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Astrocytes and the evolution of the human brain

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ABSTRACT

Cells within the astroglial lineage are proposed as the origin of human brain evolution. It is now widely accepted that they direct mammalian fetal neurogenesis, gliogenesis, laminar cytoarchitectonics, synaptic connectivity and neuronal network formation. Furthermore, genetic, anatomical and functional studies have recently identified multiple astrocyte exaptations that strongly suggest a direct relation to the increased size and complexity of the human brain.

Introduction

The enlargement of the human brain is the prima facie example of punctuated equilibrium [1]. "A progressive enlargement of the hominid brain started by about 2–2.5 million years ago, probably from a bipedal, australopithecine form with a brain size comparable to that of a modern chimpanzee" [2].

Comprehensive surveys of vertebrate brains fail to explain human cognitive abilities based on relative or absolute brain size [3–5]. Importantly, these studies focus on the density of neurons, excluding glia, which account for approximately 85% of cells of the human neocortex. Additionally, electrical and histological studies show no significant differences in neuronal electrical properties, neural cell types, or depth of cortical lamination among mammals [6–10].

Striedter concludes that "the origin of the neocortex cannot be explained as a simple, automatic consequence of increased absolute brain size. Instead, it probably involved size independent (and largely mysterious) changes in neurogenesis, migration and axon guidance" [11]. It is now firmly established that all three are functions of cells within the astroglial lineage.

To further underscore the crucial contribution of astrocytes to human brain evolution, significant genetic, functional and anatomical exaptations have recently been discovered that strongly support a substantial role of astrocytes in development of human cognitive abilities.

Empirical studies support an astrocytic origin of human brain evolution

Accumulating empirical data from multiple disciplines over the past two decades reveals that the long-held belief that brain information processing is an exclusive function of neurons is erroneous. Protoplasmic astrocytes, the predominant cell in mammalian gray matter, are essential for normal synaptic function and maintenance. Additionally, they are instrumental in expression, storage and consolidation of synaptic information from individual synapse to global neuronal networks (reviewed by [12–20]).

Recent anatomical and functional exaptations and genetic alterations specific to humans strongly support a critical role of astrocytes in human brain evolution. Additionally, a recent in vivo study infers that human astrocytes independently contribute to cognition.

Developmental studies

Numerous studies confirm that radial glia cells (RGCs) are embryonic pluripotent precursors that direct mammalian neurogenesis and gliogenesis in a highly ordered chronological fashion [21–24].

Gould emphasizes that "diversification has occurred primarily through changes in developmental regulatory networks rather than the genes themselves, which evolved much earlier" [25]. Relative to human brain evolution, this explains

"how the genetic information contained within progenitor cells regulates the number, phenotype, migration and allocation of neurons in developing brain, where they establish species-specific circuits" [8].

For instance, an increase in the number of divisions of progenitor cells by seven would "account for the 1000-fold difference in total cortical surface area between mice and humans" [8]. Two

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extra divisions in chimpanzees would do the same [6]. Therefore, "when evolution changes absolute brain size, it simply expands or contracts a highly conserved schedule of neurogenesis" [11].

Neurogenesis

Neurons are born following asymmetric divisions of RGCs. Each migrates along the extended processes of the parent RGC for proper placement within the laminated neocortex [7]. The daughter cells of RGCs maintain traces of their astrocytic origins even at the "peak of neurogenesis" [26].

Although humans and chimpanzees have similar gestational periods (38 weeks in humans and 35 weeks in chimpanzees), fetal brain volume in humans increase dramatically in the second half of gestation compared to chimpanzees. Just prior to birth, the velocity of brain growth in humans is fivefold greater than in chimpanzees [27].

A well demarcated neurogenic zone was recently discovered in the outer subventricular zone of the human fetal neocortex. RGCs in this area "accelerate the expansion of the neuronal population" [28] and contributes to the rapid intrauterine growth of human brains.

Development of neuronal pathways

Astrocytes direct axonal trajectories by acting as guide cells that produce chemoattractant and chemorepellent molecules to guide axonal terminal processes to their correct targets [24,29]. Therefore, phyletically highly conserved neuronal pathways are assured.

In addition, astrocytes act as "glial slings" to guide axons across the corpus callosum. Huxley notes that "the appearance of the 'corpus callosum' in the placental Mammals is the greatest and most sudden modification exhibited by the brain in the whole series of vertebrated animals ..." [30]. This probably accounts for bihemispheric functional specialization, since RGCs in each hemisphere are free to evolve independently, with cross hemispheric communication through the corpus callosum [31].

