Prefrontal cortex: the ultimate human evolution

Lígia Palhete-Ferreira[1-2]

1. Departamento das Ciências do Diagnóstico, Terapêutica e Saúde Pública, Escola Superior de Tecnologia da Saúde de Lisboa, Instituto Politécnico de Lisboa. Lisboa, Portugal. ligia.ferreira@estesl.ipl.pt
2. Investigadora colaboradora do Centro de Investigação em Saúde e Tecnologia (H&TRC).

ABSTRACT: The prefrontal cortex (PFC) is responsible for the acquisition, execution, and control of a wide range of functions, from basic motor responses to complex decision-making. Brain development and maturation begin during gestation and terminate, presumably, in late adolescence and early adulthood. PFC is the latest developing region of the neocortex, explaining adolescence's emotional imbalance and immature, impulsive, excited, and risky behaviour. Despite researchers' efforts to clarify human brain maturation and hight-abilities, the early adulthood development stage is not fully understood. The aim of this review is to describe the role of frontal lobes, particularly of PFC, in differentiating human behaviour and high functions and the impact of its development during late adolescence and early adulthood.

Keywords: Prefrontal cortex; Brain development; Adolescence; Early adulthood.

Córtex pré-frontal: o culminar da evolução humana

RESUMO: O córtex pré-frontal (CPF) é responsável pela aquisição, execução e controlo de várias funções cerebrais, desde respostas motoras básicas a complexos processos de decisão. O desenvolvimento e maturação cerebral inicia-se durante o período gestacional e termina, presumivelmente, na fase final da adolescência e início da vida adulta. O CPF é a última região neocortical a atingir a fase final de maturação, o que explica a labilidade emocional e imaturidade, impulsividade, excitação e comportamento arriscado, típico da adolescência. Apesar dos inúmeros esforços para clarificar o processo de maturação do cérebro humano e as suas capacidades diferenciadoras, o desenvolvimento no adulto jovem não é totalmente compreendido. Com a presente revisão pretende-se descrever o papel dos lobos frontais, particularmente o CPF, no comportamento humano e suas capacidades distintivas, e o impacto do seu desenvolvimento na fase final da adolescência e início da vida adulta.

Palavras-chave: Córtex pré-frontal; Desenvolvimento cerebral; Adolescência; Adulto jovem.

Introduction

Over the past three decades, there has been a collective effort to understand the basic principles of neural and brain formation, development, and maturation that can explain human behaviour and abilities.

Brain development and outstanding complexity contributed to the differentiation of human high functions, particularly associated with frontal areas[1]. Cognition, language, executive functions, socio-emotional behaviour, motricity, problem-solving, and environment adaptation skills are some of the human most distinct features, gained across human evolution. Despite being the core of such human abilities, which justifies two-thirds of human brain occupation, frontal lobes functions stayed in the dark for a long time and, partially, still remain[2].

The prefrontal cortex (PFC), the frontal lobe association region, is the latest developing region of the neocortex, presumably, until late adolescence and early adulthood. PFC neural system is responsible for the acquisition, execution, and control of a wide range of functions, from basic motor responses to complex decision-making. Such executive functions include the organization of sensory input, attention engaging, processing information in working memory, and the coordination of goal-directed behaviours engaged by emotion and cognition[1,3]. These abilities contributed to the management of complex social groups and unpredictable/dangerous environments along with human evolution.

Several authors postulate that PFC functions continue to develop throughout late adolescence and early adulthood. Nonetheless, few studies have been able to link structural brain changes to functional behavioural modifications[4].

Even fewer determined the development end-point for each executive function, cognitive and behavioural abilities[5-6].

The aim of this review is to describe the role of frontal lobes, particularly of PFC, in differentiating human behaviour and high functions and the impact of its development during late adolescence and early adulthood.

