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Developmental Neuroscience Relevant to Child Neurology

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Developmental neuroscience has become increasingly relevant to clinical child neurology so that it is important to include selected areas of this knowledge into residency training. It is now common for journals such as *Journal of Neuroscience*¹, *Cell*², and *Neuron*³ to publish articles that deal with the pathogenesis of pediatric neurological disorders while neurology journals such as *Annals of Neurology*⁴ commonly report on molecular aspects of these disorders. Accordingly it is important for training in child neurology to include didactic presentations and group discussion of the relevant neurobiology literature and when possible some exposure to hands on research.

There are many examples of basic science advances that are directly relevant to child neurology, and a few will suffice to illustrate the point. Research on neurotransmitters has grown from a very specialized field of research thirty years ago to a topic for bedside rounds today. Although knowledge about the role of dopamine in Parkinson's disease and serotonin in depression are important topics, it is also very important for the child neurologist to understand that the excitatory neurotransmitter glutamate is the most ubiquitous neurotransmitter in the brain and is counter-balanced by gamma-amino-butyric acid (GABA), the most prominent inhibitory neurotransmitter⁵. The excitatory actions of glutamate are very important early on in brain development to promote growth and development of synapses, and without this excitatory activity neurons would die. This is probably the reason why the actions of GABA are transiently excitatory in the fetal and early neonatal brain, and why the brain in the neonatal period and early childhood is more excitable and prone to seizures than later in life⁶. Glutamate is able to fit into several conformations that bind to different receptor subtypes including the N-methyl-D-aspartate (NMDA) receptor channel complex, AMPA receptors and metabotropic glutamate receptors. Each of these receptors plays a role in learning and memory and in the process called long term potentiation (LTP) by which synaptic neurotransmission is enhanced by prior activity. Drugs that block these receptors, such as the AMPA antagonist anticonvulsant topiramate, are powerful anticonvulsants but can also impair learning and memory at high doses. Glutamate receptors have gained even more prominence in child neurology with the recognition that they can be the targets for antibody mediated syndromes including temporal lobe epilepsy associated with anti-AMPA receptor antibodies and limbic encephalitis associated with antibodies to NMDA receptors⁸. These syndromes often respond to immunologic therapies such as IVIg and plasma exchange. Knowledge of the actions of GABA and its receptors are also quite important for child neurologists because disorders of GABAergic neurotransmission are important in the pathogenesis of epilepsy and drugs that

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enhance GABAergic neurotransmission are first line drugs for controlling status epilepticus⁵. This section highlights areas of developmental neuroscience that seem most relevant to clinical child neurology: 1) cellular, synaptic and metabolic events in the developing brain; 2) the principle of selective vulnerability during development; 3) neurogenetic mechanisms of disease; 4) the quest for neuroprotection to salvage brain tissue; 5) mechanisms of brain plasticity that are enhanced in the developing brain and contribute to recovery of function.

Cellular, Synaptic and Metabolic Development of the Brain

Knowledge of the formation and maturation of the central nervous system provides an important background for understanding the pathogenesis of many pediatric neurological disorders. Neural tube closure occurs at 30 days gestation and interventions such as addition of folic acid to the diet and avoidance of certain anticonvulsants such as valproic acid before that time are required to prevent spina bifida in pregnant women. In the second trimester the migration of neurons differs according to neurotransmitter type with glutamate-containing principle pyramidal neurons migrating outward from the ventricular and subventricular zones along glial guides and the GABA containing inhibitory neurons migrate tangentially into cerebral cortex from the ganglionic eminence in the ventral basal telencephalon⁹. Recent data from human and non-human primate fetuses indicate that cortical GABAergic neurons also arise from proliferative zones in the dorsal telencephalon that are absent in rodent brains and may have arisen to serve the more complex primate brain⁹. GABAergic neurons help to integrate and coordinate cortical function and plasticity through regulation of activity in the principal glutamate neurons, and dysfunction or reduction in the number of GABAergic neurons have been implicated in a variety of disorders including epilepsy, autism, Rett syndrome, schizophrenia and fetal alcohol syndrome¹⁰. Basic neuroscience has also made it clear that neurogenesis is not restricted to the developing brain but persists into adulthood in selected regions including the sub-ventricular zone of the lateral ventricle and the subgranular zone of the dentate gyrus of the hippocampus¹¹. Disorders of this process may be related to specific disorders such as depression.

