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Programmed to be human?

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Abstract

Pletikos et al., demonstrate in this issue of Neuron that the human neocortex has an “hourglass” temporal gene expression pattern with robust and dynamic transcriptome differences during the prenatal and adolescent/adult periods. Similar changes are not observed in the non-human primate – is this what makes us human?

Keywords

Neocortex; brain development; transcriptome; WGCNA; human uniqueness; evolution; asymmetry

Perhaps the biggest marvel of nature is the development of the human brain. It is estimated that an average human brain has ~86 billion neurons, >100 trillion synapses and > 100,000 miles of myelin-covered nerve fibers. The final organization of this immensely complex structure is dependent on merely 20,000 protein encoding genes, 23 pairs of chromosomes and 4 nucleotide bases (Table 1). Yet, the final product of development, the human brain, is a tridimensional jigsaw puzzle, made up by thousands of different kinds of projection neurons, local circuit neurons and glial cells. They are arranged in elaborate neural networks, serve special functions, and lead to a unique condition of being human. The anatomical, neurochemical and physiological differences across the different brain regions are tremendously complex, and the patterning and development of such an intricate system has been the focus of intense research endeavors for more than a century.

A particular characteristic of neocortical tissue is the precise specification and coordinated development of brain regions. Although this basic neocortical map is shared among mammals, there are multiple, unique organizational differences that are a hallmark of the human brain. Neurons are born from a uniform neuroepithelial sheet by a set of extracellular signals and transcription factor gradients acting on neocortical stem cells(Sansom and Livesey, 2009).Like other mammals, the human neocortical regions develop from rostral to caudal, but in humans the different cortical regions show distinct maturation rates(Levitt, 2003).The first areas to mature are those with the most basic functions such as senses and movement, while the prefrontal cortex, responsible for problem solving and reasoning is the last to fully develop (Gogtay et al., 2004). Synaptogenesis and synaptic pruning also show

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prominent inter-areal differences unique to humans(Huttenlocher and Dabholkar, 1997). Brain laterality emerges during the late mid-fetal period, becomes more prominent in early postnatal life, and develops in concert with functional neocortical asymmetry(Hill et al., 2010).

The current study by the Sestan laboratory analyzed the temporal dynamics and laterality of gene expression in human and macaque monkey neocortex(Pletikos et al., 2014).In an indirect way it asks a central question of our existence – what makes us human, and are we defined by our gene expression patterns? This clever, well designed study builds on their previous findings that there are robust transcriptional differences among topographically defined areas of the fetal and, to a lesser extent, adult human neocortex(Kang et al., 2011).The follow-up analysis of this already published and publicly available dataset, assessing the gene expression of 11 neocortical areas from 886 tissue samples from early fetal development to old age, revealed an inter-areal transcriptional divergence of an unexpected pattern. Pletikos, Sousa, Sedmak and colleagues uncovered a surprising “hourglass” pattern emerged over the lifespan that suggested robust and dynamic differences in the transcriptome in prenatal and adolescent/adult periods, but not during infancy and childhood in specific neocortical regions. The spatial pattern of inter-areal divergence was mainly driven by a subset of primary sensory and motor areas, such as primary visual cotex, and peri-limbic areas such as the medial frontal and inferior temporal cortices.

Pletikos, Sousa, Sedmak and colleagues hypothesized that the temporal hour glass pattern of neocortical transcriptome development was due to the differences in the underlying molecular and cellular processes that occurred at each time point. To test this, they performed an unbiased weighted gene co-expression network analysis (WGCNA) and annotated them using a secondary Gene Ontology analysis. This approach is well-suited to identify groups of co-expressed genes (“modules”) that are functionally related to each other (Mirnics, 2008). Not surprisingly, the fetal neocortex was uniquely enriched in transcripts related to developmental categories such as phosphoprotein, mitosis, cell cycle, cell morphogenesis, neuron differentiation, and development, and cell adhesion. In addition to temporal specificity, the fetal expression patterns also showed strong rostrocaudal specificity across the neocortical areas, which was lost during the postnatal period. In contrast, the adolescent/adult brains showed a different enrichment pattern primarily related to synaptic function and membrane events, encompassing transcripts encoding synaptic vesicles, plasma membrane transport, clathrin-coated vesicles, neurotransmitter binding, and monovalent inorganic cation transport. Adolescence and adulthood co-expression modules exhibited more stability over time and less complex spatial patterns than the fetal and infant brains. Taken together, these findings suggest that the transcriptome describes the different molecular processes at work: in the fetal brain, the construction of the brain areas is the driving force of the gene expression patterns, while the adolescent/adult brain is geared toward functional specification and refinement of the neocortical areas.

These patterns of gene expressions were, at least partially, unique to the human brain as quantitative PCR studies revealed that the inter-areal expression pattern of a set of selected genes was not very well correlated between the healthy human and the non-human primate brains and raise the possibility that the developmental program responsible for the precise patterning of the brain is species-specific. In other words, individual transcripts appear to act as common building blocks of the brain and it is their species-specific regulation that makes the brain of any species, including humans, unique. This argument is also strengthened by their finding that inter-areal differences in maturational rates of the human neocortexdo not strictly follow the global antero-posterior or medio-lateral neurogenetic gradients previously described in rodents.