Gliogenesis and neuronal apoptosis

RGCs subsequently switch to gliogenesis. This final stage is a massive production of astrocytes that occurs primarily after birth when the human brain enlarges the most. The postnatal transformation into the mature astrocytic phenotype occurs while the total number of neurons is decreasing by 20–80% depending on the brain region [32]. The diminished neuronal population is a consequence of astrocyte-directed apoptosis [33,34].

Establishment of neurogenic zones in the adult brain

Astrocytes in the subgranular zone (SGZ) of the adult hippocampus and subventricular region maintain the ability to undergo neurogenesis. SGV astrocytes contribute to memory formation and are sensitive to environmental factors, such as experiences that may lead to depression. There is interest in utilizing this phenomenon as a therapeutic approach to treat neurodegenerative and mood disorders (reviewed by [35]).

Anatomical studies

Magnocellular exaptation of human protoplasmic astrocytes

The volume of human protoplasmic astrocytes, the most common cell in the neocortex, is 27-fold greater with a 2.55-fold increased diameter compared to rodents. Protoplasmic astrocytes of both species demarcate specific non-overlapping anatomical and functional compartments (i.e. domains) within the neuropil that encompass ~90,000 synapses in rodents and ~2,000,000 synapses in humans [9,10].

Protoplasmic astrocytes occupy all six laminae of the cortex, and each domain is contiguous and continuous with its neighbors, resulting in three-dimensional tiling of the entire cortical grey matter. This complex geometric matrix is proposed as the platform for three-dimensional and seamless expression of consciousness and explicit memories [19].

Protoplasmic astrocytes of both species are characterized by extensive peripheral processes that account for 80% of the total membrane surface area of each cell. They ensheath virtually all excitatory synapses within each domain. However, human astrocytic processes are 10-fold more numerous and 2.6-fold longer than those of rodents [9,10].

Distal astrocytic processes contain innumerable perisynaptic functional microdomains [36–41] that "contain elements essential for astrocyte signalling and response to neuroligands (receptors, transporters, endoplasmic reticulum, transmitter vesicles), energy production (mitochondria and glycogen), motility (actin filaments), and intercellular communication (gap junctions)" [19]. They are activated simultaneously with dendritic excitatory post synaptic currents [39]. Therefore, astrocyte microdomains are considered the site of astrocyte postsynaptic information processing [19].

Human and primate-specific cortical astrocytes

Three astrocytes that are specific to humans and higher primates have recently been discovered [9,10,42,43]. Interlaminar astrocytes are located in lamina 1 and send processes within lamina 1 and others downward to terminate in lamina 4. Polarized astrocytes are found in lamina 5 or 6 and send 1 mm long processes upward. Varicose projection astrocytes are likely specific to humans. They are located in lamina 5 or 6 and characterized by very long processes that contain evenly spaced varicosities [10]. All three extend through innumerable protoplasmic astrocyte domains, and have been proposed to function as "alternative pathways for long-distance communication across cortical layers perhaps forming links between functionally related domains in different laminae" [9].

The extreme magnocellular exaptation of protoplasmic astrocytes in humans and the appearance of three primate and human-specific astrocytes leads to the conclusion "that this astrocytic complexity has permitted the increased functional competence of the adult human brain" [10].

Physiological studies

A recent in vivo study provides evidence to "strongly support the notion that the evolution of human neural processing, and hence the species-specific aspects of human cognition, in part may reflect the course of astrocytic evolution" [44].

Human glial precursor cells, implanted into the brains of immune-suppressed neonatal mice, exhibit an extensive population of human protoplasmic astrocytes in the neocortex and hippocampi of chimeric mice as adults. Primate-specific interlaminar astrocytes are also observed [9,10].

The xerographic human astrocyte morphology and function is essentially indistinguishable from previous studies in humans. The human astrocytes in the chimeric mice maintain the same increased velocity of intracellular calcium signaling compared to mice previously recorded in human subjects (average of 15.8 μm/s versus 5.7 μm/s). "The faster propagation speed of calcium in human astrocytes therefore has the potential to improve the computational speed of human brains" [45].

Most remarkable is the extremely rapid learning of auditory fear conditioning and three hippocampal-related memory test in the chimeric mice compared to their normal counterparts. This indicates the "importance of human astrocytes in the unique cognitive abilities of human brains" and "identify astrocytes as an important player in the improvement of cognitive abilities during

human evolution" [45]. One can only speculate on cognitive enhancements that may well occur if similar techniques are applied to species closer to humans, such as monkeys or closely related primates.