Development of the formidable cortical structures that make human intelligence possible is a story of waxing and waning of the total number of neurons as well as cortical thickness and synapse number. Approximate half the neurons produced during fetal neurogenesis will die by the time the brain matures, providing a surplus that allows for selection based on activity and neuronal interconnections. The pioneering studies of Conel and Huttenlocher showed us that the number of synapses in cortex peaks at two years of age at approximately twice the number found in adults¹². This means that from two years of age to the late teens stable synaptic contacts are chosen from a surplus to make stable networks. Chugani and colleagues showed that the curve for overshoot in synapse numbers followed by pruning in cerebral cortex is paralleled by the pattern of uptake of glucose using positron emission tomography (PET). Spectroscopic studies with labeled glucose showed that energy consumption is tightly linked to synaptic reuptake of the neurotransmitters glutamate and GABA¹³. These studies demonstrate the tight linkage between synapses and the glia that surround them and take up neurotransmitters in order to rapidly lower synaptic neurotransmitter levels. Because of this coupling between synapses and glia, glucose consumption by glia is a marker for synaptic activity and reflects the close symbiotic relationship between neurons and glia¹⁴.

Emerging studies with magnetic resonance imaging (MRI) are revealing how synapse development is disrupted by common disorders seen in pediatric neurology practice such as attention deficit hyperactivity disorder¹⁵. MRI has shown that cortical thickness varies with age in children in ways that resemble the changes in synaptic number reported by

Huttenlocher in postmortem brain specimens. Longitudinal study of normal children shows changes in cortical thickness that resemble the overshoot and then pruning of synapses numbers and suggests that these changes may be related to intelligence¹⁶. Profiles of change in cortical thickness in brighter children show higher peaks and relatively delayed thinning compared with changes in cortical thickness in more average children, especially in the pre-frontal cortex. Children with attention deficit hyperactivity syndrome (ADHD) have significant reductions in overall brain and gray matter volume and mean cortical thickness compared to healthy age-matched controls especially in frontal, temporal, parietal and occipital association cortices but white matter volumes are significantly increased¹⁵. These changes are consistent with reports of diminished response inhibition in children with ADHD¹⁷. Diffusion tensor imaging (DTI) is an MRI method that can examine local microstructure characteristics of water diffusion in tissue in multiple directions and yields information about the directionality of specific tracts as well as the quality and/or maturation of white matter. In addition to visualizing acute pathology such as strokes, DTI is proving very important for understanding the pathogenesis of developmental disorders such as autism and cerebral palsy¹⁸. In autism DTI imaging has revealed disrupted regional changes in white matter volume in the brain as well as altered connectivity among different cortical regions¹⁸. DTI imaging in children with the spastic diplegia form of cerebral palsy associated with periventricular leukomalacia (PVL) has shown important disruption in thalamocortical pathways that equal or exceed those in corticospinal tracts, and supporting the importance of sensory inputs into motor cortex in the pathophysiology of CP¹⁹. Development of MRI scanners with higher magnetic strength as well as new imaging sequences and more powerful analysis paradigms promise to make MRI a more powerful tool for pediatric neurology in many areas including epilepsy surgery, fetal neurology and neuro-oncology. Magnetic resonance spectroscopy will also benefit from stronger scanners as the ability to distinguish certain peaks such as glutamate and glutamine from each other will enhance ability to monitor neurotransmitter metabolism²⁰.

Selective Vulnerability During Development

The child's brain is vulnerable to numerous acquired disorders including hypoxiaischemia, stroke, status epilepticus, and traumatic brain injury as well as degenerative disorders for which neuroprotective therapy would be useful. The developing nervous system is a moving target for noxious influences since it is constantly changing throughout childhood, especially in infancy and the first several years of life. The brain can be likened to a house under construction with new structures and electrical circuits being added over time and some components such as extra neurons and synapses being deleted²¹. Accordingly, the premature brain is different from the brain of a term neonate and both are different from the brains of school age children or adolescents. These underlying structural and functional differences are also reflected in the patterns of selective vulnerability at specific times. One important example of changes in the pattern of selective vulnerability with age is the enhanced vulnerability of the white matter in the premature infant at 24–32 weeks compared to the term infant²². Oligodendrocyte progenitors present in white matter during this period are vulnerable to excitotoxicity and oxidative stress but lose this vulnerability as term approaches. These immature cells are especially vulnerable to excitotoxicity because they express AMPA and NMDA ionotropic receptors as well as excitatory amino acid transporters that regress later in gestation²³. Recent electrophysiologic analysis of the NG2⁺ oligodendrocyte progenitors shows that they express voltage gated sodium channels as well as ionotropic glutamate receptors and they form synapses with glutamate neurons and generate action potentials, making them vulnerable to excitotoxicity²⁴. Maturation of these cells leads to loss of action potentials and down-regulation of AMPA and NMDA receptors and sodium channels. These molecular changes, as well as changes in intracellular buffering of oxygen free radicals by glutathione and other oxidative buffers lead to reduced

