Brain Development: Critical Periods for Cross-Sensory Plasticity

Recent work has shown that visual deprivation of humans during a critical period leads to motion area MT+ responding to auditory motion. This cross-sensory plasticity, an important form of brain reorganization, may be mediated by top-down brain circuits from pre-frontal cortex.

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Ever since Hubel and Wiesel's landmark paper [1], the concept of the *critical period* has been fundamental to understanding brain development. Critical periods are defined as the age range during which developing brains can be altered in a profound and permanent way by abnormal experience. Nowadays, most researchers agree that there are multiple critical periods associated with various brain functions, and that critical periods for early sensory processing are shorter and earlier than critical periods for higher complex functions or cognitive/executive functions. Very seldom does postnatal sensory deprivation influence sub-cortical processes: for example, short visual deprivation has little or no effect on the retina or the lateral geniculate nucleus (LGN), but causes a pronounced alteration of primary and associative visual cortex resulting in abnormal visual function, such as the impaired visual acuity observed in amblyopia. Over the last 20 years, much research effort has been directed at understanding the basic cellular mechanisms responsible for modulating the critical period, such as the regulating role of neurotrophic factors (including BDNF and NGF), the mechanisms mediating competition between neuronal circuitry (GABAergic inhibition) and the role of perineuronal nets that could stabilize synaptic contacts (for reviews see [2,3]). These mechanistic insights have largely come from studies with nonhuman animals, however, and much less is known about the critical period of brain function in humans.

In this issue of *Current Biology*, Bedny *et al.* [4] report evidence for the existence of an early critical period for an important brain area, the MT complex, or MT+. This is a region of the cortex that, in visually normal humans, is particularly important for the perception of visual motion. It contains several sub-areas specialised for the various types of complex motion, and for eye movements and vestibular signals. In monkeys, this area also receives direct input from auditory cortex, but these anatomical connections have not been demonstrated in humans. Bedny *et al.* [4] have found that, in the absence of visual input early in life, MT+ can be recruited by other modalities, such as audition.

The ability to perceive visual flow motion — probably mediated by MT+ — develops in infancy during the first few months of life (for review see [5,6]), and the critical period of motion perception closes early in life. Children born with congenital bilateral cataracts have large deficits in motion processing, whereas children with cataracts beginning at 6–12 months develop normal flow perception, indicating that normal development of MT+ requires normal visual input during the first year. More direct evidence about the MT+ critical period has come from a subject blind from the age of three who, after regaining vision, showed a nearly complete recovery of BOLD activity within MT+, but not of responses within many other visual areas [7].

Bedny *et al.* [4] examined the critical period for recruiting MT+ for auditory motion processing — a phenomenon termed *cross-modal plasticity*. A vast fMRI literature consistently reports that, in a sighted adult, MT+ cannot be stimulated by an auditory stimulus, even when the source of that stimulus is in motion. The authors first demonstrated that, in congenitally blind subjects, auditory motion evokes strong BOLD responses in an area that corresponds anatomically to MT+ in the sighted, confirming previous evidence. They further demonstrated that this recruitment did not occur within subjects who became blind later in life: in patients with acquired blindness, MT+ was never activated by auditory motion. It seems that visual experience in the first decade of life is sufficient to keep at bay the invasion of MT by information derived from auditory motion. Interestingly, one of their subjects, who lost sight at age three, also showed no response to auditory motion, indicating that audio-visual cross-modal plasticity is not possible after three years of age. This result is clearly at odds with the observations on subject MM, who also lost vision at age three [7] but showed a response to auditory motion in MT+ after restoration of sight at age 47 [8]. Perhaps three years could be near the limiting age for cross-modal plasticity, where subtle differences in types of stimulus, prior visual experience and individual differences may play a role.

A behavioural study published recently in *Current Biology* similarly also points to three years of ages as the upper limit of the critical period for cross-modal interactions: Gori *et al.* [9] showed that congenitally blind children are better (predictably) than sighted controls in haptic discrimination of objects, but worse for haptic discrimination of orientation. They argued that this result is predictable from their previous research suggesting that young children (younger than eight) do not fuse information across the senses to increase perceptual precision (as is done by adults [10]), but rather use cross-sensory information for calibration: touch calibrates vision for size discrimination and vision calibrates touch for orientation discrimination. Lack of vision during early development may interfere with this calibration process. Interestingly, one of their subjects who became blind at the age of three had better haptic-orientation thresholds than sighted subjects, suggesting that early vision before the age of three was sufficient to establish the calibration process.

