Modeling genetic control of the early development of thalamo-cortical connections and area patterning

Jan Karbowski[1,*] and G.B. Ermentrout[2]

[1] *Sloan-Swartz Center for Theoretical Neurobiology, Division of Biology 216-76, California Institute of Technology, Pasadena, CA 91125, USA*

[2] *Department of Mathematics, University of Pittsburgh, Pittsburgh, PA 15260, USA*

Abstract

The mammalian cortex is divided into architectonic and functionally distinct areas. There has been growing experimental evidence that their emergence and development is controlled by both epigenetic and genetic factors. The latter were recently implicated as dominating the early cortical area specification. In this paper, we present a theoretical model that explicitly considers the genetic factors and that is able to explain several sets of experiments on cortical area regulation involving transcription factors Emx2 and Pax6, and fibroblast growth factor FGF8. The model consists of the dynamics of thalamo-cortical connections modulated by signaling molecules that are regulated genetically, and by axonal competition for neocortical space. The model can make predictions and provides a basic mathematical framework for the early development of the thalamo-cortical connections and area patterning that can be further refined as more experimental facts become known.

Keywords: cerebral cortex, development, thalamo-cortical connections, cortical area patterning, signaling molecules.

Presentation: oral only

[*] Presenting and corresponding author at:

Email: jkarb@cns.caltech.edu

Phone: (626)-395-5840

Fax: (626)-795-2397

Presentation: oral only

Neocortex is organized into many functional subdivisions called areas that have sharp boundaries. The areas can be identified anatomically by investigating their distinct cytoarchitectonic properties and unique connectivity patterns. One interesting feature is that the neocortical map composed of these areas is highly conserved within the same species, and has common properties across different species with different brain sizes (Nauta and Feirtag, 1986; Hofman, 1989; Finley, 1995; Northcutt and Kaas, 1995; Krubitzer, 1995; Karbowski, 2003).

One of the main questions in the development of the mammalian cortex is what factors control the specification and differentiation of cortical areas. In the past, there were two opposing views. One proposition was that areas are specified by intrinsic genetic factors (Rakic, 1988) - the so-called protomap model. Another proposition was that areas are specified by extrinsic influence, i.e. by thalamo-cortical inputs (O'Leary, 1989). In recent years, however, the consensus has been growing that both of these factors, i.e. genetic and epigenetic contribute to the cortical area patterning (Krubitzer and Huffman, 2000; O'Leary and Nakagawa, 2002). The genetic effects are thought to dominate the early stages of the development, while the epigenetic effects influence the later stages. This view has been stimulated by recent experiments demonstrating a direct genetic involvement in cortical arealization (Bishop et al, 2000; Mallamaci et al, 2000; Fukuchi-Shimogori and Grove, 2001, 2003; Bishop et al, 2002; Muzio et al, 2002; Garel et al, 2003). In particular, it has been found that the genetic transcription

factors Emx2 and Pax6 control area specification even before thalamo-cortical input arrives (Bishop et al 2000; Mallamaci et al 2000; Muzio et al, 2002; Bishop et al, 2002). Both of these factors are expressed in a graded and complementary manner along antero-posterior (A/P) axis in the neocortical ventricular zone. In mice with Emx2 mutation, anterior areas expand and posterior areas shrink, in Pax6 mutants the opposite is observed. Another set of experiments has found that cortical maps can be disrupted by modifying fibroblast growth factor FGF8 (Fukuchi-Shimogori and Grove, 2001, 2003; Garel et al, 2003), which is also involved in embryonic patterning. In wild type mouse neocortex, the FGF8 source is located in the anterior pole giving rise to an expression concentration decaying towards the posterior end. Under such regular conditions, the barrel field (S1 area) is positioned in the center along A/P axis. However, increase in the expression of FGF8 at the anterior pole, displaces the barrel field more posteriorly. In contrast, blocking the FGF8 activity with a soluble FGF8 receptor moves the field in the opposite direction. Moreover, introduction of an extra source of FGF8 at the posterior pole creates an additional barrel field that partly duplicates the original field. Taken together, all these results suggest that genetic perturbations can have a profound effect on the development of thalamo-cortical connections and area patterning. Additionally, these results are consistent with a hypothesis that the above signaling molecules provide positional information for neuroepithelial cells (Wolpert, 1969, 1996; Grove and Fukuchi-Shimogori, 2003).

Area-specific TC projections are probably controlled by axon guidance molecules, similar to what happens in the retino-tectal system (O'Leary et al, 1999). Although

several molecules have been found that are able to guide TC axons, there are some experimental indications that the plausible candidates for the late phase of accurate TC targeting are ephrins and their receptors that are expressed both in the neocortex and in the thalamus (Vanderhaeghen et al, 2000; Mackarehtschian et al, 1999; Mann et al, 2002; Uziel et al, 2002; Takemoto, 2002). It is well established that these molecules direct axons to appropriate locations in many systems, in particular, in the retino-tectal system (Goodhill and Richards, 1999), which, like the neocortex, preserves the topography of projections.

The relationship between the axon guidance molecules and Emx2, Pax6, and FGF8 is not known at present. It is likely, however, that the latter control the expression level and gradients of the guiding molecules. Thus, if the transcription factors and FGF8 concentrations are modulated, then it should affect the concentration pattern of the axon guidance molecules. This hypothesis is consistent with the experiments on cortical areas shifting described above.

