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LETTER TO THE EDITOR

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GOING BEYOND BRAIN SIZE: AN EVOLUTIONARY OVERVIEW OF SEROTONERGIC REGULATION IN HUMAN HIGHER CORTICAL FUNCTIONS

CHALLENGING TRADITIONAL CONCEPTS ON BRAIN ANATOMY

Historically, anthropology has focused on brain volume size as a principal indicator of human intelligence. The theory of brain size/encephalisation as a correlative of intelligence in *H. sapiens* is both limited and unclear in describing the complexity of human cognitive abilities (Saniotis *et al.* 2019). We would argue that neurochemical regulation such as the serotonergic system plays an important role in human cognitive abilities. Large mammalian brains contain a number of intersecting neural circuits that can continue to work incessantly and produce a large number of neural stimuli as evidenced in schizophrenia or in epilepsy. In this situation the efficient adaptive work of the central nervous system is not dependent so much on the number of neuronal connections that are present – as there is an abundance of those – as it is on orderly selective inhibition of some inputs that would overstimulate and confuse executive signalling of body's systems.

The serotonergic system probably evolved during the Cambrian era (550 Ma ago) when multicellular species began to appear. This system has been remarkably preserved for over 500 million years (Allman 1999). In humans, serotonin (5HT) is involved in learning, memory, sleep, sociality and cortical regulation (Azmitia 1999, Patrick, Ames 2015).

Serotonin has been hypothesised to regulate impulse control and modulate inhibition. Dysfunction

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in the serotonergic system has been implicated with various mental disorders (schizophrenia, ADHD, bipolar, depression, impulse behaviour) (Patrick, Ames 2015) as well as with triggering adult hippocampal neurogenesis (Klempin *et al.* 2010).

It should be noted that approximately 95% of serotonin is produced, stored and released not in the brain, but by the enteric microbiome mainly by enteroendocrine cells in the intestinal mucosa (Waclawikova, El Aidy 2018).

SEROTONERGIC REGULATION IN HIGHER CORTICAL FUNCTIONS

While the different types of serotonin receptor sites are not fully understood, a variety of serotonin receptors is known to modulate and moderate higher cortical functions in the human brain, especially behavioural inhibition (Azmitia 1999, Raghanti *et al.* 2010, Soubrié 1986). This ability to instigate "self control in delay maintenance tasks" in order to attain future reward is also evident in chimpanzees (Raghanti *et al.* 2010, Beran, Evans 2006). Humans and chimpanzees also seem to have denser serotonergic input in layers V/VI in the 9 and 32 areas of the prefrontal cortex (PFC) (Raghanti *et al.* 2008). Consequently, it has been hypothesised that greater density of serotonergic afferents in the infragranular layers of the PFC of humans and chimpanzees may have augmented behavioural inhibition and gratification delay (Raghanti *et al.* 2010).

According to Lew *et al.* (2019), serotonergic receptive neurons in the amygdala correlate with human evolutionary social patterns. In their comparative study between humans, bonobos and

TABLE 1: Mean serotonin transporter immunoreactive (SERT-ir) axon density (μm/μm^3) in humans, bonobos and chimps. Adapted from Simpson (2015) and Lew *et al.* (2019).

Species	Central nucleus	Accessory basal nucleus	Basal nucleus	Lateral nucleus
Humans	0.00656	0.00572	0.00458	0.00368
Bonobos	0.00481	0.00306	0.00543	0.00407
Chimps	0.00288	0.00257	0.00279	0.00316

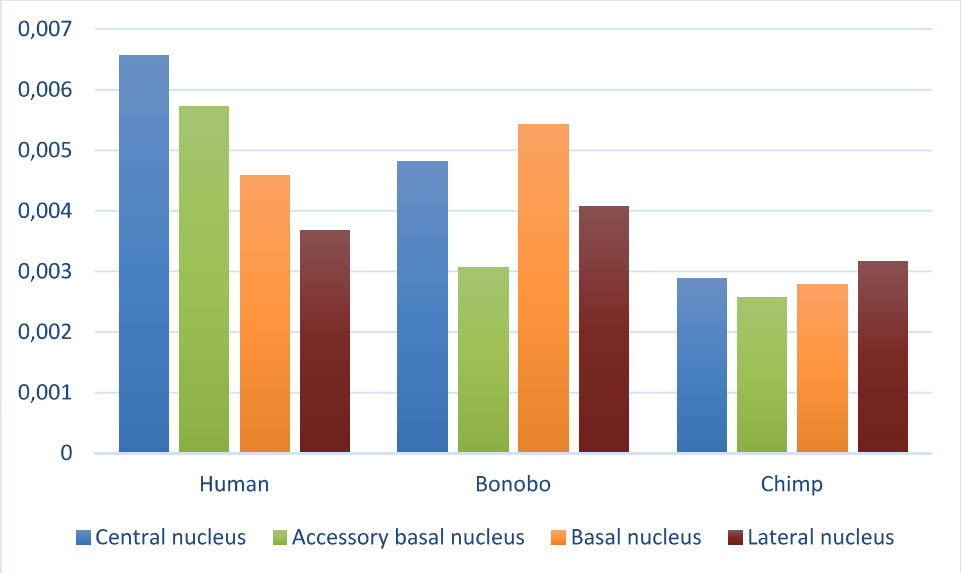

FIGURE 1: Mean SERT-ir axon density (μm/μm^3) in humans, bonobos and chimps. Adapted from Simpson (2015) and Lew *et al.* (2019).

chimps, there was greater serotonergic innervation in the amygdala in humans and bonobos suggesting that both species have increased "behavioral flexibility in response to social stimuli" (Lew *et al.* 2019). Their study also highlights the importance of serotonergic influence on subcortical structures in facilitating behavioural complexity and greater emotional control to environmental stimuli. One explanation for species' variation in serotonergic innervation of the amygdaloid is that the limbic system underwent selective pressures which facilitated prosocial behaviours – necessary for enhanced cooperation and problem solving (Lew *et al.* 2019, Hare *et al.* 2007).