How are these cross-modal connections established in congenitally blind children? Brain reorganization during development can be extraordinary. Perhaps the most striking demonstration is that the auditory cortex can develop finely tuned maps for orientation of visual stimuli when experimenters force rerouting of visual input to an otherwise deafferented auditory cortex (for review see [11]). So the obvious interpretation of the Bedny *et al.* [4] result is that in the absence of competition from visual

input, MT+ receives direct auditory input. Many visual cortical areas, including V1, receive auditory inputs after bilateral enucleation in the cat [12], probably through cortical connections. It is also well known that, during development, there is wide and unspecific sprouting of connections, particularly strong for cortico-cortical connections [13]. There are a variety of nearby associative and auditory cortical areas that respond to auditory motion stimuli, including the superior temporal sulcus cortex (STS), which might provide auditory input to the MT+ during development (Figure 1A).

In normal adult monkeys, STS has a patched or columnar organization that interleaves pure auditory, pure visual and multisensory neurons [14]. It seems plausible that the auditory input within STS may spread to nearby MT+ during development and these aberrant contacts may stabilize during the visual deprivation period. To investigate the origin of the auditory input in MT+, Bedny *et al.* [4] performed a functional connectivity analysis on BOLD resting state activity. Results showed that the functional connectivity between MT+ and occipital cortex was weakened, as might be expected. But surprisingly they also found that the connections between MT and both primary auditory cortex and multimodal STS were not stronger in congenitally blind subjects (Figure 1C). This is clearly at odds with what we would have predicted from the physiology of deprived animals. Although the possibility that some auditory input reaches MT+ from nearby multimodal areas — as well as from V1, which may represent auditory signals during deprivation [15] — cannot be completely dismissed, these inputs are probably not the dominant source of auditory input to MT+, given the reduced functional connectivity between these pathways.

So how do the auditory signals in congenitally blind individuals reach MT+? Bedny *et al.*'s [4] results indicate a very different route, via prefrontal cortex (Figure 1C). The authors found that widespread regions of prefrontal cortex showed enhanced functional connectivity with MT+ in congenitally blind individuals. The monkey dorsolateral prefrontal cortex (DLPFC) provides direct inputs to MT, and the activity of their neurons show directional selectivity for visual stimuli, for example when remembering the

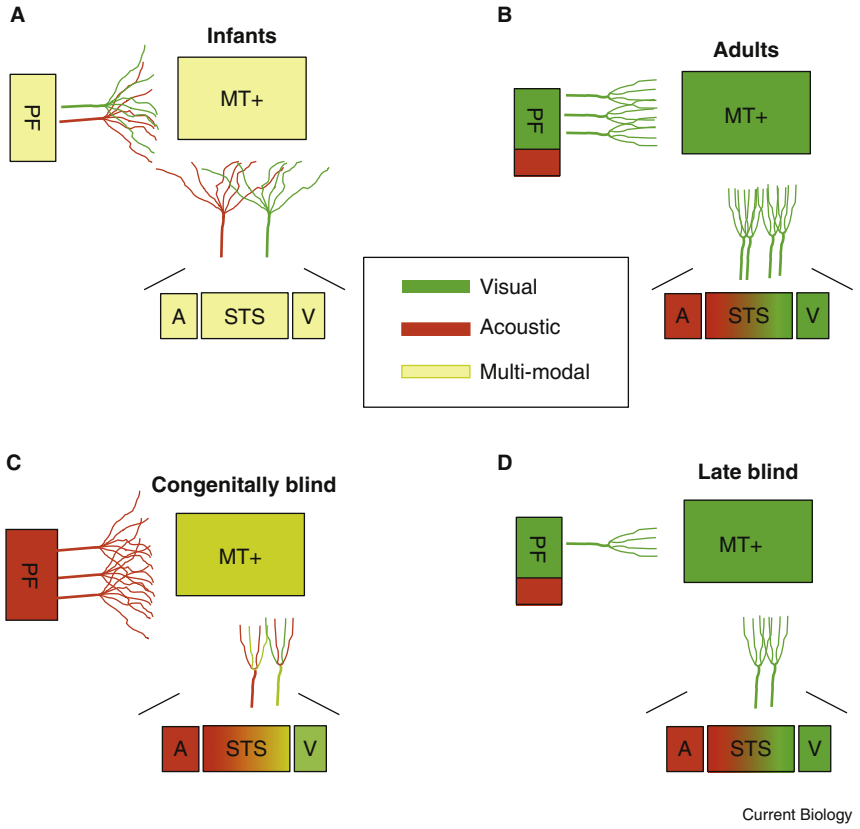

Figure 1. Schematic illustration of hypothetical input connections to MT at three different developmental stages in humans, suggested by the results of Bedny *et al.* [4].