The purpose of this work is to provide a theoretical model of the early TC projections and cortical area patterning (Karbowski and Ermentrout, 2003). The key assumption we make is that the signaling molecules Emx2, Pax6, and FGF8 control the axon guidance molecules, which in turn control TC pathfinding. We assume that there are three main types of the axon guidance molecules, which we call A, B and C (and relate them to ephrins), that are expressed in the neocortical ventricular zone in a graded and complementary manner along A/P axis. In the model, these molecules repel and attract different TC axons, which diffuse around the cortex, with specific forces,

different for different classes of axons. Additionally, axons interact among themselves by competing for neocortical space. As a consequence of these interactions, a pattern of TC connectivity emerges (from initial uniform state) that divides the neocortex into regions with sharp boundaries defined by distinct TC axon types. In this framework, area shifting experiments described above can be understood as a result of shifts in the patterns of expression of the signaling molecules.

References

Bishop, K.M., Goudreau, G., and O'Leary, D.D. (2000). Regulation of area identity in the mammalian neocortex by Emx2 and Pax6. Science 288, 344-349.

Bishop, K.M., Rubenstein, J.L.R., and O'Leary, D.D. (2002). Distinct actions of Emx1, Emx2 and Pax6 in regulating the specification of areas in the developing neocortex. J. Neurosci. 22, 7627-7638.

Finlay, B.L., and Darlington, R.B. (1995). Linked regularities in the development and evolution of mammalian brains. Science 268, 1578-1584.

Fukuchi-Shimogori, T., and Grove, E.A. (2001). Neocortex patterning by the secreted signaling molecule FGF8. Science 294, 1071-1074.

Fukuchi-Shimogori, T., and Grove, E.A. (2003). Emx2 patterns the neocortex by regulating FGF positional signaling. Nature Neurosci. 6, 825-831.

Garel, S., Huffman, K.J., and Rubenstein, J.L.R. (2003). Molecular regionalization of the neocortex is disrupted in FGF8 hypomorphic mutants. Development 130, 1903-

1914.

Goodhill, G.J., and Richards, L.J. (1999). Retinotectal maps: molecules, models and misplaced data. Trends Neurosci. 22, 529-534.

Grove, E.A., and Fukuchi-Shimogori, T. (2003). Generating the cerebral cortical area map. Annu. Rev. Neurosci. 26, 355-380.

Hofman, M.A. (1989). On the evolution and geometry of the brain in mammals. Prog. Neurobiol. 32, 137-158.

Karbowski, J. (2003). How does connectivity between cortical areas depend on brain size? Implications for efficient computation. J. Comput. Neurosci. 15, 347-356.

Karbowski, J., and Ermentrout, G.B. (2003). Model of the early development of thalamo-cortical connections and area patterning via signaling molecules. Submitted for publication.

Krubitzer, L. (1995). The organization of neocortex in mammals: Are species differences really so different? Trends Neurosci. 18, 408-417.

Krubitzer, L., and Huffman, K.J. (2000). Arealization of the neocortex in mammals: genetic and epigenetic contributions to the phenotype. Brain Behav. Evol. 55, 322-335.

Mackarehtschian, K., Lau, C.K., Caras, I., and McConnel, S.K. (1999). Regional differences in the developing cerebral cortex revealed by $Ephrin - A5$ expression. Cereb. Cortex 9, 601-610.

Mallamaci, A., Muzio, L., Chan, C.H., Parnavelas, J., and Boncinelli, E. (2000). Area identity shifts in the early cerebral cortex of $Emx2^{-/-}$ mutant mice. Nature Neurosci. 3, 679-686.

Mann, F., Peuckert, C., Dehner, F., Zhou, R., and Bolz, J. (2002). Ephrins regulate the formation of terminal axonal arbors during the development of thalamocortical projections. Development 129, 3945-3955.

Muzio, L. et al (2002). Emx2 and Pax6 control regionalization of the pre-neuronogenic cortical primordium. Cereb. Cortex 12, 129-139.

Nauta, W.J.H., and Feirtag, M. (1986). *Fundamental Neuroanatomy.* (Freeman, New York).

Northcutt, R.G., and Kaas, J.H. (1995). The emergence and evolution of mammalian neocortex. Trends Neurosci. 18, 373-379.

O'Leary, D.D.M. (1989). Do cortical areas emerge from a protocortex? Trends Neurosci. 12, 400-406.

O'Leary, D.D.M., Yates, P.A., McLaughlin, T. (1999). Molecular development of sensory maps: representing sights and smells in the brain. Cell 96, 255-269.

O'Leary, D.D.M., and Nakagawa, Y. (2002). Patterning centers, regulatory genes and extrinsic mechanisms controlling arealization of the neocortex. Curr. Opin. Neurobiol. 12, 14-25.

Rakic, P. (1988). Specification of cerebral cortical areas. Science 241, 170-176.

Takemoto, M., et al (2002). Ephrin-B3-EphA4 interactions regulate the growth of specific thalamocortical axon populations in vitro. Eur. J. Neurosci. 16, 1168-1172.

Uziel, D. et al (2002). Miswiring of limbic thalamocortical projections in the absence of ephrin-A5. J. Neurosci. 22, 9352-9357.

Vanderhaeghen, P. et al (2000). A mapping label required for normal scale of body

representation in the cortex. Nature Neurosci. 3, 358-365.

Wolpert, L. (1969). Positional information and spatial pattern of cellular differentiation. J. Theor. Biol. 25, 1-47.

Wolpert, L. (1996). One hundred years of positional information. Trends Genet. 12, 359-364.