An earlier experiment hypothesised that the amount of serotonin in the orbito-frontal region of vervet monkeys correlated to pro-social or anti-social behaviours (Raleigh *et al.* 1991). Their conclusion was that higher levels of serotonin fostered more pro-social behaviour and inhibited anti-social behaviour. Furthermore, it was found that subordinate vervet monkeys which were administered serotonin markers increased dominance by exhibiting mutuality and creating group support. Interestingly, during this period aggressive behaviour noticeably decreased in these treated monkeys in favour of affiliative activity (Ziomkiewicz-Wichary 2016).

According to a neurochemical hypothesis of human cognition, striatal serotonin levels in early hominins may have been associated with decreasing impulse control vital for fostering cooperative activities with social others such as tool making, cooperative subsistence activities and language (Raghanti *et al.* 2018). Additionally, there have been few studies on cooperative behaviours during human evolution and their neurohormonal basis. For example, both human and non-human animals show marked variation in co-operative behaviours (Raihani, Bshary 2011).

Another serotonergic theory of hominin evolution purports that periods of starvation in evolutionary environments placed energy demands on neuro-hormonally complex hominin brains, especially affecting more energetic male brains. Intermittent

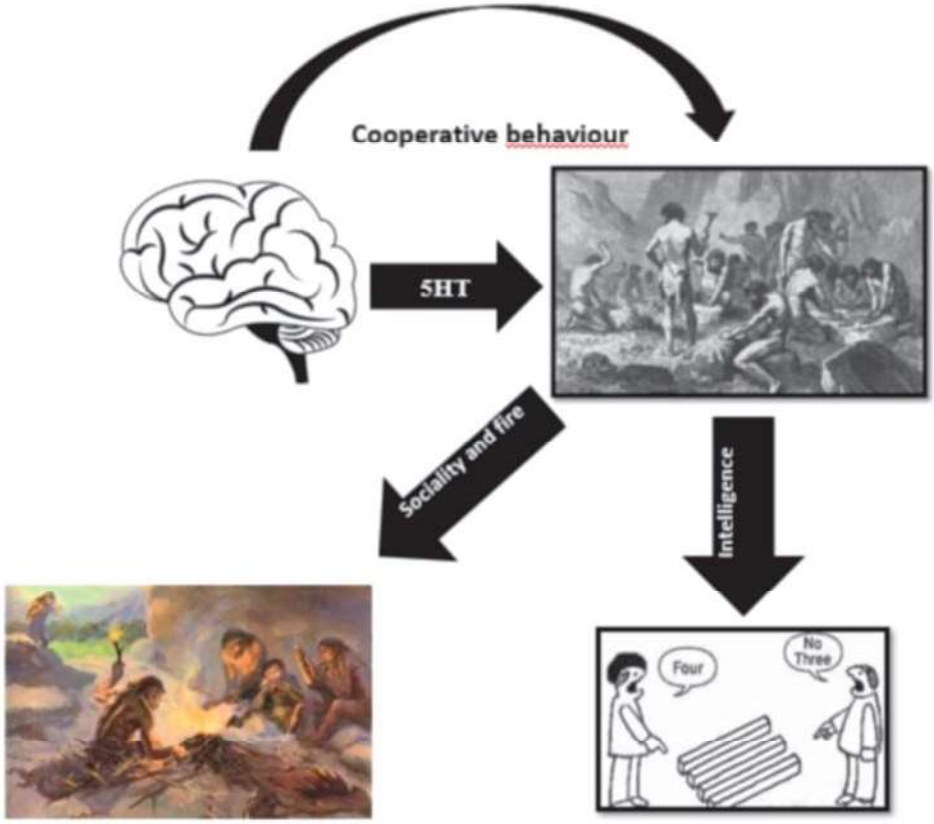

FIGURE 2: Correlation between serotonin and higher order cortical functions in ancestral hominins. For example, increasing social cooperation which led to social complexity in human societies.

periods of starvation could have resulted in decreasing neuromembrane cholesterol concentrations, leading to lowering of serotonin pre-synaptic re-uptake. Thus, reduced serotonin may have prompted ancestral males to become more impulsive and engage in high risk behaviours such as hunting. Consequently, this neurophysiological process may have led to diminished aggression as hunting demanded high cooperation between males leading to greater food sharing and affiliative behaviour between other group members (Wallner, Machatschke 2009).

Both Ziomkiewicz-Wichary (2016) and Kiser *et al.* (2012) note that while aggressiveness and physical strength may have defined social dominance amongst ancestral hominins, it was affiliative and co-operative behaviour that was required for maintaining group ties. Thus, the serotonergic system would have been important in informing both dominant/aggressive and co-operative behaviours (Ziomkiewicz-Wichary 2016).

It is plausible that the social manipulation of serotonin in post Neolithic societies might have been intrinsic to further reducing non-conformist behaviours, delaying of gratification and up-regulating impulse control mechanisms which were crucial for developing complex, stratified societies (Allman 1999) and for fostering cognitive flexibility (Raghanti *et al.* 2018). Additionally, current use of neurotransmitter agonists and antagonists for treating neurohormonal dysregulation supports the role of serotonin and other neurotransmitters in human cognitive abilities (Saniotis *et al.* 2019).

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