Human brain development and maturation: a lifespan perspective

Gestational period

Human brain development begins in the third gestational week (GW) and evolves at least util late adolescence or, possibly, throughout the lifespan. At the end of the third GW, a three-layered structure forms the embryo. The epiblast cells of the upper layer will differentiate into primary stem cells lines, precursors of every other embryo's structures, while hypoblast cells of the lower layer form extraembryonic structures (i.e. placenta). Neural stem cells, self-renewing multipotent cells, emerge from the stem cell lines and generate the nervous system precursor cell. Rostral migration of embryo cells originates the head while caudal cells migration forms the neck and trunk of the body[7-8].

During the third GW, the first brain structure (neural tube) is formed. When completed, the embryo's neural tube has a cylindrical hollowed structure in the middle line, which becomes larger and more complex originating from the ventricular system of the brain. The rostral region of the neural tube evolves to the brain, while the caudal hindbrain and spinal column emerge. Through the eighth GW, major compartments of the nervous system are formed and continue developing into rudimentary structures of the central nervous system, including the brain[8]. During brain formation, three primary brain vesicles (rostral to caudally: prosencephalon, mesencephalon, and rhombencephalon) develop as precursor structures of the forebrain, midbrain, and hindbrain, respectively. Later prosencephalon divides into telencephalon and diencephalon; the mesencephalon stays undivided; and the rhombencephalon divides into metencephalon (pons and cerebellum) and myelencephalon (medulla oblongata)[8-10]. Corpus callosum growth takes place from 9 to 14 GW and, a couple of weeks later, the first sulci appear. From 22 to 33 GW, fissures formations become evident and all primacy sulci are present[11-12]. These structural developments contribute to lobes differentiation in each brain hemispheres (frontal, parietal, temporal, and occipital lobes) with specific functions attributed[13].

Brain microstructure also exhibits major fetal development. Neurons production begins on embryonic day 42 and continues throughout midgestation. After formation, neurons grow processes, form synaptic connections, and migrate to different areas extending neural networks. By the end of the prenatal period, major fiber pathways are completed. Environmental changing settings, supported by gene expression, promote a series of dynamic and adaptive responses that lead to the formation and differentiation of new neural structures and functions[8,11].

Early and late childhood

During the early postnatal period, exuberant connectivity of the developing brain markedly exceeds that of adults and suffers progressive downward pruning, by means of competitive processes. Early neural plasticity and adaptation skills contribute to the maintenance of the most recruited neural circuits and mitigate less used ones, as a hallmark of early brain development. In fact, plasticity and learning are thought to be crucial mechanisms of human development and behaviour consolidation[8,14].

Magnetic resonance (MR) images reflect considerable changes in children's brains. Over the first two to three years of life, brain mirrors and myelinization in white matter regions becomes more evident. Myelinization processes are responsible for one of the most relevant changes in brain structure during childhood, with a clear impact on human nervous system development and unique differentiation. Electrical isolating multi-layer sheaths of myelin are formed by oligodendrocytes (in the central nervous system). Furthermore, oligodendrocytes not only dramatically increase axonal conduction velocity, but to maintain axonal integrity and neuronal survival by synthesizing trophic factors. As myelinization proceeds during infancy, faster pathways are potentiated while unmyelinated structures, with slower conductive properties, are diminished and replaced[8].

During the preschool period, the human brain increases in size four-fold, reaching 90% of adult volume by age 6. MR morphometry also shows increased gray matter volumes, both in the cerebral cortex and in subcortical nuclei, in school-aged children when compared to young adults. From birth to teenage years, brain volume asymmetrical increase is observed. The maturation timeline is distinct across cerebral regions, with frontal lobe formation for last[8,14].

Adolescence and adulthood

In adolescence tumultuous time, major changes and transformations occur with a close impact on puberty gonadal and behavioural maturation[15]. Continuous white matter increased through adolescence into adulthood, presumably, reflecting interregional communication in the developing brain[14,16]. In addition, the frontal lobe's last peak of myelinogenesis has a relevant impact on adolescent cognitive processes and behaviour[15]. These structural changes are the foundation of the functional organization of the mature human brain and cognitive high-functions differentiation[8]. For those reasons, myelinization's impact on late brain development remains a topic of interest for researchers.

