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REVIEW

Development of axonal pathways in the human fetal fronto-limbic brain: histochemical characterization and diffusion tensor imaging

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Abstract

The development of cortical axonal pathways in the human brain begins during the transition between the embryonic and fetal period, happens in a series of sequential events, and leads to the establishment of major long trajectories by the neonatal period. We have correlated histochemical markers (acetylcholinesterase (AChE) histochemistry, antibody against synaptic protein SNAP-25 (SNAP-25-immunoreactivity) and neurofilament 200) with the diffusion tensor imaging (DTI) database in order to make a reconstruction of the origin, growth pattern and termination of the pathways in the period between 8 and 34 postconceptual weeks (PCW). Histological sections revealed that the initial outgrowth and formation of joined trajectories of subcortico-frontal pathways (external capsule, cerebral stalk–internal capsule) and limbic bundles (fornix, stria terminalis, amygdaloid radiation) occur by 10 PCW. As early as 11 PCW, major afferent fibers invade the corticostriatal junction. At 13–14 PCW, axonal pathways from the thalamus and basal forebrain approach the deep moiety of the cortical plate, causing the first lamination. The period between 15 and 18 PCW is dominated by elaboration of the periventricular crossroads, sagittal strata and spread of fibers in the subplate and marginal zone. Tracing of fibers in the subplate with DTI is unsuccessful due to the isotropy of this zone. Penetration of the cortical plate occurs after 24–26 PCW. In conclusion, frontal axonal pathways form the periventricular crossroads, sagittal strata and 'waiting' compartments during the path-finding and penetration of the cortical plate. Histochemistry is advantageous in the demonstration of a growth pattern, whereas DTI is unique for demonstrating axonal trajectories. The complexity of fibers is the biological substrate of selective vulnerability of the fetal white matter.
Key words axonal pathways; development; fronto-limbic connectivity; human fetal brain; subplate.

Introduction

The establishment of long-range axonal pathways is a crucial neurogenetic event in the development of the expanded cerebral cortex of the large primate brain. The long-range axonal pathways form a basis for expanded connectivity related to the increased number and size of cortical areas which, in turn, have also increased the number and size of cortico–subcortical connections. The process of axonal growth of the long pathways is the most complex in the human cerebrum, where an increased number of areas and projection neurons (Rakic, 1988, 2009) is accompanied by an enormous expansion of axonal pathways (Von Monakow, 1905; Polyak, 1927, 1932; Makris et al. 1997; Schmahmann & Pandya, 2006; Petrides & Pandya, 2007). The expanded system of axonal pathways in the human cerebrum develops over a prolonged period of time. It begins at the end of the embryonic period (His, 1904; Hochstetter, 1909; Bartelmez & Dekaban, 1962, Kostović, 1990a,b) and lasts until the neonatal period (Kostović, 1990b; Kostović & Judaš, 2002, 2006; Berman et al. 2005; Huang et al. 2006, 2009; Huppi & Dubois, 2006; Kostović & Jovanov-Milošević, 2006; Counsell et al. 2007; Kasprian et al. 2008; Kostović et al. 2008; Ment et al. 2009). During this period of growth, the axonal pathways (i) pass the critical morphogenetic points at the diencephalic–telencephalic border and corticostriatal junction (pallial–subpallial boundary) and (ii) change the direction of the growth trajectory passing through the periventricular crossroads (Judaš et al. 2005).

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