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Transcriptomic insights into human brain evolution: acceleration, neutrality, heterochrony

Mehmet Somel[1], Rori Rohlfs[2] and Xiling Liu[3]

Primate brain transcriptome comparisons within the last 12 years have yielded interesting but contradictory observations on how the transcriptome evolves, and its adaptive role in human cognitive evolution. Since the human-chimpanzee common ancestor, the human prefrontal cortex transcriptome seems to have evolved more than that of the chimpanzee. But at the same time, most expression differences among species, especially those observed in adults, appear as consequences of neutral evolution at *cis*-regulatory sites. Adaptive expression changes in the human brain may be rare events involving timing shifts, or heterochrony, in specific neurodevelopmental processes. Disentangling adaptive and neutral expression changes, and associating these with human-specific features of the brain require improved methods, comparisons across more species, and further work on comparative development.

Addresses
[1] Department of Biology, Middle East Technical University, Ankara, Turkey
[2] Department of Integrative Biology, University of California, Berkeley, CA, USA
[3] Key Laboratory of Computational Biology, CAS-MPG Partner Institute for Computational Biology, Shanghai Institutes for Biological Sciences, Shanghai, China

Corresponding author: Somel, Mehmet (somel.mehmet@gmail.com, somel.mehmet@googlemail.com)

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Introduction

Humans are efficient cultural accumulators and niche constructors [1,2]. However, this is not because they are individually superior over other animals in every cognitive aspect. Chimpanzee performance in physical intelligence tests [3] or working memory tasks [4,5] appears comparable to infant or adult humans. The difference rather lies in human social intelligence and abilities, including spoken language, prosocial and cooperative behavior, and inclination to learn and teach [1,6•]. These characters, in turn, are associated with human-specific changes in brain development, anatomy, and physiology.

Comparative anatomical studies indicate that human and chimpanzee brain structure and developmental patterns closely resemble one another, relative to other primates (reviewed in [7–9]). Thus, most major characteristics of the human brain evolved in the great ape common ancestor. But species differences do exist, including three times more neurons and lower neuron density in the cortex, increased dendritic arbor, new connections, and prolonged development of the human brain relative to the chimpanzee brain (Table 1). The aim is, on the one hand, to predict the cognitive and behavioral consequences of these structural novelties; on the other, to identify the underlying human-specific genetic changes. The latter will inform on how human evolution unfolded, for example, whether it involved numerous genetic changes of small effect, or few with large effect. It can also allow partial reconstruction of human evolutionary history by comparison with extinct hominins with known genomes, such as Neanderthals and Denisovans (e.g. [10•,11,12]).

Evolutionary changes in brain structure, developmental timing, or neuronal physiology can arise from two types of effects. The first type is rather qualitative; it involves changes in protein activity through emergence of new genes, protein domains, or single amino acid changes. Between human and chimpanzee, coding differences are common (about two amino acids per ortholog), but most of these substitutions are predicted to be neutral [13]. Also, there exist very few human *de novo* genes [14,15]. The second type is relatively quantitative and involves expression changes, that is, changes in mRNA and protein abundance. These occur through *cis* effects (copy number, enhancer, promoter, UTR sequence changes) or *trans* effects (changes in transcription factor [TF], microRNA, DNA methyltransferase and chromatin modifier activity or post-translational modifications) [16].

Comparative developmental studies in animal models clearly demonstrate the role of gene expression changes, in the level, timing, location, or splicing pattern, as major contributors to the evolution of new forms and adaptive functions [17•,18]. Developmental expression changes are frequently driven by small alterations in *trans* effectors' coding or regulatory sequence, modifying gene expression networks and reorganizing existing modular processes (e.g. extension of progenitor mitotic activity).

Table 1

Anatomical, histological and molecular features of the human brain relative to those of chimpanzees.