The mature brain is composed of more than 100 billion neurons, five times more glial cells, and more than 60 trillion neuronal synapses, with enlargement volume mass due to sulci and gyri formation. Brain folding dramatically expands brain size but fits small cranial areas. The coronal cross-section of the mature brain shows a thin (2-5mm) external layer of the neocortex, followed by white-coloured brain cortex (formed by myelin wrapped axons), and subcortical nuclei formed by clusters of neurons that connect the neocortex,

various cortex areas, and the rest of the body. Both neocortex and subcortical structures are formed by gray matter cells (cell bodies of neurons). Resulting from neuron migration, the mature brain presents a six-layered mantel neocortex (I-VI layers)[8].

Along with the human lifespan, the cerebral cortex and deep nuclei show the greatest amount of volume variance of nervous structures. Decreasing cerebral cortex volume of adults seems to have high consistency with age. On the other end, cerebral white matter is relatively preserved with age, showing an initial increase in volume before accelerated volume loss sets in[17].

Brain structure changes during adolescence are at least as dramatic as those observed in the elderly. Imaging demonstrates structural development throughout childhood, adolescence, and even brain degeneracy into elderliness, but no robust data is related to the final brain development processes[8,18]. Despite various studies showing evidence of a developing brain until late adolescence and elderly degeneracy, data reporting early adulthood brain consolidation is scarce[8].

Frontal lobes: functions and circuits

Frontal lobes are divided into prefrontal, premotor, and motor cortices, limited posteriorly by the central sulcus. Anterior cingulate, from the limbic system, takes also part in frontal lobe divisions[1-2,19].

As early mentioned, the frontal lobes are the ultimate brain areas to develop and mature. Relative delayed time course of human brain development not only leads to larger cortex volume, especially the frontal lobes but also promotes benefits of longer influence of environment interaction in construction and shaping of brain's circuitry[14]. Development of the frontal lobe is crucial to the acquisition, execution, and control of a wide range of functions, from basic motor responses to complex decision-making[3].

Motor functions and language are complex and well-studied functions of the frontal lobes, but knowledge of their other functions was sparse for many years. Increasing interest in cognitive processing, such as executive functions, attention, memory, mood, emotions, personality, social and moral reasoning, has become evident in recent years. Frontal lobes functioning reflects our identity as autonomous beings[20], capable of living both in complex social apparatus and unpredictable environments[1], which may motivate further investigation.

Human behaviour is determined by frontal lobe processes of management of incoming information and selection of appropriate actions to achieve one's goals. This behaviour response is modulated by motivation mechanisms, such as maintenance of approach and avoidance[3]. Both approach and avoidance neural circuitry seem to be located at ventromedial regions of the PFC. The striatum is also involved in reward-related approach behaviour; while limbic circuitry (amygdala, hippocampus, insula) is also related to the aversive response that leads to avoidance behaviour. Neural interaction between approach and avoidance is not yet clear: some studies suggest circuitry overlap[21-23], but others suggest otherwise[24-25]. Reward and cost/punishment modulation is also implicated in human behaviour development and reorganization.

Although frontal lobe volume has not been differentially enlarged across human evolution, neural structures have increased their complexity, reorganization, and network connections, especially in prefrontal regions. PFC is the late-developing region of the neocortex, even later than caudal regions, and exhibits more complex dendritic arborization and myelinization[1,26].

Human PFC forms a large part of a neural system associated with many cognitive abilities, socio-emotional and executive functioning, related to high-level functions processes. Its complex circuitry has been recognized as a considerable factor in human behaviour compared to related primates' species. The PFC can be divided into ventromedial and dorsolateral regions: the primer has reciprocal connections with the amygdala (emotional processing), hippocampus (memory), and temporal visual association areas (sensory processing); and the latter has reciprocal connections with basal ganglia and premotor cortex (motor processing), cingulate (performance monitoring) and parietal cortex (sensory processing). These anatomical and functional networks support functions involving emotion, memory, behaviour, and environmental stimuli processing and control[1,27].

