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Review

The Cellular and Molecular Landscapes of the Developing Human Central Nervous System

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The human CNS follows a pattern of development typical of all mammals, but certain neurodevelopmental features are highly derived. Building the human CNS requires the precise orchestration and coordination of myriad molecular and cellular processes across a staggering array of cell types and over a long period of time. Dysregulation of these processes affects the structure and function of the CNS and can lead to neurological or psychiatric disorders. Recent technological advances and increased focus on human neurodevelopment have enabled a more comprehensive characterization of the human CNS and its development in both health and disease. The aim of this review is to highlight recent advancements in our understanding of the molecular and cellular landscapes of the developing human CNS, with focus on the cerebral neocortex, and the insights these findings provide into human neural evolution, function, and dysfunction.

The human CNS exhibits the organizing principles and developmental pattern typical of all mammals; it begins as a simple neural tube that breaks off from the embryonic ectoderm and gradually acquires mature organizational features through immensely complex and strictly regulated molecular and cellular processes. Studies of model organisms have provided fundamental insights into many human neurodevelopmental processes (Bae et al., 2015; Leone et al., 2008; Lui et al., 2011; Molyneaux et al., 2007; Nord et al., 2015; O'Leary et al., 2007; Rakic et al., 2009; Rash and Grove, 2006; Shibata et al., 2015; Taverna et al., 2014). However, despite commonalities in neurodevelopmental processes in mammals, there are compelling interspecies differences that yield clade and species-specific (or defining) features and, ultimately, differences in cognition and behavior. For example, the human brain as a whole, but most especially the association areas of the cerebral neocortex, develops more slowly than the brains of other primates, and humans have a particularly long gestational time as well as childhood and adolescence (Figure 1) (Bogin, 1994; Gogtay et al., 2004; Petanjek et al., 2011; Stiles and Jernigan, 2010; Tau and Peterson, 2010; Yakovlev and Lecours, 1967). This prolonged developmental course and period of dependency allows, more so than in other primates, environmental factors to shape the development of cognitive, emotional, and social capacities. In addition, the developing human CNS possesses certain divergent and highly derived features, such as expanded proliferative zones and diverse subtypes of neural stem and progenitor cells with enhanced proliferative capacities that facilitate brain expansion, especially of the neocortex (Bae et al., 2015; Bystron et al., 2006; Dehay et al., 2015; Gulden and Sestan, 2014; Howard et al., 2008; Lui et al., 2011; Taverna et al., 2014).

Indicative of the biological challenge of precisely regulating diverse molecular and cellular processes over a protracted period of time and across myriad cell types and regions, the CNS exhibits regionally and temporally distinct patterns of vulnerability to various diseases and insults (Figure 2) (Kessler et al., 2007; Lee et al., 2014; Semple et al., 2013; Tebbenkamp et al., 2014). Thus, the emergence of the many neurodevelopmental processes that have enabled human brain complexity may have required a trade-off that rendered it particularly susceptible to certain disorders. Not surprisingly, it has become increasingly evident that studies involving commonly used experimental animals can neither fully model human neurodevelopment or disorders nor reliably predict if potential therapeutic compounds will work against human disease or have adverse effects. Moreover, the use of model organisms is limited by our evolutionary distance from these species. As such, null mutations of orthologous genes can result in vastly different phenotypes across species (Liao and Zhang, 2008). Therefore, a true understanding of how the human CNS is built and functions also requires direct analyses of human neural tissues and cells.

Unfortunately, the human CNS, in particular its development, is challenging to study for many reasons. However, the procurement of high-quality post-mortem tissues from different periods of development, as well as recent advances in directed differentiation of induced human pluripotent stem cells (iPSCs) towards neural fates and other neural cell preparations (Brennand et al., 2011; Lancaster et al., 2013; Mariani et al., 2015; Paşca et al., 2015; Stein et al., 2014; van de Leemput et al., 2014; van den