vulnerability in more mature white matter²². The excitability of oligodendrocyte progenitors probably provides an advantage during development by stimulating early myelination near electrically active axons, but this advantage makes also them selectively vulnerable damage from hypoxia-ischemia. This is one of numerous examples of adaptive developmental differences that can create selective patterns of vulnerability to stresses or injuries.

Selective vulnerability also plays a role in neuropathology associated with epilepsy and metabolic disorders. Chronic changes in the hippocampus associated with temporal lobe epilepsy include a marked reduction in GABA receptors which is expected to cause reduced sensitivity to GABAergic anticonvulsants²⁵. Reduced activity of GABAergic activity also seems to be responsible for seizures and status epilepticus in Dravet syndrome and generalized epilepsy with febrile seizures plus (GEFS⁺) because these disorders are caused by loss of function mutations in the SCN1A subunit of sodium channels localized selectively on GABAergic interneurons²⁶. Hyperammonia associated with urea cycle disorders and other metabolic diseases produces toxicity at several steps involved in metabolism of glutamate and GABA²⁷. Ammonia is normally combined with glutamate to form glutamine in glia associated with excitatory synapses and build-up of ammonia leads to edema associated with increased intracellular glutamine. High ammonia levels also lead to excitotoxicity by activation of NMDA type glutamate receptors as well as through increased production of reactive oxygen species and impaired mitochondrial oxidative phosphorylation²⁷. Non-ketotic hyperglycinemia and sulfite oxidase deficiency associated with molybdenum co-factor deficiency also cause injury through over-activity of NMDA glutamate receptors^{28, 29}. Genetically determined mitochondrial disorders often show selective patterns of injury on MRI scans with complex I disorders including Leigh disease having bilateral brainstem and putamenal lesions³⁰ and mitochondrial encephalopathy with stroke like episodes (MELAS) usually have posterior cortical lesions in a non-vascular distribution associated with hemiparesis, hemianopsia and seizures³¹. In contrast, children with methylmalonic aciduria often have metabolic “strokes” associated with bilateral lesions in the globus pallidi and other disorder including pyruvate dehydrogenase deficiency and kernicterus also damage the globus pallidi^{32,33}. Many other disorders in pediatric neurology exhibit this kind of selectivity including the inherited leukodystrophies (e.g. posterior white matter in adrenoleukodystrophy), juvenile Huntington’s disease (caudate and putamen) and pantothenate kinase associated degeneration (PKAN, globus pallidus)³⁴.

The Quest for Neuroprotection

An important facet of developmental neuroscience related to child neurology has been devoted to the goal of protecting the immature brain from injury or interrupting damage in early stages after an insult to salvage brain tissue³⁵. The goal seemed plausible based on experience from the 1950’s that deep hypothermic arrest could protect young infants from injury during complex congenital heart surgery. This information was supported by the observation that brain injury from intrapartum asphyxia was linked to signs of encephalopathy such as seizures, coma and need for ventilator assistance which usually evolved over a day or more after a latent interval of several hours³⁶. The observation that damage was not uniform but was relatively selective across the nervous system also supported the concept. In addition, work in experimental animals showed that a cascade of biochemical steps including excitotoxicity, oxidative stress, and inflammation mediated by cytokines and microglia was responsible for the delayed evolution of encephalopathy and delayed neuronal death³⁵. After many years of work, three recently reported randomized controlled trials of mild hypothermia administered over three days in term babies with asphyxia showed benefit by significantly reducing death or disability at 18 months of age^{37–39}. This is a noteworthy accomplishment given the failure of several other pharmacologic neuroprotection trials in adults with stroke or in children or adults with