Executive functions of PFC have been a topic of research in neuroscience, neuropsychology, and other related fields for many years. These complex functions are related to human purposeful, goal-directed behaviours, achieved by intention, planning, selection, sequential organization of input from different sensory modalities, and self-monitorization. The ability to persevere on task termination relies also on attention, while memory processes contribute to executive functions mediation[1-2,28].

The undeniable importance of PFC in human behaviour and high functions have promoted hide-spectral investigation of frontal lobe development, network, and maturation. Unfolding such mechanisms over a lifespan perspective can contribute to understanding the processes related to human cognition, behaviour, motivation, personality, socio-emotional dimension, and moral compass. At the final maturation stage of the frontal (and prefrontal) areas, important changes occur that need further clarification.

Adolescence and early adulthood: the hallmark of the prefrontal cortex

The human brain remains in an active state of development during adolescence and early adulthood. Significant brain growth and development occur in adolescence due to the formation and strengthening of regional circuitry and pathways in the brain stem, cerebellum, occipital, parietal, temporal, and frontal lobes. Furthermore, in adolescence, PFC continuing formation, consolidation, and maturation are seen. As PFC is responsible for the ability to apply good judg-

ment within difficult life situations but being the last region of the brain to reach maturation, adolescent immature behaviour is expected. Typical adolescent development imbalance can also be explained by early maturation of subcortical affective brain regions while cognitive control of fronto-cortical regions matures slowly[4,15].

PFC myelinogenesis and neurocircuitry process, which continues from childhood, are vulnerable to significant adolescent sex hormone increase. Adding, PFC glutamatergic neurotransmission predominance also seems to contribute to the functional vulnerability of immature, impulsive, and excited behaviour, common in adolescence[15]. In fact, in this stage of human development, social maladjustments and risky behaviours are a result of an immature limbic system and PFC. Delayed development of gamma-aminobutyric acid (GABA)ergic neurotransmission and sex hormones mediated dopaminergic neurotransmission are present in the adolescent PFC. These neurochemical features appear to have a role in neuro-behavioural excitement and risk-taking behaviour. As dopamine action is associated with emotional response and pleasure/pain experiencing, its decreased levels during adolescence promote drug-seeking behaviour, mood swings, and emotion regulation difficulties[5]. Similarly, other central nervous system neurotransmitters play important role in adolescent brain maturation and operation. Serotonin decreases and promote diminished impulse control, and the melatonin releasing profile alters the sleep-wake cycle[15]. Along with environmental inputs, the described mechanisms influence not only behaviour, self-control, emotional status, social and sexual interactions, but also eating habits and sleep patterns[6,15].

Cognitive development and executive functional maturity can only be reached after structural development and maturation of frontal lobe regions. Despite global acceptance that brain development, mainly PFC, is completed in early adulthood around the age of 25 years[15], the majority of studies only address age until 21-22 years[4]. Thus, the final development stage is still poorly understood. Further clarification could contribute to clarifying neurobiological, socio-economical, environmental, and educational aspects able to influence adults' cognition, personality, behaviour, and action-driven influencers.

Concluding remarks

Development and maturation of the human brain follow a path that mirrors our evolution as a species, characterized by differentiated and complex adaptive survival skills, cognitive, motor, and socio-behavioural functions, and creative capabilities. Firstly, the most basic structures are formed and are responsible for the most primitive survival mechanisms, progressively giving rise to the sensorial and motor skills, integrative and responsive functions, and later, executive functions, moral reasoning, and further. Nonetheless, it is not clear when maximum brain maturation is achieved; nor the brain underlying changes related to the final mechanisms that arise in typical human behaviour and high functions.

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Conflict of interests

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