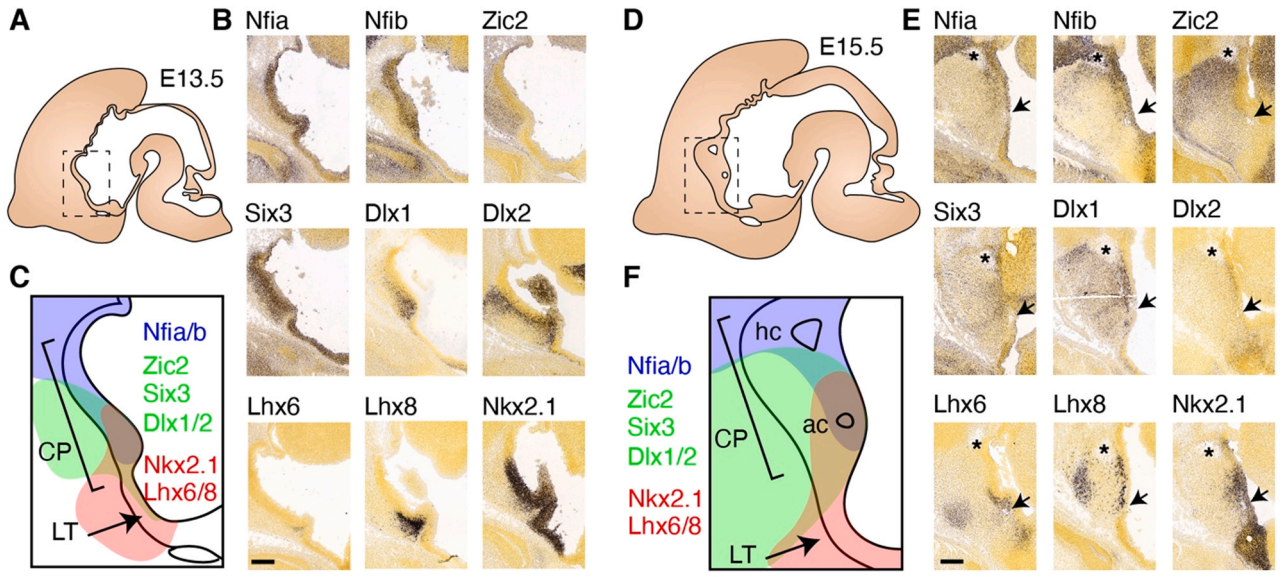

Fig. 4. Confluence of transcriptional specification at the presumptive anterior commissure territories. Midsagittal views, schematics and in situ hybridisations of cortical (blue), septal (green) and preoptic (red) transcription factors at E13.5 (A-C, before midline crossing) and E15.5 (D-F, after midline crossing). By E15.5, the anterior commissure (ac, arrows) and hippocampal commissure (hc, asterisks) have crossed the midline. ac anterior commissure; E embryonic day; hc hippocampal commissure; CP commissural plate; LT lamina terminalis. Rostral is to the left; scale bars: 50 μm.
In situ hybridisation figures modified from Allen Institute, developing mouse brain datasets.

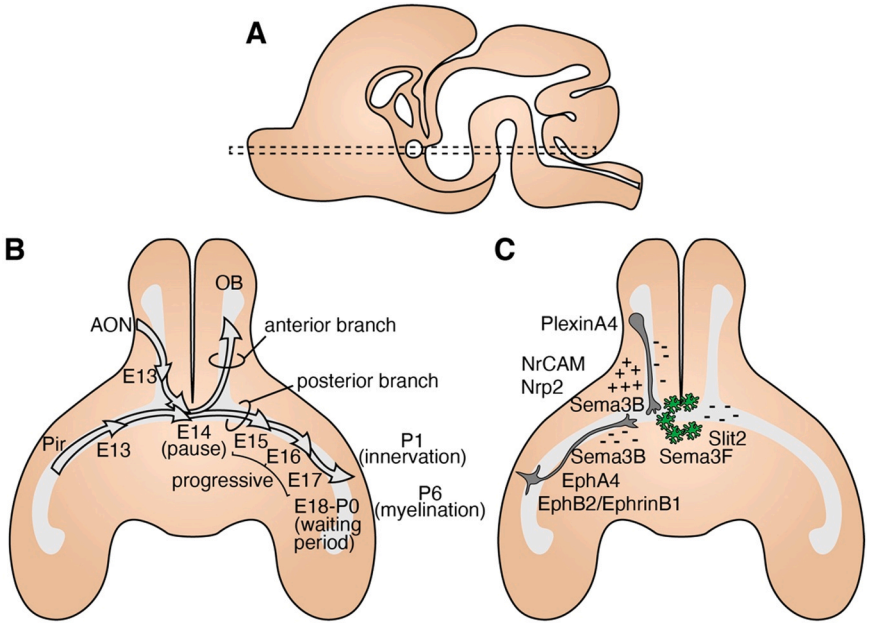

Fig. 5. Dynamics of anterior commissure circuit development. A, midsagittal schematic of a perinatal mouse brain indicating the horizontal plane of anterior commissure development described below. B, the anterior and posterior branches are shown and approximate embryonic days (E) of wiring milestones. C, axon guidance cues and midline glial populations help channel growing axons of the anterior commissure. AON, anterior olfactory nucleus; OB, olfactory bulb; Pir, piriform cortex. See text and Supplementary Table 1 for further details and references.

