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Cross-modal plasticity in sensory deprived animal models: From the thalamocortical development point of view

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ABSTRACT

Over recent decades, our understanding of the plasticity of the central nervous system has expanded enormously. Accordingly, it is now widely accepted that the brain can adapt to changes by reorganizing its circuitry, both in response to external stimuli and experience, as well as through intrinsic mechanisms. A clear example of this is the activation of a deprived sensory area and the expansion of spared sensory cortical regions in individuals who suffered peripheral sensory loss. Despite the efforts to understand these neuroplastic changes, the mechanisms underlying such adaptive remodeling remains poorly understood. Progress in understanding these events may be hindered by the highly varied data obtained from the distinct experimental paradigms analyzed, which include different animal models and neuronal systems, as well as studies into the onset of sensory loss. Here, we will establish the current state–of-the–art describing the principal observations made according to the time of sensory deprivation with respect to the development of the thalamocortical connectivity. We will review the experimental data obtained from animal models where sensory deprivation has been induced either before or after thalamocortical axons reach and invade their target cortical areas. The anatomical and functional effects of sensory loss on the primary sensory areas of the cortex will be presented. Indeed, we consider that the comparative approach of this review is a necessary step in order to help deciphering the processes that underlie sensory neuroplasticity, for which studies in animal models have been indispensable. Understanding these mechanisms will then help to develop restorative strategies and prostheses that will overcome the functional loss.

1. Introduction

Neuroplasticity is the ability of the nervous system to adapt its functional and/or structural organization to internal or external stimuli derived from developmental events, experience, the environment, damage or insult (Pascual-Leone et al., 2005). For example, when a sensory modality is lost or impaired, as in blindness or deafness, the adaptive reorganization associated with neuroplasticity affects both the sensory modality that is lost and those that remain (for review see (Bavelier and Neville, 2002; Merabet and Pascual-Leone, 2010). These changes in the intact sensory systems are referred to as **cross-modal plasticity**. By characterizing the structural and functional rearrangements that occur in the regions susceptible to cross-modal plasticity, it might be possible to define the intrinsic mechanisms and environmental inputs responsible for determining cortical specificity. It is widely accepted that intrinsic factors associated with early development may influence subsequent cortical development, such as restricted gene expression, the factors that define regional identity in distinct cortical areas, and the arrival of thalamic inputs (for review see López-Bendito and Molnár, 2003). However, to what extent thalamocortical (TC) afferents drive the functional specification of cortical areas remains unclear. Specifically, and in the context of cross-modal plasticity, it is unknown whether modality-specific afferents can be redirected to cortical regions that do not receive the appropriate sensory inputs and if this is the case, whether this is relevant for the reorganization that occurs when peripheral sensory inputs are lost. Different species have been used as models to investigate these issues. In the present review, we will present the cross-modal effects induced on the cortex by sensory deprivation, with a special focus on the timing of TC development

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with respect to the time of sensory deprivation. Therefore, we will first make a distinction between two groups of animal models used in the experiments, when sensory deprivation is achieved before or after the arrival of thalamocortical connectivity to the cortex. Then, we will summarize the developmental program that establishes TC connectivity and highlight the impact of thalamic input on the patterning of cortical areas. Finally, we will describe the cortical changes found following sensory deprivation in the two distinct groups of animal models and the impact that these manipulations have on the development of TC connectivity. Tables 1 and 2 summarize the most relevant pioneer works for each animal model of the two groups.

2. General considerations on the animal models of sensory loss

The classical cross-modal plasticity paradigm was developed in the 1970s when it was demonstrated that the primary auditory cortex of congenitally deaf cats could be driven by visual or somatosensory stimuli (Rebillard et al., 1977). Since then, sensory deprivation has been induced in different animal models to study cross-modality. It is now well accepted that sensory loss of one modality has striking effects on the development and function of the remaining modalities (Bronchti et al., 2002; Chabot et al., 2008; Karlen et al., 2006; Piché et al., 2007). Indeed, cross-modal plasticity, such as the hypertrophy of spared cortical areas, is thought to serve as a compensatory strategy to improve the function of the remaining sensory systems. Although this has been shown at the behavioral and functional level, some controversy exists regarding the mechanisms that trigger these neuroplastic changes in the brain. This is partly due to the variability of the results obtained when using distinct animal models or sensory deprivation paradigms, and more importantly, the time at which sensory loss occurs. In terms of the latter, it is quite apparent that the earlier the peripheral lesion, the more striking the adaptive effects that can be seen in the brain, which becomes less receptive to changes as development proceeds. Therefore we will consider here animal models in these two categories: the ones where sensory loss was induced after TC axons invade the cortex and the ones where sensory loss was induced before TC axons invade the cortex (Fig. 1).

