Brain Development in Neuroscience

A Brief Look at its Beginnings and the Current Trends

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"The immature brain is not simply a small adult brain, and normal development of the brain depends on a complex series of interactions between nature and nurture during the critical period. Studies of the developing visual system have provided many insights into the roles of experience and neural plasticity mechanisms in cortical development" (Murphy, 2005).

One of the most exciting frontiers in neuroscience today is the study of brain development. A global empirical initiative has been underway to understand how the brain develops. Volumes of books would be required to encompass the breadth of this research. The aims of this article, however, are to briefly touch upon some of the important historical findings, and to highlight a few of the contemporary lines of inquiry to illustrate the field's continued advances. Classically speaking, one of the most fiercely debated topics within this area and in all areas of developmental biology is whether neural development is a consequence of one's genetic make-up or the environment in which they are reared. Researchers today willingly acknowledge that the development of one's brain is the product of a complicated sequence of events that is determined by both genetic and environmental factors. Neuroscientists around the world are continuing to elucidate the relationship between these factors and brain development. Some of this research takes place here at McMaster University.

History

The development of the brain has long been at the forefront of neuroscience research. In 1906, Santiago Ramon Y Cajal and Camillo Golgi won the Nobel Prize in Physiology and Medicine for their research on the anatomical organization of the brain. In the process, Cajal became one of the founders of modern neuroscience.

Using Golgi's staining procedure involving silver chromate, Cajal successfully learned how to darkly stain the neuronal cell membrane, and thus isolated individual neurons. He was able to see how neurons were interconnected through axonal "arborizations" - treelike branchings that connect one neuronal cell to multiple parts of another single neuronal cell or multiple cells (Eichenlaum, 2002). This discovery led physiologists and anatomists to believe that, although each neuron is a separate entity, each one is in contact with other cells. This ultimately led to the idea that the nervous system is made up of billions of individual neuron units. Cajal continued to make many contributions to what would become modern-day neuroscience, including the introduction of "plasticity" (Eichenlaum, 2002). Plasticity refers to, in a very basic sense, changes that occur in the organization of the brain as a result of experience (Eichenlaum, 2002). More specifically, plasticity involves changes that occur to the location of specific neural information processing functions and structures as a consequence of experience (Kandel et al., 2001). Though the precise definition of this term continues to be widely debated, plasticity is a theme that has permeated all areas of neural development research.

Another major contribution to the field of brain development came in the form of Hebbian learning, coined after the influential Canadian psychologist Donald Hebb in 1949. This theory describes how, at the level of the synapse, a basic mechanism exists for plasticity, whereby an increase in synaptic efficacy arises from the presynaptic cell's repeated and persistent stimulation of the postsynaptic cell (Hebb, 1949). This led to what has become a very common theme in neuroscience research: cells that "fire together, wire together." In other words, the connection between cells that are stimulated simultaneously are strengthened. In 1966, Hebbian learning saw true empirical validation through a phenomenon known as "long-term potentiation" (Bliss & Lomo, 1973). Long-term potentiation, or LTP, is a neurophysiological term used to describe high-frequency stimulation trains that produce larger, prolonged excitatory post-synaptic potentials (EPSPs) compared to the responses evoked by a single stimulus train (Bliss & Lomo, 1973). In effect, the connection between two neurons was observed to be stronger. With this observation, a whole new way to view brain development, as well as learning and memory, came to fruition.

Around the same time, other landmark work in brain development was explored by David Hubel and Torsten Wiesel. Hubel and Wiesel showed that competition exists between both eyes in the visual cortex of cats during early development, ultimately affecting the adult visual system (Hubel and Wiesel, 1965). During this critical period, neural connections are particularly susceptible to being changed based on environmental input and are governed by the rules of Hebbian synaptic plasticity (Hubel and Wiesel, 1965). Through these experiments, the scientific community was able to see directly that experience does in fact affect cortical organization, and the idea that nature and nurture acted as two discrete forces was no longer intellectually feasible.