development during which axons halt underneath the cortex, waiting until P1 to commence innervation [42] (Fig. 5B). The latter observation of an axonal pause prior to contralateral innervation of the overlying cortical target is comparable to callosal development in the rat, where fibres accumulate in the white matter for a few postnatal developmental days before innervation [60]. Such pauses in axonal growth have been hypothesised to underlie subsequent axon guidance decisions.

Finally, once axons have innervated their targets, oligodendrocytes start to become evident around anterior commissure axons, reaching adult-like levels of myelination between the third and fourth postnatal week in rodents [58,61–63]. In monkeys, myelination of the anterior commissure occurs progressively, before the bulk of fibre elimination, such that around 95% of surviving axons are myelinated by the end of development [59].

5. Genetic regulation of anterior commissure development

The genes that regulate the formation of the anterior commissure in eutherian mammals have predominantly been deduced by observations of knockout mouse lines showing defects in this tract. These can broadly be divided into two categories: genes that affect the anterior commissure in isolation, and those that also affect other structures, particularly the other commissures. Within the categories of genes thought to regulate rodent anterior commissure development via abnormal neuronal and/or glial proliferation (group 1), abnormal midline patterning (group 2) and abnormal neuron migration/specification (group 3; Supplementary

Table 1), only a handful of genes specifically affect the anterior commissure, suggesting that many of these processes may be overlapping in the cells of origin that give rise to the corpus callosum and anterior commissure (for a review of the function of the genes shared between the corpus callosum and anterior commissure see [64]). The exceptions to this are mutant mice that have absent or severely reduced structures that are known to project through the anterior commissure, such as the olfactory bulbs (*Kif1b* and *Ndst1*) or amygdala projections (*Tbr1*), likely explaining the reduction of this tract (Supplementary Table 1).

The largest group of genes identified as being involved in the development of the anterior commissure are axon guidance molecules (group 4; see Supplementary Table 1 for further details and references). This includes the receptors *Dcc* (and its ligands *Ntn1* and *Draxin*) and *Robo*1 (and its ligand *Slit2*), with *Slit2* being expressed in midline guidepost cells, as is the case for callosal midline guidance. Interestingly, models involving knockout of *Fzd3* (a receptor for *Wnt* ligands) exhibit deficits in both the corpus callosum and anterior commissure, but knockout of three other receptors known to interact with the *Fzd3* pathways (*EphA*, *Celsr3* and *Islr2*) results in isolated defects of the anterior commissure, suggesting that Fzd3 might perform different functions in the development of each commissure. In addition to these, knockout of several genes involved in intracellular signalling and cytoskeletal regulation (e.g., *Cdk5r1*, *Gap43*, *Map1b*, *Rac1*, *Shtn1*, *Vasp*, *Enah*, *Tsku*, *Trio*) also result in defects of both commissures, potentially via effects on these axon guidance pathways and/or other mechanisms.

Given the aforementioned hypothesis that the anterior commissure was likely an evolutionary forerunner to more recent forebrain commissures, a key goal of this review is to pinpoint the developmental mechanisms unique to the anterior commissure and thereby identify candidates for future isolated genetic manipulations. Some of the earliest studies to identify an axon guidance gene that specifically regulates anterior commissure development (i.e. where its perturbation does not result in an abnormal corpus callosum and hippocampal commissure) reported that *Ephb2* knockout mice showed aberrant positioning of the posterior branch of the anterior commissure, possibly through signalling with the *Efnb1* receptor [65], although later studies reported a higher penetrance of corpus callosum abnormalities [66] (Fig. 5C). Another member of the Eph family, *Epha4*, has also been shown to be required for anterior commissure development, likely through its kinase activity, with the knockout showing a loss of the anterior commissure in addition to disruption of spinal cord architecture and a reduction of the dorsal funiculus [67–69]. However, the precise mechanisms of action and downstream effectors of these molecules during anterior commissure formation remain to be determined.