In the first group there are mice, rats and cats. In mice and rats, the arrival of TC axons to the cortex begins at embryonic stages as they start to invade the cortical plate few days before birth (E19 in rats and E17 in mice) and continue until the first days after birth when they start invading cortical layer IV (Erzurumlu and Jhaveri, 1990; Molnár et al., 1998). In cats the process of cortical invasion starts at late embryonic stages and it persists into the first postnatal week (Shatz and Luskin, 1986). In these animals, sensory deprivation is induced no earlier than at birth, which means that TC connectivity was already established when the peripheral input was removed.

In the second group, sensory manipulations are performed before TC axons invade the cortex, here species such as the ferret, hamster and opossum have been extensively used. These species are less mature at birth and thus, their TC axons reach target cortical regions after birth (Crossland and Uchwat, 1982; Herrmann et al., 1994), therefore, the effect of sensory deprivation can be studied through postnatal manipulations. Monkeys, in which thalamic axons invade the cortical plate before birth, also belong to this group. Indeed peripheral sensory organs can be manipulated in embryos in order to study the effect of sensory loss prior to the establishment of TC connections, as has been performed in Rhesus monkeys (Bourgeois and Rakic, 1993, 1996; Rakic, 1976, 1977a). Finally, belonging to this group, we will also present the data obtained from congenitally deprived animals where neuroplastic changes are enhanced.

In addition, a distinction should be done here between sensory deprivation and a lesion or a lack of a sensory afferent. Taking the visual system as example, the first paradigm is achieved by eyelid suture or dark rearing, which cause that the pattern of spontaneous retinal waves is replaced by uncorrelated noise. When induced in one eye (monocular deprivation, MD) this has been the method of choice to study the consequences of the lack of functional afferents on the development, function and plasticity of the cortex. Since the pioneer work of Hubel and Wiesel, this kind of manipulation has been used to study cortical networks and the correlation of binocular inputs, unraveling the mechanisms of ocular dominance plasticity (Burnat et al., 2012; Espinosa and Stryker, 2012; Hubel and Wiesel, 1963, 1970; Konur and Yuste, 2004; Morales et al., 2002; Zapasnik and Burnat, 2013). By contrast, lesions like enucleation implies a complete removal or the retinal input, leading to the irreversible elimination of both spontaneous waves and light-driven activity. It has been shown that monocular enucleation (ME) causes alterations in subcortical (Chan et al., 2011; Furman and Crair, 2012; Lund et al., 1973; Yagi et al., 2001) and cortical (Hada et al., 1999; Toldi et al., 1994, 1996; Yagi et al., 2001) visual centers. In this review we will consider manipulations that imply the complete removal of the sensory input, mainly enucleation, but additionally, we will focus on those experiments where the manipulation was performed bilaterally, thus avoiding compensatory mechanisms and inducing more drastic effects.

3. Thalamocortical influence over cortical area patterning

A large proportion of the cerebral cortex is engaged in processing sensory information or delivering motor commands. These sensory or motor areas include several specialized areas, defined as primary, secondary or tertiary in accordance with their function in the hierarchical order. The three primary sensory neocortical areas, the primary visual (V1), somatosensory (S1), and auditory (A1) areas, process information received from the eye/retina (vision), body (somatosensation), and inner ear/cochlea (audition), respectively. The fourth primary cortical area, the motor area (M1), controls the voluntary movements of the body. Primary cortical areas mainly receive inputs in layer IV from TC axons whose cell bodies are located in specific thalamic nuclei, and

Table 1
Summary of the experimental animal models of cross-modal plasticity where sensory loss is induced after TC axons invasion.

Specie	Sensory deprivation	Cross-modal effect	References
Mouse	Bilateral enucleation at birth	Barrelfield expansion in S1; A1 activation upon visual stimuli	Bronchti et al. (1992), Rauschecker et al. (1992), Chabot et al. (2007)
Rat	Bilateral enucleation at birth	Innervation of S1 by the rostral part of V1; A1 activation upon visual stimuli	Toldi et al. (1994, 1996), Piché et al. (2007)
Cat	Bilateral lid suture or enucleation at birth	AEV activation by auditory and tactile stimulation A1 activation upon visual stimuli	Rauschecker and Korte (1993), Jiang et al. (1994), Yaka et al. (1999)

S1, primary somatosensory cortex; A1, primary auditory cortex; V1, primary visual cortex; AEV, visual part of anterior ectosylvian cortex.