A — Anatomy and connections
a. ~3 times larger volume; ~3 times more neurons; higher encephalization [105].
b. Higher proportion of neocortex, especially the prefrontal and temporal cortices; increased cerebellar connections; increased connections within the prefrontal cortex [8,105].
c. Slightly higher cortical folding (gyrification) in the neocortex, especially in the PFC [106].
d. Larger temporal cortex white matter [107].
e. Relative enlargement and increased left-right asymmetry in the Broca's area [108].
f. Expanded white-matter connection between frontal and temporal cortices, which could be related to language use [109].
g. Possible loss of a network hub in the medial PFC [110].
B — Cell types and histology
a. Higher glia to neuron ratio [38••].
b. Higher proportion of large spindle projection neurons in layer V (but little difference in pyrimidal or fusiform cells) [111].
c. Wider interneuronal spacing, or neuropil, in the PFC than in other cortical regions, indicating higher dendrite, spine, axon density [112,113] (a feature which develops after adolescence [114]).
d. Wider interneuronal spacing in the Broca's area [115].
e. Wider minicolumns and more interneuronal spacing on the left hemisphere [116].
f. Assymetry in interneuronal spacing in the left hemisphere [116].
g. Longer dendrites in cortical neurons [117]
h. Higher total number but lower density of von Economo neurons (spindle cells) [118].
C — Development and aging
a. Faster brain growth starting from 16 weeks of gestation [119] and continuing into infancy [120].
b. Faster PFC white matter volume growth during postnatal development [121].
c. Extended duration of cortical myelination [36].
d. Delayed peak of synapse numbers in PFC [64••] (but see [95]).
e. Relatively earlier initiation of white matter decay [122].
f. Prominent brain shrinkage at old age [123].
D — Physiology
a. Higher levels of resting-state brain activity in language areas [124].
b. Higher activity of metabolic pathways [22,30•,125,126].

Intuitively, developmental expression changes might have played similar roles in human brain evolution [19••]. Hence, once microarray technology became available, multiple groups moved to compare mRNA abundance between human and chimpanzee adult cortical regions and other tissues. The expectation was that a few genes would exhibit prominent activation shifts on the human lineage, and these could be readily associated with human-specific traits. On the contrary, the first studies found that hundreds to thousands of genes showed significant mRNA abundance differences between humans and chimpanzees [20,21••,22], most with ambiguous functional roles. Furthermore, many of these species differences were shared across brain regions with distinct functions [23] (reviewed in [24]).

Human acceleration?

Despite this initial disappointment, some of the early studies found an excess of gene expression change on the human lineage, or human acceleration. One study detected five times more human-specific expression changes than chimpanzee-specific ones, and only in the brain, but not blood or liver [21••]. Another found dozens of genes with elevated expression only in humans, including genes with roles in synaptic plasticity (e.g. calcium/calmodulin-dependent protein kinase II alpha, *CAMK2A*, and carbonic anhydrase II, *CA2*) [20].

Human brain acceleration is intriguing, as the brain transcriptome is highly conserved compared to most other tissues, and brain-specific genes' coding sequences are under strong negative selection [25,26•]. Also notably, these studies had investigated expression levels in the prefrontal cortex (PFC), a region involved in high order, partly human-specific cognitive processes such as abstract thinking and planning [27]. An abundance of human-specific molecular changes in a highly conserved tissue with human-specific functions was suggestive of adaptive evolution. It supported the old notion that the human brain transcriptome divergence could explain human cognitive divergence [19••].

Subsequent work, however, revealed equivocal results. Some, using different brain regions [22] or technology [28], reported similar magnitude of change on the human- and chimpanzee lineages. Another found higher similarity between human and gorilla brain transcriptomes than with the chimpanzee, implying chimpanzee acceleration (although the effect here was not quantified) [26•].

Yet others reported human acceleration but in specific contexts. An investigation into metabolome and metabolite-related enzymes did find more adult human-specific changes in the PFC than chimpanzee-specific changes