A well-described pathway that specifies the anterior commissure independently from other forebrain commissures comprises the transmembrane receptor *Nrp2* and the secreted ligands *Sema3b* and *Sema3f* [70,71] (Fig. 5C). *Nrp2* knockout mice were initially described as lacking an anterior commissure, or having a severely reduced and defasciculated anterior commissure in both the anterior and posterior branches, whereas the corpus callosum, hippocampal commissure and lateral olfactory tract appeared normal. Beta-galactosidase and mRNA staining in these knockout lines revealed *Nrp2* expression in many of the regions known to project through the anterior commissure in mice, including the piriform cortex, amygdala and accessory olfactory nucleus, with a relative absence in the dorsal neocortex [72,73]. The knockdown of both *Sema3f* and *Sema3b* have also been shown to result in abnormalities or absence of the anterior commissure [74,75]. Indeed, an elegant study by Falk et al. [74] provided one of the most complete mechanisms of anterior commissure formation to date, by showing that NRP2, expressed on axons of both the anterior and posterior branches of the anterior commissure, mediates growth cone collapse via interaction with SEMA3B on the posterior branch. In contrast, axons comprising the anterior branch of the anterior commissure are instead attracted by SEMA3B and repelled by SEMA3F (Fig. 5C). The differential responses of NRP2 to SEMA ligands in the two anterior commissure branches are thought to be mediated by the FAK/SRC signalling cascade. mRNA staining revealed *Sema3f* expression in the neonatal striatum and *Sema3b* expression in the subventricular zone lining the lateral ventricles. This finding accords with the phenotype of *Sema3b* mutants, which exhibit an anterior branch displaced away from the lateral ventricle, whereas it is closely apposed in the wildtype, in line with its attractive role for this branch. This study also showed that NrCAM, which is known to form a receptor complex with NRP2, is involved in this process, as mutants for the gene resemble *Sema3b* knockouts (a ventral and lateral shift of the anterior commissure and defasciculation). These findings highlight the most promising mechanisms to target in future studies seeking to specifically label and manipulate the anterior commissure independently from other forebrain commissures.

Very little is known about the molecular regulation of the anterior commissure in vertebrates other than eutherian mammals. In zebrafish, many homologues of the pathways known to affect the development of this structure in mammals are conserved, including Slits [76,77], Wnts [78–81], Netrin [82,83], Neuropilins/Semas [84] and Fgfs [85,86]. In non-eutherian mammals, such as marsupials, the molecular regulation of the neocortical portion of the anterior commissure has only recently been investigated. Marsupials lack a corpus callosum and their neocortices are connected via the anterior commissure (Figs. 1 and 2). In marsupial fat-tailed dunnarts the transcription factor *Satb2*, a “callosal specifier” in eutherians, is also responsible for the development of neocortical commissural neurons projecting through the anterior commissure [87], with Crispr/Cas9 knockdown resulting in ectopic projections that descend via the internal capsule in both dunnarts and mice. Interestingly, the timing of developmental SATB2 expression was revealed to be crucial for neocortical axons to make the decision between callosal or anterior commissural routes.

6. Function of the anterior commissure

Despite the evolutionary conservation of the anterior commissure and its broad connectivity throughout the mammalian brain, relatively little is understood about its function, although this presumably varies depending on the regions it connects in different species. A role in olfactory function in rodents is supported by the finding that olfactory memory is disrupted following transection of the anterior, but not the posterior, branches of the anterior commissure in rat pups [88]. Transection of the anterior commissure in mice has also been shown to induce higher locomotor activity, aberrant social interaction and a reduction in associative memory, potentially via disrupted connections between amygdaloid areas [89]. Humans who have had their corpus callosum surgically severed retain interhemispheric transfer of olfactory and some auditory and visual information, but not somatosensory or language functions, which are thought to be largely mediated by the corpus callosum [90]. Selective sectioning or inactivation of the anterior commissure in monkeys results in memory and visual defects [91,92]. This is consistent with a human case who presented with an incidental haematoma involving the anterior commissure who exhibited severe anterograde amnesia for visual stimuli [93]. Although it remains unclear whether other brain structures were also affected in these cases, such visual deficits may point to additional functional roles for the anterior commissure in primates.