Human-specific genetic variations

Comparative analysis of genomic microarrays in mice, monkeys, chimpanzees and humans indicates that there have been significant modifications in the human genome that contribute to enhanced cognitive abilities [46].

On a cellular level, comparisons of genomic profiles of neurons, astrocytes and oligodendrocytes from birth to adulthood in mice show that as many, if not more, variations have occurred in astrocytes as neurons. In fact, these studies indicate that the term glia should be eliminated as an inclusive group, since astrocytes differ more genetically from oligodendrocytes than neurons [47]. Therefore, each brain cell type should be considered separate entities.

Two human-specific genes are of particular interest relative to the increased size and cognitive abilities of human brains. These are members of the Thrombospondin group of genes and the SRGAP2C SLIT-ROBO Rho GTPase activating protein 2C (SRGAP2C) paralog of the ancestral SRGAP2 SLIT-ROBO Rho GTPase activating protein 2 (SRGAP2A) gene.

Thrombospondin genes

Thrombospondins are astrocyte-secreted extracellular-matrix glycoproteins that control fetal synaptogenesis and neurite outgrowth [48–52].

One gene of the thrombospondin family, thrombospondin 4, occurs in adult humans and was "upregulated during human brain evolution" [53]. Most interesting is that the protein expression is primarily increased in adult forebrains, the most enlarged area of the human neocortex, that functions to facilitate abstract cognitive abilities and reasoning.

This is the "first gene expression changes in human evolution that involve specific brain regions, including portions of the cerebral cortex. Increased expression of thrombospondins in human brain evolution could result in changes in synaptic organization and plasticity, and contribute to the distinctive cognitive abilities of humans ..." [53].

SRGAP2C paralog of the ancestral SRGAP2A gene

Neoteny is one of the most important advances in human brain evolution that accounts significantly for increased brain size and intellectual development. The extended postnatal period of brain development, lasting until the age of thirty, permits experience-driven learning in a protected environment as dense synaptic connections, characteristic of human brains, slowly form relative to other primates.

An incomplete segmental duplication of ancestral SRGAP2 has recently been discovered that accounts for the neurological developmental characteristic of neoteny [54,55]. Importantly, this alteration is estimated to have occurred 2–3 million years ago, "corresponding to the transition from Australopithecus to Homo and the beginning of neocortex expansion" [55]. Furthermore, it is also present in Neanderthal DNA, another large brained hominid [54].

The ancestral SRGAP2 decelerates the migration of neurons and promotes maturation of dendritic spines within the developing cortex. However, the novel gene, SRGAC2, has the opposite effect. It antagonizes the actions on SRGAP2 at birth by promoting neuronal migration and slowing spine maturation. Subsequently, the dendrite spines become longer and more complex and numerous. These results in the high level of synaptic densities in the human cortical neuropil compared to other primates and rodents [11].

Discussion

RGCs are instrumental in timing and directing corticogenesis. Novel genetic variations in these cells, through the process of natural selection, may profoundly influence brain size and functions [56]. As discussed earlier, empirical data over the past two decades demonstrates that protoplasmic astrocytes in adult mammals are critical for brain information processing and integration essential for higher cognitive functions.

Human protoplasmic astrocytes, the most abundant cell in the brain, have a 27-fold increase in volume compared to their mouse counterparts [9,10]. Therefore, this exaptation contributes significantly to the massive increase in human brain size. This primate-specific astrocyte magnocellular exaptation must be considered one of the most important recent findings in comparative neuroanatomy and paleoneurology.

The functional roles of human protoplasmic astrocytes was forced to expand to accommodate the enormous increase in white matter needed to relay action potentials over wider areas of the expanded cortex as the human brain enlarged. Additionally, there was a concomitant decrease in the concentration of neurons relative to smaller brains. For instance, the adult mouse brain is estimated to have 142,000 neurons per mm^3, whereas elephants have 6000 per mm^3 [11].

Therefore, enormous pressures developed for alternatives to information processing and cognition as neurons became fastidious in order to maintain the rapid transfer of information encoded in actions potentials over ever-increasing distances. A logical conclusion is that the enormously enlarged human protoplasmic astrocytes and their exapted primate and human-specific cohorts assumed these sentient functions.

Conclusion

Cells within the astroglial lineage determine the phyletic expression of mammalian brains, including humans. The increased size and complexity of the human brain clearly correlates with astrocyte anatomical and functional exaptations and genetic variations. Furthermore, the earlier concept that neurons and glia are derived from separate progenitor cells has been dispelled. Therefore, there is no compelling evidence supporting a neurocentric role in human brain evolution.

Conflict of interest

None.

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