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Wiring the developing brain

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The brain must be wired correctly in order to function. The process of wiring the brain occurs both pre- and postnatally through a series of highly orchestrated molecular, cellular and activity dependent events. An excellent model system for studying brain wiring is the corpus callosum, the largest fibre tract in the brain connecting the two cerebral hemispheres. Formation of the corpus callosum requires the specification of callosal neurons that send axons across the midline to find their targets in the contralateral hemisphere. We are particularly interested in identifying the molecular and activity dependent cues involved in guiding these axons. At the midline, highly evolutionarily conserved molecules such as Netrin, Slit, Draxin, Wnts, BMP's, Semaphorins and Ephrins and their respective receptors are involved. We want to determine how an axonal growth cone is able to sense and integrate all of this information in order to find the correct path for growth. Specifically, at certain stages of development axonal growth cones express receptors for both attractive and repellent molecules expressed in their environment. How are these growth cones able to continue to grow in a repulsive environment and utilise each of these signals to find their correct path of growth? Recent data from our laboratory has shown that receptors from different axon guidance families interact modulating the attractive and repulsive response of the axon. These mechanisms allow axons to approach and cross the midline and then grow away from the midline to innervate their targets in the contralateral hemisphere. Callosal axons reach the contralateral hemisphere at late prenatal and early postnatal stages but do not innervate the contralateral cortex until the period of sensory experience. Sensory activity is then essential for the formation of both the final crude wiring but also the fine synaptic specificity required for a functional circuit. Together, these are the fundamental mechanisms in wiring the brain during development.