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Contralateral targeting of the corpus callosum in normal and pathological brain function

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The corpus callosum connects the two cortical hemispheres of the mammalian brain and is susceptible to structural defects during development, which often result in significant neuropsychological dysfunction. To date, such individuals have been studied primarily with regards to the integrity of the callosal tract at the midline. However, the mechanisms regulating the contralateral targeting of the corpus callosum, after midline crossing has occurred, are less well understood. Recent evidence suggests that defects in contralateral targeting can occur in isolation from midline-tract malformations, and may have significant functional implications. We propose that contralateral targeting is a crucially important and relatively under-investigated event in callosal development, and that defects in this process may constitute an undiagnosed phenotype in several neurological disorders.

Development of the corpus callosum

The formation of precise connections between the two hemispheres of the brain is essential for many aspects of neural function, including integration of lateralised sensory input and regulation of higher-order cognitive, social, and emotional processing [1]. Such bilateral integration between the two cortical hemispheres is largely mediated by axons forming the corpus callosum, the largest fibre tract in the human brain. The development of the corpus callosum involves a precise sequence of events [2,3] (Figure 1). First, newborn cortical neurons committed to a callosal-projection fate extend an axon medially. Next, aided by a complex interaction of secreted and contact-mediated axon-guidance cues, axons extend towards, across, and then away from the midline, defined as midline crossing. Finally, callosal axons continue coursing through the contralateral intermediate zone and turn into the cortical plate, ultimately arborising and stabilising to form functional connections in a layer- and cortical area-specific manner. We will refer to these later stages of contralateral callosal axon innervation and stabilisation as contralateral targeting. Thus, callosal development involves numerous stages, and it is necessary to understand the progression and mechanisms underlying all of these to fully comprehend this process and the errors that may arise in it.

Callosal malformations

Once callosal neurons and axons are formed, several different outcomes could result from coordinated or isolated misregulation of the subsequent stages during development. For instance, failure of midline crossing often results in callosal dysgenesis, a congenital brain malformation that includes complete (agenesis) or partial absence of the corpus callosum as well as callosal hypoplasia [4–6]. This may lead to an absence of contralateral connectivity

Glossary

Axon-tracing techniques: can include anterograde (marker taken up by the cell body and transported to the axon terminal) or retrograde (marker taken up by terminals and transported back to the cell body) transport. Includes methodologies such as:

Molecular tracing: includes degeneration-based techniques and injectable molecular dyes [anterograde and retrograde methods, such as horseradish peroxidase, injection of tritiated amino acids (autoradiography), cholera toxin subunit B, or DiI]. Limitations include variable injection site/size and inability to transfect specific populations of neurons.

Genetically targeted tracing: includes viral tracing (anterograde, retrograde, and *trans*-synaptic methods, involving infection of a population of neurons with a viral vector) and *in utero* electroporation (anterograde, involving the transfection of a genetic construct encoding a fluorescent protein). Has the advantage of labelling cells in a developmentally and/or genetically constrained manner.

Callosal dysgenesis: a group of disorders of the corpus callosum that includes its absence (agenesis), partial absence, and hypoplasia (global decrease in size).

Diffusion magnetic resonance imaging (dMRI): an MRI method that detects the diffusion of water molecules in biological structures and consequently provides information about the structure and organisation of the internal tissue. It is commonly used to evaluate white-matter tracts in the brain non-invasively.

Functional anisotropy: a value extracted from dMRI data that describes the directionality of water diffusion in a given structure, with a high value suggesting a single ordered direction (i.e., along a single axis) and a low value suggesting unrestricted diffusion in all directions.

Functional magnetic resonance imaging (fMRI): a non-invasive method of MRI of living brains that measures the presence and extent of neuronal activation in different brain regions via changes in blood flow over time.

Neuropsychological assessment: non-invasive tests performed on human subjects to assess factors such as intelligence, sensory processing, motor functioning, and speed of processing.

Tractography: a technique that uses dMRI data to create 3D maps of neuronal tracts.

Transcranial magnetic stimulation: non-invasive method often applied to humans that involves the application of a constrained magnetic field to the outside of the head, allowing the specific activation of underlying brain regions.