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With the characterization of the temporal dynamics of inter-areal gene expression defining three phases of human neocortical development, the authors turned their attention to examining whether a left-right asymmetry of the developing transcriptome might also drive the lateralizatlion and functional specification of the human brain hemispheres. Disappointingly, this did not turn out to be the case:at the population level, the transcriptomes of the different brain areas were globally symmetric across the full course of human neocortical development and adulthood, suggesting that either the level of the resolution was too crude to detect the critical expression differences, or the hemispherical differences do not develop in a global transcriptome-dependent manner.

What can such an inter-areal, longitudinal, descriptive study tell us about the development and function of the human brain? First, it argues for three distinct phases of human brain development: a prenatal, genetics-driven patterning, a childhood, experience-driven functional specification, and an adolescent/adult regional refinement. From these, it is a significant finding that only the first and the third phase are predominantly gene expression-dependent. Second, as mentioned earlier, this study reminds us that the building blocks of the brain are quite similar across the various species while revealing that the exact gene expression pattern and its regulation over time is the critical driving force of the human brain development. This clearly orchestrated, tightly regulated and genetically encoded process, suggests that any deviation from this process early in life can result in neurodevelopmental disorders and depending on specific timing, might lead to preferential disruption of the various neocortical areas with distinct pathology later in life. Yet, as the developmental process proceeds to the stage with less inter-areal differential transcriptome activity, the deviation from the “typical” development at the “patterning stage” might not be obvious at the phenotypic level. Rather, the later “brain refinement phase” in adolescence, even without additional insults is the one that would likely uncover the behavioral manifestations of the disease: synaptic pruning, refinement of synaptic transmission, reorganization of neural networks, myelination and other processes reveal the long-existing, hidden deficits, leading to establishment of such diagnoses as schizophrenia or bipolar disorder.

There are at least three questions that emerge from the study. First, does the decline in inter-areal transcriptional divergence described from infancy thru childhood mean that human brain development is quiet and without significant refinement during this period of life? Not at all:the data merely suggest that this phase of development is not dominated by areal-driven gene expression patterns. Rather, the developmental events in this period of life are likely to be driven more by pan-neocortical transcriptional programs or post-transcriptional mechanisms that are dependent on activity and experience with input from subcortical brain regions potentially contributing to the maturation process.

Second, what is the relationship between morphological changes of a neuron and gene expression patterns? Clearly, gene-encoded expression changes can lead to changes in the morphology of neurons, but morphological changes have the potential to alter gene expression. This becomes particularly intriguing when considering changes in transcription that coincide with synaptic refinement or growth. Is the observed change in transcription driving the synapse elimination or are the observed gene expression changes the result of synapse elimination? The causal dynamics of this relationship remains much of a mystery to date, but vitro and in vivo experiments suggest that both mechanisms lilkely work in concert(citations).

Finally, the absence of an asymmetry in the inter-areal transcriptomes in the current analysis by Pletikos and colleagues leaves the long standing question of how brain asymmetry develops unanswered. The lateralization of brain functions emerges well before

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preadolescence(Hill et al., 2010) and the morphological left-right asymmetry appears to be the rule across various biological systems rather than the exception (Geschwind and Galaburda, 1985). Thanks to early seminal work by Broca, Wernicke, Sperry, and Geschwind it is clear the functional differences between the left and the right brain are even more striking than the anatomical differences (Hugdahl, 2005). For example, speech is a clearly lateralized, uniquely human process, and handedness is also a hemisphere-encoded process. Yet, if this is not driven by global changes in the transcriptome, does it depend on a very few number of transcripts, or it is regulated purely by activity-dependent mechanism? Are the epigenetic or non-coding RNA regulatory mechanisms the driving force of postnatal brain development? The symmetric inter-areal transcriptome in this study from the Sestan group will spur the field to identify the factors that establish this critical feature of the human neocortex.

It is staggering to be reminded how much we do not know about the development of our own brain. However, studies like this work by Pletikos, Sousa, Sedmak and colleagues advance our knowledge, and underscores that (regardless of significant limitations and confounds), post-mortem human brain tissue is a unique, essential resource for understanding brain function and disease pathophysiology of neuropsychiatric disorders. After all, we are a unique species, and for understanding our own individual phenotypic variability we must first decipher what is specific about homo sapiens.

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01	**Weight:** ~1,375 grams in male, ~1,275 grams in females
02	**Number of neurons:** ~86,000,000,000
03	**Number of synapses:** ~100,000,000,000,000
04	**Number of neocortical neurons:** >20,000,000,000
05	**Number of neocortical glial cells:** >35,000,000,000
06	**Asymmetry:** left side has 186,000,000 more neurons
07	**Total length of myelinated fibers:** ~100,000 miles
08	**Total length of blood vessels:** ~100,000 miles
09	**Number of fibers in corpus callosum:** ~250,000,000
10	**Body's energy usage:** 20%
11	**Energy generation:** 10–23 watts (could power a light bulb)
12	**Oxygen consumption:** 94% gray matter, 6% white matter
13	**Organic composition:** 60% fat
14	**Maximum transmission speed :** >250 mph
15	**Membrane surface area of neurons:** 25,000 m2
16	**Birth of neurons during peak of neurogenesis:** 250,000/minute
17	**Average loss of neocortical neurons:** ~85,000/day
18	**Sensory system input:** 11 million bits/second
19	**Conscious awareness of sensory input:** less than 50 bits/second
20	**Number of thoughts:** 70,000/day