traumatic brain injury, but is in agreement that hypothermia can improve outcome in adults in coma after resuscitation following cardiac arrest. These results have stimulated to organization of a number of neonatal centers across the US and other countries to provide the cooling protocol for infants with encephalopathy generally with signs of encephalopathy within six hours of birth⁴⁰. Continuous monitoring of electroencephalogram (EEG) activity with integrated EEG (aEEG) units is currently thought to be an important part of the cooling protocol which is of interest to child neurologists⁴¹. The early apparent success of this form of neuroprotective therapy has stimulated greater interest on the part of neonatologists in neonatal neurology and in the involvement of child neurologists as collaborators in the nursery. Current laboratory research is focused on combining hypothermia with addition of drugs such as erythropoietin or anticonvulsants such as topiramate which might be used in human infants to improve outcome even more³⁵. This aspect of neonatal care involving child neurologists can be expected to grow with time and to require more detailed knowledge of the details of neonatal neurointensive care and neuroprotection.

Neurogenetic Mechanisms of Disease in Child Neurology

Aside from neuroimaging, the area of child neurology that has changed the most over the last thirty years is neurogenetics. Tomorrow's child neurologist needs to have a working knowledge of molecular genetics together with an understanding of how to use rapidly changing genetic diagnostic tests and choose current treatment options. The term "chromosomal microarray (CMA)" is now commonplace when diagnostic discussions take place in child neurology and refers to array based comparative genomic hybridization (aCGH) or the sometimes more sensitive single nucleotide polymorphism (SNP) arrays that detect copy number variations including deletions, duplications and inversions. A recent consensus statement from an international consortium of geneticists recommended that CMA's be used rather than G-banded chromosomes for initial testing of children with unexplained developmental delay or intellectual disability⁴². CMA as an initial test has a diagnostic yield of 15–20% in this group of children compared with karyotype techniques. This underscores the importance of copy number variation (CNV) as causes of neuropsychiatric diseases as well as epilepsy.

Genes for epilepsies, neuromuscular disorders and autism and related disorders are being identified at a rapid rate and the only way to keep up is through use of on-line databases such as Online Mendelian Inheritance in Man (OMIM) and Genetests. Testing itself is progressing at a rapid rate and the cost of tests like whole exome or whole genome sequencing is getting cheaper each day⁴³. Child neurologists need in-depth training in genetics as they are on the front line for many of these disorders. Knowledge in pharmacogenetics will also be useful to them as specific genotypes can predict altered pharmacokinetics of anticonvulsants and other drugs as well as propensity to develop Stevens Johnson syndrome and other serious adverse reactions⁴⁴.

Aside from making a diagnosis, one of the most useful aspects of neurogenetics has been to open the door to understanding pathogenesis and potential therapies for previously mysterious disorders. One good example is the X-linked disorder Rett syndrome which was found to be due to mutations in the transcription factor MeCP2 which is controlled by neuronal activity and itself controls activity dependent synapse formation and synaptic plasticity⁴⁵. The pathogenesis of Fragile X syndrome and tuberous sclerosis complex (TSC) have also been illuminated by genetic discoveries which facilitated the creation of mouse models⁴⁶. With deeper genetic understanding of these three disorders has come the realization that they disrupt activity-dependent signaling cascades within synapses^{47–48}. For Fragile X syndrome, new genetic knowledge led to a promising hypothesis that synaptic plasticity is disrupted by over-activity of a metabotropic glutamate receptor that impairs

trafficking of AMPA type glutamate receptors⁴⁸. This hypothesis is now being tested in several clinical trials of investigational drugs. Molecular genetic studies in TSC led to the hypothesis that synaptic plasticity and other manifestations such as tubers, subependymal giant cell astrocytomas (SEGA), as well as skin manifestations and tumors in lung and other organs are due to up-regulation of mTOR (mammalian target of rapamycin), the serine/threonine protein kinase enzyme that regulates cell growth and proliferation as well as protein synthesis and transcription⁴⁹. Medications that block mTOR are clinically approved for reduction in the size of SEGA and tubers, and are being tested for their effect on seizures, behavior and mental ability⁵⁰. Similar work is being done to unravel the pathogenesis of other genetic disorders that produce severe impairments such as Angelman syndrome². Autism has been shown to be caused by numerous different mutations but many of them are linked to synaptic function, such as neuroligin and neurexin molecules⁵¹ that hold pre- and postsynaptic elements together, and molecules such as Shank3 that form the scaffolding that anchors postsynaptic receptors⁵². These translational advances are likely to be replicated with other neurogenetic disorders in the future, leading to a broader focus of child neurology on therapy for previously untreatable encephalopathies.