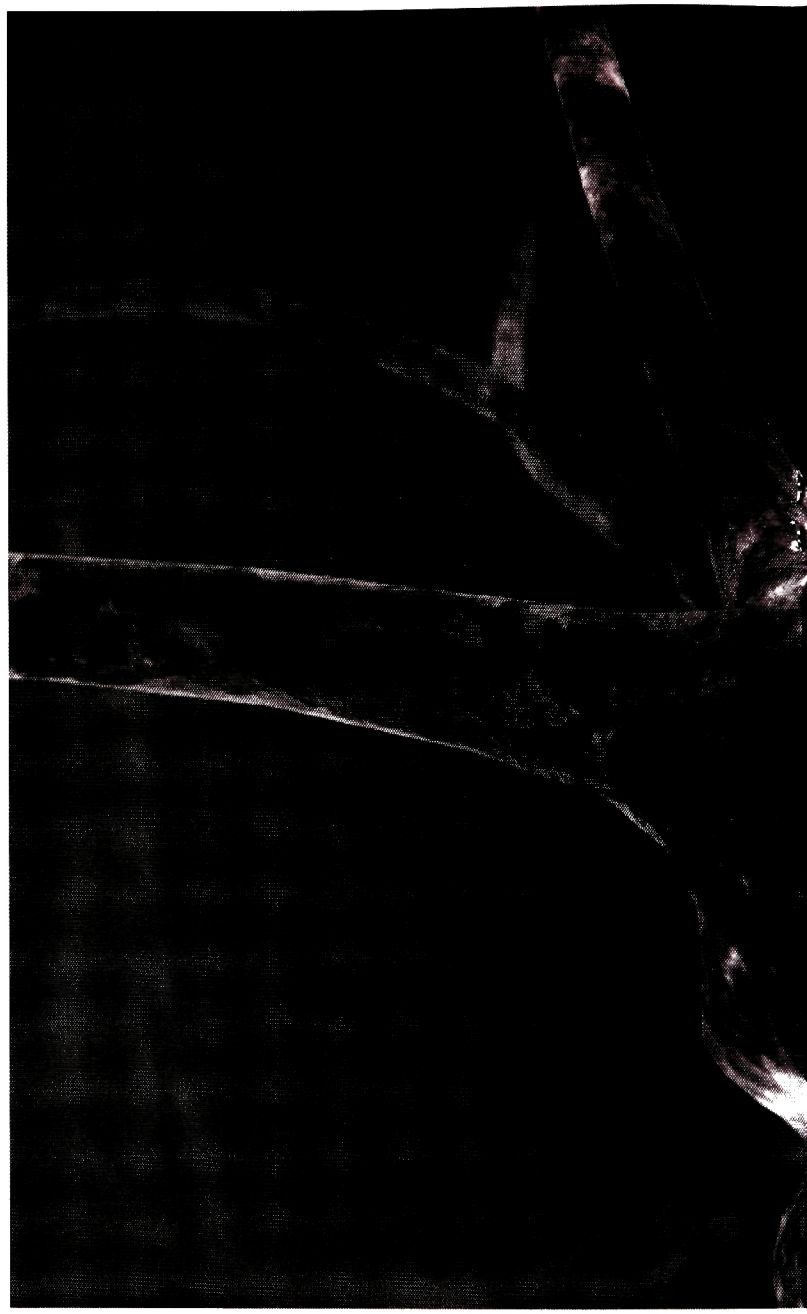
From the 1970's to the present, many genetic techniques employed in all areas of biological science (which include the

advent of cloning and gene knock-out strategies, sophisticated biochemical and molecular tools) have seen a steady integration into the study of how the brain develops. Today, these tools, such as the Polymerase Chain Reaction (PCR) are commonplace and often part of the large ensemble of laboratory methods inextricably linked to how many researchers conduct their studies.

Present Research

As mentioned earlier, neuroscientists all over the world are constantly breaking new ground in learning how the brain develops. McMaster neuroscientist Dr. Kathryn Murphy, for example, is affiliated with both the Departments of Psychology and the Department of Medical Physics and Applied Radiation Sciences, and investigates brain development from the perspective of the visual system. Using a wide variety of neurobiological, computational and psychophysical techniques, Dr. Murphy explores the effect of visual experience on the shape of the brain over time. Her career has seen many unique and important contributions to the world of neuroscience, including the discovery of "colour blobs" in the primary visual cortex of the cat (the area of the visual cortex where colour is processed) (Murphy et al., 1995). However, the last number of years has seen a particular emphasis on the role of plasticity in critical periods at the neuronal level, focusing on synaptic excitation and inhibition.

Cortical plasticity is widely believed to be mediated in the cortex through activation of glutamatergic N-methyl-D-aspartate (NMDA) receptors (LoTurcco et al., 1991; Watanabe et al., 1992; Hicks and Conti, 1996; Popescu, 2005). These pentameric membrane proteins, with a central ion channel pore permeable to Na^+, K^+ and Ca^{2+} ions, are composed of a primary NR1 subunit and different NR2-type subunits, the latter of which have been shown to alter receptor kinetics (McBain and Mayer, 1994). It has been demonstrated that during early development in human and animal models, repeated stimulus activation causes NMDA receptor-mediated synaptic current to become more phasic in nature through a structural shift from NR2B-type to NR2A-type subunits (Yamakazi et al., 1992; Williams et al., 1993; Takahashi, 2005; Murphy et al., 2005). On the other hand, cortical inhibition during plasticity and neuronal circuitry formation is attributed to the neurotransmitter gamma-aminobutyric acid (GABA), which binds to ionotropic GABAA receptors and allows Cl^- ion entry through a central channel pore (Murphy et al., 2005; Bosman, Rosahl, & Brussaard, 2002; Gibbs et al., 1996). GABAA receptors, the most numerous inhibitory receptors in the mammalian nervous system, are pentameric membrane proteins composed of different types of alpha, beta and gamma subunits – most commonly, 2 alpha, 2 beta and a gamma (Farrant & Nuser, 2005). Similar to NMDA receptors, a shift in subunit composition occurs during development which leads to an increase in overall receptors kinetics, with GABAAalpha1 subunits replacing the GABAAalpha3-type (Murphy et al., 2005; Bosman et al., 2005). This confers a more phasic quality to Inhibitory Post-Synaptic Current (IPSC) (Hensch et al., 1998, Bosman et al., 2002). In contrast to NMDA receptors, this shift in subunit structure, specifically the upregulation GABAAalpha1, has been shown to be independent of stimulus perception (Bosman et al., 2002). In both cases, this switch from tonic to more transient synaptic currents is viewed as a progression toward "mature" synapse formation.



