PET in the Assessment of Pediatric Brain Development and Developmental Disorders

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KEYWORDS

- Alpha methyl tryptophan (AMT)
- Brain development • Developmental disorder • FDG
- Flumazenil (FMZ) • Functional imaging • Pediatric
- Positron emission tomography (PET)

Positron emission tomography (PET), along with various molecular imaging agents in its arsenal, can play an invaluable role in understanding the structural and functional changes that occur during brain development, and how these changes relate to behavioral and cognitive development in the infant and child. Although the application of PET technology has had an important impact in the study of human brain functional maturation, it is important and appropriate to begin with a brief review of the salient features of developmental neuroanatomy. In this regard, the contribution of MR imaging has been equally important and complementary to PET studies.

SOME BASICS ON DEVELOPMENTAL NEUROANATOMY

The human brain remains structurally and functionally immature at the time of birth and continues to undergo multiple complex and dynamic processes consisting of anatomic, molecular, functional, and organizational changes. In fact, brain development is orchestrated through the interaction of numerous synchronized processes, some of which continue even after birth, while some others start postnatally and take different courses, depending upon the specific brain region. For example, the neural tube is formed by 4 weeks of gestation, with neurogenesis taking place between 4 and 20 weeks and neuronal migration to their cortical destination from 12 to 20 weeks.[1] Although neurogenesis and migration was previously believed to be completed by birth, it is now known that some degree of neurogenesis continues into adulthood in the hippocampus and probably in other structures.[2] Neurogenesis is followed by apoptosis, peaking after neuronal migration, and reducing the number of neurons by half from 24 weeks of gestation to 4 weeks after birth.[3]

Although neocortical dendritic growth takes place between the third trimester of pregnancy and 2 years of age,[4] some regions, such as the calcarine cortex, show earlier dendritic growth (as compared with the prefrontal cortex), with about one-third of the growth completed by birth followed by some decline between 2 and 7 years of age.[5] Dendritic growth and synaptogenesis are

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PET Clin 3 (2009) 487–515
doi:10.1016/j.cpet.2009.04.006

closely linked and have a similar time course.[6] Synaptogenesis also begins around the twentieth week of gestation, increases rapidly after birth, and reaches peak synaptic density, 50% more than adult levels, by 2 years of age.[7] However, the peak in synaptic density depends upon the brain region; the peak is earliest in the primary sensory areas, followed by the prefrontal cortex.[8] In the visual cortex, it is almost 90% of the maximum at birth, reaches the maximum number by 8 months of age, and then decreases to about half the maximum between 1 and 5 years of age.[9] It reaches the peak in the auditory cortex at 3 months, but only at about 15 months in the prefrontal cortex.[8] Synaptic density starts decreasing around 7 years of age, reaching adult values by 12 years of age in the auditory cortex and by mid-adolescence in the prefrontal cortex.[8]

Myelination starts prenatally at around 28 weeks in the brain stem and generally proceeds from inferior to superior and posterior to anterior.[10] Myelination of the optic radiation and occipital white matter begins 1 to 2 months after birth and gradually extends to the frontal lobe by 9 months postnatally.[11,12] Myelination appears to follow the maturational pattern of functional circuitries; sensory fibers myelinate first, followed by motor fibers and associations fibers.[13] The surface of the growing brain begins to fold into sulci and gyri around 15 weeks of gestational age with all major gyri, except for the occipital lobe, formed by 28 weeks.[3,14] All gyri are present by birth, though relatively immature in terms of their inter- and intraregional connectivity.

Average brain weight at birth is about 370 g and increases rapidly to achieve 80% of adult weight by 2 to 3 years and 90% by 5 to 6 years of age.[15] Total cerebral volume peaks at 14.5 years in males and 11.5 years in females, with approximately 50% variation of brain volume in normal children of the same age.[16] One cubic millimeter of adult brain may contain between 35 and 70 million neurons and up to twice as many glial cells,[17] and about 500 billion synapses[18] in the cortical gray matter, or up to 20 miles of myelinated fibers in white matter.[19]

Although human brain development closely follows the sequence of events observed in other primates, it proceeds on a slower timescale. According to the model that predicts the timing of different neural developmental events in various mammalian species,[20,21] a delayed developmental time course leads to a relatively larger volume of the later developing structures, which may be the reason for the larger frontal cortex in human beings. Brain growth is further underscored by various remodeling processes, all undergoing simultaneously, and leading to variable growth of gray and white matter in a region-specific fashion. Cortical gray-matter volume peaks differently in different brain regions, peaking in the frontal lobe at 11 years in girls and 12 years in boys, in the parietal lobe at 10 years in girls and 12 years in boys, and in the temporal lobe at 17 years in girls and 16 years in boys, followed by a gradual decrease.[3,16] It seems that primary sensorimotor areas attain their peak thickness before secondary areas, followed by higher-order association areas.[22,23] Caudate size peaks at age 7.5 years in girls and 10 years in boys.[3] While total temporal lobe volume appears relatively stable from 4 to 18 years of age, the amygdala, which contains a high number of androgen receptors, increases in size in males and the hippocampus, having a higher number of estrogen receptors, significantly increases in size in females only, although no direct relationship between receptor density and growth patterns has been found.[24–26] The volume and density of white matter, including corpus callosum, usually increases with age until the fifth decade, with an almost similar pattern of change seen in all the lobes.[16,27–29] Although brain size is approximately 9% larger in males, the volume of frontal gray matter is higher in females, and the volume of occipital white matter is higher in males across all ages and after adjusting for the different overall brain sizes.[30]

Maturation of different parts of the brain also proceeds differently and is usually associated with thinning of gray matter and thickening of white matter. Longitudinal MR imaging studies have shown that cortical thickness generally decreases throughout late childhood and adolescence, with thinning of gray matter occurring first in sensorimotor areas, followed by parietal, superior temporal, and dorsolateral prefrontal cortices.[27,28,31,32] Regions subserving primary functions, such as motor and sensory systems, mature earliest, with temporal and parietal association cortices associated with basic language skills and spatial attention maturing next. Higher-order association areas, such as the prefrontal and lateral temporal cortices, which integrate primary sensorimotor processes and modulate basic attention and language processes, seem to mature last.[27,33] The cortical thinning may be a consequence of the pruning of neural connections that has been documented in animal models,[34] or may be related to increased myelination of axons within the cortical gray matter, leading to apparent thinning of gray matter.[28,33] Increase in white-matter volume appears to be associated with myelination. Both these regressive and progressive processes, occurring