(A) In newborns it seems likely that input connections to MT+ are relatively unspecified, receiving and transmitting both visual and acoustic signals. (B) In visually normal adults MT+ probably only receives visual input from visual, associative and pre-frontal cortices. (C) In early blind individuals inputs from visual cortex is reduced; there is no direct input from acoustic cortex, but prefrontal cortex connections to MT+ increase. The pre-frontal cortex, which tends to be primarily visual in the normally sighted, presumably responds more extensively to acoustic signals in early blind subjects. (D) In subjects that became blind after the age of three years no great re-organization occurs, apart from a loss of functional connectivity between MT+ and visual areas. Red: acoustic signals and cortices; green: visual signal and cortices; yellow: audio-visual signals and cortices. The less saturated colour represents higher potential for plasticity.

direction of motion during a delayed sample-to-match motion discrimination task [16]. However, DPFC, and pre-frontal cortex in general, is mainly involved with cognitive tasks, executive functions, decisions and memory. Why should cross-modal plasticity rely upon complex circuits that normally mediate higher cognitive functions?

A potential explanation has only indirect evidence, but it is fascinating. It has been shown in blind subjects that performing verbal memory tasks and grammaticality judgments can activate many occipital cortices [17,18], which would suggest that these deprived sensory cortices are recruited to resolve memory tasks more efficiently, effectively increasing memory capacity. The stronger connection between MT+ and pre-frontal not only would mediate the motion auditory signal to be processed by MT, but also would use the spare capacity of MT for memory storage and the demands of other cognitive tasks. If so, the results of Bedny *et al.* [4] should be interpreted as plasticity of pre-frontal cortex and not of MT (Figure 1C), and would define the cross-modal critical period of the pre-frontal circuits. This last hypothesis would also sit well with the behavioural results of Gori *et al.* [9], showing cross-modal calibration within the critical period around three years, given that calibration probably heavily involves decision stages and the pre-frontal circuits.

The dense reciprocal connections between sensory and prefrontal associative cortex may provide a general and convenient circuit for reorganization of function. If their role in mediating cross-sensory plasticity is confirmed by direct anatomical measures, and in primates, then we will have to revaluate the assumed high plasticity potential of early sensory cortices.

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Mechanosensitive Channels: In Touch with Piezo

Mechanosensory transduction underlies touch, hearing and proprioception and requires mechanosensitive channels that are directly gated by forces; however, the molecular identities of these channels remain largely elusive. A new study has identified Piezo1 and Piezo2 as a novel class of mechanosensitive channels.

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The activity of mechanosensitive channels has been detected in nearly every organism [1]. These channels are directly gated by forces to convert mechanical stimuli into electrical signals and thus function as the force transducer in mechanosensory transduction [1,2]. They are also called mechanotransduction channels or mechanically activated channels. Mechanosensitive channels open very rapidly with short latency, usually less than 5 milliseconds [2], which makes it unlikely that second messengers are involved in channel gating [2]. It has also been argued that mechanical stimuli may not always result in direct gating of ion channels by forces, but instead may trigger second-messenger signaling that leads to activation of downstream ion channels [3]. In this case, the ion channels are mechanically sensitive but not mechanically gated. Nevertheless, it is generally believed that the three common mechanical sensory modalities — touch, hearing and proprioception — are mediated by mechanosensitive channels that are directly gated by forces [1]. The molecular identities of these channels, however, remain largely elusive, particularly in mammals. A new study by Coste *et al.* [4], published recently in *Science*, has now shed light on this enigma.

The best characterized mechanosensitive channels are the bacterial Msc proteins [5], but the quest for mechanosensitive channels in the animal kingdom has turned out to be rather difficult for several reasons [6]. First, the expression level of mechanosensitive channels is typically low, making it difficult to identify them through biochemical approaches [6]. Second, it is relatively difficult to functionally express mechanosensitive channels in heterologous systems. Unlike voltage-, ligand-, or temperature-gated channels, the proper function of many mechanosensitive channels may require tethering of the channel to the cytoskeleton and/or extracellular matrix and may also depend on auxiliary subunits, a setting that is difficult to recapitulate in heterologous systems [1,6]. Third, the biophysical properties of mechanosensitive channels recorded from different cell types show large variation, suggesting that the molecular nature of mechanosensitive channels is highly heterogeneous [6].

The first breakthrough came from studies in the genetic model organism *Caenorhabditis elegans*. Using genetic and electrophysiological approaches, Chalfie and colleagues have identified a mechanosensitive channel complex comprising MEC-4, MEC-10, MEC-2 and MEC-6 that senses gentle body touch in *C. elegans* [6–8]. In this complex, MEC-4 and MEC-10 form the channel pore, while MEC-2 and MEC-6 are the auxiliary subunits that link the channel to the cytoskeleton and