Through developmental expression profiles acquired from performing western blots on tissue samples taken at various stages throughout development, Dr. Murphy and her students were able to quantify the amount of specific NMDA and GABA receptor subunit protein present at each stage. The benefit of this technique is that one can take as many samples as necessary for an unlimited duration, with whatever experimental parameters required, in order to test whether there is a change in subunit expression and by how much in relative terms (See Figure 1). For instance, one of the most widely studied developmental profiles are monocularly deprived animals – one eye is deprived of sight during some time in early development, typically the critical period. In 2004, Murphy and her colleagues demonstrated that NMDAR1 receptor subunit expression is decreased in the case of

monocular deprivation (Murphy et al., 2004). One interpretation of this result is that diminished NMDAR1 expression would ultimately lead to lower excitatory input in the deprived eye's projections to the visual cortex. Consequently, this lower level of excitation would not be adequate to activate the existing NMDA receptors, and the connections would become weakened. This would ultimately cause loss of acuity in the visual field, as seen in children with unilateral cataracts (as cited by Murphy et al., 2004). Dr. Murphy's research, along with others who do similar work, have given great insight into disorders of the visual system such as congenital amblyopia and cataracts, and have also served as a paradigm for generalized brain development, including cases of genetic abnormality.

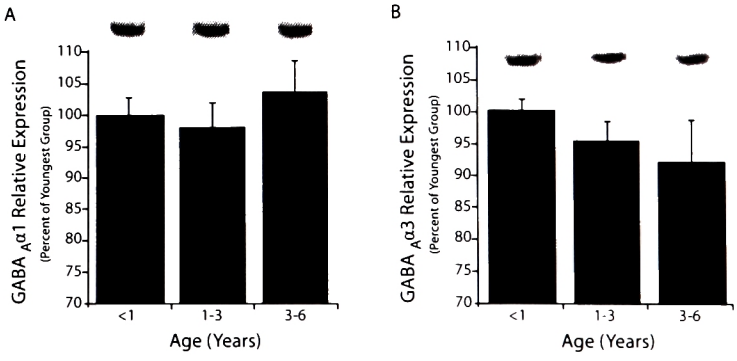


Figure 1: Western blots of tissue samples taken at various stages of development (Murphy et al., 2004).

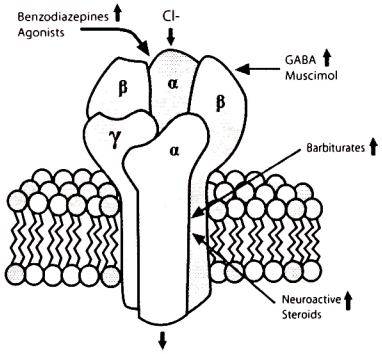


Figure 2: GABAA receptor. A pentameric membrane protein commonly composed of 2 alpha, 2 beta and a gamma subunit (Farrant & Nuser, 2005).

Future Directions

With the continued advancement of brain development research through strides made in other areas of molecular science, the field is constantly being enhanced with the latest and most advanced laboratory tools. For example, one of most interesting areas of research in genetics today involves making use of gene chip technology: a device that allows one to quantify the relative expression of thousands of genes simultaneously through a microarray. Recently, Ueno and colleagues (2006) used microarray analysis to study how neuronal progenitor cells in early neural development regulate DNA replication in the face of extrinsic stress (i.e. factors that cause DNA damage). They found a correlation between gene product expression and the checkpoints that neurons go through during early development. Based on the local environment, these cells can decide to undergo apoptosis (programmed cell death) or continue proliferation (Ueno et al., 2006).

The study of how the brain develops has always been at the forefront of neuroscience research; it remains a very exciting and constantly growing field. It has helped explain the complex relationship between environment and genetic constitution. It has also elucidated many of the molecular causes behind neuropathology, developmental disorders and general brain functioning. This is impressive and very important research. In order to better understand the world around us, it is imperative that we also obtain a better understanding of ourselves. With contributions from McMaster's Dr. Murphy, and others like her, our understanding of how the brain functions and supports the incredible processes of the human mind will not only benefit the scientific community, but society at large.

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