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How evolution informs the fate of ancient inhibitory interneurons, in relationship to the cerebrospinal fluid contacting neurons, in the human neocortex

Alexandra Kunz[1], Andras Csokay[2]
[1] *Harvard University (Extension), Cambridge, MA, USA*
[2] *Department of Neurosurgery, BAZ County Hospital, Miskolc, Hungary*

Introduction: 600 Mya marks an evolutionary milestone: 1st internal fluid brain-tissue environment: the chordate lancelet's hindbrain inhibitory interneurons (INS) in direct contact with cerebrospinal fluid-contacting (CSF-c) neurons, whose cilia transduced diffusible growth-promoting, non-synaptic signals to INS' progenitor cell bodies. In time with evolutionary increases of INS in phylogenetically differentiated vertebrates, the CSF-c neurons migrated from the ventricles, communicating now synaptically, their cilia extending into intracellular fluid.

Methods: This paper explores the ontological fate of evolutionary ancient interneurons/their significance for human neocortex functioning.

Results/Discussion: Energy metabolism sets humans apart from primates: evolutionary increases in synaptic signaling/connectivity, quadrupled glial cells, an unexpected 46% greater glial:neuron density, $p<0.001$. INS' **energy efficiency** exceeds excitatory neurons': 85% energy consumption associated with excitatory glutamate recycling, using *both* glycolytic/glycogenolytic processes, *only* glycolytic ATP for INS' synaptic-cleft recycling.
Key in evolution's INS' origins is recruitment of other mechanisms of greater number/diversity for primates'/human's neocortex: primitive vertebrate lampreys' (450Mya) INS' circuits devoid of sense organs/pallium/ geniculate eminence (GE); vertebrate gnathostomes' (350Mya) INS' *tangential* migration from GE to pallium highly conserved; INS' competence to enter neocortex subventricular zone (SVZ) established in amniotes (310Mya); competence to enter cortical plate (CP) from GE, mammalian unique (185-210Mya). 40Mya primates' INS' number/diversity/complexity increased more than excitatory neurons': a pre-existing developmental mechanism's boosting, a **bipartite process**: INS' lateral ventricular neuroepithelium progenitors migrating *radially.*
Relaxed phylogenetic brain/body constraints to a behavioral evolutionary shift was the adaptive force for anthropoid primates' **social acumen**. An extrinsic supply neuromodulators for behavioral flexibility, dopamine(DA), acetylcholine(ACh), serotonin(5-HT) with slower/longer neuromodulation, altered INS' terminal neocortical axon patterns; humans'/chimps' axonal density increased as DA/5-HT/ACh "coils"/"clusters" for plasticity; subtle human evolutionary shift favored cortex layers V/VI's increased innervation, $p<0.05$.

Conclusion: Evolutionary ancient INS were vitally important to brain function 600 Mya; their legacy today ontologically as neocortical INS help define our preeminent human identity.