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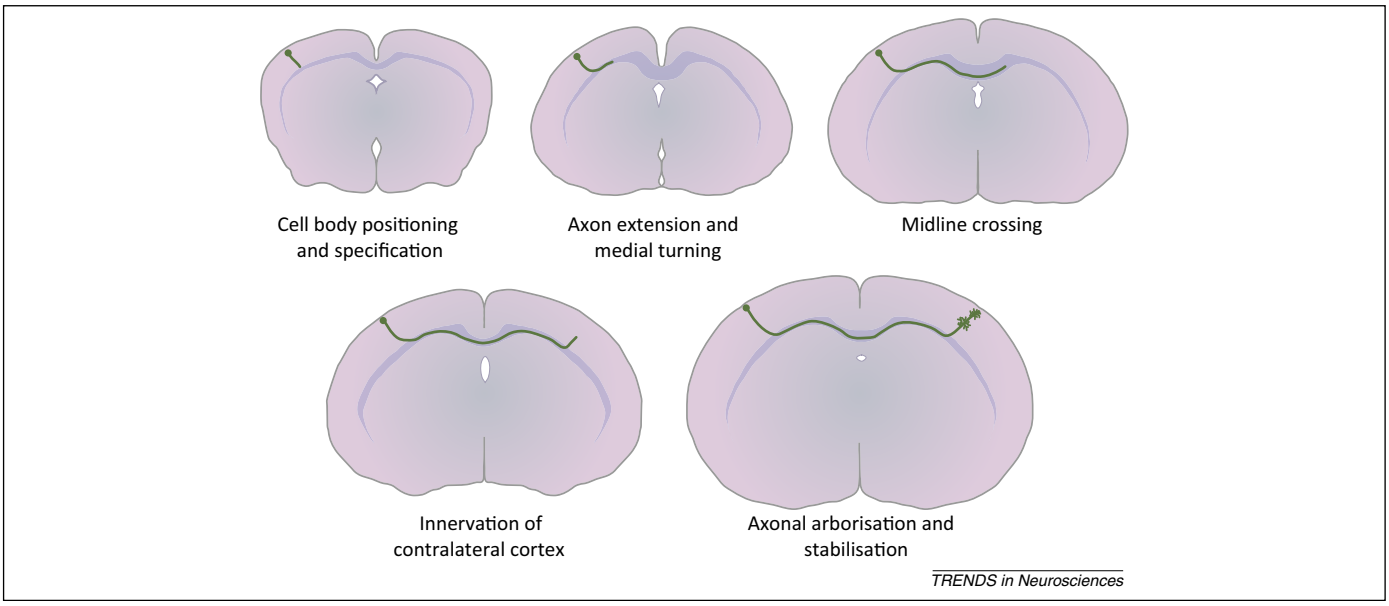

Figure 1. Stages of callosal development. Schematic illustrating the different stages of callosal targeting, using callosal neurons from the L2/3 somatosensory neocortex of a mouse as an example. First, callosal cell bodies migrate from the ventricular zone where they are born to their cortical layer and are specified as callosal projection neurons at around postnatal day (P) 0 in the mouse. Next, axons extend and turn medially in the intermediate zone towards the midline (P2). Axons then cross the midline and continue to follow the white-matter tract in the other hemisphere (P4). Projections turn to innervate the contralateral cortical plate (P6) and finally arborise and stabilise in their final contralateral locations (beginning at P8). These last two stages of innervation, arborisation and stabilisation, are collectively termed contralateral callosal targeting.

because callosal axons that are unable to cross the midline stall in the ipsilateral hemisphere (for instance, forming Probst bundles [7,8]). Interhemispheric cortical axons that are unable to cross the midline may also reroute through alternate commissures and correctly innervate their contralateral targets. Evidence for this has come from studies showing that some human patients with callosal agenesis display little/no interhemispheric disconnection in neuropsychological tasks [9–15], as well as an enlarged anterior commissure [9,10]. A recent report has also provided direct evidence of rerouting of cortical axons through the anterior and posterior commissures that positively correlates with functional interhemispheric connectivity [13]. The majority of callosal research has focused on midline crossing [2], and all human callosal disorders are clinically diagnosed based solely on the detection of gross structural defects at the sagittal midline. However, midline callosal dysgenesis represents the most severe form of callosal malformation, and many other neurological disorders are likely to involve more subtle defects in this commissure.

Recent research in mice indicates that the final stages of callosal targeting in the contralateral hemisphere may be more important than previously thought. For instance, several genetic and environmental manipulations can result in severe alteration of contralateral callosal targeting without any structural changes at the midline [16–21]. This suggests that, under a midline-based diagnostic paradigm, callosal defects arising from isolated errors in contralateral targeting may remain undiagnosed in humans. Contralateral callosal targeting is therefore a significant research topic given its importance in the development of correct functional connections and its potentially isolated disruption in humans.

Process of contralateral callosal targeting

Although contralateral callosal targeting is a significant event in the accurate functional wiring of cortical regions, the developmental processes involved are still poorly understood. Nevertheless, it has been shown that once callosal axons arrive at the contralateral white matter, there are dynamic waiting periods lasting a few days before they innervate the cortical plate in the visual [16,22], motor [23], frontal, and parietal [24] systems of rodents, as well as the cat visual system [25]. However, no waiting period has been found in the rodent somatosensory cortex [17], suggesting that this phenomenon may differ between cortical areas. Next, axons innervate the cortical plate, possibly using radial glial processes as a scaffold [26,27]. Callosal projections then arborise and form synapses with neurons located in cortical layers 2/3 and 5, and to a lesser extent 6 in rodents [28]. It is largely accepted that callosal axons innervate similar (homotopic) contralateral regions to those in which their cell bodies are located [29]. However, there is also evidence that callosal axons branch and project to other regions within the same hemisphere [30,31], as well as to contralateral heterotopic areas such as other cortical areas [19,32–34], secondary sensory regions, and the contralateral striatum [35,36].

There is a general consensus in the literature that there is an initial exuberance of callosally projecting neurons during development, and the cell bodies of these neurons frequently occupy cortical areas that are not callosally projecting in the adult ([37] for review). Further, it seems that these neurons cease to be contralaterally connected during development by retracting their contralateral axon, rather than via apoptosis [38–40]. However, the contralateral destination(s) of these transient axons

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