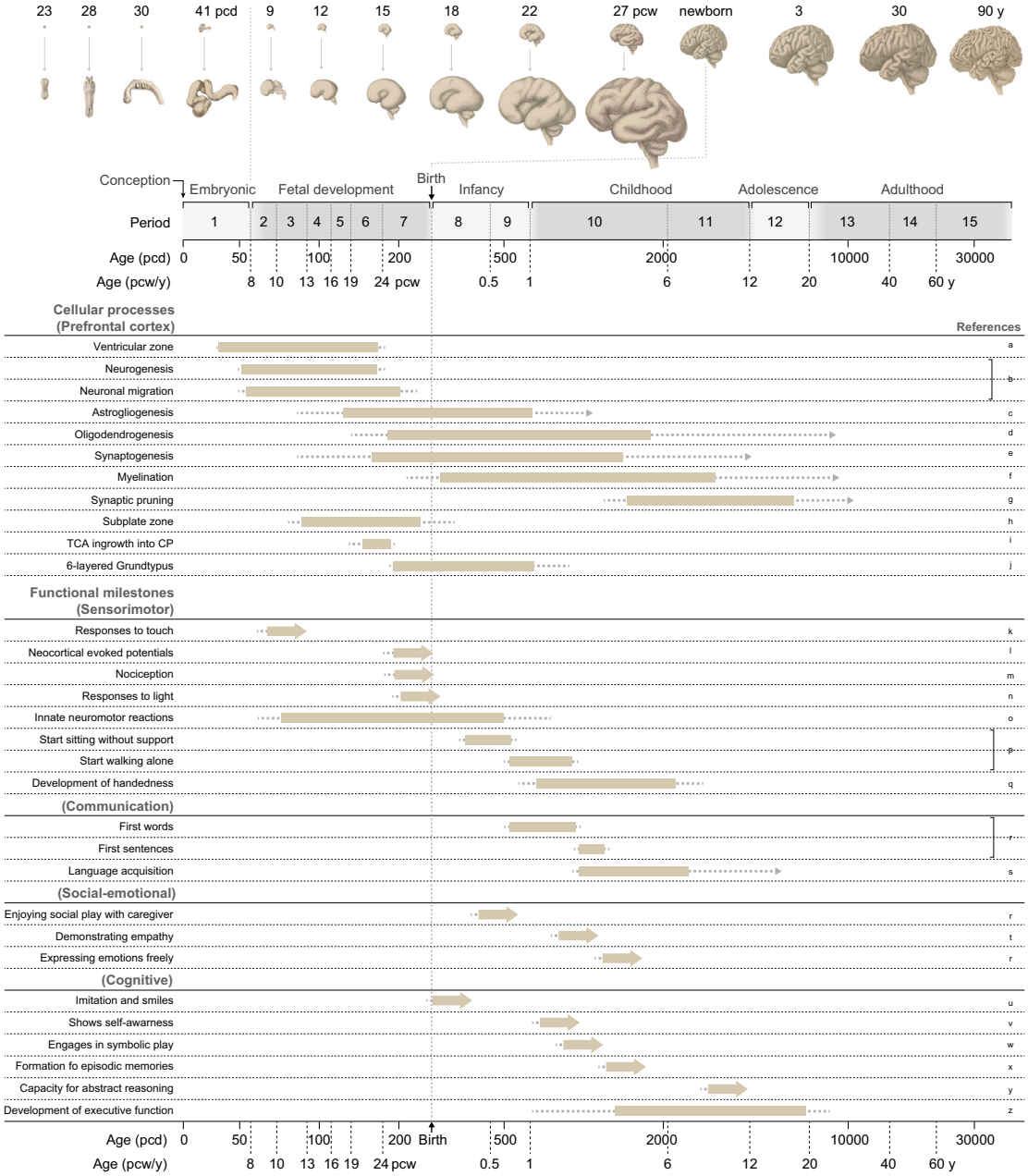

Figure 1. Timeline of Key Human Neurodevelopmental Processes and Functional Milestones

The figure provides a summary of some key cellular processes in the developing prefrontal cortex and functional milestones. Illustrations in the top panel show the gross anatomical features of the developing and adult CNS, with prenatal brain features magnified. The second panel, which is duplicated at the bottom of the figure, provides a timeline of human development and the associated periods (designed by Kang et al., 2011), and age in postconceptional days (pcd), postconceptional weeks (pcw), and postnatal years (y). The schematic below details the approximate timing and sequence of key cellular processes and developmental milestones. Bars indicate the peak developmental period in which each feature is acquired; dotted lines indicate that feature acquisition occurs at these ages, though to a relatively minor degree; and arrows indicate that the feature is present thereafter. Relevant references pertaining to each process or milestone are provided in the rightmost column: a, Gould et al. (1990) and Malik et al. (2013); b, Bystron et al. (2006), Meyer (2007), and Workman et al. (2013); c, Choi and Lapham (1978), deAzevedo et al. (2003), and Kang et al. (2011); d, Kang et al. (2011) and Yeung et al. (2014); e, Huttenlocher (1979), Kwan et al. (2012), Molliver et al. (1973), and Petanjek et al. (2011); f, Miller et al. (2012) and Yakovlev and Lecours (1967); g, Huttenlocher (1979) and Petanjek et al. (2011); h, Kostovic and Rakic (1990); i, Kostovic and Judas (2006) and Kwan et al. (2012); j, Aldama (1930) and Brodmann (1909); k, Humphrey and Hooker (1959); l, Eswaran et al. (2007); m, Bellieni and Buonocore (2012); n, Polishuk et al. (1975); o, Clowry (2007), de Vries et al. (1985), Ianniruberto and Tajani (1981), Johnson and Blasco (1997), and Van Dongen and Goudie (1980); p, WHO Multicentre Growth Reference Study Group (2006); q, McManus et al. (1988) and Ramsay (1980); r, Dosman et al. (2012), Gerber et al. (2010), and Johnson and Newport (1989); s, Johnson and Newport (1989); t, Zahn-Waxler et al. (1992); u, Meltzoff and Moore (1977); v, Amsterdam (1972) and Butterworth (1990); w, Harris (2000); x, Dumontheil (2014); y, Rajan et al. (2014); z, Catts et al. (2013) and Heaton et al. (1993).