In addition to cases of callosal damage or loss, there are also cases of congenital absence or malformation of the anterior commissure that may inform its function. It has been well established that an absent or hypoplastic anterior commissure occurs in 50–60% of patients with agenesis of the corpus callosum [94,95], as well as occasionally in patients with a normal corpus callosum [96]. There are also reported cases of gene disruptions underlying developmental anterior commissure reduction or absence in humans, for instance in association with mutations of *PAX6* [97–99], *TUB1A*, *TUBB2B* [100] and *HESX1* [101]. As many of these cases of anterior commissure agenesis occur concomitant

with defects in other forebrain commissures or brain areas, it is difficult to attribute the associated functional deficits specifically to the absence of the anterior commissure. Nevertheless, functional defects in these case studies often include reduced olfaction [98] and some visual impairment/visuospatial difficulties, a decline in working memory and perhaps an increased incidence of epilepsy [96,99]. There have also been reports of changes in the organisation, size or axonal density of the anterior commissure in conditions such as schizophrenia [102,103], bipolar disorder [104,105], language impairment [106] and Down's syndrome [107], and in a marmoset model of autism spectrum disorder (valproic acid exposure) [108]. In these cases, the severity of symptoms sometimes correlates with the altered parameter, such as more severe language impairment correlating with decreased size and connectivity of the anterior commissure [106].

7. Plasticity of the anterior commissure

Interpretations of the functional significance of the anterior commissure from lesion or congenital cases are further complicated by the possibility that this commissure may compensate for seasonal requirements across the lifespan of an animal (e.g. in the case of the ground squirrel [109]), as well as for injuries to or absence of other brain connections, such as in cases of congenital blindness [110] lesions of the lateral olfactory tract [111] or disruption of the corpus callosum. Some of the first evidence for such plasticity came from autopsies of humans with agenesis of the corpus callosum, a number of whom had a relatively enlarged anterior commissure [112]. This enlargement was soon hypothesised to be a potential substrate for "The Sperry Paradox" outlined by Roger Sperry in 1968 [113], whereby people born without a corpus callosum do not display the same disconnection syndrome as those who have undergone callosotomies in adulthood. The potential for behavioural developmental plasticity was solidified by subsequent observations that callosotomies in children produce a milder disconnection syndrome than those in adults [114], as well as tractographic studies highlighting the many primate brain regions that are interconnected by both commissures, potentially indicating redundancy and the prospect of compensation between the two [115].

Sporadic evidence for a larger and/or denser anterior commissure in some humans and mice with acallosal brains subsequently emerged [116]. However, this has often been accompanied by other contradictory reports of an unchanged or smaller anterior commissure in those with callosal agenesis [117,118], with a recent investigation finding that, on average, children who are born acallosal exhibit a larger anterior commissure, although the range in size is greater than that seen in a neurotypical brain [119]. It remains unclear whether or not this variability, as well as the anecdotal reports of better outcomes in callosal agenesis individuals with a normal or larger anterior commissure [120], is due to developmental axonal plasticity or instead reflects the variable aetiologies of the disorder.

The advent of diffusion tensor imaging tractography has resulted in new evidence of ectopic routes of neocortical axons through the anterior commissure in humans with callosal agenesis, including connections between visual areas [121,122], the temporal lobes [123,124] and the parietal lobe [125]. Although a handful of knockout mouse models have been confirmed to show rerouting of neocortical axons through the anterior commissure from would-be callosal neurons [126,127] or corticofugal neurons [128–130], such rerouting has not been definitively histologically demonstrated in humans or in the majority of mouse models of callosal agenesis. Nevertheless, the potential for compensatory mechanisms is an intriguing area for future research into recovery from brain traumas and malformations.

8. Conclusion

The remarkable conservation of the anterior commissure throughout the vertebrate lineage suggests deep homology of developmental, anatomical and functional processes that likely arose more than 400 million years ago. Moreover, lineage-specific features of the anterior commissure highlight its flexibility in being able to carry diverse connections from different telencephalic areas across both phylogeny and ontogeny, possibly facilitating the origin of new commissural routes in early limbed vertebrates (e.g. the hippocampal/pallial commissure) and in mammals (e.g., the fasciculus aberrans, corpus callosum), as well as putatively mediating plastic developmental compensation in humans with neurodevelopmental defects that affect commissural circuits. The early emergence of the anterior commissure both during evolution and in development is likely related to such circuit innovations, by establishing developmental constraints on neural wiring while allowing for circuit variability. However, despite its phylogenetic and ontogenetic importance, a detailed understanding of the developmental mechanisms and function of the anterior commissure across species requires ongoing investigation. Renewed attention to this topic aided by modern techniques for neuronal labelling, axonal transections, live imaging and transgenic manipulation may help to address these questions.

Acknowledgements

We are grateful for insightful discussions and suggestions for the manuscript from Rowan Tweedale, Annalisa Paolino, Yunan Ye and Elizabeth Haines. This work was supported by a National Health and Medical Research Council (NHMRC) Investigator Grant to LRF (GNT1175825), a NHMRC Principal Research Fellowship to LJR (GNT1120615), a University of Queensland Amplify Fellowship to RS and a University of Queensland Research Training Scholarship and QBI Top-Up Scholarship (ZL).

Competing interests

Declarations of interest: none.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.semcdb.2021.04.009.

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