Mechanisms of Brain Plasticity

Brain plasticity is another area of developmental neuroscience that is expanding rapidly and highly relevant to child neurology^{12,21,46}. The concept of plasticity permeates child neurology as it relates to both normal child development as well as response to acquired and genetic diseases. Evidence continues to emerge showing that plasticity is enhanced in the developing brain and includes functional plasticity whereby synapses may be strengthened or weakened based on previous electrical activity and structural plasticity which involves the loss or gain of synapses. The surplus of synapses in cerebral cortex in early childhood supports plasticity by allowing the brain to choose which will be maintained and which will be deleted during the rest of childhood based on experience.

Brain plasticity can be divided into four types: adaptive plasticity, impaired plasticity associated with intellectual disability or other neurodevelopmental disorder, excessive plasticity and plasticity as the brain's "Achilles' heel"²¹. Adaptive plasticity includes molecular mechanisms of learning and memory as well as acquisition of skills which may be associated with physical organization of neuronal maps or networks in cerebral cortex. Examples of impaired plasticity included genetic disorders that impair synaptic plasticity such as Fragile X syndrome, neurofibromatosis 1, tuberous sclerosis complex and Rett syndrome⁴⁶. In these disorders, signaling cascades that carry messages from synapses to the nucleus where messenger RNA's are encoded to change synaptic structure and function are defective. Enhanced plasticity refers to disorders such as phantom pain syndromes following limb amputation and focal dystonia associated with over-practice of musical instruments such as the piano. In these situations, reorganization of sensory or motor maps in cerebral cortex in response to aberrant sensory input from the limbs are thought to lead to maladaptive function in sensory or motor programs^{53,54}. The hippocampus is also thought to be prone to maladaptive plasticity through excessive stimulation of neuronal circuits by seizures or status epilepticus leading to aberrant synaptic organization that is responsible for chronic seizures⁵⁵. Plasticity as the Achilles' heel refers to over-activity in circuits responsible for plasticity that leads to permanent damage mediated by excitotoxicity. Many circuits in the infant and child's brain can be damaged by excessive stimulation of synapses containing NMDA type glutamate receptors leading to neuronal damage and synaptic reorganization³⁵.

Therapies to harness plasticity are increasingly being accepted into clinical practice. Constraint induced movement therapy (CIMT) appears to be effective for improving the

functional use of the affected hand and arm in children with congenital hemiplegia⁵⁶. In this therapy, use of the normal limbs is constrained with a cast or other device while the weak side is exercised for several hours each day using a salient behavioral paradigm⁵⁷. Activity based therapies that guide the movement of the arms and legs using robots are also being used for patients with the spastic diplegia and other forms of cerebral palsy⁵⁸. Activity based therapies that stimulate the movement of paralyzed extremities of patients with spinal cord injury using skin electrodes connected to a computerized stimulation are also successful at stimulating more voluntary use of the extremities⁵⁹. At the experimental level, transcranial magnetic stimulation (TMS) is being used to increase or decrease activity in the cerebral cortex to enhance plasticity and functional recovery after injuries. In patients with stroke, it has been reported that the undamaged hemisphere inhibits the opposite damaged hemisphere through fibers in the corpus callosum⁶⁰. TMS sequences that inhibit the good hemisphere have been used to improve function of damaged hemisphere. The techniques of low voltage transcranial direct current stimulation (TDCS) and retrograde stimulation through peripheral nerves have also been reported to modify cortical plasticity and facilitate return of function^{61–63}. TMS has also been used to measure cortical excitability in children with attention deficit hyperactivity syndrome and showed that inhibition is reduced in these children¹⁷. These techniques for modifying cortical plasticity show promise for treating a variety of pediatric motor and cognitive disorders in the future.

How Competencies in Developmental Neuroscience Are Obtained

Lectures, journal club/seminars, scientific meeting attendance, concentrated courses and laboratory research are the best way to achieve competencies in developmental neuroscience. Some training programs have a weekly seminar/journal club that deals with developmental neuroscience and review portions of books or articles that are directly relevant to clinical practice. There now many articles in the basic neuroscience literature dealing with models of pediatric neurological disorders. Short intensive courses such as the Annual Short Course on Medical and Experimental Mammalian Genetics held at Jackson Laboratory in Bar Harbor each July are good ways to present this information to residents in pediatric neurology.

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